Review

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Advances in Preventive and Therapeutic Strategies for Oral Cancer: A Short Review

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Oral cancer is a major global health concern, with high incidence and mortality rates, especially in high-risk populations. Early diagnosis remains a challenge, and current treatments, such as surgery, radiation, and chemotherapy, have limited effectiveness, particularly in advanced stages. Recent advances in targeted therapies and immunotherapy offer promising alternatives, providing more precise and personalized treatment options. Targeted therapies, such as epidermal growth factor receptor inhibitors, aim to disrupt specific molecular pathways in tumor growth, while immunotherapies, including immune checkpoint inhibitors and chimeric antigen receptor-T cell therapy, enhance the body's immune response to fight cancer. Combination therapies, integrating both targeted and immune strategies, are being explored to overcome the limitations of single-agent treatments. This review highlights the current strategies in the prevention and treatment of oral cancer, discusses emerging therapies, explores future research directions, focusing on optimizing existing treatments, identifying new biomarkers, and developing innovative therapeutic approaches. The potential of personalized medicine and combination therapies offers new hope for improving survival rates and quality of life for oral cancer patients.

Key Words Oral cancer, Targeted therapy, Immunotherapy, Combination therapy, Prevention

INTRODUCTION

Oral cancer, characterized by malignant growths within the oral cavity, represents a significant global health burden with high incidence and mortality rates, especially in high-risk populations [1]. It is strongly associated with lifestyle factors, such as smoking, alcohol consumption, and poor oral hygiene. The epidemiological trends indicate a rising prevalence of oral cancers in developing regions, largely due to increased tobacco use and changing dietary patterns [2]. Figure 1 shows the risk factors of the oral cancer. Early diagnosis remains a major challenge in oral cancer management due to its subtle early symptoms and the lack of routine screening protocols. This has resulted in a substantial number of patients being diagnosed at later stages, limiting treatment efficacy and survival rates [3]. Existing treatment modalities such as surgery, radiation therapy, and chemotherapy offer limited success, especially in advanced cases [4-6]. As a result, there is an urgent need to explore innovative prevention and therapeutic strategies, including targeted therapies and immunotherapy,

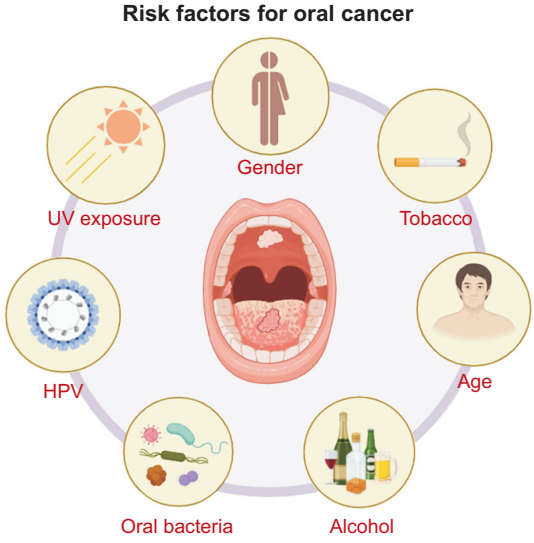

Figure 1. Risk factors of oral cancer (created with BioRender.com, https://BioRender.com/r75j585). HPV, human papillomavirus.

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which show promising potential in improving patient outcomes.

ORAL CANCER PREVENTION STRATEGIES

Effective prevention of oral cancer is critical, as it offers the best opportunity to reduce the burden of the disease [1,7]. Early screening and detection methods, including routine oral examinations, imaging techniques, and emerging liquid biopsy technologies, have the potential to significantly improve the early diagnosis of oral cancer [8,9]. The ability to detect precancerous lesions before they progress into full-blown malignancies could significantly enhance survival rates [10]. In addition to early detection, vaccines have emerged as a preventive tool, particularly for human papillomavirus (HPV)-related oral cancers [11]. HPV vaccination programs have shown promise in reducing the incidence of oral cancers associated with HPV infection, although their long-term effectiveness remains under investigation [12,13]. Chemoprevention strategies, including the use of certain compounds to inhibit carcinogenesis, are also being explored but require further validation. Lifestyle interventions, such as smoking cessation, alcohol moderation, improved dietary habits, and better oral hygiene practices, are crucial in reducing the risk of oral cancer [14]. These interventions, although challenging to implement on a global scale, could have a profound impact on reducing the prevalence of oral cancer in at-risk populations [15,16].

