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REVIEW

Nanomaterials for Theranostic Management of Oral Cancer: Advances in Imaging, Biosensing, Targeted Delivery, and Multimodal Synergistic Therapy

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Abstract: Oral squamous cell carcinoma (OSCC), which accounts for over 90% of oral cancer cases, is often diagnosed at advanced stages, resulting in a five-year survival rate of less than 40%. Current diagnostic methods, such as visual examination, biopsy, and conventional imaging, have limitations in sensitivity, specificity, and invasiveness. Conventional treatments like surgery, radiotherapy, and chemotherapy also pose significant challenges due to functional loss, toxicity, and poor patient compliance. These issues have prompted the exploration of nanomaterials as promising theranostic tools. Due to their tunable properties, high surface area, and biocompatibility, nanomaterials offer innovative solutions for OSCC diagnosis and therapy. They enable enhanced imaging resolution, ultrasensitive biomarker detection, and targeted, stimuli-responsive drug delivery systems that improve therapeutic outcomes while minimizing side effects. Additionally, nanoplatforms can combine chemotherapy, photothermal therapy (PTT), photodynamic therapy (PDT), gene therapy, and immunotherapy to address challenges like multidrug resistance and tumor hypoxia. This review highlights the novel role of nanomaterials in OSCC, focusing on their use in diagnostic enhancement, targeted therapies, and multimodal treatment strategies. Finally, we discuss the challenges of clinical translation, including synthesis scalability, regulatory standards, and long-term safety, while suggesting future directions, such as biodegradable nanomaterials, AI-based personalized treatment platforms, and improved clinical trial designs.

Keywords: oral cancer, nanomedicine, drug delivery, combination therapy, precision medicine

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Introduction

Oral cancer, a critical subtype of head and neck malignancy, has emerged as one of the most prevalent malignant tumors worldwide. Among these cases, oral squamous cell carcinoma (OSCC) accounts for over 90% of the total.[1] Epidemiological data reveal that global deaths attributed to oral cancer exceeded 170,000 in 2020, imposing an extremely heavy disease burden.[2] The high mortality is largely associated with delayed diagnosis. The concealment of early clinical symptoms of oral cancer, coupled with inadequate public awareness of the disease, contributes to this widespread diagnostic delay.[3] Clinical statistics indicate that more than 50% of patients are diagnosed at an advanced stage, directly leading to a poor prognosis in which the five-year survival rate remains only around 40%.[4] Currently, oral potentially malignant disorders (OPMDs), tobacco exposure, alcohol consumption, betel nut chewing, and human papillomavirus (HPV) infection are recognized as the primary risk factors for oral cancer (Figure 1).[1] In clinical practice, the diagnosis of oral cancer remains primarily reliant on oral mucosa macroscopic observation, tissue biopsy, and conventional imaging examinations (eg, CT, MRI, fluorescence imaging).[5,6] However, these diagnostic methods exhibit significant limitations: naked-eye observation strongly depends on the clinician's experience and is therefore subjective; tissue

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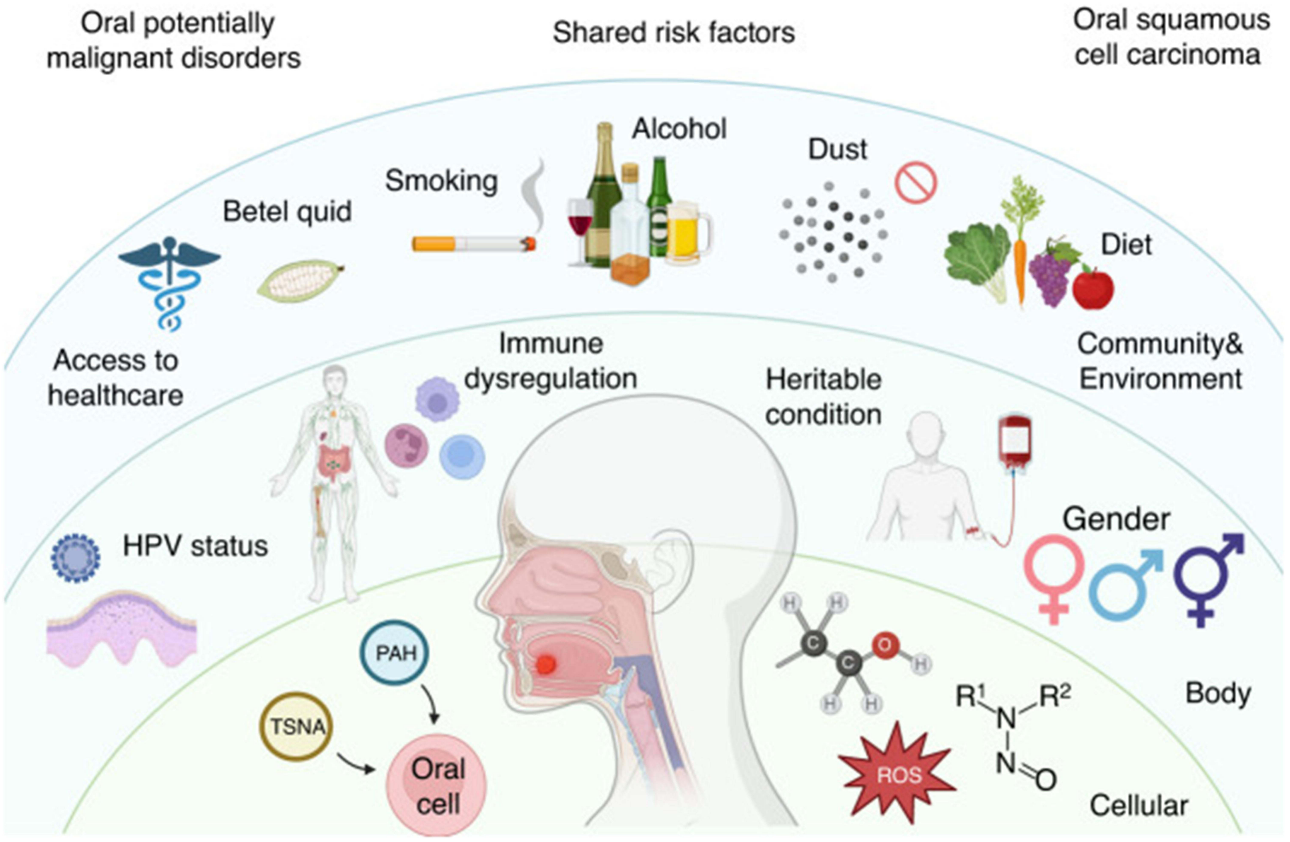

Figure 1 Multifactorial risk factors for OSCC and oral potentially malignant disorders (OPMDs). The diagram illustrates interconnected contributors: environmental (eg, alcohol, smoking, betel nut, dust, polycyclic aromatic hydrocarbons [PAH], tobacco-specific nitrosamines [TSNA]); dietary and immune factors; genetic traits (eg, RUNX2); human papillomavirus (HPV) infection; gender; reactive oxygen species (ROS)-mediated cellular damage; and social determinants (eg, healthcare access, community awareness). These elements collectively drive malignant transformation of oral epithelium. Reproduced from,[1] Copyright © 2023 by the authors.

biopsy, while accurate, is invasive and reduces patient compliance; and conventional imaging is constrained by limited resolution, while the potential toxicity of contrast agents remains unresolved.[4,5,7] Surgical resection, radiotherapy, and chemotherapy remain the mainstay of treatment.[8] Nevertheless, each approach carries clear drawbacks. Surgical resection may result in disfigurement and functional impairments in speech and taste.[9] Although radiotherapy and chemotherapy can exert certain therapeutic effects, damage to normal tissues is inevitable and may even induce long-term complications such as cardiovascular diseases.[10] Additionally, the presence of biological challenges including multidrug resistance (MDR), abnormal tumor microenvironment, and immune escape further diminishes the therapeutic efficacy in oral cancer.[11–13] Therefore, the development of minimally traumatic precision diagnostic and therapeutic strategies with early detection capabilities, precise delivery properties, and multimodal treatment functions has become an urgent need in the field of oral cancer research.[14,15] This approach seeks to minimize harm in both the diagnostic and therapeutic processes, ensuring less invasive and more patient-friendly solutions.

The rapid development of nanomaterials has opened up a novel avenue for addressing the clinical challenges in oral cancer diagnosis and therapy. Nanomaterials, with their unique physicochemical properties, such as tunable size, high specific surface area, facile surface functionalization, and excellent biocompatibility, offer promising solutions to overcome the limitations of current imaging and drug delivery systems.[16–19] These properties enable nanomaterials to significantly enhance both diagnostic and therapeutic approaches in oral cancer management. For instance, nanomaterials can integrate multimodal imaging agents, thus significantly enhancing diagnostic resolution and specificity, allowing for early and accurate detection of oral cancer.[20,21] Furthermore, nanomaterials can be utilized to construct ultrasensitive detection platforms for salivary or serum tumor markers, facilitating non-invasive diagnosis and overcoming the drawbacks of invasive traditional diagnostic methods.[22] In addition, nanomaterials can be engineered into targeted, stimulus-responsive drug delivery systems, allowing for real-time control of drug release. This precise, controllable drug delivery addresses the inefficiencies of conventional systems, ensuring targeted and effective therapeutic outcomes while minimizing systemic side effects.[16–18,23] Nanomaterial-based theranostic platforms have the potential to synergize with chemotherapy, photodynamic therapy (PDT), photothermal therapy (PTT), gene therapy, and immunotherapy, offering a combined therapeutic effect that enhances the overall efficacy in targeting and treating oral cancer cells.[24–26] By integrating multiple treatment modalities, nanomaterials offer a comprehensive approach to overcoming the complex challenges in oral cancer therapy, such as multidrug resistance, tumor heterogeneity, and poor therapeutic targeting.[14,27]

Despite the increasing in-depth research on nanomaterials in the field of cancer diagnosis and treatment, studies on their applications in OSCC remain fragmented, and their clinical translation process is constrained by multiple factors.[28] These include challenges in biosafety assessment, limitations in large-scale production technologies, ambiguity in regulatory classification standards, and the lack of experimental models that accurately recapitulate the human oral microenvironment.[29,30] Existing literature predominantly focuses on single dimensions of diagnosis or treatment, lacking a comprehensive and cross-disciplinary systematic summary tailored to OSCC.[31] Concurrently, the interaction mechanisms between key design parameters of nanomaterials (such as size, morphology, and surface chemical properties) and OSCC-specific microenvironmental barriers have not been systematically elaborated.[32] In view of these unmet needs, this review comprehensively summarizes the latest research progress and application strategies of nanomaterials in OSCC diagnosis and treatment, with a focus on their core role in theranostic integration. To streamline the discussion, we organize the content by key applications and mechanisms: diagnosis (including imaging enhancement and biosensing platforms), targeted delivery systems, and multimodal synergistic therapies (encompassing PTT, PDT, gene/immunotherapy, and combinations). This structure highlights nanomaterial functionalities across diverse platforms while avoiding redundancy in material-specific descriptions The content covers key areas such as nanomaterial-based imaging enhancement systems, biosensor platforms, targeted and stimulus-responsive delivery systems, and multimodal combination therapies. Finally, this paper discusses the clinical translation challenges of nanomaterials in OSCC diagnosis and treatment and proposes future research directions, aiming to provide a scientific basis and development pathway for the design of nanomaterial-based precision theragnostic platforms for OSCC.

Classification of Nanomaterials in Oral Cancer

In the clinical practice of oral cancer diagnosis and treatment, the traditional model is confronted with multiple practical dilemmas.[33] First, the accuracy of early screening remains insufficient, hindering timely detection and diagnosis of the disease.[34] Second, invasive examination methods, characterized by low patient acceptance, restrict the smooth implementation of clinical diagnosis.[35] In the context of treatment, the efficacy of existing therapeutic regimens is limited by factors such as tumor heterogeneity and multidrug resistance, while their significant toxicity and side effects further compromise patients' quality of life.[36] Therefore, breaking through the technical bottlenecks of the traditional diagnosis and treatment model has become a key problem to be addressed in clinical practice.

