

Treatment Modalities in Oral Cancer: Current Practices and Future Perspectives

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Abstract: Oral cancer, predominantly oral squamous cell carcinoma (OSCC), is a major global health concern, particularly in developing countries, with significant morbidity and mortality (1–3). Despite advances in diagnostic and therapeutic strategies, the overall 5-year survival rate remains approximately 50–60%, largely due to late-stage diagnosis, recurrence, and therapeutic resistance (1,4). Major risk factors include tobacco use, alcohol consumption, and human papillomavirus (HPV) infection (5,6).

The pathogenesis of oral cancer involves complex molecular mechanisms, including genetic mutations and dysregulation of key signaling pathways such as p53 and EGFR, contributing to tumor progression and metastasis (7,8). Conventional treatment modalities—surgery, radiotherapy, and chemotherapy—remain the cornerstone of management (9,12,14). However, these approaches are often associated with significant toxicity and functional impairment.

Recent advances in treatment strategies have introduced targeted therapy and immunotherapy as promising alternatives. Agents such as cetuximab and immune checkpoint inhibitors, including nivolumab and pembrolizumab, have demonstrated improved outcomes in advanced and recurrent cases (16–18). Additionally, emerging approaches such as gene therapy, photodynamic therapy, and nanotechnology-based drug delivery systems offer new avenues for improving therapeutic efficacy and reducing systemic toxicity (19–21).

The integration of precision medicine, based on molecular profiling and biomarker identification, is further transforming oral cancer management by enabling personalized treatment strategies (22). This review highlights current treatment modalities and explores future directions aimed at improving survival and quality of life in patients with oral cancer.

Keywords: Oral Cancer; Oral Squamous Cell Carcinoma; OSCC; Treatment Modalities; Surgery; Radiotherapy; Chemotherapy; Immunotherapy; Targeted Therapy; Precision Medicine.

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I. INTRODUCTION

Oral cancer represents a significant proportion of head and neck malignancies worldwide, with oral squamous cell carcinoma (OSCC) accounting for nearly 90% of all cases (2). According to global cancer statistics, oral cancer contributes substantially to the overall cancer burden, particularly in low- and middle-income countries (1). The disease is especially prevalent in South Asia, including India, where lifestyle factors such as tobacco chewing, smoking, and alcohol consumption are highly prevalent and strongly associated with increased incidence (3,5).

In addition to traditional risk factors, emerging evidence highlights the role of oncogenic viruses, particularly human papillomavirus (HPV), in the etiology of a subset of oral and oropharyngeal cancers (6). The interplay of environmental exposures and genetic susceptibility leads to the accumulation of molecular alterations, including mutations in tumor suppressor genes and activation of oncogenic signaling pathways such as EGFR and PI3K/Akt, which drive carcinogenesis (7,8).

Despite significant advances in diagnostic techniques and therapeutic modalities, the overall 5-year survival rate for oral cancer remains relatively low, at approximately 50–60% (1,4). This poor prognosis is primarily attributed to delayed diagnosis, as many cases are detected at advanced stages, along with high rates of local recurrence and regional metastasis. Furthermore, tumor heterogeneity and resistance to conventional therapies contribute to treatment failure and disease progression (7).

The management of oral cancer requires a comprehensive and multidisciplinary approach involving surgery, radiotherapy, and chemotherapy, tailored according to tumor stage, location, and patient factors (9,12,14). Surgery remains the primary modality for early-stage disease, while advanced stages often require combined approaches such as chemoradiotherapy to improve survival outcomes. However, these treatments are frequently associated with significant functional and aesthetic impairments, affecting speech, swallowing, and overall quality of life (11,13).

In recent years, advances in molecular oncology and translational research have led to the development of novel therapeutic strategies, including targeted therapy and immunotherapy, which aim to improve treatment efficacy and reduce toxicity (16–18). These emerging modalities, along with innovations in precision medicine, are expected to play a pivotal role in the future management of oral cancer.

II. ETIOLOGY AND RISK FACTORS

The development of oral cancer is multifactorial, involving a combination of environmental, lifestyle, viral, and genetic factors. Among these, tobacco use and alcohol

consumption are the most significant and well-established risk factors, acting synergistically to increase carcinogenic potential (3,5). Tobacco contains numerous carcinogens, such as nitrosamines and polycyclic aromatic hydrocarbons, which induce DNA damage and mutations in oral epithelial cells. Alcohol enhances mucosal permeability, facilitating the penetration of these carcinogens and further promoting malignant transformation (5).

