

## **Nano -Approaches in Oral Cancer: From Detection to Targeted Therapy -**

### **A review**

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## Abstract

Oral cancer, primarily oral squamous cell carcinoma (OSCC), represents a significant global health burden, characterized by high morbidity and mortality rates, largely due to late diagnosis and the limitations of conventional therapeutic approaches. Despite advancements in surgery, radiotherapy, and chemotherapy, patient outcomes for advanced-stage disease remain suboptimal, necessitating the development of novel strategies for early detection and more effective, targeted treatments. Nanotechnology offers a revolutionary paradigm shift in addressing these challenges by enabling precision medicine at the molecular and cellular levels. This review explores the transformative potential of nanotechnology in oral cancer, focusing on its applications in enhancing diagnostic accuracy through advanced imaging and biosensing, and improving therapeutic efficacy via targeted drug delivery, photodynamic/photothermal therapies, and immunomodulation. We discuss various nanomaterials, including metallic nanoparticles, liposomes, polymeric nanoparticles, and quantum dots, highlighting their unique properties that facilitate improved bioavailability, reduced systemic toxicity, and overcoming biological barriers. Current challenges, such as biocompatibility, regulatory hurdles, and the need for rigorous clinical translation, are also addressed. The integration of nanotechnology holds immense promise for revolutionizing the management of oral cancer, paving the way for personalized and highly effective interventions.

**Keywords:** Oral cancer, Nanotechnology, Diagnosis, Therapy, Nanoparticles, Targeted drug delivery

## Introduction

Oral cancer, predominantly oral squamous cell carcinoma (OSCC), accounts for a substantial proportion of head and neck cancers, ranking among the top ten most common cancers

worldwide <sup>(1)</sup>. Its etiology is multifactorial, strongly associated with tobacco use, alcohol consumption, betel quid chewing, and human papillomavirus (HPV) infection <sup>(2)</sup>. Despite significant progress in medical science, the 5-year survival rate for oral cancer has remained largely stagnant over the past decades, particularly for patients diagnosed at advanced stages <sup>(3)</sup>. This grim prognosis is primarily attributed to the challenges in early detection, leading to diagnoses often occurring when the disease has already progressed to regional lymph node metastasis or distant sites. Furthermore, conventional treatment modalities, including surgery, radiation therapy, and chemotherapy, frequently result in significant side effects, recurrence, and the development of resistance, underscoring an urgent need for more precise and efficacious interventions <sup>(4)</sup>.

The advent of nanotechnology, the manipulation of matter on an atomic, molecular, and supramolecular scale (typically 1-100 nm), has opened unprecedented avenues for innovation in oncology. Nanomaterials possess unique physicochemical properties, such as high surface-to-volume ratio, tunable size, shape, and surface chemistry, which enable them to interact with biological systems in novel ways <sup>(5)</sup>. These characteristics make them ideal candidates for overcoming many limitations of traditional cancer diagnostics and therapeutics, including poor drug solubility, non-specific biodistribution, and inadequate cellular uptake <sup>(6)</sup>.

In the context of oral cancer, nanotechnology offers a multifaceted approach to improve patient outcomes. For diagnosis, nanoparticles can enhance the sensitivity and specificity of imaging techniques, facilitate the detection of early molecular biomarkers, and enable non-invasive liquid biopsies. Therapeutically, they can be engineered for targeted drug delivery, minimizing systemic toxicity while maximizing drug concentration at the tumour site. Moreover, nanoparticles can serve as platforms for novel treatment modalities like photodynamic therapy (PDT) and photothermal therapy (PTT), or for enhancing immunotherapy <sup>(7)</sup>. This review aims to provide a comprehensive overview of the current

state and future prospects of nanotechnology in the diagnosis and therapy of oral cancer, highlighting key advancements, challenges, and the potential for clinical translation.

## **Nanomaterials for Oral Cancer Applications**

A diverse array of nanomaterials has been explored for oral cancer applications, each offering distinct advantages based on its composition and properties. The selection of a specific nanomaterial depends on the intended application, whether it is for imaging, drug delivery, or a combination thereof.