Endowed with unique physicochemical properties (such as the quantum size effect and surface effect) and excellent biological function-regulating capabilities, nanomaterials offer novel strategies and technical support for overcoming the aforementioned clinical challenges.[37,38] They not only compensate for the inherent limitations of conventional diagnostic and therapeutic methods but also open promising research avenues for establishing a precision theragnostic system tailored to oral cancer. The following section will outline the categories and application characteristics of nanomaterials commonly utilized in the field of oral cancer diagnosis and treatment.

Gold Nanomaterials

Owing to their unique optical and physicochemical properties, especially, gold nanomaterials have demonstrated significant application advantages in the field of oral cancer diagnosis and treatment.[39] The high specific surface area of gold nanoparticles enables the enhancement of the surface plasmon resonance (SPR) effect.[40] Meanwhile, their inherent non-immunogenic characteristics confers low biological toxicity.[41] In addition, gold nanomaterials possess excellent ductility, allowing the acquisition of diverse morphological features through the regulation and control of preparation processes. Importantly, morphological variations lead to distinct physicochemical behaviors: for example, the catalytic efficiency of gold nanorods surpasses that of spherical nanoparticles, whereas gold nanocubes demonstrate enhanced bactericidal effects. These observations suggest that particle geometry directly modulates surface atom exposure and binding capacity, and such structure–function correlations are essential for rational design in diagnostic applications.[41,42]

In terms of diagnostic applications, surface-enhanced raman scattering (SERS) technology leverages the robust SPR effect of gold nanoparticles to achieve efficient enhancement of Raman scattering signals, thereby significantly improving the sensitivity of tumor detection.[41] Compared with conventional fluorescent probes, SERS provides higher photostability and signal specificity; however, the reproducibility of "hot spot" generation at the molecular level remains a major technical challenge. Given the challenges in early detection and surgical margin determination posed by the irregular anatomical structure of the oral cavity, the SPR properties of gold nanomaterials can enhance the contrast of oral imaging, leading to a marked improvement in diagnostic accuracy.[43] David et al successfully sorted and identified 12–17% of tumor cells by constructing a gold-coated magnetic nanoparticle system and combining magnetic sorting with SERS technology for the detection of colorectal cancer tumor cells. This study confirmed that the integration of gold nanoparticles, magnetic nanomaterials, and SERS technology can effectively enhance the sensitivity of tumor detection.[44] This integration illustrates a synergistic mechanism: magnetic nanomaterials enable efficient physical enrichment of tumor cells, while gold nanomaterials amplify Raman signals at the molecular level, together producing higher diagnostic sensitivity. However, the approach requires further validation in oral cancer models, and issues such as probe stability, background interference, and large-scale clinical applicability remain unresolved.[44]

As an emerging imaging technology, diffuse reflectance spectroscopy (DR) enables tumor diagnosis by identifying the specific optical characteristics of tissues across different wavelengths.[40] Endowed with unique optical properties, gold nanoparticles can be selectively enriched in tumor tissues, thereby altering their optical profiles and enhancing the diagnostic sensitivity of DR technology.[40] For example, Sudri et al confirmed that after anti-epidermal growth factor receptor (EGFR) monoclonal antibody-coupled gold nanorods specifically bound to EGFR on the surface of tumor tissues, DR detection revealed a marked enhancement of optical signals in OSCC model rats.[45] This study underscores the importance of molecular targeting: antibody conjugation ensures selective nanoparticle accumulation at tumor sites, while anisotropic nanorods amplify optical responses through shape-dependent SPR effects. Compared with untargeted nanoparticles, such active targeting strategies improve tumor-to-normal tissue contrast. Nevertheless, practical challenges—including antibody stability, immunogenic risk, and the high cost of bioconjugation—may hinder widespread clinical translation. Overall, these findings indicate that diagnostic strategies based on the optical properties of gold nanomaterials hold great promise for the early and accurate detection of oral cancer.[40,46]

In the field of therapeutic applications, gold nanoparticles can efficiently achieve the conversion of light energy to thermal energy under near-infrared (NIR) light irradiation. By generating local hyperthermia in tumor tissues, they exert a photothermal therapeutic effect, enabling the selective killing of tumor cells.[47] Meanwhile, due to their excellent biocompatibility and surface modifiability, gold nanoparticles are frequently engineered as drug delivery carriers.[48] In particular, surface functionalization enhances their targeted delivery capability by enabling specific binding to tumor-associated receptors or microenvironmental cues. Khamaikawin et al demonstrated that when gold nanoparticles loaded with docetaxel, cisplatin, and fluorouracil were applied in the treatment of head and neck squamous cell carcinoma models, the system achieved precise targeted drug delivery and efficient intracellular accumulation, while maintaining therapeutic efficacy with reduced doses of chemotherapeutic drugs.[49] This not only highlights their potential to minimize systemic toxicity but also underscores the synergistic advantage of combining photothermal properties with controlled drug release.

While gold nanomaterials excel in exploiting SPR for enhanced imaging and photothermal effects, their molecular interactions with OSCC cells primarily involve receptor-mediated endocytosis via ligands such as anti-EGFR antibodies, which bind to overexpressed EGFR on tumor surfaces (affinity Kd ~10–100 nM).[40,45] This interaction facilitates clathrin-dependent uptake and subsequent lysosomal escape, thereby improving intracellular delivery efficiency. In the acidic tumor microenvironment (TME, pH 6.5–6.8), thiolated coatings on AuNPs can protonate, triggering pH-responsive drug release and mitigating hypoxia-induced resistance by enhancing ROS generation.[50] Comparative studies show that gold nanorods (AuNRs) outperform spherical AuNPs in NIR absorption (peak at ~800 nm vs 520 nm), achieving 20–30% higher photothermal conversion efficiency (η ~50%).[51] However, AuNRs are prone to shape-dependent aggregation in the viscous oral mucosa, which reduces tumor penetration depth by up to 40% compared with magnetic nanomaterials.[40]

Targeting strategies typically combine active mechanisms (eg, antibody conjugation) with passive accumulation via the enhanced permeability and retention (EPR) effect.[52] Yet, the reliability of the EPR effect in OSCC remains controversial, as dense stromal architecture and elevated interstitial pressure restrict nanoparticle extravasation. Despite these advances, several limitations persist. Long-term hepatotoxicity due to Au^3+ ion leaching has been reported in 15–20% of preclinical models.[53] Moreover, early AuNR-PEG clinical attempts failed due to poor clearance kinetics, leading to off-target splenic accumulation and immune activation.[54] Recent strategies employing zwitterionic coatings show promise in improving circulation stability and reducing immune recognition, but large-scale GMP validation remains necessary.[55,56] Taken together, these insights highlight both the mechanistic advantages and translational challenges of Au-based systems, underscoring the need for hybrid nanoplatforms that balance efficacy and safety in the heterogeneous TME of OSCC.

Magnetic Nanomaterials

Magnetic nanomaterials are primarily composed of magnetic metal elements such as iron, cobalt, nickel, and manganese. By adjusting parameters including the size, morphology, and elemental composition of these nanomaterials, their physicochemical properties can be optimized, thereby enabling them to exert more significant effects in the diagnosis and treatment of oral cancer.[57] These materials possess excellent magnetic properties and structural stability, and their biocompatibility can be effectively enhanced through surface coating or ligand functionalization. In addition, some magnetic nanomaterials exhibit controlled biodegradability, with iron oxide nanoparticles (IONPs) serving as a representative example. In this case, Fe^2+/Fe^3+ ions can be metabolized through normal iron pathways, thereby reducing long-term toxicity.[58,59]

As one of the most widely utilized magnetic nanomaterials, IONPs can serve as contrast agents for MRI in diagnostic applications. By shortening the relaxation time of water molecules, tumor tissues enriched with magnetic nanoparticles exhibit a significantly low signal in T_2-weighted imaging, thereby enabling precise tumor localization and diagnosis.[60] Montiel et al confirmed that folic acid-modified IONPs, when used for MRI detection, can specifically target ovarian cancer cells with overexpressed folic acid receptors and successfully achieve targeted imaging of ovarian cancer.[59] This finding highlights the importance of molecular interactions between targeting ligands and tumor cell receptors, suggesting that receptor-mediated endocytosis plays a critical role in improving imaging specificity. More recently, iron carbide has emerged as a novel magnetic nanomaterial, with magnetization reaching 140 emu/g—significantly higher than that of traditional IONPs—and strong corrosion resistance that enhances stability in physiological environments. Compared with IONPs, iron carbide offers superior magnetic responsiveness and imaging contrast; however, its biocompatibility and biodegradability remain insufficiently validated, raising concerns for long-term clinical application.[57]

In the field of therapeutic applications, magnetic nanomaterials are frequently engineered as drug delivery carriers. For instance, hyaluronic acid-modified Fe_3O_4 magnetic nanoparticles can specifically target oral cancer cells with overexpressed CD44, enabling the precise delivery of therapeutic siRNA to oral cancer lesions under the guidance of an external magnetic field.[61] In this system, the molecular interaction between hyaluronic acid and CD44 ensures selective binding and internalization, illustrating how passive magnetic targeting can be synergistically combined with active receptor-mediated uptake. In addition, magnetic nanomaterials can generate local hyperthermia under the action of an alternating magnetic field, exerting a hyperthermic effect to kill tumor cells.[62] Legge et al demonstrated that when magnetic nanoparticles modified with anti-αVβ6 monoclonal antibodies acted on OSCC cells with high αVβ6 expression, high temperatures could be rapidly generated through alternating magnetic field induction, effectively inducing the death of OSCC cells.[63] This strategy exemplifies a dual-targeting mechanism: antibody conjugation improves tumor specificity, while the magnetic field enables spatial control over therapeutic heating. However, limitations—including uneven heat distribution, the risk of off-target thermal damage, and potential immune activation—remain significant challenges that must be addressed prior to clinical translation.

Mechanistically, magnetic nanomaterials such as IONPs interact with OSCC cells through their superparamagnetic properties.[64,65] Under external magnetic fields (0.5–2 T), the alignment of Fe^3+/Fe^2+ spins shortens T_2 relaxation times ($r_2 >$ 100 $mM^{-1}s^{-1}$), thereby enhancing water proton dephasing and producing high-contrast MRI signals, particularly in hypoxic regions of the TME.[66] Targeting is often achieved through folate or hyaluronic acid (HA) ligands binding to CD44 (Kd ~1 nM), which promotes caveolae-mediated endocytosis and facilitates magnetic hyperthermia (SAR > 500 W/g).[67] This hyperthermia

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disrupts mitochondrial membranes and alleviates hypoxia by vasodilating tumor vessels, increasing oxygen perfusion by 25–50%.[67,68] In comparative evaluations, IONPs provide superior magnetic guidance for deep-seated oral lesions, whereas gold nanomaterials offer greater optical versatility, achieving 50% photothermal efficiency compared to only 30–40% for IONPs.[69] However, limitations remain. Excess Fe^2+ can trigger Fenton reactions, producing hydroxyl radicals that exacerbate TME inflammation in 20–30% of preclinical models.[70] Debates persist regarding biodegradability: although IONPs can degrade into ferritin and be metabolized via normal iron pathways, incomplete clearance within fibrotic OSCC stroma may lead to chronic toxicity.[71,72] To address these concerns, Mn-doped IONPs have been explored, which enhance r_1/r_2 ratios and potentially reduce oxidative stress while improving imaging performance.