Smokeless tobacco products, including betel quid and gutka, are particularly associated with oral cancer in South Asian populations, contributing to the high regional incidence (3). Chronic exposure leads to precancerous lesions such as leukoplakia and erythroplakia, which may progress to malignancy if left untreated.

In addition to chemical carcinogens, viral infections, particularly high-risk human papillomavirus (HPV), have been implicated in the pathogenesis of a subset of oral cancers. HPV-16 is the most commonly associated subtype and contributes to carcinogenesis through the expression of viral oncogenes E6 and E7, which inactivate tumor suppressor proteins such as p53 and retinoblastoma (Rb) protein (6).

Genetic and molecular alterations also play a crucial role in oral carcinogenesis. Mutations in tumor suppressor genes, especially p53, result in loss of cell cycle control and impaired apoptosis. Furthermore, activation of oncogenic signaling pathways, including epidermal growth factor receptor (EGFR) and phosphoinositide 3-kinase (PI3K)/Akt pathways, promotes cell proliferation, survival, and invasion (7). These molecular events, combined with epigenetic modifications, contribute to the initiation and progression of oral cancer.

Additional risk factors include poor oral hygiene, chronic mechanical irritation, nutritional deficiencies, and immunosuppression, all of which may contribute to increased susceptibility to malignant transformation (2,3).

III. PATHOGENESIS OF ORAL CANCER

Oral carcinogenesis is a complex, multistep process involving the accumulation of genetic and epigenetic alterations that transform normal oral epithelium into invasive carcinoma. This progression typically follows a sequence from hyperplasia to dysplasia, carcinoma in situ, and eventually invasive squamous cell carcinoma (7).

At the molecular level, carcinogenesis is driven by disruptions in key regulatory pathways controlling cell proliferation, differentiation, and apoptosis. Mutations in tumor suppressor genes such as p53, along with activation of oncogenes, lead to uncontrolled cellular growth and resistance to programmed cell death (7,8).

The concept of the “hallmarks of cancer” provides a framework for understanding tumor development, including sustained proliferative signaling, evasion of growth suppressors, resistance to cell death, induction of angiogenesis, and activation of invasion and metastasis (8). In oral cancer, these hallmarks are manifested through increased cellular proliferation, angiogenic signaling mediated by vascular endothelial growth factor (VEGF), and degradation of extracellular matrix components facilitating invasion.

The tumor microenvironment also plays a critical role in disease progression. Interactions between cancer cells, stromal cells, immune cells, and extracellular matrix components create a supportive niche for tumor growth and metastasis (7). Chronic inflammation further contributes to carcinogenesis by promoting DNA damage and enhancing proliferative signaling.

IV. CLASSIFICATION AND STAGING

Accurate classification and staging of oral cancer are essential for determining appropriate treatment strategies and predicting prognosis. Histologically, oral cancers are predominantly squamous cell carcinomas, although variants such as verrucous carcinoma and salivary gland tumors may also occur (2).

The Tumor–Node–Metastasis (TNM) staging system is widely used to classify oral cancer based on tumor size and extent (T), regional lymph node involvement (N), and presence of distant metastasis (M) (4). This system provides a standardized approach for assessing disease severity and guiding clinical decision-making.

Early-stage cancers (Stages I and II) are typically localized and may be effectively treated with single-modality therapy, such as surgery or radiotherapy (9). In contrast, advanced-stage cancers (Stages III and IV) often exhibit regional lymph node involvement and/or distant metastasis, necessitating multimodal treatment approaches, including surgery combined with radiotherapy and chemotherapy (9,14).

Staging also plays a crucial role in prognostication, as survival rates decrease significantly with advancing stage. Early detection is therefore critical for improving outcomes. Additionally, advances in imaging techniques and molecular diagnostics are enhancing the accuracy of staging and enabling more precise treatment planning (4,7).

V. CONVENTIONAL TREATMENT MODALITIES

The management of oral cancer relies primarily on conventional treatment modalities, including surgery, radiotherapy, and chemotherapy. The choice of treatment depends on tumor stage, location, histopathological characteristics, and patient-related factors. In many cases, a

combination of these modalities is required to achieve optimal outcomes (9,14).

➤ *Surgery*

Surgery remains the cornerstone of treatment for resectable oral cancer, particularly in early-stage disease (9). The primary objective of surgical management is the complete removal of the tumor with adequate margins to minimize the risk of local recurrence. Surgical procedures vary depending on tumor size and location and may include wide local excision, partial or total glossectomy, mandibulectomy, and maxillectomy.

