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Research progress on carcinogenic factors and personalized treatment of oral cancer

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Abstract

Oral cancer, particularly oral squamous cell carcinoma (OSCC), represents a significant global health burden, with notably high incidence in regions such as South and Southeast Asia. In China, both the incidence and mortality of oral cancer have been steadily rising, posing a growing threat to public health. Despite the identification of major risk factors—including tobacco use, alcohol consumption, betel quid chewing, and high-risk human papillomavirus (HPV) infection—the disease often remains asymptomatic in its early stages, leading to delayed diagnosis and poor prognosis. These clinical challenges are closely linked to the complex molecular pathogenesis of OSCC, involving genetic alterations, epigenetic dysregulation, tumor microenvironment remodeling, and immune evasion. Recent advances in multi-omics profiling, liquid biopsy, and immunotherapeutic strategies offer promising avenues for early detection, accurate staging, and personalized treatment. This review synthesizes cutting-edge research from both domestic and international scholars, focusing on the interplay between carcinogenic exposures, molecular mechanisms, and emerging therapeutic paradigms, thereby providing a comprehensive reference for future studies in oral cancer prevention and precision oncology.

Keywords Oral squamous cell carcinoma, Carcinogenesis, Molecular pathogenesis, Risk factors, Tumor microenvironment, Liquid biopsy, Immunotherapy

1 Introduction

Oral cancer is one of the most common malignancies within the spectrum of head and neck cancers, the sixth most common malignant tumour worldwide [1]. Oral cancer includes the gingiva (gums), buccal mucosa, floor of the mouth or sublingual, lips, anterior part of the tongue, hard palate, posterior triangle of the molar teeth and may spread to the oropharynx, and the lower portion of the oral cavity including the laryngeal wall, posterior part of the tongue, soft palate, and tonsils, of which about 90% are squamous cell carcinomas [2]. The low survival rate of oral cancer (OC) is primarily attributed to delayed diagnosis, which results in delayed treatment initiation, limited therapeutic options, and increased treatment-related morbidity and mortality.The major determinant of survival is the stage of cancer diagnosis. As more than 2/3 of OC lesions are detected late after metastasis has occurred, treatment outcomes and prognosis are

extremely poor [3]. According to the Global Cancer Statistics Database (GLOBOCAN) data released by the World Health Organisation's International Agency for Research on Cancer (WHO/IARC) in 2022, oral cancer was ranked 15th in the global mortality rate, resulting in approximately 188,438 deaths in that year, with 130,808 deaths in men and 57,630 deaths in women. From 1990 to 2021, the global incidence of oral cancer increased significantly, from 3.26 (95% uncertainty interval UI 3.14–3.41) to 5.34 (95% UI 4.94–5.77) cases per 100,000 people. During the same period, the mortality rate also showed an increasing trend, from 1.83 cases/100,000 (95% UI 1.73–1.92) to 2.64 cases/100,000 (95% UI 2.42–2.84). In addition, the impact of oral cancer on global disability-adjusted life years (DALYs) is also increasing, with the associated value rising from 55.05 (95% UI 52.38–57.97) to 74.44 (95% UI 67.50–80.44.50.44) [4, 5], posing a significant burden on global health (Fig.1).

2 Carcinogenic factors

2.1 Smoking and drinking alcohol

Despite the increasing awareness of the health hazards of smoking, there are still about 1.1 billion smokers worldwide, and over 8 million people die each year due to smoking. Smoking not only causes various oral and systemic diseases, such as increased periodontal pocket depth, loss of alveolar bone, loose teeth, oral lesions, ulcers, bad breath, and tooth discoloration, but is also the cause of oral cancer and oropharyngeal squamous cell carcinoma (OSCC/OPSCC) [6]. Sawant S et al. found changes in oral microbiota composition from healthy populations to smokers and ultimately to oral cancer patients. The abundance of Streptococcus gradually decreased while the abundance of Prevotella increased, indicating that smoking habits can lead to dysbiosis of oral bacteria and may further promote the development of cancer [7]. In 1988, the International Agency for Research on Cancer (IARC) classified alcohol as a Group 1 human carcinogen [8]. The International Agency for Research on Cancer also listed alcohol as one of the causes of breast cancer, colorectal cancer, laryngeal cancer, liver cancer, esophageal cancer, oral cancer and pharyngeal cancer [9, 10]. Smoking and drinking habits promote cancer development through mechanisms such as activating signaling pathways, regulating cell cycle proteins, and inhibiting apoptosis pathways [11].

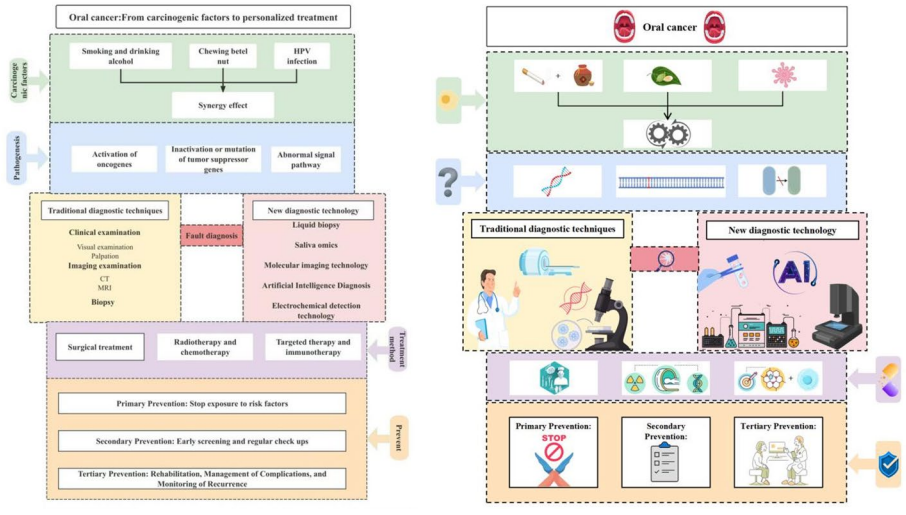

Fig. 1 Oral cancer ranging from carcinogenic factors to personalized treatment

2.2 Chewing betel nut

Betel nut is a common chewing habit in Southeast Asia and the Western Pacific region, especially in some island countries such as Palau, as well as some Asian countries such as Pakistan and Taiwan [12–14]. The main component of betel nut is arecoline, which is a major active ingredient and an important risk factor for oral cancer [15]. The habit of chewing betelnut is related to the high incidence rate of oral cancer, especially in Asian countries [13]. Chewing betel nut can promote the malignant transformation of oral lesions and trigger benign cellular and molecular changes [16]. Chewing betel nut in the oral cavity can cause changes in the composition of the oral microbiota, known as dysbiosis [17]. The relationship between betel nut chewing and oral cancer has attracted increasing attention in the global public health field [18]. Therefore, reducing the habit of chewing betel nut is crucial for preventing oral cancer and reducing its disease burden.

2.3 HPV infection

HPV has been identified as a pathogenic factor for oral squamous cell carcinoma (OSCC), with HPV types 16 and 18 being particularly prevalent in oral cancer [19]. HPV is a potential factor for an increase in certain oral squamous cell carcinomas (OSCCs). Genomic analysis shows that HPV-positive and HPV-negative OSCCs exhibit distinct mutational profiles, and both exhibit somatic mutation enrichment and copy number changes on multiple genes, indicating that virus host interactions shape the unique genetic features of HPV positive cancers [20]. In particular, the HPV-encoded early proteins E6 and E7 play a central role in carcinogenesis, with E6 targeting the host oncoprotein p53 through ubiquitin-mediated degradation to inhibit DNA damage-induced cell cycle arrest and apoptosis, and E7 releasing the E2F transcription factor through binding and inactivation of the retinoblastoma protein (pRb), which promotes cell cycle progression. Disruption of these key pathways disrupts normal cell proliferation regulatory mechanisms, leading to genomic instability and aberrant proliferation, which promotes malignant transformation of epithelial cells [21–23]. In addition, HPV-positive OSCCs often exhibit specific molecular features, such as lower TP53 and NOTCH1 mutation frequencies and higher levels of activation of cell cycle-associated pathways [24, 25]. further supporting the idea that HPV drives tumourigenesis through the interaction of its viral proteins with the genetic network of host cells. In addition, Giuliano et al. found that the oral HPV infection rate in the general population of the United States is higher in males, especially those aged 51 to 60. High risk oral HPV infection is associated with sexual factors such as male gender, older age, and more sexual partners, suggesting that this group may have a higher risk of developing oropharyngeal cancer [26]. Oleszkiewicz Spiolek et al. found that patients have limited understanding of the impact of human papillomavirus (HPV) infection on oral health. Women are more aware of HPV and its prevention than men, and age is related to their understanding of HPV causing oral cancer. Therefore, it is necessary to strengthen education and prevention plans for patients [27].