Polymer Nanomaterials

Polymer nanomaterials are composed of high-molecular-weight polymers, with a typical particle size range of 1–100 nm. These materials exhibit outstanding characteristics including strong designability, excellent biocompatibility, and favorable targeting capabilities.[73] Endowed with these superior physicochemical properties, polymer nanomaterials have garnered widespread attention and favor from researchers in the field of disease diagnosis and treatment. Through regulation of polymerization modes and surface modification, researchers can precisely tailor their physicochemical properties and targeting functions.[74] In addition, certain natural polymers (such as hyaluronic acid and albumin) or biodegradable polymers (such as PLGA and PEG) can effectively reduce immune rejection. For instance, aggregation-induced emission (AIE) photosensitizers encapsulated by bovine serum albumin (BSA) nanoparticles can significantly enhance biocompatibility, thereby facilitating preferential accumulation of photosensitizers at tumor sites.[73]

In the field of medical imaging, polymer nanomaterials are widely applied in MRI. For instance, magnetic PLGA nanoparticles modified with folate-modified chitosan can target and recognize oral cancer cells. By shortening the T_2 relaxation time, they significantly enhance the contrast of MRI images, thus improving diagnostic accuracy and providing clinicians with a more reliable basis for treatment planning.[38] Polymer nanomaterials are also widely utilized in drug delivery systems. Following surface modification, they can achieve targeted recognition of oral tumor cells and precise drug release. A representative example is the hyperbranched polymer nanoparticles (DOX/HαO-PLA@PDA-PEG-FA NPs) developed by Yin et al, which were surface-modified with polydopamine (PDA) and folic acid.[75] These nanomaterials demonstrated strong therapeutic efficacy in oral cancer, as doxorubicin (DOX) loaded onto them selectively targeted folate receptor–overexpressing tumor cells. Meanwhile, PDA provided high photothermal conversion efficiency, enabling synergistic photothermal–chemotherapy to eradicate local tumor cells.[76] Furthermore, the degradable components of these nanoparticles (HαO-PLA, PDA, and PEG-FA) effectively reduced systemic toxicity.[77]

At the molecular level, polymer nanomaterials such as PLGA interact with OSCC cells through amphiphilic self-assembly, where hydrophobic cores encapsulate doxorubicin (DOX) via π–π stacking (loading >20 wt%), while PEG shells sterically hinder protein corona formation, thereby extending systemic circulation ($t_1/_2$ >24 h).[78] Targeting strategies typically employ FA–HA conjugates that bind folate and CD44 receptors, subsequently triggering hyaluronidase-mediated degradation in the TME (with enzyme levels elevated 5–10×), which enables burst drug release and matrix remodeling to enhance nanoparticle diffusion in the dense collagen stroma.[79] In TME interplay, pH-sensitive hydrolysis of PLA ester bonds (at pH <6.8) produces lactic acid, amplifying local acidosis. This effect synergizes with PTT by denaturing HSP70 chaperones, thereby reducing treatment resistance.[80,81] Relative to lipid nanomaterials, polymer-based carriers exhibit tunable degradation kinetics (weeks vs hours) but their higher mechanical rigidity restricts endosomal escape (efficiency ~40% vs 70%).[82] Despite these advantages, key limitations remain. Heterogeneous degradation generates acidic byproducts that can damage adjacent healthy mucosa, with necrosis observed in 10–15% of xenograft models.[83] Furthermore, dendrimer-based systems have faced translational hurdles; for example, a PAMAM trial failed due to cationic toxicity that disrupted oral epithelial barriers.[84] Controversies also persist regarding the protein corona effect, which may alter targeting specificity in saliva-rich environments.[85] This has prompted exploration of mucoadhesive modifications, such as chitosan grafting, to enhance retention without compromising biocompatibility.

Lipid Nanomaterials

Lipid-based nanoparticles (LBNPs) are a class of nanomaterials with lipids as the main component. Since most of their components are natural lipids or lipid-like substances, they display excellent biocompatibility and biodegradability.[86] Through rational design and surface modification, LBNPs can be engineered into diverse forms suitable for oral cancer therapy, including liposomes, solid lipid nanoparticles, nanostructured lipid carriers, nanoemulsions, microemulsions, lipid–polymer hybrid nanoparticles, self-nanoemulsifying drug delivery systems, and lipid-core nanocapsules (Figure 2).[25,87]

Among these, liposomes are single-layer or multi-layer spherical structures composed of phospholipids and cholesterol. Their aqueous core can encapsulate hydrophilic drugs, while the lipid bilayer can carry lipophilic drugs.[25] Due to their lipid-based composition, liposomes exhibit high biocompatibility and low toxicity, making them particularly attractive for biomedical use.[88] This unique structural advantage, combined with favorable stability, underpins their broad application in the diagnosis and treatment of oral cancer. For example, Wei et al prepared liposomes of approximately 120 nm in diameter loaded with evodiamine (Evo), a natural alkaloid, and indocyanine green (ICG), a photosensitizer. Liposomes of this size efficiently exploit the EPR effect to selectively deliver therapeutic cargos to tumor sites.[89] While the hydrophobic nature of Evo limits its delivery when used alone, liposome encapsulation significantly improves its aqueous solubility and tumor accumulation. Simultaneously, encapsulated ICG exhibits

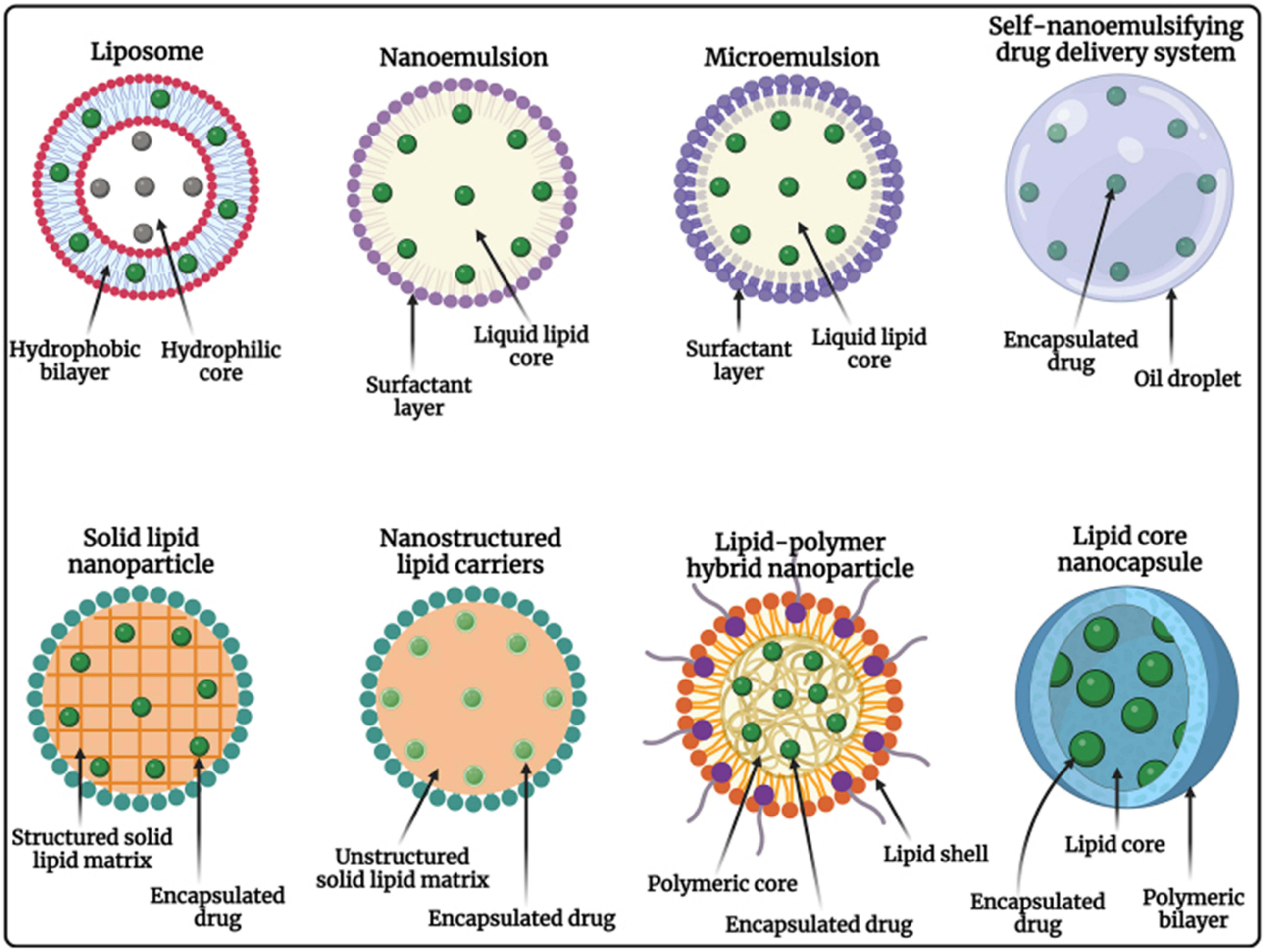

Figure 2 Overview of lipid-based nanoparticles (LBNPs) for OSCC theranostics. LBNPs encompass a family of colloidal carriers including liposomes, solid lipid nanoparticles, nanostructured lipid carriers, nano-/micro-emulsions, lipid–polymer hybrid nanoparticles, self-emulsifying drug-delivery systems and lipid-core nanocapsules. Liposomes—shown here as a representative subtype—consist of a spherical phospholipid–cholesterol bilayer that forms an aqueous core suitable for hydrophilic drugs while the lipid shell accommodates lipophilic agents, thereby enabling dual encapsulation. Other LBNPs display diverse core–shell architectures in which solid, liquid or nanostructured lipid matrices serve as reservoirs for therapeutic or diagnostic payloads. Surface functionalization with surfactants, PEG chains or targeting ligands further improves stability, biocompatibility and tumor-specific accumulation via the EPR effect and/or receptor-mediated recognition. Reproduced from,[87] Copyright © 2024 by the authors.

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reduced degradation in systemic circulation, thereby enhancing tumor accumulation and improving imaging precision.[90] In addition, liposomes can achieve targeted drug delivery to oral cancer cells through specific modification, thereby reducing damage to normal oral tissues.[91] Based on the characteristics of high folate receptor expression in breast cancer cells, Peres-Filho et al developed folate-modified liposomes to encapsulate paclitaxel and imatinib. The results demonstrated that, compared with conventional liposomes, these targeted liposomes significantly increased the mortality of breast cancer cells and reduced the expression of the vascular endothelial growth factor (VEGF) gene, thereby inhibiting tumor cell growth.[92] Although direct applications of modified liposomes in oral cancer remain limited, the confirmed overexpression of folate receptors in oral tumor cells provides a strong theoretical basis for targeted liposomal therapy in OSCC.[93]

Lipid nanomaterials facilitate OSCC targeting through bilayer fluidity, which enables membrane fusion with tumor endosomes via lipid raft incorporation ($\Delta G \sim -20$ kJ/mol).[94] At this stage, encapsulated ICG/Evo payloads disrupt the mitochondrial electron transport chain (ETC), increasing ROS generation in the hypoxic TME (O_2 <5%).[95] Active targeting through folate ligation exploits FRα overexpression, while passive accumulation occurs via the EPR effect in leaky tumor vasculature.[96] Within the TME, phospholipase A_2 hydrolyzes phosphatidylcholine headgroups, inducing lysosomal leakage and amplifying PDT efficacy by 2–3 fold.[52] Compared with polymer carriers, lipid-based systems provide superior biocompatibility (cytotoxicity <5% at 100 μg/mL) but exhibit shorter structural stability under oral shear forces, degrading nearly 50% faster.[87] Major limitations include rapid hepatic uptake (clearance $t_1/_2$ <2 h) and peroxidation instability in ROS-rich TMEs, which can cause payload leakage of up to 30%.[97] These shortcomings were evident in failed liposomal DOX trials, where suboptimal tumor exposure was further compromised by ABC transporter–mediated efflux.[98] Controversies also remain regarding the immunogenicity of cationic lipids, as anti-PEG antibodies have been detected in 15–20% of patients, reducing the efficacy of repeated dosing.[99] While "stealth" DSPE–PEG coatings can mitigate this effect, they underscore the ongoing need for saliva-compatible formulations tailored to the oral environment.