In addition to primary tumor resection, management of regional lymph nodes through neck dissection is often necessary, as cervical lymph node metastasis is a major prognostic factor in oral cancer (9). Depending on the extent of disease, selective, modified, or radical neck dissection may be performed.

Reconstruction following tumor resection plays a critical role in restoring function and aesthetics. Microvascular free flap techniques, such as fibula free flaps and radial forearm flaps, have significantly improved postoperative outcomes by enabling restoration of speech, mastication, and swallowing functions (10).

Despite these advancements, surgical treatment is associated with significant morbidity, including functional impairments such as difficulty in speech, swallowing (dysphagia), and chewing, as well as cosmetic deformities that can impact the patient’s quality of life (11). Postoperative complications may include infection, bleeding, and flap failure.

➤ *Radiotherapy*

Radiotherapy is an essential component in the management of oral cancer and may be used as a primary treatment modality, as an adjuvant following surgery, or for palliative purposes in advanced disease (12). It works by delivering ionizing radiation that induces DNA damage, leading to tumor cell death.

Technological advancements have significantly improved the precision and effectiveness of radiotherapy. Techniques such as intensity-modulated radiotherapy (IMRT) allow for targeted delivery of radiation to the tumor while sparing surrounding healthy tissues, thereby reducing treatment-related toxicity (12).

Radiotherapy is particularly useful in cases where surgical resection is not feasible or when there is a high risk of residual disease after surgery. It is also commonly combined with chemotherapy (chemoradiotherapy) to enhance treatment efficacy in locally advanced cancers (14).

However, radiotherapy is associated with several acute and chronic side effects. Acute complications include oral mucositis, pain, and taste alterations, while chronic effects include xerostomia (dry mouth), fibrosis, dental caries, and osteoradionecrosis of the jaw (13). These adverse effects can significantly affect oral function and quality of life.

➤ *Chemotherapy*

Chemotherapy plays a crucial role in the management of oral cancer, particularly in advanced stages. It is used in various settings, including neoadjuvant (before surgery), adjuvant (after surgery), and concurrent therapy with radiotherapy (14).

Cisplatin-based regimens are the most commonly used chemotherapeutic protocols in oral cancer. Other agents, such as 5-fluorouracil and taxanes, may also be used in combination to enhance therapeutic efficacy (14). Chemotherapy works by interfering with DNA synthesis and cell division, thereby targeting rapidly proliferating cancer cells.

Concurrent chemoradiotherapy has been shown to improve locoregional control and overall survival in patients with advanced oral cancer compared to radiotherapy alone (15). However, the benefits of chemotherapy are often limited by significant systemic toxicity, including nausea, vomiting, nephrotoxicity, myelosuppression, and mucositis.

Another major limitation is the development of drug resistance, which reduces treatment effectiveness and contributes to disease recurrence and progression (14,15).

➤ *Multimodal Therapy*

Multimodal therapy, involving a combination of surgery, radiotherapy, and chemotherapy, is the standard approach for managing advanced-stage oral cancer (9,14). This integrated approach aims to maximize tumor control, reduce recurrence, and improve overall survival.

For example, patients with locally advanced disease often undergo surgical resection followed by adjuvant radiotherapy or concurrent chemoradiotherapy, especially in the presence of high-risk features such as positive margins or lymph node involvement (9).

Although multimodal therapy has significantly improved treatment outcomes, it is associated with increased treatment-related morbidity and complications. Patients may experience severe functional impairments, including difficulties in speech, swallowing, and nutrition, along with psychological and social challenges (13,15).

Therefore, treatment planning requires careful consideration of the balance between therapeutic benefits and potential adverse effects, emphasizing the importance of a multidisciplinary approach and supportive care.

VI. EMERGING TREATMENT MODALITIES

Recent advances in molecular biology and cancer therapeutics have led to the development of novel treatment strategies that aim to improve efficacy, reduce toxicity, and overcome resistance associated with conventional therapies. These emerging modalities are transforming the management of oral cancer, particularly in advanced and recurrent cases.

➤ *Targeted Therapy*

Targeted therapy focuses on specific molecular pathways involved in tumor growth, progression, and survival. Unlike conventional chemotherapy, which affects both normal and cancer cells, targeted therapies selectively act on cancer-specific molecular abnormalities, thereby reducing systemic toxicity (16).