2.4 Other factors

In addition to the above, an increasing number of studies have shown that the disruption or imbalance of oral and intestinal microbiota is increasingly closely related to the development and progression of oral cancer. In oral cancer patients, the abundance of

certain specific bacteria such as Fusobacterium nucleatum and Porphyromonas gingivalis is significantly increased. These bacteria can promote the formation of the tumor microenvironment through various mechanisms such as inducing chronic inflammation, inhibiting immune surveillance, and directly damaging host DNA [28–30]. In addition, changes in the oral microbiome may also have a synergistic effect with HPV infection, affecting the persistence of the virus, immune escape, and remodeling of the tumor microenvironment, thereby further increasing the risk of cancer [31–33]. It is worth noting that some studies have also found an imbalance in gut microbiota associated with poor prognosis in oral cancer patients, suggesting that regulating gut microbiota may become a potential therapeutic target [34, 35].

The development of oral cancer is a complex process involving multiple stages and factors, gradually evolving from normal mucosa to potential malignant lesions, and ultimately developing into heterogeneous tumors, with significant differences in gene expression and biological behavior among their cell populations [36]. In addition to microbial factors, genetic variation also plays a key role, such as the polymorphism of endothelial nitric oxide synthase (eNOS) gene, which can regulate the production of NO and affect the occurrence of cancer [37, 38]. Single nucleotide polymorphisms (SNPs), as a common form of genetic variation, have been widely studied to be associated with susceptibility to oral cancer. Multiple SNPs in the MET proto-oncogene (MET, hepatocyte growth factor receptor) — such as rs41736 and rs41739 — are significantly associated with oral cancer risk and clinical features [39], While polymorphisms in DNA repair genes such as XRCC1, XRCC3, XPD, and hOGG1 may increase the risk of disease by reducing DNA damage repair ability [40]. Studies in the Karad population of India have shown significant differences in SNPs involved in oxidative stress, carcinogen detoxification, and DNA repair (such as rs3761547, rs3761548, rs3761549) among patients, suggesting an interaction between genetics and environmental exposure [41]. Genome wide association studies (GWAS) have also identified multiple genetic regions associated with oral cancer in different populations, such as susceptibility loci found in the Taiwanese population, further confirming the important role of genetic factors in the etiology [42]. In oral squamous cell carcinoma (OSCC), the Wnt pathway is abnormally activated due to genetic or epigenetic interference (such as specific SNPs or gene silencing), promoting epithelial mesenchymal transition (EMT) and tumor progression; Meanwhile, the dysregulation of the JAK-STAT pathway also promotes carcinogenesis by regulating inflammation and immune responses [43]. In summary, the pathogenesis of oral cancer is the result of multiple factors working together, including dysbiosis of the microbiota, HPV infection, genetic variations, and environmental exposure factors such as smoking, alcohol consumption, and betel nut chewing. Therefore, future prevention and treatment strategies should start from multiple dimensions and comprehensively consider these factors to achieve more precise and comprehensive interventions.

3 Pathogenesis mechanism

3.1 Activation of oncogenes

The activation of certain oncogenes plays a crucial role in the occurrence and development of oral cancer. For example, Oliveri F et al. mentioned the relationship between human papillomavirus (HPV) and oral cancer, and the activation of the HPV16 genome is associated with the development of oral cancer [44]. In addition, Liu et al. mentioned

that SPP1 + Macs (specific types of macrophages) increase the secretion of TNF - α and IL-1 β through the NF kappa B signaling pathway, thereby promoting the proliferation of head and neck squamous cell carcinoma (HNSCC) cells, as shown in Fig. 2, indicating that certain cytokines play a promoting role in oncogene activation [45].

3.2 Inactivation or mutation of tumor suppressor genes

The inactivation or mutation of tumor suppressor genes is also an important link in the pathogenesis of oral cancer. Zhai XQ et al. reported that high expression of USP20 in OSCC is associated with tumor differentiation and primary tumor size, and can accelerate tumor growth, which supports the role of tumor suppressor gene inactivation in oral cancer development [46]. Additionally, Hibino Y et al. identified mutations in BRAF and KRAS genes in OSCC, which are typically associated with the activation of the MAPK/ERK signaling pathway—a key pathway driving tumor initiation and progression [47]. Notably, while Homeobox A5 (HOXA5) functions as a tumor suppressor gene in breast cancer, Chen Y J et al. indicated that its role in OSCC has not been confirmed [48].

3.3 Signal pathway abnormalities

Proteins specifically expressed in oral tumors and their interactions play a crucial role in immune and inflammatory responses. ADSCs (adipose derived stem cells) interact with various malignant tumors, promoting their proliferation and metastasis. The aberrance and overactivation of the Wnt/PCP signaling pathway are associated with the initiation and progression of OSCC [49]. Pandey et al. found that the abnormally activated Notch signaling pathway in OSCC can lead to tumor progression and metastasis [50]. Cell adhesion proteins can interact with signaling pathways that regulate cell proliferation, migration, and survival. Dysregulation of these pathways may also promote the development and progression of oral cancer [51].

3.4 Other mechanisms

The pathogenesis of oral cancer is complex, and in addition to the above-mentioned factors, there are also important roles played by the tumor microenvironment in the occurrence, development, and progression of OSCC. Various cells in TME, including tumor associated macrophages (TAMs) and regulatory T cells (Tregs), are closely related to the progression of OSCC and patient prognosis [52, 53]. Certain types of viruses, such as poliovirus, are associated with the occurrence of oral cancer. Mousavi et al.'s study showed that individuals who are positive for Merkel cell multi tumor virus (MCV) have a 13% higher risk of developing oral cancer compared to those who are negative for MCV [54]. Cancer-associated fibroblasts (CAFs) are the most important stromal cells in the tumor microenvironment (TME), which promote the invasion and metastasis of OSCC by secreting cytokines such as transforming growth factor - β (TGF - β) and interleukin-6 (IL-6). CAFs increase tissue hardness and activate the integrin FAK signaling pathway by reshaping the extracellular matrix (ECM), thereby enhancing the migration ability of tumor cells [55]. High expression of alpha SMA in CAFs is significantly correlated with a reduced 5-year survival rate in OSCC patients (HR = 2.14, 95% CI 1.37–3.34) [56]. Tumor derived extracellular vesicles carry non coding RNA (such as miR-21, lncRNA HOTAIR) and proteins (such as PD-L1), among which extracellular vesicle PD-L1 inhibits anti-tumor immunity by binding to T cell surface PD-1, promoting the