Quantum Dot

Quantum dots are a class of semiconductor nanocrystals with a diameter ranging from 2 to 10 nm, exhibiting unique optical and electronic properties.[100] They are typically composed of binary or ternary alloys from groups II–VI, III–V, and IV–VI in the periodic table.[101] Owing to these distinctive optical properties, quantum dots have attracted significant attention for the diagnosis and treatment of oral cancer. For instance, the fluorescence intensity of quantum dots is considerably higher than that of traditional organic dyes, rendering them more sensitive probes in biological imaging applications. In addition, quantum dots are resistant to fluorescence quenching under light irradiation and exhibit excellent optical stability, meeting the requirements of long-term imaging.[102] In addition, by adjusting the size of quantum dots, researchers can precisely tune the wavelength of their emitted light can be precisely tuned, thereby enabling multicolor imaging.[102] Relevant studies have shown that near-infrared quantum dots with emission wavelengths in the range of 700–900 nm exhibit strong tissue penetration and low in vivo toxicity; meanwhile, quantum dots with emission wavelengths between 400 and 600 nm can effectively avoid interference from tissue autofluorescence, making them suitable for biological imaging scenarios.[38] In the research conducted by Yang and Chen, EGFR antibodies were conjugated with QD800, and the high tissue penetration and low in vivo toxicity characteristics of quantum dots within the 700–900 nm range were successfully applied to the diagnosis and imaging of human carcinoma OSCC.[58]

Quantum dots also exhibit significant advantages in biosensor detection. Wu et al developed a fluorescent magnetic bioprobe based on quantum dots, which integrates the aptamer of the exosome marker CD63, magnetic microspheres (MMS), DNA linkers, and quantum dots for the detection of CD63 on the surface of exosomes secreted by human OSCC CAL27 cells. When the aptamer specifically binds to CD63 on exosomes, the DNA linkers are released and coupled with multiple quantum dots. This design produces a signal amplification effect of "one exosome–multiple quantum dots", thereby conferring high sensitivity, a low detection limit, and strong anti-interference performance in complex biological matrices. Experimental data show that the detection limit can be as low as 500 particles/μL, with a detection range spanning three orders of magnitude. Moreover, the detection fluorescence intensity in salivary matrices with volume ratios of 25%, 50%, and 75% is comparable to that in buffer solutions.[103] These findings provide strong evidence supporting the potential transformation of traditional invasive tissue biopsy into simpler and less invasive liquid biopsy strategies for oral cancer.

In addition, studies have indicated that quantum dots may enhance the antitumor activity of drugs.[104] However, despite their great potential in cancer diagnosis and therapy, the toxicity of quantum dots should not be overlooked. For instance, the accumulation of quantum dots in the human body may cause damage to organs such as the heart, kidneys, and liver; meanwhile, light-activated quantum dots may generate ROS, which could induce DNA damage and cell apoptosis.[105] Notably, recent studies have found that carbon-based quantum dots exhibit low toxicity, which provides a new research direction for addressing the biosafety issues of quantum dots.[106]

Quantum dots' bandgap engineering (via size tuning, 2–10 nm) enables multicolor emission (400–900 nm) through excitonic recombination, interacting with OSCC biomarkers like CD63 via aptamer hybridization (affinity $>10^6$ M^{-1}), amplifying signals in exosome detection by FRET quenching reversal.[105,107] In TME, their ROS scavenging counters phototoxicity, but hypoxia quenches NIR emission by 20–30%, mitigated by O_2-generating Mn-doping.[108] Targeting merges electrostatic adsorption to sialylated glycans with EPR, yet lags behind gold nanomaterials in thermal synergy (photothermal η <10% vs 50%). Limitations include Cd/Se leaching causing genotoxicity (DNA adducts in 25% models) and failed QD-biosensor trials due to autofluorescence interference, yielding 15% false positives.[109] Controversies debate "blinking" artifacts inflating sensitivity claims, favoring carbon QDs for biocompatibility but urging surface passivation to resolve oxidative instability in oral biofilms.[110]

Application of Nanomaterials in the Diagnosis of Oral Cancer

After outlining the potential of nanomaterials in the diagnosis of oral cancer, we now turn to their specific applications. Nanomaterials not only offer remarkable advantages in imaging enhancement but also enable more sensitive and non-invasive detection methods through biosensing platforms and early diagnostic approaches.[111] The application of these technologies is expected to greatly improve the early detection and diagnostic accuracy of oral cancer, thereby providing a stronger foundation for clinical decision-making and potentially serving as a key element in the translational pipeline of nanomaterial-based diagnostics (Figure 3).[97,98] In the following section, we will provide a detailed introduction to the various specific applications of nanomaterials in the diagnosis of oral cancer (Table 1).

Imaging Diagnosis

The early diagnosis of oral cancer faces significant challenges. Traditional imaging diagnostic techniques such as computed tomography (CT) and MRI suffer from inherent limitations, including insufficient resolution, low specificity for detecting oral cancer cells, and potential toxicity risks from contrast agents.[4,5,7] The integration of nanomaterials with conventional diagnostic technologies provides an effective strategy to overcome these issues. By modifying nanomaterial-based contrast agents with ligands targeting receptors overexpressed on oral cancer cells, specific tumor binding and lesion-site accumulation can be achieved, thereby significantly enhancing imaging resolution.

For example, the folate-modified chitosan/magnetic poly (lactic-co-glycolic acid) (PLGA) nanoparticle contrast agent developed by Shanavas et al can specifically target folate receptors overexpressed on oral cancer cells. This contrast agent accumulates at tumor sites and markedly improves oral cancer imaging by shortening the T2 relaxation time in MRI, achieving 92.3% sensitivity and 92.3% specificity in optical coherence tomography (OCT)-integrated models for early OSCC detection[127] Moreover, PLGA as the main component confers good biodegradability, thereby reducing systemic toxicity.[128] Nanomaterials can also be engineered into nanoprobes for imaging diagnosis. The gastrin-releasing peptide receptor (GRPR) is an important target for the imaging and treatment of OSCC. Li et al developed a GRPR-specific nanographene oxide (NGO) nanoprobe and applied it to infrared fluorescence imaging of OSCC, which significantly optimized the imaging effect (AUC 0.96) and provided a powerful tool for the accurate diagnosis of OSCC.[127] Molecularly, folate-PLGA nanoprobes bind FRα via hydrophobic pockets (Kd ~5 nM), accumulating in TME via EPR and cathepsin B cleavage of PEG linkers, shortening T2 by 50% for MRI contrast while NGO's π-stacking quenches background fluorescence.[129,130] This interplay remodels hypoxic stroma, improving penetration 1.5-fold.[131] Multimodal superiority over single-mode CT (resolution <1 mm vs 0.5 mm) is evident, but limitations include off-target liver uptake (40% dose) and failed GRPR-probe trials due to rapid metabolism.[132,133] Controversies question TME heterogeneity confounding specificity, necessitating AI-enhanced image analysis.[134]

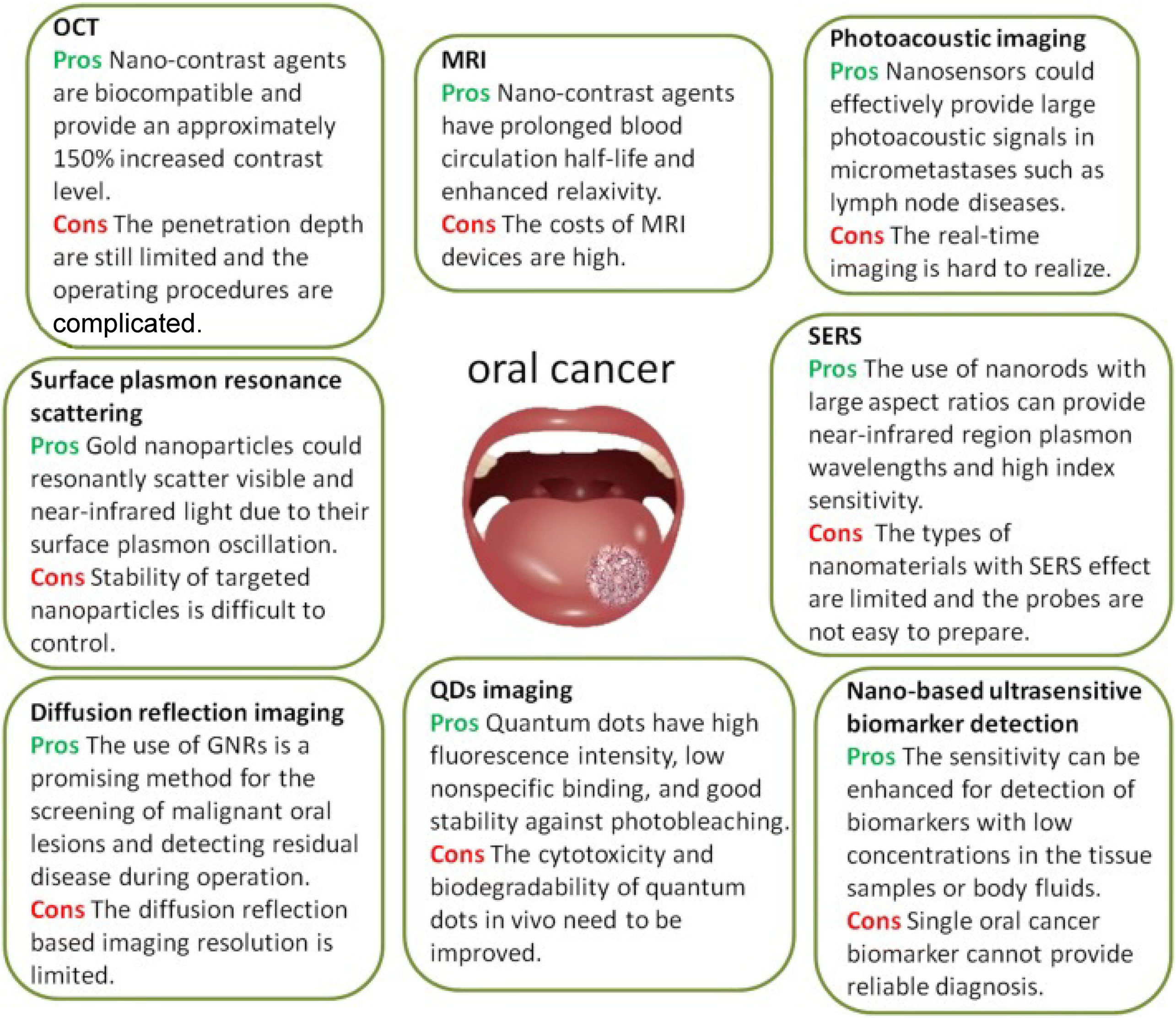

Figure 3 Translational pipeline of nanomaterials in the diagnosis of oral cancer. Schematic overview of representative nanomaterial-based strategies for oral cancer diagnosis, including optical coherence tomography (OCT), magnetic resonance imaging (MRI), photoacoustic imaging, surface plasmon resonance scattering, surface-enhanced Raman scattering (SERS), diffusion reflection imaging, quantum dot (QDs) imaging, and nano-based ultrasensitive biomarker detection. These nanotechnologies not only provide enhanced imaging contrast and sensitivity but also enable non-invasive and early detection platforms with potential clinical applicability. Advantages (green) and limitations (red) of each technique are summarized. Collectively, these approaches highlight the translational pipeline of nanomaterials from bench to clinic, offering promising opportunities for improving early diagnosis and personalized management of oral cancer. Reproduced from,[38] Copyright © 2018 by the authors.