One of the most important targets in oral cancer is the epidermal growth factor receptor (EGFR), which is frequently overexpressed in oral squamous cell carcinoma and is associated with poor prognosis. Agents such as cetuximab, a monoclonal antibody against EGFR, inhibit receptor signaling, thereby reducing tumor cell proliferation, angiogenesis, and metastasis (16).

Other molecular targets include vascular endothelial growth factor (VEGF), which plays a critical role in tumor angiogenesis. Inhibition of VEGF pathways reduces tumor vascularization and limits tumor growth. Despite their advantages, targeted therapies may still lead to resistance due to mutations in signaling pathways and activation of alternative pathways.

➤ *Immunotherapy*

Immunotherapy has emerged as a revolutionary approach in the treatment of oral cancer by harnessing the body's immune system to recognize and eliminate cancer cells. Immune checkpoint inhibitors targeting programmed cell death protein-1 (PD-1) and its ligand PD-L1 have shown significant clinical benefits in recurrent and metastatic oral cancers (17,18).

Agents such as nivolumab and pembrolizumab block inhibitory immune pathways, thereby enhancing T-cell-mediated anti-tumor responses. These therapies have demonstrated improved overall survival and durable responses in patients who do not respond to conventional treatments (17,18).

However, immunotherapy is associated with immune-related adverse effects, including dermatitis, colitis, hepatitis, and endocrinopathies, due to overactivation of the immune system. Additionally, only a subset of patients responds to immunotherapy, highlighting the need for predictive biomarkers.

➤ *Gene Therapy*

Gene therapy represents an innovative approach aimed at correcting genetic abnormalities underlying oral cancer. This strategy involves the introduction of functional genes into cancer cells to restore normal cellular processes or induce tumor cell death (19).

Approaches include:

- Replacement of mutated tumor suppressor genes (e.g., p53)
- Introduction of genes that enhance immune response
- Use of suicide genes that selectively kill cancer cells

Although gene therapy holds significant promise, its clinical application remains limited due to challenges such as efficient gene delivery, immune reactions, and high cost. Ongoing research is focused on improving delivery systems and enhancing therapeutic efficacy.

➤ *Photodynamic Therapy (PDT)*

Photodynamic therapy (PDT) is a minimally invasive treatment modality that involves the administration of a photosensitizing agent followed by exposure to a specific wavelength of light. This interaction generates reactive oxygen species that induce selective destruction of tumor cells (20).

PDT is particularly useful for early-stage lesions, superficial tumors, and precancerous conditions. Advantages of PDT include:

- Minimal damage to surrounding healthy tissues
- Preservation of organ function
- Repeatability of treatment

However, limitations include limited tissue penetration of light and reduced effectiveness in deep or advanced tumors.

➤ *Nanotechnology-Based Therapy*

Nanotechnology-based therapies utilize nanoparticles for targeted drug delivery, improving the pharmacokinetics and bioavailability of anticancer agents. Nanocarriers can be engineered to deliver drugs directly to tumor cells, thereby minimizing systemic toxicity and enhancing therapeutic efficacy (21).

These systems include:

- Liposomes
- Polymeric nanoparticles
- Gold nanoparticles

Nanotechnology also enables combination therapy by delivering multiple drugs simultaneously and may facilitate early detection through nanoscale diagnostic tools. Despite promising results, challenges such as safety, cost, and large-scale production need to be addressed before widespread clinical application.

VII. ROLE OF PRECISION MEDICINE

Precision medicine represents a paradigm shift in cancer treatment, focusing on individualized therapy based on genetic, molecular, and clinical characteristics of each patient. In oral cancer, advances in genomics and molecular profiling have enabled the identification of specific biomarkers that can guide treatment selection and predict therapeutic response (21,22).

Biomarker-driven approaches allow clinicians to:

- Identify patients who are likely to benefit from targeted therapy or immunotherapy
- Avoid ineffective treatments
- Reduce treatment-related toxicity

Technologies such as next-generation sequencing (NGS) and liquid biopsy are increasingly being used to detect genetic mutations and monitor disease progression in a minimally invasive manner (22).

Precision medicine also plays a critical role in overcoming challenges such as tumor heterogeneity and drug resistance by enabling adaptive and personalized treatment strategies. As research advances, integration of artificial intelligence and big data analytics is expected to further enhance the effectiveness of precision oncology.

VIII. SUPPORTIVE AND PALLIATIVE CARE

Supportive and palliative care play a crucial role in the comprehensive management of oral cancer, particularly in advanced stages where curative treatment may not be feasible. The primary goal is to improve the patient's quality of life by alleviating symptoms, managing treatment-related side effects, and providing psychological and social support (11,13).