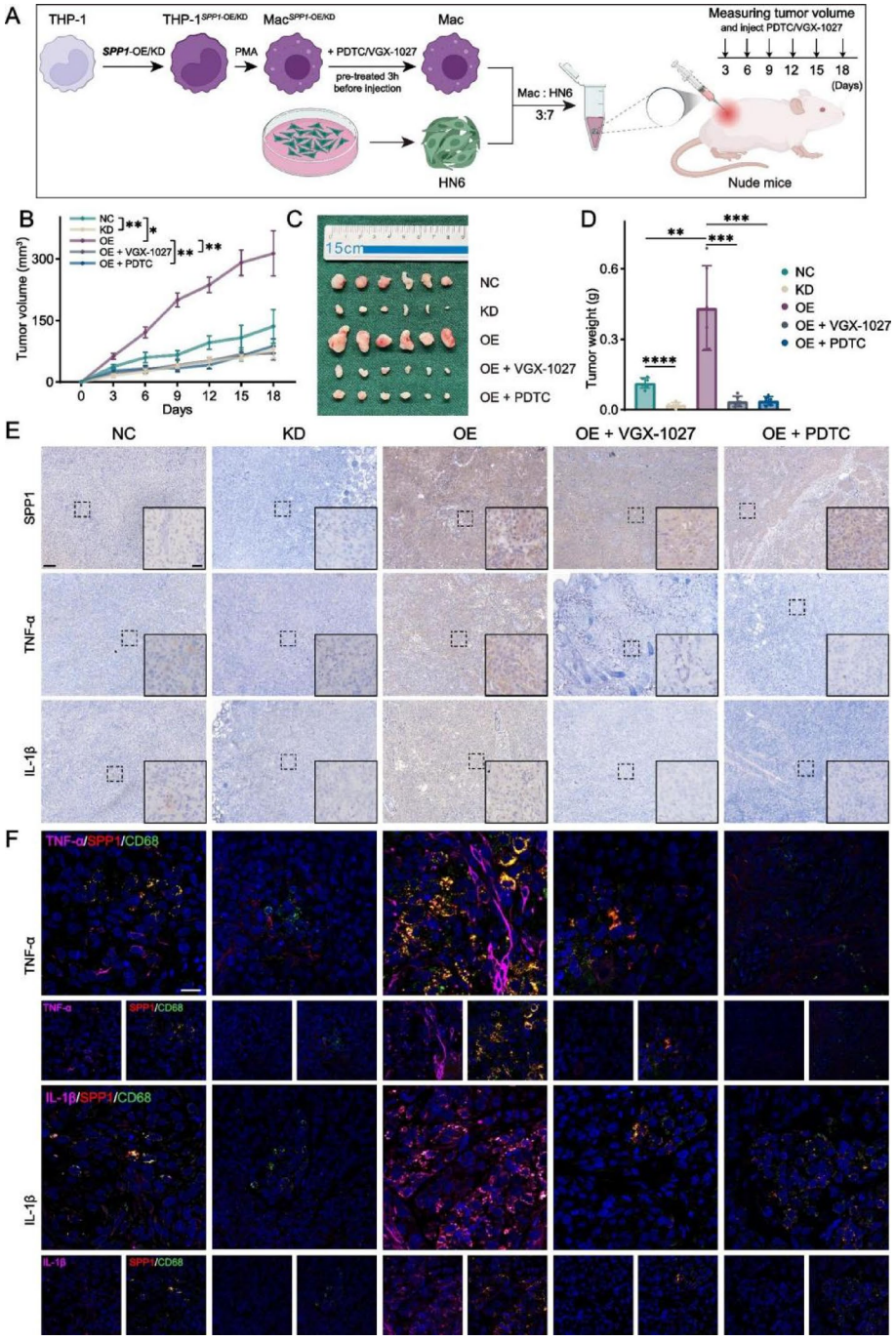

Fig. 2 SPP1+ Macs (a specific type of macrophage) increase the secretion of TNF-α and IL-1β through the NF-kappa B signaling pathway [45]

occurrence of oral cancer [57]. The vascular mimicry induced by VEGF overexpression in TME is closely related to the distant metastasis of OSCC. VM channels are formed by tumor cells themselves and can directly connect to the circulatory system, providing a pathway for OSCC cells to break through the basement membrane, enter blood vessels, and undergo distant metastasis [58]. The hypoxic environment in TME can induce the expression of HIF-1 α (hypoxia inducible factor-1 α), thereby upregulating VEGF and jointly promoting VM formation. Ma Q et al. confirmed that HIF-1 α is positively

correlated with the VM structure and recurrence risk of OSCC [59]. TrkA and nerve growth factor receptor (NGFR) are the two main receptors of NGF, highly expressed in OSCC. Experimental results have shown that targeting and knocking down these two receptors can inhibit the proliferation, invasion, and metastasis of OSCC cells, while reducing PNI and pain symptoms. Of particular note is that TrkA knockdown alone inhibits thermal hyperalgesia, while NGFR knockdown specifically alleviates mechanical allodynia, indicating that OSCC coordinates and regulates multiple pathological processes through different components of the nerve growth factor pathway [60]. In OSCC, the hypoxic environment may indirectly affect the NGF/TrkA pathway through upregulation of HIF-1 α, promoting abnormal expression of Par3 and tight junction proteins, thereby accelerating metastasis [61]. Under these pathogenic mechanisms, cells lose normal growth control and eventually form tumors.

3.5 Diagnostic method

Oral cancer (squamous cell carcinoma) is a multi-step process, in which normal mucosal lesions transform into potential malignant stages, followed by carcinogenesis [62]. Therefore, prior to oral cancer, clinically detectable chronic lesions often develop at various stages and are currently classified as oral potentially malignant disorders (OPMD), including oral leukoplakia, erythroplakia, and oral submucous fibrosis [63]. Due to the fact that OPMD usually has no symptoms, most patients do not seek medical help until persistent pain or functional disorders occur [64]. In clinical practice, the initial assessment of oral lesions typically relies on visual oral examination (VOE) and palpation by clinicians to identify suspicious areas. However, distinguishing benign from malignant lesions accurately based solely on morphological features remains challenging—particularly for early-stage or precancerous lesions—thereby increasing the risk of misdiagnosis and missed diagnosis." Therefore, in order to confirm the diagnosis, emerging diagnostic methods such as tissue biopsy, electrochemical diagnostic technology, and artificial intelligence diagnosis are used to improve the accuracy and efficiency of diagnosis.

3.6 Traditional diagnostic techniques

3.6.1 Clinical examination

Doctors examine abnormalities in the oral cavity, including lumps, ulcers, or other suspicious changes, through direct observation and palpation. This is a commonly used method for preliminary diagnosis of oral cancer [65].

3.6.2 Imaging examination

These techniques, including X-rays, CT scans, MRI, and PET-CT, can help evaluate the size, location, and presence of lymph node or distant metastasis of tumors [65, 66].

Computed Tomography (CT), also known as X-ray Computed Tomography, relies on measuring the attenuation characteristics of X-ray beams when penetrating biological samples to generate images at different depth levels. Although this technique excels in assessing hard tissues (e.g., bone), X-ray-induced artifacts and the relatively low soft tissue resolution of CT limit its performance in specific applications, thereby impeding the evaluation of in situ oral cancer [67, 68].

Magnetic resonance imaging (MRI) is a technique that provides the highest quality soft tissue images without the use of ionizing radiation and known biological risks

[69]. MRI is a very valuable tool that can provide a detailed display of the oral structure and its adjacent tissues. Due to its excellent resolution of soft tissue, MRI can clearly reveal the extent and spread of tumor invasion. It is mainly used to evaluate the degree of spread, depth of invasion, and degree of lymph node lesions of local and regional tumors. Compared to CT, the main advantage of MRI is its excellent soft tissue imaging effect and the fact that it does not expose patients to harmful radiation. In addition, MRI can detect tumor invasion of the bone marrow in the early stage, which is more sensitive than CT. MRI is particularly adept at providing information on the involvement of the tongue base and floor of the mouth, and is also very useful for observing the extension of tumors towards the oropharynx, which is often difficult to clearly display on CT images [70].

Positron emission tomography (PET) is a functional imaging technique that evaluates the metabolic activity of tissues by detecting the distribution of radioactive tracers (such as fluorodeoxyglucose, FDG) in the body [71]. However, its price is expensive and there are certain limitations to using PET alone for diagnosing oral cancer [72]. After combining PET with other imaging techniques, such as PET/CT, it has significant diagnostic accuracy in detecting local lymph node metastasis and distant metastasis of oral squamous cell carcinoma (OSCC), especially in identifying cervical lymph node metastasis. PET/CT shows higher specificity and sensitivity, which is superior to traditional CT and MRI examinations [73, 74].

3.6.3 Tissue biopsy

Tissue biopsy refers to the acquisition of tumor or suspicious lesion samples—typically via surgical excision, incisional biopsy, fine-needle aspiration (FNA), brush cytology, or core needle biopsy—for histopathological examination to confirm the presence, type, and grade of cancer [75]. In the context of oral cancer, biopsies are commonly obtained from oral mucosal lesions, primary tumors, or regional lymph nodes using surgical or minimally invasive techniques [76].

For instance, Li et al. collected paired tissue samples (normal and cancerous) from 35 oral cancer patients—totaling 70 specimens—for Raman spectroscopy analysis and the development of deep learning–based diagnostic models [77].

Tissue biopsy remains the gold standard for oral cancer diagnosis due to its ability to provide direct morphological and molecular information. However, diagnostic accuracy can be influenced by sampling adequacy, lesion heterogeneity, and pathologist expertise. Moreover, as an invasive procedure, it may cause pain, bleeding, or anxiety, leading to lower patient acceptance compared to non-invasive alternatives such as liquid biopsy or optical imaging.