TARGETED THERAPY IN ORAL CANCER

Targeted therapy represents a promising advancement in the treatment of oral cancer [17], offering a more precise approach to treatment by targeting specific molecular pathways involved in tumor growth [18-20]. These therapies work by inhibiting key molecular drivers, such as epidermal growth factor receptor (EGFR), VEGF, and phosphatidylinositol 3-kinase (PI3K)/serine-threonine kinase (Akt) signaling pathways [21], all of which are crucial in tumor development and progression.

Mechanisms of targeted therapy

Targeted therapies act by modulating molecular pathways crucial for tumor proliferation, angiogenesis, and survival. EGFR inhibitors, such as Cetuximab and Nimotuzumab, target the overexpressed EGFR in many oral cancers, preventing ligand interaction and downstream signaling that promote cell proliferation and survival [22]. VEGF inhibitors, including Bevacizumab and Aflibercept, disrupt angiogenesis [23], which is essential for blood vessel formation and tumor metastasis. Similarly, PI3K/Akt/mTOR pathway inhibitors, such as Buparlisib and Everolimus, suppress tumor growth and survival by inhibiting this dysregulated pathway frequently implicated in oral cancer progression and therapy resistance (Table 1) [24-34]. Together, these targeted therapies aim to disrupt the key biological processes sustaining tumor growth and metastasis.

Challenges of targeted therapy

Despite their promise, targeted therapies face several challenges. Resistance mechanisms, such as secondary mutations in EGFR or activation of alternative pathways like mesenchymal epithelial transition (MET) amplification or HER3 activation, often limit the long-term efficacy of these agents [35,36]. Additionally, targeted therapies are associated with side effects; for example, EGFR inhibitors can cause dermatological toxicities like rash and pruritus, while VEGF inhibitors may lead to hypertension and impaired wound healing [37]. The genetic and molecular heterogeneity of oral cancers further complicates treatment, as comprehensive genomic profiling is often required to identify effective therapies for individual patients, adding complexity and cost to clinical

Table 1. Summary of targeted therapies for oral cancer: key inhibitors and molecular pathways

Target	Therapeutic agents	Mechanism of action	Clinical status	Reference
EGFR	Cetuximab, Nimotuzumab, Erlotinib	Inhibits EGFR signaling to block tumor cell proliferation and survival	FDA-approved for advanced cases; ongoing trials for optimization	[25-27]
VEGF	Bevacizumab, Aflibercept	Blocks angiogenesis by inhibiting VEGF and VEGF receptor interactions	Investigational for oral cancer; approved for other malignancies	[28,29]
PI3K/Akt pathway	Buparlisib, Alpelisib	Targets PI3K/Akt signaling to suppress tumor growth and survival pathways	Early-phase trials; emerging therapies	[30,31]
mTOR	Everolimus, Temsirolimus	Inhibits downstream mTOR signaling, affecting cell growth and metabolism	Phase I trials for head and neck cancers, including oral cancer	[32,33]
Combination therapies	Cetuximab + PI3K inhibitors	Co-targets EGFR and PI3K/Akt pathways to overcome resistance mechanisms	Investigational; promising preclinical and early clinical results	[34]

EGFR, epidermal growth factor receptor; FDA, Food and Drug Administration; PI3K/Akt, phosphatidylinositol 3-kinase/serine-threonine kinase.

management [24].