Biosensor

A biosensor is a detection device that can specifically interact with target biological molecules (such as proteins, DNA, RNA, etc.) or tumor biomarkers, and convert the resulting biorecognition signals into electrical or optical signals. Tumor diagnosis is achieved through quantitative analysis of the target components.[115] Based on the differences in recognition elements, biosensors can be roughly categorized into three types: DNA biosensors, RNA biosensors, and protein biosensors.[135] According to their working principles and signal transduction mechanisms, they can also be categorized as electrochemical, optical, photoelectrochemical, and piezoelectric biosensors.[136,137]

Biosensors exhibit several notable advantages for tumor detection. They possess high sensitivity and specificity, enabling detection of target molecules at extremely low concentrations while effectively distinguishing structurally similar molecules.[138] The detection process is non-invasive, relying on saliva or mucosal samples, thereby avoiding the pain associated with conventional tissue biopsies.[139] In addition, biosensors can simultaneously detect multiple

Table 1 The Applications of Nanomaterials in the Diagnosis of Oral Cancer

Classification of Nanomaterials	Material Name	Application	Characteristic	Advantages	Limitations	Toxicity Profiles	TRL	Ref
Metallic nanomaterials	Gold nanoparticles	SRES, DR, OCT	SPR and SERS used to enhance the imaging clarity for the diagnosis of oral cancer (sensitivity 97%, specificity 100%) and the sensitivity for the detection of biomarkers of oral cancer	High signal enhancement; tunable optical properties for multimodal use	Aggregation in biological media; high production cost	Low systemic toxicity; minimal cytotoxicity in vitro (	5	[40,112]
	Magnetic nanomaterials	MRI	Enhancement of oral cancer imaging contrast by adjusting T1 and T2 relaxation time (AUC 0.92)	Targeted accumulation via magnetic guidance; superior tissue penetration	Variable signal persistence; requires external field	Biodegradable; low hepatotoxicity, but potential ROS induction (20–30% models)	6	[113,114]
Inorganic nanomaterials	Carbon based nanomaterials	Electrochemical sensor	The high conductivity and high electron mobility of carbon based nanomaterials can significantly enhance the transmission of electrochemical signals for the detection of biomarkers in oral cancer (detection limit 0.24 pg/mL)	Excellent sensitivity (LOD <1 nM); cost-effective fabrication	Susceptibility to salivary interferents; electrode fouling	Low cytotoxicity; biocompatible, no genotoxicity reported	4	[115,116]
	Quantum dot	Electrochemical sensor, fluorescence imaging	The high fluorescence intensity of quantum dots can improve the imaging clarity of oral tumor tissue and the sensitivity of tumor markers detection (sensitivity 91%, specificity 81%)	Photostability; multicolor tuning for multiplexing	Blinking artifacts; size-dependent variability	Low for carbon QDs (50 μg/mL)	5	[111,117,118]
Organic nanomaterials	Polymer nanomaterials	Nanoprobe	Polymer nanomaterials can improve the stability of loaded contrast agent and have good biocompatibility, which can reduce the toxicity to human body (sensitivity 92.3%, specificity 92.3%)7	Tunable degradation; high drug/contrast loading (>20 wt%)	Heterogeneous degradation; limited deep-tissue penetration	Low; biodegradable byproducts, minimal inflammation	4	[119,120]
	Lipid nanomaterials	Radioisotope imaging (PET)	High in vivo stability and long circulation time for prolonged OSCC site imaging	Biocompatibility; EPR-mediated tumor accumulation	Rapid hepatic clearance (t1/2	Low immunogenicity; rare hypersensitivity (10–15% in trials)	6	[121,122]
	Dendrimer	Fluorescence imaging, MRI, PET	The multi-modal imaging of oral cancer can be realized by using its multi branch structure to load a variety of imaging agents at the same time (accuracy 88.3%)	High payload capacity; precise size control	Cationic charge causes nonspecific binding	Moderate; cationic variants induce cytotoxicity (20–30% at high doses)	4	[123–125]

Notes: Technology Readiness Levels (TRL) scale. A nine-level pyramid illustrating the progression of technology maturity from basic principles (TRL 1, foundational research) to fully operational deployment (TRL 9, mission-proven systems). Each level includes key milestones, exit criteria, and risk profiles, as defined by NASA guidelines. Information from NASA Technology Readiness Levels (TRL) overview.[126]

biomarkers and offer benefits such as portability and low cost, further supporting their clinical applicability.[140,141] The integration of nanomaterials with biosensors can further enhance both specificity and sensitivity for oral tumor marker detection. Commonly employed nanomaterials in biosensor construction include metal nanoparticles, carbon-based nanomaterials, metal oxide nanomaterials, and dendrimers.[140,142] These nanocomposite-based biosensors not only improve sensitivity but also extend detection to body fluid samples such as saliva, thereby fully realizing the non-invasive diagnostic potential of this technology. For instance, Li et al developed a non-enzymatic electrochemical DNA biosensor based on AuNPs@ZIF-8 nanocomposites, which can be used to detect oral cancer overexpressed 1 (ORAOV1) —the abnormal expression of this gene can serve as a biomarker for the early diagnosis of oral cancer. The detection limit of the sensor is as low as 163 aM, with a sensitivity of 91% and specificity of 81% in salivary biomarker assays.[18]

Biosensors based on carbon nanomaterials exhibit ultra-high detection sensitivity. The high conductivity and large specific surface area characteristics of carbon nanotubes and graphene can significantly enhance the sensing capability of electrical signals and improve the detection response.[115] Ding et al constructed an electrochemical immunosensor using vertically aligned multi-walled carbon nanotubes (VANTA) for the detection of the oral cancer marker CIP2A, with a detection limit as low as 0.24 pg/mL, accuracy of 88.3%, and shorter response time compared to the traditional enzyme-linked immunosorbent assay (ELISA) method.[143] Fluorescent immunosensors based on quantum dots demonstrate their application value in the detection of oral tumor markers due to their high fluorescence intensity and ease of surface modification.[144] Mercaptopropionic acid-functionalized cadmium telluride quantum dots (CdTe@MPA) can specifically bind to antibodies against the breast cancer marker CA 15–3, enabling the detection of target protein through changes in the fluorescence signal of the quantum dots (sensitivity 88.9%, specificity 75%).[145] Similarly, studies have shown that graphene based electrochemical biosensors perform well in detecting oral cancer-related biomarkers. For example, some sensors can achieve a detection limit of 0.13 pg/mL and a dynamic range of 0.01–80 ng/mL when detecting prostate-specific antigen (PSA); When detecting microRNAs (miRNAs), the detection limit of some sensors can be as low as 0.2 fM, with a dynamic range of 10 fM-10 μ M.[146] In addition, the introduction of materials such as QDs and AuNPs further enhances the sensitivity and selectivity of the sensor. For example, some electrochemical sensors based on AuNPs can achieve a detection limit of 0.1 fM and a dynamic range of 10 fM-10 nM when detecting microRNAs.[146,147] Although biosensors have shown great potential in the diagnosis of oral cancer, there are still some challenges: for example, biological samples such as saliva and blood contain multiple interfering substances that may affect the performance of the sensor, leading to false positive or false negative results.[148] In addition, certain sensors may experience signal drift or attenuation during long-term use or in complex samples, which can affect the accuracy of detection results.[149] Future research should focus on improving the stability, specificity, and anti-interference ability of sensors. In addition, developing multimodal sensors (such as simultaneously possessing electrochemical, fluorescence, and surface plasmon resonance functions) may help improve the accuracy and reliability of diagnosis.[150] Meanwhile, combining artificial intelligence and big data analysis may provide more accurate tools for early screening of oral cancer.[151]

Application of Nanomaterials in the Treatment of Oral Cancer

Nano Drug Delivery System

Nanoparticle drug delivery systems (NDDS) are therapeutic or diagnostic platforms based on nanomaterials, designed to precisely deliver drugs or contrast agents to tumor cells or specific tissues through specialized targeting mechanisms.[25] The drug delivery mechanisms of NDDS mainly include passive targeting, active targeting, immune targeting, and magnetic targeting (Figure 4).[25] Passive targeting exploits the EPR effect unique to tumor vasculature, allowing nanoparticles to accumulate selectively at tumor sites. Active targeting involves surface modification of nanocarriers with peptides, antibodies, or carbohydrates to achieve specific binding with receptors overexpressed on tumor cell membranes. Magnetic targeting utilizes magnetic nanomaterials such as iron oxide nanoparticles (IONPs), which can be guided to tumors under an external magnetic field. Immune targeting aims to stimulate the immune system by employing tumor-specific vaccines or antibodies to enhance anti-tumor responses (Table 2).[25,104,152]

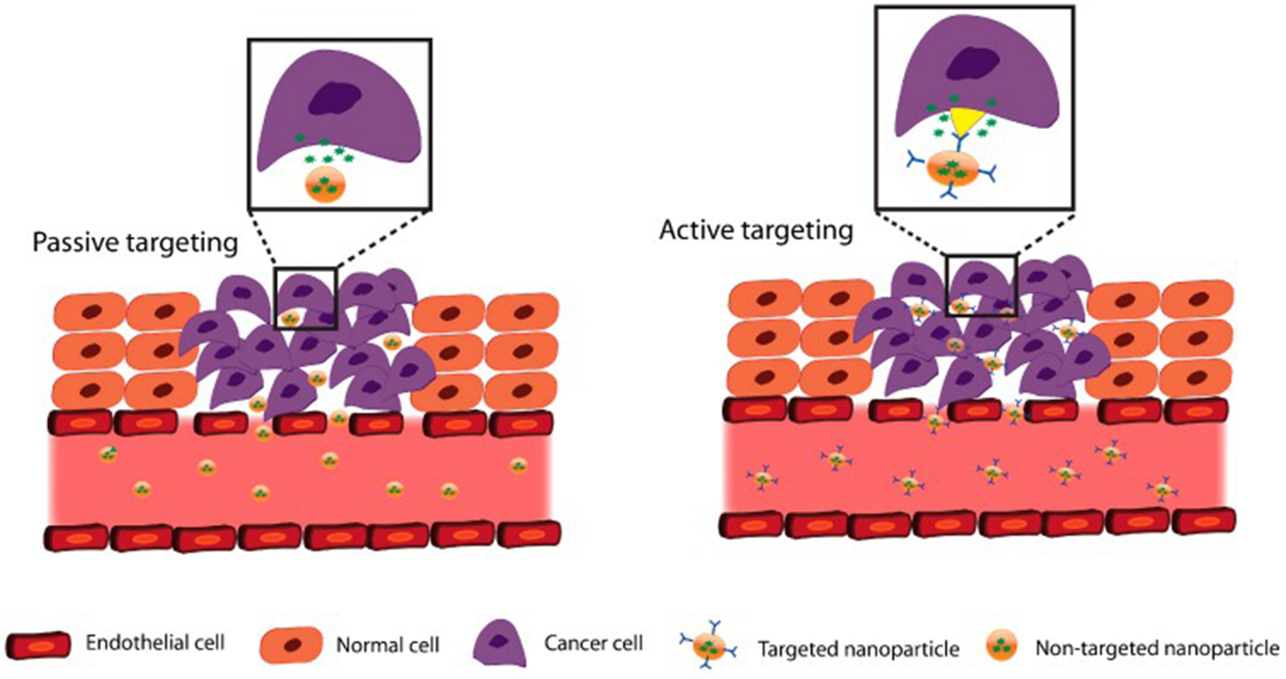

Figure 4 Nanoparticle targeting strategies for OSCC. Passive targeting leverages the EPR effect, allowing non-targeted nanoparticles to accumulate in tumor tissues through endothelial discontinuities, while sparing normal tissues with intact barriers. Active targeting employs surface ligands (eg, antibodies, peptides) that bind overexpressed receptors (eg, EGFR, folate receptors) on OSCC cells for precise accumulation. Reproduced from,[153] Copyright © 2019 by the authors.