3.7 Emerging diagnostic technologies

3.7.1 Liquid biopsy

Traditional cancer screening techniques, such as imaging examinations and protein biomarker testing, have limitations in early detection of cancer. At present, the standard methods for diagnosing oral cancer mainly rely on various forms of endoscopic examination and tumor biopsy, which are effective but relatively invasive [78]. In recent years, liquid biopsy has gradually gained attention as an emerging diagnostic tool. It can provide real-time information about cancer in a minimally invasive manner, making it an

important choice for molecular feature analysis and detection of cancer. Liquid biopsy, as shown in Fig. 3, detects emerging biomarkers such as circulating tumor DNA (ctDNA), circulating tumor cells (CTCs), and miRNA in extracellular vesicles in the blood. It not only helps with early detection of cancer, but can also be used to guide treatment planning and monitor treatment response (Comparison with conventional tissue biopsy is shown in Table 1) [79]. In addition to blood, there are other bodily fluids such as urine, saliva, semen, pleural effusion, cerebrospinal fluid, sputum, and fecal samples that can be used for liquid biopsy [84]. In addition, using liquid biopsy, we can obtain a unique molecular profile for each patient. These molecular data can provide important supplements to traditional tumor, lymph node, and metastasis (TNM) staging systems, helping

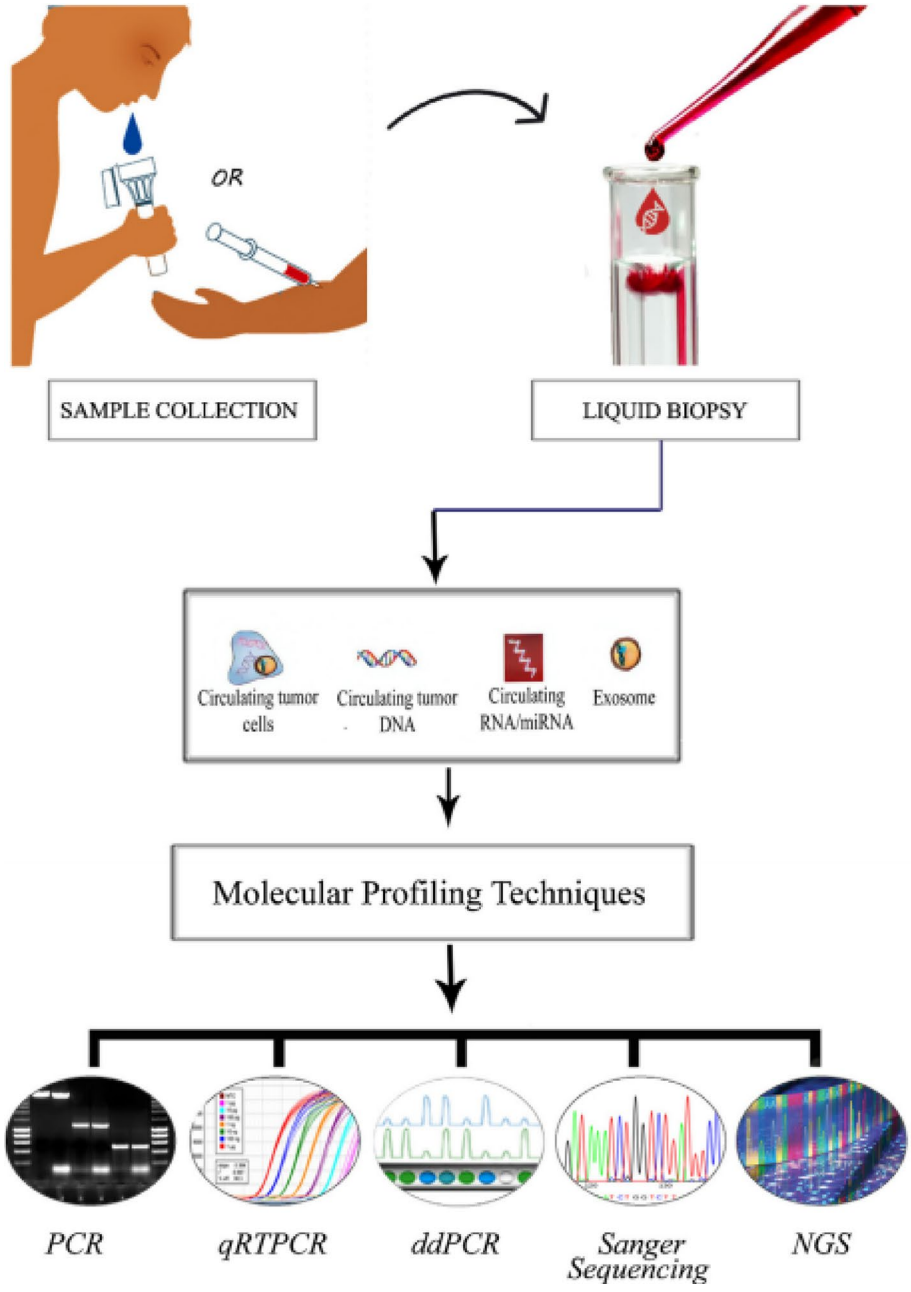

Fig. 3 Molecular profiling techniques used in liquid biopsy [79]

to more accurately distinguish different tumor subtypes [85]. Based on its non-invasive and convenient nature, allowing for frequent sampling, this enables doctors to continuously track disease progression, evaluate tumor heterogeneity, and monitor minimal residual lesions and treatment outcomes. Therefore, liquid biopsy provides a more flexible and dynamic approach for cancer management, which is expected to significantly improve the prognosis and quality of life of patients.

However, its application in resource-limited settings needs to be considered in terms of cost-effectiveness. For example, in Canada, the incorporation of liquid biopsy into tissue testing can result in cost savings and improved patient outcomes, while in Germany its cost-effectiveness is considered moderate, particularly for certain genetic subtypes [86, 87]. However, in some low- and middle-income countries such as Colombia, the current high initial cost of liquid biopsy has not yet been translated into an overall cost-effectiveness, even though the cost of the test may be lowered in the future [88]. A systematic review showed that liquid biopsies are generally cost-effective for treatment selection and can reduce unnecessary repeat testing and post-treatment costs, but their economic impact depends on local healthcare costs, drug prices, and implementation strategies [89]. In addition, liquid biopsies can provide access to precision medicine for patients who are difficult to sample tissues and can help to reduce health inequalities [90]. Overall, despite the high upfront investment, liquid biopsies streamline care with their high sensitivity and specificity, can reduce downstream costs, and are expected to further improve patient outcomes as the technology matures and costs decline.

3.7.2 Saliva omics

Saliva omics is a non-invasive, efficient, and patient friendly diagnostic method that utilizes comprehensive molecular insights provided by genomics, transcriptomics, proteomics, metabolomics, and microbiology to detect and manage oral cancer (OC). This method has revolutionary potential due to its non-invasive nature, enabling early detection and management of oral cancer [91]. Heguedusch et al. evaluated the expression patterns of five key biomarkers (β - catenin, E-cadherin, podoplanin (PDPN), CXCR4, and p53) in OSCC tissues, providing an important perspective on the fusion EMT mechanism for understanding OSCC invasion [92]. Future research directions can integrate multiple omics data to discover superior biomarkers, improve diagnostic accuracy, and enhance the ability to manage OC.

3.7.3 Molecular imaging technology

Molecular imaging techniques can help detect tumor specific biomarkers of oral squamous cell carcinoma (OSCC) using specific imaging probes such as epidermal growth factor receptor (EGFR) and programmed death ligand 1 (PD-L1), which are crucial for the treatment of OSCC [93]. Multispectral fluorescence molecular imaging (FMI) can

Table 1 Comparison of sensitivity, specificity, and detection levels between liquid biopsy and tissue biopsy in the diagnosis of oral cancer

Method	Sensitivity (%)	Specificity (%)	Invasive or not	Detection level	Ref.
Liquid biopsy	93–96	93–96	Non-invasive	Detects minimal residual disease, may miss some variants present in tissue	[80, 81]
Tissue biopsy	Gold standard	Gold standard	Invasive	Complete mutation profile, may miss tumor heterogeneity	[82, 83]

promote the detection of tumor specific biomarkers and help detect OSCC early [93]. Autofluorescence and fluorescence techniques are highly sensitive for cancer screening and are directly related to the molecular level of human tissue, making them quantitative tools for cancer detection [94]. A new NIR II fluorescence imaging probe was designed for accurate tracking of oral squamous cell carcinoma (OSCC) cells in the study of NIR II fluorescence imaging probes [95]. The development and testing of targeted imaging probes for Nimotuzumab ICG and Atezolizumab Cy5.5 imaging probes were carried out on preclinical OSCC cell lines and in situ OSCC mouse models, and further clinical mouthwash trials were conducted in OSCC patients [92]. In PET/CT imaging mode studies, it was found that [Cu] Cu-DOTA-AE105 urokinase type plasminogen activator receptor (uPAR) - PET/CT is a promising new cancer visualization imaging mode, although it has not been tested in head and neck cancer patients or preclinical models closely related to these heterogeneous tumors, namely patient derived xenograft (PDX) models [96].