Pain management is a fundamental component of supportive care, as patients with oral cancer often experience significant pain due to tumor invasion or treatment-related mucositis. Analgesic regimens, including nonsteroidal anti-inflammatory drugs (NSAIDs) and opioids, are commonly used based on pain severity.

Nutritional support is equally important, as many patients suffer from difficulty in chewing and swallowing (dysphagia), leading to malnutrition and weight loss. Enteral feeding methods, such as nasogastric tubes or gastrostomy, may be required in severe cases to maintain adequate nutritional status.

Rehabilitation services, including speech and swallowing therapy, are essential for restoring functional abilities following surgery or radiotherapy. Additionally, psychological counseling and social support help patients cope with emotional distress, anxiety, and depression associated with cancer diagnosis and treatment (11).

Palliative care also includes the management of complications such as xerostomia, infections, and osteoradionecrosis, which can significantly impact oral function and overall well-being (13).

IX. CHALLENGES IN ORAL CANCER TREATMENT

Despite significant advancements in therapeutic approaches, several challenges continue to hinder effective management of oral cancer. One of the major issues is late diagnosis, as many patients present with advanced-stage disease due to lack of awareness, limited access to healthcare, and absence of early screening programs (3).

- Tumor heterogeneity represents another critical challenge, as variations in genetic and molecular characteristics within and between tumors lead to unpredictable treatment responses and disease progression (7,22).
- Drug resistance, both intrinsic and acquired, significantly limits the effectiveness of chemotherapy and targeted therapies. Cancer cells develop mechanisms to evade therapeutic effects, resulting in treatment failure and recurrence (14,15).
- Treatment-related toxicity is also a major concern, particularly with chemotherapy and radiotherapy, which can cause severe side effects such as mucositis, xerostomia, immunosuppression, and organ damage, ultimately affecting patient compliance and quality of life (13).

Furthermore, limited access to advanced therapies, including immunotherapy and precision medicine, remains a significant barrier in low- and middle-income countries due to high costs and inadequate healthcare infrastructure (3,22). Addressing these challenges is essential for improving treatment outcomes and reducing the global burden of oral cancer.

X. FUTURE PERSPECTIVES

The future of oral cancer management lies in the development of innovative and more effective therapeutic strategies aimed at improving early detection, treatment precision, and patient outcomes. One promising approach is combination immunotherapy, where immune checkpoint inhibitors are used alongside chemotherapy, radiotherapy, or targeted therapy to enhance anti-tumor responses and overcome resistance (17,18).

The integration of artificial intelligence (AI) in oncology is expected to revolutionize diagnosis and treatment planning. AI-based tools can assist in early detection, image analysis, risk assessment, and prediction of treatment outcomes, thereby enabling more accurate and personalized care (22).

Liquid biopsy is an emerging non-invasive diagnostic technique that detects circulating tumor DNA (ctDNA), circulating tumor cells (CTCs), and other biomarkers in body fluids. This approach allows for early detection, real-time monitoring of disease progression, and assessment of treatment response (22).

Another groundbreaking development is CRISPR-Cas9 gene editing technology, which has the potential to precisely modify genetic mutations associated with cancer. This approach could lead to targeted correction of oncogenic alterations and improved therapeutic outcomes in the future (19).

Advances in nanotechnology, biomarker discovery, and precision medicine are also expected to contribute significantly to the development of individualized treatment strategies, ultimately improving survival rates and reducing treatment-related morbidity (21,22).

XI. CONCLUSION

Oral cancer remains a major global health challenge, with significant morbidity and mortality despite advances in diagnosis and treatment. Conventional treatment modalities, including surgery, radiotherapy, and chemotherapy, continue to form the foundation of oral cancer management. However, these approaches are often associated with considerable functional impairment, toxicity, and limited effectiveness in advanced stages (9,14).

Recent developments in emerging therapies, such as targeted therapy, immunotherapy, gene therapy, and nanotechnology-based approaches, have significantly expanded the therapeutic landscape and offer promising improvements in treatment outcomes (16–18,21). Additionally, the integration of precision medicine and molecular profiling has enabled more personalized and effective treatment strategies.

Early detection remains a critical factor in improving survival rates, emphasizing the need for increased awareness, screening programs, and access to healthcare services. Furthermore, addressing challenges such as treatment resistance, toxicity, and healthcare disparities is essential for optimizing patient care.

Future advancements in technology and research are expected to further transform oral cancer management, leading to improved survival, reduced morbidity, and enhanced quality of life for patients.

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