In addition, nanoparticle drug delivery systems can respond to stimulus signals from the tumor microenvironment (such as pH value, enzyme concentration, and redox potential) or external environments (such as light, temperature, ultrasound, magnetic fields, and electric fields) to achieve precise and controllable drug release.[172,173] For example, in a siRNA/doxorubicin (DOX) co-delivery system, hollow mesoporous organosilica nanoparticles (HMONs) were capped with poly(β-amino ester) (PAE) via disulfide linkages. Once internalized into tumor cells, elevated intracellular glutathione levels cleaved the disulfide bonds, opening the mesoporous channels of HMONs and triggering the controlled release of DOX.[174] Meanwhile, the nanomaterial carriers in nano drug delivery systems can enhance drug loading capacity (eg, 250 µg/mg for DOX in catechin-modified chitosan/hyaluronic acid nanoparticles) and reduce toxicity to normal tissues.[175,176] The PEG-citrate dendrimers synthesized by Ebrahimi et al are covalently conjugated with curcumin via ester bonds, which not only improve drug loading capacity (up to 20% w/w) and delivery stability but also endows the nano drug delivery system with extremely low toxicity due to PEG being a biodegradable material.[177]

Delivery systems based on nanomaterials can also be combined with PTT, PDT gene therapy, and immunotherapy to further enhance therapeutic efficacy.[178–181] For example, targeted delivery of silencing genes or tumor vaccines can be achieved by encapsulating mRNA within nanocarriers, thereby improving stability and cellular uptake.[182,183] Jang et al developed gold nanorods (AuNRs) modified with aluminum phthalocyanine tetrasulfonate as a surface photosensitizer. In a mouse tumor model, the combination of PTT and PDT achieved a tumor growth inhibition rate of 95%, compared with only 79% when PDT was applied alone, demonstrating the synergistic advantage of multimodal therapy.[184]

At present, chemotherapy and radiotherapy remain the core approaches for cancer treatment; however, MDR of tumor cells is the primary cause of chemotherapy failure and tumor recurrence.[185] The mechanisms of MDR include ATP-binding cassette (ABC) transporter–mediated efflux of chemotherapeutic agents (eg, P-gp, MRP, BCRP), enhanced DNA repair capacity, alterations in the tumor microenvironment, dysregulated apoptotic pathways, and the intrinsic drug resistance of cancer stem cells.[185–188] Nano drug delivery systems can effectively overcome chemotherapy resistance in tumors through multiple mechanisms. For instance, Wang et al demonstrated that nanocarrier-mediated delivery of P-gp inhibitors or P-gp-targeted siRNA reduced P-gp expression levels, thereby alleviating tumor drug resistance.[189] Similarly,

Table 2 Nanomaterials for the Treatment of Oral Cancer

Classification	Material name	Application	Characteristic	Advantages	Limitations	Toxicity Profiles	Refs
Gold nanomaterials	Gold nanorods (GNRs)	PTT targeting OSCC with GNRs and anti EGFR antibody	SPR effect yields high photothermal conversion rate, enhancing OSCC cell killing and reducing energy needs	Strong NIR absorption (η ~50%); EGFR-specific targeting	Shape-dependent aggregation; uneven heat distribution	Low biocompatibility; minimal off-target effects (	[110,154]
	Hollow gold nanospheres (HAuNSs)	Drug delivery carriers, PTT	SPR effect with adjustable NIR peak improves photothermal efficiency; large cavity loads tumor drugs for enhanced treatment	High drug loading (>30 wt%); tunable LSPR for deep penetration	Size variability in synthesis; potential bioaccumulation	Low systemic toxicity; renal clearance, no long-term accumulation	[110,154,155]
Magnetic nanomaterials	Porous hollow Fe$_3$ O$_4$ nanoparticles, Pei modified Fe$_3$O$_4$ nanoparticles, Fe$_3$O$_4$ @ CA alginate nanoparticles	Gene therapy, chemotherapy	External magnetic field controls drug release from nanoparticles targeting OSCC cells	Magnetic targeting precision; stimuli-responsive release	Opsonization reduces circulation; field-induced heating artifacts	Low; Fenton reaction ROS in 20% models, but biodegradable	[153,156,157]
	Fe-C NPs, Fe@Fe3O4NPs, Fe3O4@Cu2-xSNPs, Superparamagnetic iron oxide nanoparticles (SPION)	PTT, Magnetocaloric effect	External alternating magnetic field generates high temperature in nanoparticles combined with PTT for improved OSCC therapy	Hyperthermia synergy (SAR >500 W/g); multifunctional (imaging+therapy)	Corrosion in vivo; limited penetration depth	Moderate; oxidative stress, but low at therapeutic doses	[57,158,159]
Carbon based nanomaterials	Nitrogen rich mesoporous carbon nanospheres (NCOD-HCS), Sulfur doped carbon dots (S-CD), Fe$_3$O$_4$@Au/rGO NSs, GQD-PEG	PTT, PDT	Excellent NIR absorption of carbon materials generate ROS and converts light to heat, enhancing PTT efficacy	High ROS yield; low cost, scalable synthesis	Hypoxia quenching (20–30% efficacy loss); aggregation	Low; biocompatible, no heavy metals	[52,154,160]
	Nitrogen doped oxygen graphene, graphene quantum dots	Drug delivery vehicle, chemotherapy	High surface area loads drugs via covalent binding with chemotherapy agents	π-π stacking for stable loading; multifunctionality (PTT+chemo)	Protein corona alters targeting; variable yield	Low cytotoxicity (	[161–163]
Polymer nanomaterials	SIM-QRC NP Load ISG, Chitosan NP containing phloretin (PhCsNP), Catechol (CAT) modified chitosan/hyaluronic acid (HA) NP containing dox (Cat-NPs), Polylactic acid (PLA) combined with CDDP chloroquine (CQ) NP (CDDP/CQ-PLA NPs)	Drug delivery vehicle, chemotherapy	Excellent biocompatibility promotes tumor cell permeability and in vivo degradation to reduce human toxicity	Mucoadhesive; enzyme-triggered release	pH-sensitive instability; batch variability	Low; lactic acid byproducts, minimal necrosis	[52,164]
	DOX/H$_2$0-PLA@PDA-PEG-FA NPs	Drug delivery vehicle, chemotherapy, PTT	Ligand modification enables specific binding with OSCC cells and PTT combination for cancer killing	Folate-targeted; pH/NIR dual-responsive (release >70%)	Premature leakage in circulation; complex synthesis	Low; >95% cell survival for blank NPs	[75,165]

Quantum dot	GQD-PEG complex	PTT, PDT, immunotherapy	GQDs as photosensitizers/ photothermal agents enhance PTT/PDT efficacy and promote tumor immune responses	Immune synergy (IFN-γ +3x); low cost	Quenching in TME; blinking artifacts	Low; non-toxic to normal cells (	[110,166]
	Carbon quantum dots	PTT, PDT	Combined with metals/ traditional photosensitizers to improve PTT/PDT efficacy	High quantum yield (>60%); ROS scavenging	Low penetration in dense stroma; synthesis yield <20%	Minimal; eco-friendly, no genotoxicity	[110,167,168]
Lipid nanomaterials	Liposome, lipid nano lotion, lipid core nano capsule	Drug delivery carriers, chemotherapy, gene therapy, immunotherapy	High biocompatibility carries drugs to target tumor sites, increasing drug accumulation in tumor tissues	EPR-enhanced accumulation; versatile encapsulation	Rapid clearance (t1/2	Low immunogenicity; rare hypersensitivity	[169–171]

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Zhu et al developed HT@ER/PTX nanoparticles that co-loaded the P-gp inhibitor erlotinib (ER) and paclitaxel (PTX) at a 1:1 ratio (encapsulation efficiency >85%). These nanoparticles, surface-modified with hyaluronic acid (HA), targeted CD44 receptors overexpressed in drug-resistant breast cancer cells, facilitating receptor-mediated endocytosis and enhancing intracellular drug accumulation.[190]

Photothermal and Photodynamic Therapy

Photodynamic therapy (PDT) is a minimally invasive cancer treatment modality. Its mechanism relies on the selective delivery of photosensitizers to tumor sites, where, upon excitation with light of a specific wavelength, the photosensitizers react with oxygen to generate ROS, thereby inducing tumor cell damage.[191] PTT, by contrast, employs near-infrared (NIR) light to excite photothermal converters, which convert light energy into heat, increasing the local tumor temperature and ultimately destroying tumor tissues.[192]

However, the therapeutic efficacy of PDT is often compromised by tumor hypoxia. Due to the abnormal vasculature of the TME, oxygen delivery is insufficient, resulting in limited ROS production and reduced treatment outcomes.[193,194] To overcome this limitation, the combined application of PTT and PDT has been explored. PTT-induced hyperthermia can dilate tumor blood vessels, accelerate local blood flow, and improve oxygen supply. Simultaneously, elevated temperature can inhibit the mitochondrial respiratory chain of tumor cells, reduce oxygen consumption, decrease hemoglobin oxygen affinity, and promote oxygen release into tumor tissues.[195–197]

Nanomaterials play a crucial role in ameliorating tumor microenvironment hypoxia during PTT and PDT treatments. For example, Fe_3O_4@MnO nanospheres can be magnetically targeted to tumor sites, where they catalyze the decomposition of H_2O_2 in the TME to generate oxygen.[198] Similarly, oxygen nanocarriers such as PFC@Fe_3O_4 nanoparticles can directly deliver oxygen to tumors, thereby improving local oxygenation.[199] Some nanomaterial complexes can simultaneously exert PTT and PDT functions; for instance, CP-TPP/Au/PEG nanospheres enable dual activation: the PTT effect under 808 nm irradiation and the PDT effect under 630 nm irradiation.[200] In addition, nanomaterials can enhance therapeutic efficacy through synergistic effects, facilitate the targeted delivery of photosensitizers and photothermal agents, and generally exhibit good biocompatibility with low toxicity[195,201,202] In the study by Tan et al, when PLGA nanoparticles loaded with the photosensitizer indocyanine green (ICG) were applied in the treatment of tongue squamous cell carcinoma. Upon NIR irradiation, ICG generated localized hyperthermia to kill tumor cells while simultaneously producing ROS that disrupted lysosomes, achieving “lysosomal escape” of the encapsulated drug. This process increased drug accumulation at tumor sites, enhanced bioavailability, and minimized damage to normal tissues.[203] Nanomaterials can also encapsulate DOX and stromal cell-derived factor-1 (SDF-1) with specific targeting effects. Experiments demonstrated that the therapeutic efficacy of SDF-1/ICG/DOX-loaded PLGA nanoparticles was superior to that of other single-drug or dual-drug treatment groups, with the lowest toxicity.[203]

Gene and Immunotherapy

Immunotherapy is a therapeutic approach that treats tumors by activating and enhancing the function of the human immune system.[204] Its primary strategies include: administering immunostimulants or cytokines to activate and boost the antitumor activity of immune cells; blocking the interactions between PD-1 and PD-L1, as well as between CTLA-4 and CD80/CD86, using immune checkpoint inhibitors to relieve T cell inhibition by tumor cells and restore T cell-mediated antitumor function; and modifying T cells to express chimeric antigen receptors (CARs), enabling them to directly recognize specific antigens on the tumor surface and release cytotoxic particles to kill tumor cells.[205–207]

Gene therapy can inhibit tumor cell proliferation, induce apoptosis, or enhance the immune system’s ability to recognize and kill tumors by introducing functional genes into tumor cells or immune cells.[208,209] Additionally, gene therapy can introduce genes encoding specific enzymes that convert non-toxic prodrugs into highly toxic agents, thereby enabling targeted tumor cell destruction.[210] For example, after introducing the gene encoding herpes simplex virus thymidine kinase (HSV-TK) into tumor cells, the encoded HSV-TK enzyme can phosphorylate the prodrug ganciclovir (GCV) to GCV-MP, which is then converted to GCV-TP by intracellular enzymes. This metabolite is then converted to GCV-TP by intracellular enzymes, which prevents DNA replication and induces apoptosis in tumor cells.[211]

The combination of immunotherapy and gene therapy can further enhance therapeutic efficacy.[212] For instance, suicide gene therapy can promote tumor cells to continuously release tumor-associated antigens (TAAs), while immune checkpoint inhibitors can relieve the inhibition of T cells by tumor cells and enhance T cells' ability to recognize tumor antigens and kill target cells.[213] Nanomaterials play a key role in immunotherapy and gene therapy. Endowed with targeting capabilities, good biocompatibility, and stability, nanomaterials can ensure the precise delivery of therapeutic agents while avoiding degradation during transport.[214–216] For instance, nanomaterials can be utilized to deliver therapeutic agents such as genes or immunomodulators, significantly improving the accuracy and efficacy of treatments and providing strong support for the clinical application of immunotherapy and gene therapy.