3.7.4 Artificial intelligence diagnosis

Artificial intelligence assisted diagnosis is an automated diagnostic method based on artificial intelligence that has shown promising results in the field of oral cancer. It can evaluate various information including histopathological sections and intraoral images. AI technology, such as surgical robots and early histopathological diagnosis, significantly affects the future of oral oncology. Although its accuracy still needs to be improved to adapt to practical diagnostic scenarios [97]. Deep learning techniques have shown promising results in early cancer detection and have shown promise in accurate diagnosis [98]. Models such as Vision Transformers (ViT) have shown better accuracy than traditional convolutional neural networks in oral cancer image classification tasks [99]. Oral intraepithelial neoplasia (OED) is a preliminary histopathological diagnosis of oral cavity lesions, and its grading exhibits significant inter - and intra observer variability, which cannot reliably predict malignant progression and may lead to suboptimal treatment decisions. The development of AI algorithms aims to address this issue [100]. Reproducibility remains a major challenge when applying AI to diagnose oral cancer. Although AI models, particularly deep learning algorithms, have demonstrated high accuracy, sensitivity, and specificity in detecting oral cancer-sometimes outperforming traditional clinical methods-these results typically stem from the use of small, single-centre datasets and limited external validation studies, raising concerns about generalisability and overestimated performance rates [101–103]. To address these concerns, future research must prioritise the development of larger multicentre datasets, transparent reporting, external validation, and regulatory frameworks to ensure safe and effective clinical integratio [104, 105]. It is only through this rigorous approach that the promise of AI in oral cancer diagnostics can be in routine practice reliably realised in practice.

3.7.5 Electrochemical detection technology

Electrochemical detection technology plays an important role in early detection of oral diseases such as dental caries, periodontal disease, and oral cancer. Electrochemical technology, which is non-invasive, rapid, sensitive, accurate, and low-cost, is crucial for screening and diagnosing oral cancer [106]. Electrochemical biosensors have shown great potential in the detection and diagnosis of oral cancer. They can use anti biological

pollution hydrogels to detect early oral cancer in body fluids [107], and confirm the effectiveness of this technology by diagnosing oral squamous cell carcinoma in clinical cases [108]. Predictive biomarkers can be used to identify high-risk populations for oral cancer (such as long-term smokers, drinkers, or HPV infected individuals) and intervene in the precancerous stage. HPV infection is an important cause of oral squamous cell carcinoma (OSCC). Electrochemical DNA sensors based on nanomaterials such as graphene modified with gold nanoparticles can detect HPV DNA in saliva with a sensitivity of 0.1 fM, making them suitable for large-scale screening [109]. TP53 gene mutation is an early event in OSCC. Electrochemical CRISPR sensors can non invasively detect TP53 mutations in saliva, and 60% –80% of cases have TP53 molecular changes [110]. The electrochemical microfluidic array has been optimized for measuring four protein biomarker plates in the diagnosis of oral cancer, and this protein plate has been validated to accurately diagnose oral cancer. Malhotra R et al. used a low-cost and easy to manufacture immune array to rapidly detect oral cancer in blood, demonstrating 89% clinical sensitivity and 98% specificity [111]. Emran et al. proposed a non-invasive bioimpedance spectroscopy (BIS) method to overcome the pain and discomfort caused by traditional biopsies and achieve regular screening of high-risk patients [112]. At present, various electrochemical immunosensors have also been developed, as shown in Fig. 4, for detecting biomarkers such as Cyfra 21.1 in human saliva samples [113]. Titanium carbide MXene nanosheets decorated with silver nanoparticles (TiC_AgNPs) were used as electroactive interfaces for non-invasive diagnosis of oral cancer [114]. Researchers have also developed various electrochemical biosensors for early detection of oral cancer using nanomaterials such as carbon nanotubes, silver nanoparticles, and two-dimensional electroactive reduced graphene oxide (RGO) [115–117]. Electrochemical sensors can detect OSCC specific markers in body fluids (saliva, serum) with high sensitivity, assisting pathological biopsy. Cyfra 21.1 is significantly elevated in saliva of OSCC patients. The detection limit of the electrochemical immunosensor based on RGO/carbon nanotubes is as low as 0.5 pg/mL, with a clinically validated sensitivity of 91% [113]. Tumor derived extracellular vesicle miRNA is an ideal non-invasive biomarker. The sensor based on Ti3C2Tx MXene can detect miR-21 in saliva and distinguish early OSCC from healthy controls (AUC = 0.94) [118]. Prognostic biomarkers can be used for treatment monitoring and recurrence prediction, such as dysregulated ncRNAs (such as miRNA-675-5p) that affect oral cancer progression by regulating the cell cycle and have prognostic value [119].

The diagnostic techniques for oral cancer have evolved from traditional clinical examinations, imaging evaluations (such as X-rays, CT, MRI, and PET-CT), and tissue biopsies to emerging liquid biopsies, sialomics, molecular imaging, AI assisted diagnosis, and electrochemical testing. The comparison between traditional and emerging diagnostic methods for oral cancer is shown in Table 2.

3.8 Therapeutic method

The treatment of oral squamous cell carcinoma (OSCC) can adopt multiple modes, which can be used alone or in combination. These treatment methods include surgical resection, radiation therapy (such as external beam radiotherapy or close range therapy), and adjuvant systemic therapy (such as chemotherapy or immunotherapy) [126]. About one-third of oral cancer patients suffer from early-stage diseases, and these patients

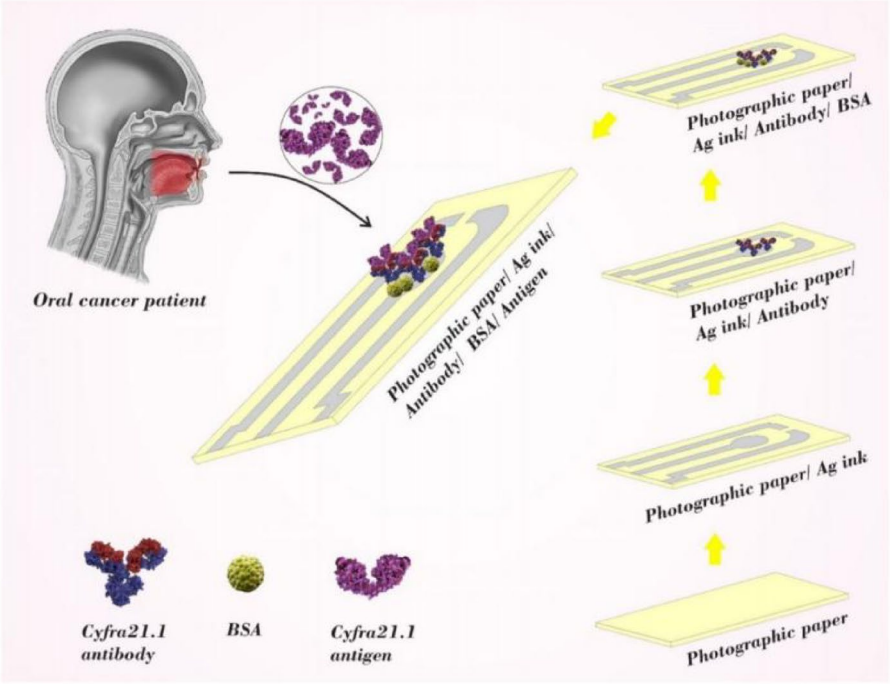

Fig. 4 Electrochemical immunosensor detection of human saliva samples [113]

receive postoperative radiation therapy with good prognosis. Patients with locally advanced oral tumors are mainly treated with surgery combined with postoperative radiotherapy and chemotherapy [127]. For oral squamous cell carcinoma (OSCC), surgery is considered the gold standard for treatment when it involves safe margin resection of the jawbone edge or segment. The surgical plan can be selected based on the specific condition of the lesion, whether to combine selective cervical lymph node dissection. Postoperative adjuvant radiotherapy (RT) and/or chemotherapy (CRT) are usually considered based on pathological results and clinical staging to reduce the risk of recurrence and improve survival rates. The multimodal treatment strategy is mainly formulated based on the extent of lesion expansion and initial staging [128].