Emerging trends and future directions

Research continues to explore ways to enhance the efficacy and overcome the limitations of targeted therapies. Combining targeted agents with other modalities, such as immunotherapy or chemotherapy, has shown promise in preclinical and early clinical studies, as seen with Cetuximab combined with PI3K inhibitors to address resistance mechanisms [38]. Advances in personalized medicine, driven by genomic and proteomic technologies, enable the identification of biomarkers that predict patient response, allowing for a more tailored therapeutic approach. Novel targets such as HER2, fibroblast growth factor receptors, and c-MET are being investigated alongside innovative agents like antibody-drug conjugates and bispecific antibodies to improve therapeutic precision [39]. Additionally, nanotechnology-driven delivery systems are being developed to enhance drug bioavailability and minimize off-target effects, as evidenced by EGFR-targeted nanoparticles showing improved drug accumulation in oral cancer cells in preclinical studies [40]. By addressing these challenges and advancing research, targeted therapy has the potential to transform the treatment landscape of oral cancer, offering patients more effective and less toxic therapeutic options.

IMMUNOTHERAPY IN ORAL CANCER

Immunotherapy has emerged as a game-changing approach to cancer treatment, harnessing the body's immune system to combat cancer cells [41]. By targeting tumor-induced immune evasion mechanisms, immunotherapy offers the potential for long-lasting responses and improved survival outcomes in oral cancer [42]. Below, we elaborate on key immunotherapeutic strategies, including immune checkpoint inhibitors, chimeric antigen receptor (CAR)-T cell therapy, and other emerging approaches, along with their associated challenges and future prospects (Table 2) [43-52].

Immune checkpoint inhibitors

Immune checkpoint inhibitors are among the most established immunotherapy strategies. These agents block inhibitory pathways that tumors exploit to suppress the immune system, reactivating T cells to attack cancer cells. The programmed cell death protein 1 (PD-1)/programmed death-ligand 1 (PD-L1) axis is the most studied target in oral cancer [47]. Drugs like Pembrolizumab and Nivolumab have demonstrated efficacy in enhancing immune responses by preventing PD-1 on T cells from binding to PD-L1 on tumor cells [48]. Clinical trials have shown that these inhibitors can improve overall survival in patients with recurrent or metastatic oral cancer, particularly in those with high PD-L1 expression [49]. Despite these successes, limitations such as primary and acquired resistance remain significant challenges, necessitating biomarkers to predict patient response and combination therapies to overcome resistance mechanisms.

CAR-T cell therapy

CAR T-cell therapy represents a highly personalized approach by genetically engineering a patient's T cells to recognize and destroy tumor-specific antigens [50]. While CAR-T therapy has shown remarkable success in hematological malignancies, its application in solid tumors, including oral cancer, is still in its infancy [51]. Challenges include identifying appropriate tumor-specific antigens and overcoming the immunosuppressive tumor microenvironment. Recent research focuses on engineering CAR-T cells to target antigens such as EGFR or HPV-associated E6 and E7 proteins in oral cancers [52]. Although promising preclinical results exist, clinical translation is limited by issues such as off-target toxicity, high costs, and the need for improved persistence of CAR-T cells in the solid tumor milieu.

Other emerging immunotherapeutic approaches

Beyond immune checkpoint inhibitors and CAR-T therapy, other innovative immunotherapy strategies are being explored for oral cancer treatment [53]. Tumor vaccines aim to stimulate the immune system to recognize and attack cancer cells, with ongoing trials investigating their efficacy against HPV-related oral cancers [54]. Oncolytic viruses, which selectively infect and kill tumor cells while stimulating an anti-tumor

Table 2. Summary of current immunotherapeutic strategies

Therapy	Mechanism	Outcome	Challenge	Reference
Immune checkpoint inhibitors	Block PD-1/PD-L1 or CTLA-4 pathways	Improved survival in metastatic cases	Resistance, patient selection	[47-49]
CAR-T cell therapy	Engineer T cells to recognize tumor-specific antigens	Preclinical promise; limited clinical data	High cost, tumor microenvironment barriers	[50-52]
Tumor vaccines	Stimulate immune system against tumor antigens	Ongoing trials for HPV-related oral cancers	Limited efficacy in solid tumors	[43,44]
Oncolytic viruses	Selectively infect and kill tumor cells	Early-phase trials	Delivery challenges, off-target effects	
TIL therapy	Expand and reinfuse TILs	Enhanced immune response	Complex manufacturing, cost	[45,46]

PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; CTLA-4, cytotoxic T-lymphocyte associated protein 4; CAR, chimeric antigen receptor; HPV, human papillomavirus; TIL, tumor-infiltrating lymphocyte.

immune response, are another area of active research. Additionally, adoptive T-cell therapies, such as tumor-infiltrating lymphocytes, are under investigation for their potential to enhance immune responses in oral cancer [55]. While these approaches are in early developmental stages, they offer potential to complement existing immunotherapies and address current treatment gaps.

Challenges and future directions

Despite the promise of immunotherapy, several challenges hinder its widespread application in oral cancer. Tumor immune escape mechanisms, such as reduced antigen presentation and the immunosuppressive tumor microenvironment, limit the effectiveness of current therapies. Adverse effects, including immune-related toxicities like colitis and pneumonitis, also pose significant risks to patients [54]. To address these challenges, future research should focus on identifying predictive biomarkers for patient selection, optimizing combination therapies (e.g., immune checkpoint inhibitors with targeted therapies or chemotherapy), and developing novel delivery systems to enhance therapeutic efficacy [56]. Advances in understanding the interplay between the immune system and the tumor microenvironment will be crucial for unlocking the full potential of immunotherapy in oral cancer.

COMBINATION THERAPY OF TARGETED AND IMMUNOTHERAPIES

The combination of targeted therapies and immunotherapy holds great promise in enhancing the treatment outcomes of oral cancer [39,53]. This combination approach aims to harness the strengths of both modalities: the precision of targeted therapy and the broad immune activation induced by immunotherapy. By using targeted agents to block specific molecular pathways and combining them with immune checkpoint inhibitors to reactivate the immune system, this strategy could overcome the limitations of monotherapy. Preliminary clinical trials and studies have shown that combining these two treatment strategies may improve tumor response rates and extend survival in oral cancer patients, especially those who are refractory to conventional treatments [57,58]. Ongoing studies are investigating the optimal timing, dosing, and patient selection criteria for this combination approach, as well as the identification of biomarkers that could predict patient response.

FUTURE RESEARCH DIRECTIONS

Looking ahead, several areas of research promise to further improve the treatment of oral cancer. First, there is a need to optimize both targeted therapies and immunotherapies through a better understanding of the molecular mechanisms driving resistance and identifying novel biomarkers for patient selection [59,60]. Personalized treatment strategies, particularly those that combine genetic profiling with therapeutic targeting, are likely to be the future of oral cancer treatment [60,61]. New treatment approaches, such as tumor microenvironment modulation, gene editing technologies like clustered regularly interspaced short palindromic repeat (CRISPR)-CRISPR associated protein 9, and the development of novel immunotherapeutic agents, are also on the horizon. These innovations could offer new ways to overcome current treatment limitations and improve patient outcomes [62,63]. Additionally, exploring novel drug delivery systems, including nanomedicine, could increase the efficacy of current therapies while minimizing toxicity. As research continues, the integration of these emerging strategies into clinical practice holds great promise for improving the prognosis of oral cancer patients [40,64].

CONCLUSION

In summary, the prevention and treatment of oral cancer have witnessed significant advancements, particularly with the emergence of targeted therapies and immunotherapies. These innovative treatment strategies have the potential to greatly improve survival rates and quality of life for oral cancer patients. However, despite the progress made, challenges remain in optimizing treatment regimens, overcoming drug resistance, and managing adverse effects. The integration of targeted therapies and immunotherapy into multimodal treatment plans represents a promising avenue for enhancing treatment outcomes. Future research focusing on the optimization of these therapies, the discovery of new biomarkers, and the development of innovative therapeutic strategies will be crucial in transforming the management of oral cancer. Continued scientific discovery and clinical innovation should follow, with the ultimate goal of improving the prognosis for patients diagnosed with this devastating disease.

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CONFLICTS OF INTEREST

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