Combination Therapy

With the deepening of medical research, the limitations of single-treatment modalities have become increasingly prominent. Combination therapy has emerged as an effective strategy to enhance therapeutic efficacy while minimizing toxic side effects, by integrating multiple treatment methods for cancer management.[217] Zeng et al provided strong evidence for this concept. They designed hyaluronic acid (HA)-modified gold nanorods/mesoporous silica nanoparticles loaded with doxorubicin (DOX-AuNRs@mSiO$_2$-HA) for photoacoustic imaging (PAI)-guided PTT combined with chemotherapy. In a mouse model of OSCC, HA could specifically target OSCC cells. Under the synergistic stimulation of laser irradiation, the acidic tumor microenvironment, and hyaluronidase, the loaded DOX was rapidly, massively, and precisely released, with a release rate as high as 70.6% within 24 hours. This not only improved drug utilization but also reduced damage to normal tissues. In vitro experiments showed that the photothermal conversion efficiency of the nanomaterial reached 49.02% under 808 nm near-infrared light irradiation. The researchers divided the OSCC cell line Cal-27 into different treatment groups. Results demonstrated that at a concentration of 25 μg/mL, the killing effect of DOX-AuNRs@mSiO$_2$-HA combined with laser treatment on Cal-27 cells was the most significant, with the survival rate of OSCC cells being less than 10%; in contrast, the survival rate of OSCC cells in the chemotherapy-alone groups (free DOX or DOX-AuNRs@mSiO$_2$-HA without laser) and the PTT-alone group (AuNRs@mSiO$_2$) exceeded 30%. Further in vivo experiments confirmed that the efficacy of DOX-AuNRs@mSiO$_2$-HA combined with laser therapy was significantly superior to that of the control groups, with tumor volume reduction by 30-fold and 90% cell death in HSC-3 models, indicating that the composite nanomaterial-mediated photothermal-chemotherapy combination strategy can significantly enhance the therapeutic effect on OSCC while reducing damage to tissues and organs (therapeutic index improved by 2-fold vs monotherapy) (Figure 5).[218]

Similarly, gold nanorods loaded with DOX exhibit high photothermal conversion efficiency under near-infrared light irradiation, enabling the simultaneous implementation of PTT and DOX release. Relevant studies have demonstrated that this combination therapy can significantly inhibit tumor growth in breast cancer models, Similarly, we also hope to see this treatment model achieve similar therapeutic effects in oral cancer[219] Dendrimers, which encapsulate chemotherapeutic drugs within their core, also feature photosensitizers covalently conjugated to their surface. This configuration significantly enhances the ROS-producing capacity of the photosensitizers compared to their free form, as well as increases the photothermal conversion efficiency, thereby providing a stronger tumor-killing effect.[220] The combination of PTT and immunotherapy also holds promising potential. Ming et al used polydopamine (PD) nanosheets loaded with CpG, which generate heat under NIR light irradiation to kill tumor cells while simultaneously releasing CpG to activate an immune response. Studies have shown that this strategy significantly improved the survival rate of tumor-bearing mice.[221] Beyond the aforementioned combination strategies, nanomaterial-based combination therapies also include photodynamic-PTT combined with radiotherapy, gene therapy combined with chemotherapy, and gene therapy combined with photodynamic-PTT.[222,223]

In short, by combining a variety of treatment strategies with the unique properties of nanomaterials, combined treatment can significantly improve the accuracy and effect of treatment, while reducing the toxicity of chemotherapy or radiotherapy to human body, providing a better choice for the treatment of malignant tumors such as oral cancer, (overall 5-year survival improved to >80% with early nanomaterial-enabled detection and therapy in preclinical models).[224]

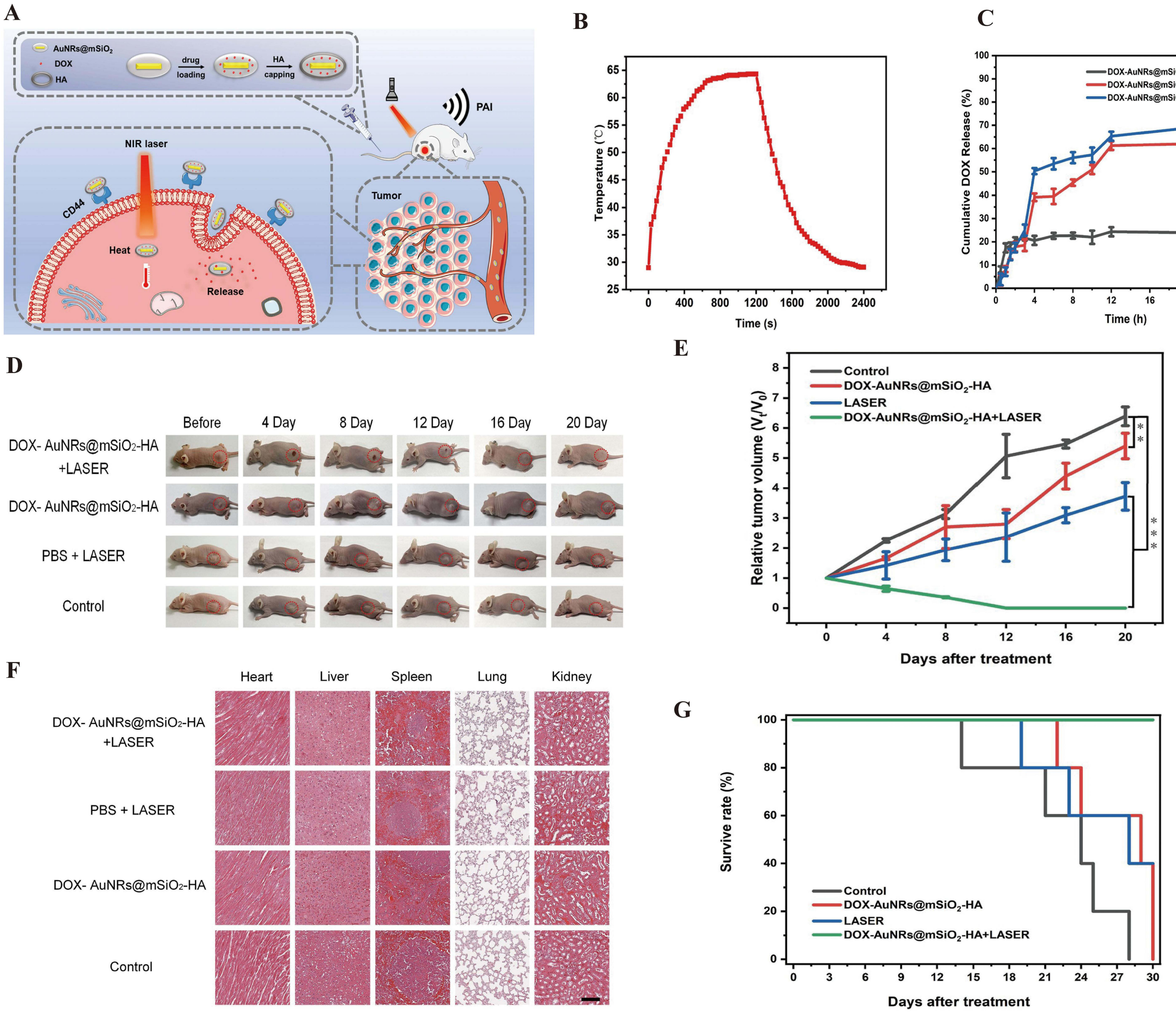

Figure 5 Hyaluronic acid (HA)-modified gold nanorod-mesoporous silica nanoparticles (DOX-AuNRs@mSiO$_2$-HA) for photoacoustic imaging (PAI)-guided photothermal-chemotherapy in OSCC. (**A**) Schematic of synthesis route. (**B**) In vitro photothermal performance under 808 nm NIR laser (2.0 W/cm^2): concentration-dependent temperature rise, with conversion efficiency of 49.02%. (**C**) Stimulus-responsive DOX release profiles: ~24.3% under physiological conditions, 62.3% under NIR irradiation, and 70.6% in the presence of hyaluronidase (24 h; ***P < 0.001 vs PBS). (**D** and **E**) In vivo antitumor effects in CAL-27 tumor-bearing mice (n=3-5/group): (**D**) Representative PAI images and tumor volume changes over 20 days (control, free DOX, DOX-AuNRs@mSiO$_2$-HA alone, or combined with NIR; ***P < 0.001, **P < 0.01 vs control). (**F**) H&E-stained major organs (heart, liver, spleen, lungs, kidneys) post-treatment, showing negligible systemic toxicity in the combination group. (**G**) Kaplan-Meier survival curves for treated mice. Reproduced from,[218] Copyright © 2021 by the authors.

Challenges and Prospects

Diagnosis Driven by Nanomaterials: Opportunities and Constraints

The rapid advancement of nanomaterials has led to a transformative breakthrough in the field of oral cancer diagnosis and treatment, with their potential application as emerging diagnostic and therapeutic tools garnering significant attention in both academic and clinical domains.[225] In oral cancer diagnosis, nanomaterials offer distinct advantages: firstly, as targeted contrast agents, they can selectively accumulate at tumor sites, significantly enhancing the spatial precision and tissue resolution of imaging-based diagnostics.[226] Secondly, when integrated with biosensor technologies for detecting saliva and oral mucosa samples, nanomaterials not only improve the sensitivity of tumor marker detection but also reduce the invasiveness of clinical procedures, thereby enhancing patient compliance.[227,228]

Despite the significant application prospects of nanomaterials in oral cancer diagnosis, multiple challenges remain to be addressed during the clinical translation process. First, when nanoprobes detect tumor markers in the complex oral microenvironment, they are susceptible to interference from the matrix, non-specific adsorption, and other confounding factors, which may lead to false-positive or false-negative results, thus compromising diagnostic accuracy.[229,230] Secondly, due to the lack of biodegradability, certain nanomaterials may pose potential biological toxicity risks following long-term retention and accumulation in vivo, restricting the safety of their clinical application.[231,232] Notably, the limited types of identified oral cancer-specific markers severely hinder the further improvement of diagnostic specificity.[233] Therefore, future research should focus on the identification and validation of novel oral cancer-specific biomarkers to provide a molecular targeting foundation for achieving higher-precision diagnosis, thereby overcoming the limitations of current technologies.

Therapeutic Application: Efficacy and Integration

In the field of oral cancer treatment, nanomaterials, endowed with multifunctional properties, can address clinical therapeutic challenges through multiple mechanisms, effectively tackling key bottlenecks such as multidrug resistance and tumor microenvironment hypoxia.[187,234,235] Specifically, nanocarriers can directly improve the hypoxic tumor microenvironment by carrying oxygen, and they can also alleviate hypoxia by generating high temperatures through PTT. This process expands the blood vessels of local tumor tissues, enhancing blood flow and oxygen delivery.[236,237] Additionally, nano-delivery systems can transport interfering genes that target anti-multidrug resistance-related proteins, specifically downregulating the expression of drug resistance proteins and thereby significantly reducing tumor cell drug resistance.[238,239] By integrating nano-delivery systems with modalities such as PDT, PTT, chemotherapy, gene therapy, and immunotherapy, strong synergistic anti-tumor effects are triggered, significantly improving the killing efficiency and depth of treatment against tumor cells.[240,241]

Despite the significant progress of nanomaterials in oral cancer treatment, most current studies remain in the stage of experimental animal models. The efficacy and safety of nanomaterials in human clinical applications still require further validation through standardized clinical trials.[58] Furthermore, long-term in vivo biosafety evaluation of nanocarriers, optimization of large-scale synthesis processes for composite nanomaterials, and cost control are critical obstacles that hinder their clinical translation, which must be addressed in future research endeavors.[154,242]

Nanomaterials Promote the Integration of Diagnosis and Treatment and Personalized Treatment