However, surgical resection has trauma and limitations, generally applicable to primary lesions, cannot eliminate metastatic cancer cells, and cannot come into contact with cancer cells in the bloodstream. In addition, surgical treatment is required for patients with high physical demands; Otherwise, it will accelerate the spread and metastasis of cancer cells due to weakened immunity. Radiation therapy is the use of radiation to irradiate cancer tissue, destroy the DNA strands of cancer cells, and achieve local treatment of cancer [129]. Radiation therapy usually has a long treatment cycle, high cost, and can cause various complications, damage bodily functions, and weaken the body's immune system. Oral chemotherapy is emerging as a promising treatment option for various cancers due to its high safety and convenience, low cost, and high patient compliance. This may be good news for oral cancer patients who require CRT treatment [130]. Therefore, there is an urgent need to develop new cancer treatment strategies that can not only provide effective tumor treatment, but also significantly reduce toxicity and adverse reactions during the treatment process, ultimately improving the overall quality of life and long-term prognosis of patients.

Table 2 Comparison of traditional and emerging diagnostic methods for oral cancer

Comparative items	conventional diagnostic methods	Ref.	Emerging diagnostic methods	Ref.
virulence	Invasive procedures such as tissue biopsy are required	[76]	Non-invasive or minimally invasive, as salivary omics	[91]
Patient comfort	May cause patient discomfort	[120]	Provide a more comfortable diagnostic experience	[120]
sensitivity and specificity	May be a lack of sensitivity, leading to difficulties in early diagnosis	[121]	Usually with higher sensitivity and specificity, facilitate early diagnosis	[122]
Molecular features	Depend on morphological and histological features	[67, 76]	Using molecular features, such as genomics, transcriptomics, proteomics, metabolomics, and microbiome	[85, 91, 94]
Deagnostic tool	Including both imaging and protein biomarkers	[66, 77]	Including advanced nanoscale preparations, long non-coding RNA (lncRNA), computer-aided analysis and deep learning algorithms	[123, 124]
Real-time information provision	Real-time information is not normally provided	[78]	Liquid biopsy can provide real-time information on tumor dynamics	[125]
Biomarker development	Relying on a single biomarker may not meet all diagnostic needs	[120]	Study and develop biomarker combinations to improve diagnostic and management accuracy	[120]
technological development	Technology is more mature, but it may lack innovation	[78]	With rapid development, new technologies and methods are constantly emerging, such as molecular imaging technology, electrochemical detection, artificial intelligence diagnosis, etc.	[93, 97, 106]
Cost and resources	More often requires more medical resources and costs	[65, 66, 76]	New technologies may require more investment in research and development, but could reduce costs in the long term	[120]

In recent years, with the rapid development of molecular targeted therapy and immunotherapy, new hope has been provided for the precise treatment of OSCC. In terms of targeted therapy, RAS signaling pathway inhibitors (such as KRAS G12C inhibitors) have shown certain therapeutic effects in clinical trials, but due to the existence of adaptive resistance mechanisms, they often need to be combined with MEK inhibitors or immune checkpoint inhibitors (ICI) to enhance efficacy and delay the occurrence of resistance [131, 132]. Histone deacetylase (HDAC) inhibitors can overcome drug resistance in preclinical studies, but their efficacy in clinical practice still needs further optimization [133]. Microtubulin targeted drugs such as paclitaxel have also shown potential in locally advanced oral cancer, especially when combined with EGFR inhibitors or immunotherapy [134]. In order to improve response rates, strategies are currently being explored to combine ICI with targeted therapies (such as tyrosine kinase inhibitors TKIs), anti VEGF therapy, or STING agonists. Combining ICI with STING agonists can reshape the tumor immune microenvironment and activate stronger T cell responses [135–137]. CAR-NK cell therapy, as a new generation immunotherapy technology, has demonstrated good safety and anti-tumor activity in preclinical studies, and related clinical trials are currently underway [138]. Unlike traditional cancer treatment methods, targeted therapies, these new drugs specifically interfere with the growth and survival mechanisms of cancer cells by interacting with specific receptors and intracellular signaling pathways. Selecting appropriate therapeutic drugs based on specific carcinogenic sites has the advantages of high selectivity, low toxicity, and high treatment index [139]. This type of treatment includes anti-tumor monoclonal antibodies (mAbs), small molecule inhibitors, signal transduction receptor inhibitors, and cancer vaccines

[140, 141]. Some plant extracts have shown targeted anti-cancer effects on oral cancer cells, showing more targeted anti-cancer effects compared to traditional chemotherapy drugs such as cisplatin [142]. HPV infection (especially HPV16) plays a key role in the occurrence of OSCC, with 20–30% of OSCC patients detecting HPV DNA, but only 2–6% of patients showing E6/E7 mRNA expression (indicating active infection) [143]. The KEYNOTE-048 trial confirmed that the PD-1 inhibitor pembrolizumab, in combination with or without chemotherapy, can serve as the first-line standard treatment for platinum sensitive recurrent/metastatic head and neck squamous cell carcinoma (including oral cancer), significantly improving survival [144]. In recurrent/metastatic OSCC, PD-1 inhibitors combined with chemotherapy (such as cisplatin + docetaxel) can significantly prolong median progression free survival (PFS) to 7.9 months (vs. 5.4 months) and overall survival (OS) to 24.2 months (vs. 16.7 months) [145]. Some new drugs, such as the combination of metformin and verteporfin, have shown anti-cancer effects against head and neck squamous cell carcinoma (HNSCC) [146]. Secondly, the introduction of immune checkpoint inhibitors marks a significant breakthrough, significantly improving overall survival rates. By using monoclonal antibodies to block inhibitory immune checkpoint molecules such as PD-1 and PD-L1, these therapies enhance the immune response to tumors, effectively controlling the growth and spread of tumor cells. Immune checkpoint blockade eliminates inhibitory signals for T cell activation, allowing tumor reactive T cells to overcome regulatory mechanisms and produce effective anti-tumor responses. This type of immunotherapy aims to restore or enhance the immune system's ability to detect and destroy cancer cells, by overcoming the tumor's immune evasion mechanism and rebalancing a state that is favorable for immune protection [147, 148]. In addition to the above treatment strategies, new treatment methods are also constantly emerging. Photodynamic therapy (PDT) uses photosensitizers such as indigo green (ICG) combined with near-infrared light (NIR) for local treatment. Due to its high selectivity and FDA certified safety, it has become a promising local control method and can be used in combination with chemotherapy or immunotherapy to improve efficacy [149, 150]. Epigenetic regulatory drugs such as BET inhibitors have shown anticancer activity in preclinical models, but need to be combined with other drugs (such as HDAC inhibitors) to improve clinical response rates [151]. The oncolytic virus therapy is based on vectors such as Sindbis virus and has shown good anti-tumor effects in models such as ovarian cancer. Its application in oral cancer still needs further exploration [152–154]. Drugs targeting metabolic pathways, such as statins, have also been found to enhance the sensitivity of tumors to existing treatments, suggesting that their combination with chemotherapy or targeted therapy may have a synergistic effect [155]. Although the above-mentioned new therapies have shown encouraging results in preclinical studies, they still face many challenges in the actual translation process. For example, about 95% of new therapies are effective in preclinical trials but fail in clinical trials, mainly due to the lack of preclinical models that closely resemble human pathological and physiological characteristics (such as PDX, organoids), as well as insufficient guidance on biomarkers, making it difficult to accurately screen beneficiaries [156]. Meanwhile, combination therapy may increase toxicity and side effects, making it crucial to evaluate safety in preclinical models [157, 158]. In addition, changes in the tumor oxygen microenvironment can also affect drug sensitivity, and under hypoxic conditions, it is necessary to adjust the combination therapy strategy to improve efficacy [159]. The

Table 3 Progress in clinical trials of immunotherapy/targeted therapy for oral cancer

Type of treatment	Current progress	Ref.
Immunotherapy	Immune checkpoint inhibitors (PD-1/PD-L1 antibodies) have shown clinical value in recurrent or metastatic oral squamous cell carcinoma (OSCC), significantly improving progression free survival and overall survival	[166–168]
Targeted therapy	Monoclonal antibodies targeting specific signaling pathways (such as EGFR, VEGF) have been used in clinical trials, but the issue of drug resistance has not yet been resolved	[169, 170]
Combination therapy	Immune + targeted combination: such as PD-1 inhibitors combined with anti angiogenic drugs, can improve the survival rate of late stage patients by 11–12.	[171, 172]

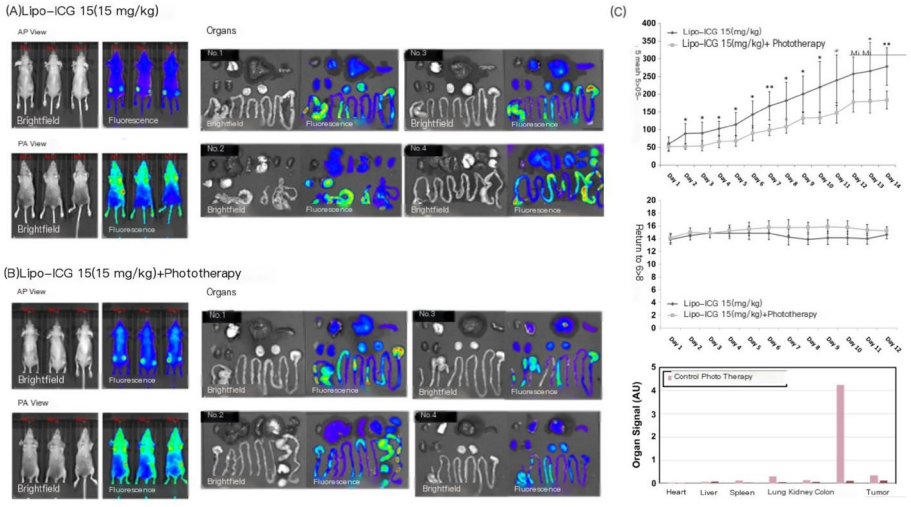

Fig. 5 Near-Infrared (NIR) light absorption characteristics for treating oral cancer [160]

progress of clinical trials of immunotherapy/targeted therapy for oral cancer is shown in Table 3. Meanwhile, studies have also shown that natural killer (NK) cells, as an important component of the innate immune system, have been explored for the treatment of oral squamous cell carcinoma (OSCC) due to their inherent ability to kill tumor cells [160]. Near infrared (NIR) light absorption, as shown in Fig. 5, demonstrates the potential of photodynamic and photothermal therapy using indigo green (ICG) for treating oral cancer due to its unique NIR light absorption characteristics and FDA approved safety profile [161]. These treatment strategies provide a framework for the treatment of oral cancer and help improve treatment outcomes. However, due to the high invasiveness and malignant tendency of oral cancer, early diagnosis is difficult, resulting in poor overall survival rates [162]. Therefore, continuous research on the molecular and cellular mechanisms underlying the development and progression of oral cancer, as well as innovative treatment trials, is crucial for optimizing strategies to prevent malignant progression.

With the advancement of science and technology, the field of precision medicine has ushered in new breakthroughs, pointing the way to the development of future therapeutic strategies. For example, CRISPR-Cas9 gene editing technology has been used to correct disease-causing mutations in hereditary diseases, including mutations in the TP53 gene [163]. As the 'guardian of the genome', the loss of function of TP53 is closely related to the development of many types of cancers, and the application of CRISPR-Cas9 technology offers the possibility of restoring its normal function. The application

of CRISPR-Cas9 technology has made it possible to restore its normal function, marking a significant advance in the field of gene therapy. Meanwhile, microbiota-targeted drug delivery systems represent an emerging field of nanomedicine, which aims to improve disease states through precise modulation of the gut microbiota [164]. Studies have shown that the gut microbiota has a profound impact on human health, ranging from immune regulation to metabolic homeostasis to direct involvement in certain disease processes. Microbiota-targeted drug delivery systems are capable of delivering therapeutic agents specifically to the target microorganisms, thereby improving therapeutic efficacy and reducing side effects. Combined with these advances, future therapeutic frontiers are likely to focus on the following: firstly, personalised gene therapy will become a reality, using advanced technologies such as CRISPR-Cas9 to target patient-specific genetic variants. Second, developments in microbiomics will further reveal the complex relationship between microbiota and human health, driving the development of microbiota-based diagnostics and therapeutics. Finally, interdisciplinary collaboration will become even more important based on the need for professionals such as oncologists, dentists, geneticists, and microbiologists to work closely together to develop more effective therapeutic options. This multidisciplinary teamwork not only integrates the expertise and technologies of each field, but also accelerates the process of translating from basic research to clinical application. For example, the success of this collaborative model has been demonstrated by several NCI-supported consortia, which, by pooling resources and technological strengths, have not only improved early detection rates and treatment efficacy, but have also fostered the development of personalised treatment protocols to ensure that each patient receives the treatment that is best suited to his or her specific condition [165]. In summary, as CRISPR-Cas9 gene editing technology and microbiota-targeted drug delivery systems continue to advance, we are moving into a whole new era in which precision medicine and personalised therapies will dramatically change our understanding of how diseases are prevented, diagnosed and treated.

3.9 Preventive methods

Oral cancer, as a serious life threatening disease, its incidence rate is increasing year by year worldwide, which has brought heavy economic and emotional burden to patients and their families. Early detection and prevention are key to reducing the risk of oral cancer and improving cure rates. By gaining a deep understanding of risk factors, taking effective preventive measures, and conducting regular professional examinations, we can reduce the likelihood of illness and improve the prognosis of patients.

3.10 Primary prevention: stop exposure to risk factors

The key to primary prevention of oral cancer is to stop exposure to known risk factors. According to an article released by the International Agency for Research on Cancer (IARC) working group in 2022, the revised oral cancer prevention strategy emphasizes the importance of smoking cessation and alcohol restriction in reducing the risk of oral cancer. Studies have shown that the risk of cancer gradually decreases over time after quitting smoking. In addition, stopping the use of betel nut products - whether accompanied by smoking or not - has also been shown to be beneficial for preventing oral cancer [173]. A prospective cohort study showed that quitting smoking, especially before diagnosis, can significantly reduce the overall mortality rate and cancer specific

mortality rate of HNSCC patients [174]. Long-term abstinence (>10 pack-years) confers significant overall survival and HNSCC-specific survival benefits. In a randomized controlled trial conducted in India, it was found that intervening in tobacco use through centralized education programs can significantly improve smoking cessation rates and effectively reduce the incidence of precursor lesions (such as oral leukoplakia, OL) associated with oral cancer [175]. The decrease in the incidence rate of dental plaque also supports this conclusion, indicating an improvement in overall oral health. Therefore, this study demonstrates the feasibility and effectiveness of primary prevention of oral cancer, emphasizing the important role of educational interventions in preventing oral cancer. Secondly, as alcohol is a risk factor for oral cancer, the risk increases when alcohol is used in combination with tobacco products [176]. Another study found that there is a significant synergistic effect among risk factors, especially when multiple factors are present simultaneously, such as exposure to tobacco (including cigarettes, smokeless tobacco (SLT), secondhand smoke (SS)), BQ, and alcohol, the combined risk of OPMD is extremely high [177]. In a meta-analysis, the potential for reversing the risk of oral and pharyngeal cancer after discontinuing betel nut use (BQ-T) was emphasized for the first time, as well as the significant reduction in oral cancer risk after long-term withdrawal from betel nut use and smoking cessation (BQ + T, over 10 years). These findings further support the urgent need to develop strong policies to reduce the use of betel nut and incorporate betel nut cessation interventions into cancer control efforts, particularly in geographic areas where betel nut chewing is prevalent [178]. Community-based betel nut (areca nut) cessation programmes have been conducted in South Asia, partly through health education, training of local health workers, and raising public awareness of the health risks associated with betel nut. Studies have shown that these measures have been effective in increasing the knowledge and health awareness of adults and children about the dangers of betel nut, as well as positive attitudinal changes [179, 180]. Such community-centred intervention strategies not only enhance the sense of participation of the residents, but also lay the foundation for behavioural change. In the future, by incorporating cultural practices and utilising the influence of religious sites and local leaders, it is possible to achieve wider and sustainable betel nut control, thereby reducing the incidence of oral cancer and other related diseases.