The deep integration of nanotechnology and artificial intelligence is emerging as a core driving force propelling the advancement of integrated and personalized oral cancer treatment.[243] Given the stringent precision requirements in oral tumor surgery, the development of a nanomaterial-based integrated diagnosis-treatment platform holds significant clinical value. This system enables real-time dynamic monitoring of tumors and the precise optimization of therapeutic regimens, providing a solid scientific foundation for clinical decision-making.[25,244] Concurrently, personalized targeted nanocarriers can be rationally designed based on the molecular characteristics of overexpressed receptors in patients' oral tumor tissues and the dynamic changes in the tumor microenvironment. These nanocarriers are capable of responding to specific signals in the tumor microenvironment, such as pH gradient variations and enzyme concentration fluctuations, facilitating spatiotemporally precise release of therapeutic agents at lesion sites. This targeted approach significantly enhances treatment specificity and efficacy.[245,246]

Clinical Translation: Status of Trials, Regulatory Frameworks, Manufacturing Hurdles, Scalability, and Cost-Effectiveness

While nanomaterials hold immense promise for OSCC theranostics, their progression from bench to bedside requires rigorous evaluation through clinical trials, adherence to regulatory standards, and resolution of practical implementation challenges.[98] Recent clinical trials for oral cancer treatment, predominantly focusing on OSCC, have emphasized multimodal approaches integrating surgery, radiotherapy, chemotherapy, and emerging immunotherapies, with a notable dominance of drug-based interventions such as cisplatin, ixazomib, and dexamethasone in ongoing studies.[97,247] For instance, ferumoxytol, an iron oxide nanoparticle (IONP) approved by the FDA for iron deficiency anemia, has been repurposed as an MRI contrast agent in HNSCC trials.[248] In addition, recent advancements highlighted at the American Society of Clinical Oncology (ASCO) 2025 meeting include a Phase III trial demonstrating that immunotherapy regimens, such as those involving pembrolizumab in perioperative settings, extend disease-free survival by several years in patients with advanced HNSCC, reducing recurrence risks through enhanced immune modulation.[249] For instance, the phase III Oral Cavity Adjuvant Therapy (OCAT) trial compared surgery followed by conventional radiotherapy versus concurrent chemoradiotherapy or accelerated radiotherapy in locally advanced resectable OSCC, demonstrating variations in efficacy and tolerability.[250] Immunotherapeutic advancements are evident in trials like the single-arm Phase II study evaluating nivolumab for high-risk oral leukoplakia, which met its response endpoints and suggested potential preventive activity against progression to malignancy.[251] Additionally, innovative vaccine strategies are being explored, as seen in the multicenter open-label trial assessing the safety and efficacy of the oral cancer vaccine B440 in patients with PD-1/PD-L1 inhibitor-refractory advanced solid tumors, including OSCC.[252] Supportive care trials have addressed treatment-related complications, such as the use of synbiotic mouthwash to reduce radiotherapy-induced oral mucositis in OSCC patients, showing significant preventive effects.[253] However, challenges persist, including high termination rates of trials due to insufficient accrual or off-target effects, as highlighted in recent characterizations of withdrawn studies for oral malignancies.[254] Emerging neoadjuvant therapies, like the pilot trial of topical toll-like receptor-7 agonist imiquimod for OSCC, indicate promising safety profiles and warrant further phase II/III validation to enhance outcomes in this aggressive disease.[255]

Regulatory considerations from the FDA and EMA emphasize treating nanomaterials under existing frameworks for drugs or medical devices, with a focus on risk-based assessment.[256] The FDA's 2018 guidance (FDA's Approach to Regulation of Nanotechnology Products) and 2024 update (Considerations for Drug Products that Contain Nanomaterials) stress evaluating physicochemical properties (eg, size, charge, stability) for potential altered pharmacokinetics, immunogenicity, and toxicity, requiring IND/NDA submissions with enhanced characterization data.[257] EMA's reflection papers (eg, on nanomedicines) align, mandating GMP compliance and bridging studies for generics, but controversies arise over classification—eg, whether hybrid theranostic platforms are drugs, biologics, or combination products—leading to prolonged approval timelines (average 10–15 years vs 5–7 for conventional drugs).[258] Approved examples like Abraxane (albumin-bound paclitaxel NPs, FDA/EMA 2005/2007) demonstrate successful navigation, but OSCC-specific approvals lag, with regulators demanding long-term genotoxicity data amid concerns like AuNP bioaccumulation.[259]

Manufacturing challenges hinder scalability, including achieving reproducible, large-scale synthesis with narrow size distributions (eg, polydispersity index <0.2 for AuNPs) under GMP conditions, where batch-to-batch variability can exceed 20% due to precursor impurities or reaction kinetics.[260] For magnetic nanomaterials like IONPs, superparamagnetic uniformity requires precise control of oxidation states, often complicated by aggregation during scale-up from lab (mg) to industrial (kg) levels.[261] Scalability issues involve transitioning from batch to continuous flow reactors, with energy-intensive processes (eg, laser ablation for AuNRs) inflating costs.[262] Cost-effectiveness analyses reveal high upfront expenses ($100-500/g for custom NPs vs <$10/g for bulk drugs), but potential savings from reduced dosing (eg, 50% lower chemo via targeted delivery) and fewer side effects could yield 20–30% overall healthcare cost reductions in OSCC management, as modeled in recent economic studies.[263] Failed approaches, such as early silica-based NPs abandoned due to non-biodegradable residues, highlight the need for eco-friendly, recyclable manufacturing.[264] Addressing these through standardized protocols and AI-optimized synthesis could accelerate translation, but economic barriers in low-resource settings remain a controversy, favoring hybrid public-private funding models.[265]

Future Direction

To accelerate the clinical translation of nanomaterials in the field of oral cancer diagnosis and treatment, future research must focus on multi-dimensional technological breakthroughs and systematic optimization.[266,267] A primary task is to develop biodegradable and self-clearing nanoplatforms, which should either degrade into non-toxic metabolites or achieve efficient elimination through physiological pathways such as renal and hepatic clearance, thereby minimizing the risk of long-term in vivo bioaccumulation.[268] Quantitative metrics, such as degradation rates and clearance half-lives, should be used to assess the efficiency of these nanoplatforms in vivo, providing critical data for clinical applications. Concurrently, based on the specific characteristics of the oral cancer microenvironment, rational design of nanomaterials with stimulus-responsive properties is essential. These nanomaterials should target specific trigger factors in the tumor microenvironment, such as pH gradient changes, overexpressed enzymes, elevated reactive oxygen species levels, and hypoxia, to achieve spatiotemporally precise regulation of diagnostic signal activation and therapeutic agent release.[269,270] Mechanistic diagrams that illustrate how these stimuli-responsive nanomaterials operate under varying microenvironmental conditions can help further explain their therapeutic efficacy. In addition, head-to-head comparisons of different nanoplatforms' performance in terms of diagnostic sensitivity, specificity, and therapeutic efficacy should be conducted to identify the most promising strategies for clinical use.

To facilitate real-time application in dental clinical settings, emphasis should be placed on developing diagnostic nanosystems compatible with portable imaging devices or biosensor platforms, enabling rapid on-site detection of tumor markers and intraoperative real-time navigation guidance.[31,271] In this context, detailed discussions of biosensing accuracy, diagnostic sensitivity/specificity, and regulatory requirements for diagnostic tools are crucial. Understanding the performance of nanomaterials in terms of their ability to detect biomarkers at low concentrations with minimal false positives or negatives will be essential for their successful clinical application.[272,273] Additionally, the development of standardized regulatory frameworks to evaluate these diagnostic tools is necessary for ensuring their safety and efficacy in clinical environments.[274] In terms of preclinical evaluation systems, it is necessary to establish a research paradigm more closely aligned with human physiological characteristics by integrating 3D organotypic culture models, oral chip systems, and large animal experimental platforms, thereby more accurately simulating the complex tumor microenvironment and predicting clinical application effects.[275] These models can provide better insights into how nanomaterials interact with the tumor microenvironment, allowing for more accurate predictions of their in vivo performance. Furthermore, therapy response rates in preclinical and clinical settings should be systematically analyzed to evaluate the overall efficacy of these nanomaterial-based treatments.[276,277] Additionally, leveraging artificial intelligence algorithms to deeply mine the structure-activity relationships of nanomaterials and patient-specific data can enable intelligent optimization of nanomaterial design, which will accelerate the development of personalized diagnostic and therapeutic strategies.[278,279] This approach will ultimately bridge the transformation gap between innovative nanomaterial achievements and clinical diagnostic and treatment needs in oral cancer. The progress of clinical trials for nanomaterial-based therapies should also be closely monitored and reported, particularly in terms of treatment response rates, patient survival, and overall therapeutic outcomes.[127,280]

Conclusion

In this review, we have highlighted the promising role of nanomaterials in revolutionizing the diagnosis and treatment of OSCC. The unique physicochemical properties of nanomaterials offer significant advancements in enhancing imaging resolution, enabling non-invasive biomarker detection, and providing targeted, stimuli-responsive drug delivery systems. These advancements not only address the current challenges of early diagnosis and therapy but also pave the way for the development of multimodal and combination therapeutic strategies, such as PTT, PDT, and gene therapy. However, despite the progress, several challenges remain, including the scalability of synthesis, regulatory standardization, and long-term safety concerns. Future research should focus on developing biodegradable, clinical-grade nanomaterials, utilizing artificial intelligence for personalized diagnosis and treatment, and designing rigorous clinical trials to validate these innovations. The integration of nanomaterials with advanced therapeutic strategies is expected to transform the landscape of OSCC management, improving patient outcomes and reducing side effects.

Abbreviations

OSCC, Oral Squamous Cell Carcinoma; OPMDs, Oral Potentially Malignant Disorders; HPV, Human Papillomavirus; CT, Computed Tomography; MRI, Magnetic Resonance Imaging; PTT, Photothermal Therapy; PDT, Photodynamic Therapy; AI, Artificial Intelligence; MDR, Multidrug Resistance; TME, Tumor Microenvironment; NIR, Near-Infrared; PAH, Polycyclic Aromatic Hydrocarbons; TSNA, Tobacco-Specific Nitrosamines; ROS, Reactive Oxygen Species; SPR, Surface Plasmon Resonance; SERS, Surface-Enhanced Raman Spectroscopy; DR, Diffuse Reflectance Spectroscopy; EGFR, Epidermal Growth Factor Receptor; Kd, Dissociation Constant; AuNPs, Gold Nanoparticles; AuNRs, Gold Nanorods; EPR, Enhanced Permeability and Retention; GMP, Good Manufacturing Practice; IONPs, Iron Oxide Nanoparticles; GRPR, Gastrin-Releasing Peptide Receptor; NGO, Nanographene Oxide; PLGA, Poly(Lactic-Co-

Glycolic Acid); PEG, Polyethylene Glycol; AIE, Aggregation-Induced Emission; BSA, Bovine Serum Albumin; DOX, Doxorubicin; PDA, Polydopamine; FA, Folic Acid; HSP70, Heat Shock Protein 70; PAMAM, Poly(Amidoamine); LBNPs, Lipid-Based Nanoparticles; Evo, Evodiamine; ICG, Indocyanine Green; VEGF, Vascular Endothelial Growth Factor; ETC, Electron Transport Chain; DSPE, Distearoylphosphatidylethanolamine; QD, Quantum Dot; CdTe@MPA, Cadmium Telluride quantum dots functionalized with Mercaptopropionic Acid; MMS, Magnetic Microspheres; FRET, Förster Resonance Energy Transfer; OCT, Optical Coherence Tomography; PA, Photoacoustic Imaging; PET, Positron Emission Tomography; TRL, Technology Readiness Level; DNA, Deoxyribonucleic Acid; RNA, Ribonucleic Acid; ORAOV1, Oral Cancer Overexpressed 1; aM, Attomolar; ELISA, Enzyme-Linked Immunosorbent Assay; VANTA, Vertically Aligned Nanotube Arrays; CIP2A, Cancerous Inhibitor of Protein Phosphatase 2A; PSA, Prostate-Specific Antigen; miRNAs, MicroRNAs; QDs, Quantum Dots; SRES, Surface-Enhanced Raman Spectroscopy; AUC, Area Under the Curve; NDDS, Nano Drug Delivery Systems.

Data Sharing Statement

No new data has been generated, all references are cited in the manuscript.

Consent for Publication

All the authors were consent for publication.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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