3.11 Secondary prevention: early screening and regular physical examinations

Due to the fact that many cases of oral cancer are only diagnosed in the late stage (stage III or IV), the difficulty of treatment increases and the prognosis for patients is poor. According to statistics, up to 50% of oral cancers are diagnosed in the advanced stage, which seriously affects treatment effectiveness and patient survival rates [181]. Therefore, early screening and regular physical examinations are crucial for preventing oral cancer. In 1996, India launched a cluster randomized controlled trial using visual oral examination to evaluate its impact on oral cancer mortality rates among the average risk population. Although the initial results showed a 22% reduction in overall mortality, this result is not statistically significant. However, in subgroup analysis after 9 years of follow-up, studies targeting tobacco or alcohol users (or both) showed a significant 34% reduction in mortality rates [182]. It is worth noting that due to limited statistical ability, this significance only appears in males, while the results in females did not reach statistical significance. After 15 years of follow-up, the mortality rate of oral cancer in high-risk

populations continued to decrease by 24% (95% CI: 3% –40%), further confirming the importance of early screening in these populations [183]. Based on this study in India, Cramer et al. simulated the effect of oral cancer screening program for Americans, especially men with a long history of smoking [184]. It was found that targeted screening of high-risk populations for oral cancer may maximize screening efficiency and have a meaningful impact on oral cancer mortality rates. Oral cancer mainly includes malignant tumors of the mouth, including lips, tongue, bottom of the mouth, palate, and gums. Its symptoms usually manifest as persistent ulcers, red or white patches, lumps, or chronic pain, which can be visible or palpable in the mouth. These early signs and symptoms can be easily identified through visual examination and manual palpation during dental examination [185]. Therefore, regular dental checkups can help detect oral cancer early by assessing risk factors, conducting comprehensive oral examinations, and identifying potential malignant lesions. In addition, HPV vaccines were initially developed to prevent cervical cancer, but their benefits can have a broader scope in preventing other HPV related diseases such as oropharyngeal cancer and oral squamous cell carcinoma [186]. A systematic review found that participants who received the HPV vaccine had significantly reduced vaccine type oral or oropharyngeal HPV infections [187]. In addition, a large proportion of participants developed IgG antibodies in their oral fluid after vaccination. In an early screening in the United States and Texas, the potential role of dental service providers in reducing the incidence rate of oral cancer and oropharyngeal cancer was emphasized. It can be seen that secondary prevention can be achieved through prevention and screening [188]. Caponio et al. mentioned that inflammatory cells induce host immune responses at the forefront of tumors, preventing tumor spread, indicating that secondary prevention can be achieved by monitoring and enhancing immune responses [189]. Khanna et al. discussed the diagnostic accuracy and epidemiological value of mobile health (mHealth) technology in early detection of oral precancerous lesions or oral cancer (OPML/OC). This indicates that the use of modern technology can improve the efficiency and accuracy of early detection [190]. In addition, multiple studies have shown that important reasons for delayed diagnosis may be self neglect, patients' lack of understanding of the cause, and asymptomatic and subtle clinical manifestations of the lesion [191–193]. Therefore, it is very important and necessary to promote and educate about oral cancer.

3.12 Tertiary prevention: rehabilitation and complication management, as well as recurrence monitoring

For patients diagnosed with oral cavity cancer, if it has progressed to advanced stages or after treatment, the purpose of tertiary prevention is to control the condition, prevent recurrence, alleviate pain, and improve quality of life. This includes post treatment management of patients after using treatment methods such as surgery, radiation therapy, and chemotherapy. After treatment for head and neck cancer (HNC), patients' oral function and quality of life (QoL) may be affected, therefore targeted rehabilitation therapy is needed [193]. Nagarathna P J et al. emphasized the important role of oral cancer stem cells (OCSCs) in treatment resistance and tumor recurrence. The treatment strategy for OCSCs can reduce recurrence and metastasis, and is an important part of tertiary prevention [194]. Oral mucositis caused by radiotherapy and chemotherapy is a common side effect of cancer treatment, and prevention and treatment of oral mucositis are

crucial for improving patients' quality of life [195]. Oral cancer patients require special management and treatment to prevent the occurrence of serious complications. Mercadante V et al. mentioned that reducing radiation dose on salivary glands can lower the incidence and severity of dry mouth syndrome and reduce treatment side effects, which is part of reducing treatment-related complications in tertiary prevention [196].

4 Summary and prospect

This article reviews the latest developments in cancer research, comprehensively exploring the carcinogenic factors, pathogenesis, diagnostic methods, treatment methods, and prevention strategies of oral cancer. Oral cancer is a significant global health concern, with particularly high incidence in certain regions such as South and Southeast Asia. In China, both the incidence and mortality of oral cancer have been steadily increasing, making it one of the major malignancies threatening public health—especially given its strong association with risk factors like tobacco use, alcohol consumption, betel quid chewing, and HPV infection. In terms of diagnostic methods, traditional techniques such as clinical examinations and imaging examinations have certain effectiveness, but also have limitations. Emerging technologies such as tissue biopsy, salivary omics, molecular imaging, artificial intelligence diagnosis, and electrochemical detection provide more possibilities for early diagnosis of oral cancer. In terms of treatment methods, multimodal treatment strategies such as surgical resection, radiation therapy, chemotherapy, and immunotherapy have been developed based on the severity of the lesion. However, there is an urgent need to develop new treatment strategies to reduce toxicity and adverse reactions. In terms of prevention, primary prevention emphasizes etiological prevention, secondary prevention emphasizes early screening and regular physical examinations, and tertiary prevention focuses on patient management after treatment, including preventing recurrence and metastasis, reducing treatment side effects, and comprehensive treatment. Future research should focus on several key directions to address the unmet challenges in oral cancer management. Firstly, in-depth research on the mechanisms of carcinogenesis, especially the molecular mechanisms under the interaction of multiple factors, provides a solid theoretical basis for precision treatment. Secondly, explore and develop efficient non-invasive diagnostic techniques, such as saliva diagnosis based on multi omics and more precise molecular imaging techniques, to improve the accuracy and efficiency of early diagnosis. Thirdly, develop new treatment strategies, including targeted therapy, immunotherapy, and gene therapy, to address the high invasiveness and malignancy of oral cancer, and reduce toxicity and adverse reactions during the treatment process. In addition, strengthening interdisciplinary cooperation, promoting collaborative innovation in fields such as dentistry, oncology, molecular biology, genetics, and immunology, and jointly advancing and developing research on oral cancer. Finally, improve public health literacy by strengthening publicity and education, advocating a healthy lifestyle, reducing exposure to carcinogenic factors, and thereby reducing the risk of illness. These comprehensive measures will help to effectively control the incidence rate and mortality of oral cancer, and improve the prognosis and quality of life of patients. In the future, further in-depth research should be conducted on the carcinogenic mechanism of oral cancer, especially the molecular mechanism under the interaction of multiple factors, to provide theoretical basis for precision treatment. Continue to explore and develop new, efficient, non-invasive diagnostic

techniques, such as saliva diagnosis based on multi omics and more precise molecular imaging techniques, to improve the accuracy and efficiency of early diagnosis. Develop new treatment strategies, such as targeted therapy, immunotherapy, and gene therapy, to address the high invasiveness and malignancy of oral cancer, thereby reducing toxicity and adverse reactions during the treatment process, improving the overall quality of life and long-term prognosis of patients. Strengthen the research and implementation of primary, secondary and tertiary prevention strategies, especially the screening and intervention of high-risk groups, to effectively reduce the incidence rate and mortality of oral cancer. Promote interdisciplinary cooperation in dentistry, oncology, molecular biology, genetics, immunology, and other fields to jointly advance and develop research on oral cancer. The findings from our study highlight the potential of the 3D cancer-immune co-culture model in elucidating the STAT3 interactome and its role in immune regulation in oral squamous cell carcinoma (OSCC). Moving forward, this model should be further optimized to better mimic the in vivo tumor microenvironment, incorporating additional immune cell types and stromal components to enhance its physiological relevance. Future studies should also focus on validating the functional roles of key STAT3-binding partners, such as EGFR, PRMT1, and SUMO2, in immune evasion using genetic and pharmacological approaches. Moreover, the integration of single-cell proteomics and spatial transcriptomics with 3D co-culture systems could provide deeper insights into the dynamic interactions between cancer and immune cells. As emphasized in our recent work [197] such advanced models are crucial for identifying novel therapeutic targets and developing more effective immunotherapies for aggressive and metastatic OSCC. Through these comprehensive measures, we are expected to significantly enhance our understanding and control capabilities for oral cancer in the future, bringing better treatment outcomes and quality of life to patients worldwide.

Author contributions

Kebin Xu Writing: original draft, Methodology, Investigation. Qiaozhi yang and Weiyun Chen: Writing original draft, Investigation. Zhijian Li: Methodology.Yudong Wu: Investigation. Data curation. Review & editing, Funding acquisition. Fu Ren and Xin Li: Writing review & editing, Supervision, Conceptualization.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

This is a review article that only synthesizes and analyzes data from previously published studies. No original human or animal experiments were conducted, so ethical approval was not required. This review does not involve human participants or collection of original individual data, so consent to participate is not applicable.

Consent for publication

This review relies on publicly available published data and does not contain any unpublished individual information or personal data. Thus, consent to publish is not required.

Competing interests

The authors declare no competing interests.

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