### **Metallic Nanoparticles**

Metallic nanoparticles, particularly gold nanoparticles (AuNPs) and silver nanoparticles (AgNPs), have garnered significant attention due to their unique optical, electronic, and catalytic properties <sup>(8)</sup>. AuNPs are highly biocompatible and can be easily functionalized with targeting ligands (e.g., antibodies, peptides) or therapeutic agents. Their surface plasmon resonance properties make them excellent contrast agents for imaging techniques like surface-enhanced Raman scattering (SERS) and photoacoustic imaging (PAI), enabling highly sensitive detection of oral cancer cells and biomarkers <sup>(9)</sup>. AgNPs exhibit potent antimicrobial and anticancer activities, often inducing apoptosis in cancer cells through oxidative stress mechanisms <sup>(10)</sup>. However, their potential toxicity *in vivo* requires careful consideration.

### **Polymeric Nanoparticles**

Polymeric nanoparticles are versatile platforms for drug delivery, offering controlled release kinetics, improved drug stability, and the ability to encapsulate a wide range of hydrophobic

and hydrophilic drugs <sup>(11)</sup>. Common polymers include poly (lactic-co-glycolic acid) (PLGA), polyethylene glycol (PEG), chitosan, and dendrimers. PEGylation, the process of conjugating PEG to nanoparticles, is frequently employed to enhance biocompatibility, reduce immunogenicity, and prolong circulation time by evading reticuloendothelial system uptake <sup>(12)</sup>. Polymeric nanoparticles can be engineered to respond to specific tumour microenvironment stimuli, such as pH, temperature, or enzyme activity, allowing for on-demand drug release <sup>(13)</sup>.

### **Liposomes and Lipid Nanoparticles**

Liposomes are self-assembling spherical vesicles composed of lipid bilayers, capable of encapsulating both hydrophilic drugs in their aqueous core and hydrophobic drugs within their lipid bilayer <sup>(14)</sup>. They have a long history of clinical use, with several liposomal drug formulations approved for cancer therapy. For oral cancer, liposomes offer advantages such as improved drug pharmacokinetics, reduced systemic toxicity, and the potential for targeted delivery through surface functionalization <sup>(15)</sup>. Solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs) are newer generations of lipid-based carriers that offer enhanced stability and drug loading capacity compared to traditional liposomes <sup>(16)</sup>.

### **Quantum Dots (QDs)**

Quantum dots are semiconductor nanocrystals that exhibit unique photophysical properties, including high quantum yield, broad absorption spectra, and narrow, tunable emission spectra <sup>(17)</sup>. These properties make them excellent fluorescent probes for high-resolution imaging and multiplexed detection of biomarkers in oral cancer. For instance, QDs can be conjugated to antibodies specific for oral cancer markers, allowing for highly sensitive and specific *in vitro* and *in vivo* diagnostic applications <sup>(18)</sup>. Concerns regarding the potential toxicity of heavy

metal-containing QDs (e.g., cadmium) have led to the development of less toxic alternatives, such as carbon dots and silicon QDs <sup>(19)</sup>.

**Table 1. Illustrative summary of common nanomaterials and their applications in oral cancer.**

Nanomaterial Type	Key Properties	Oral Cancer Diagnostic Applications	Oral Cancer Therapeutic Applications
Gold Nanoparticles	Biocompatible, tunable optical properties, easy functionalization	SERS imaging, photoacoustic imaging, biosensors for biomarker detection	Photothermal therapy, targeted drug delivery, radio sensitization
Polymeric Nanoparticles	Biodegradable, controlled release, high drug loading, tunable size	Targeted imaging, <i>in vivo</i> biosensing	Targeted chemotherapy, gene therapy, immunotherapy
Liposomes	Biocompatible, low toxicity, encapsulate hydrophilic/hydrophobic drugs	Contrast agents for imaging, <i>in vivo</i> drug tracking	Targeted drug delivery, combination therapy
Quantum Dots	High quantum yield, tunable emission, photostable	High-resolution fluorescent imaging, multiplexed biomarker detection	Photodynamic therapy (less common), theragnostic

## Nanotechnology in Oral Cancer Diagnosis

Early and accurate diagnosis is paramount for improving oral cancer prognosis. Nanotechnology offers several innovative approaches to overcome the limitations of conventional diagnostic methods, such as visual inspection, biopsy, and histopathology, which often lack sensitivity for early-stage lesions or are invasive.

### Enhanced Imaging and Biosensing

Nanoparticles can significantly improve the resolution and sensitivity of various imaging modalities. For instance, AuNPs functionalized with specific antibodies can target tumour cells, acting as superior contrast agents for optical coherence tomography (OCT) or photoacoustic imaging (PAI), allowing for the visualization of precancerous lesions or small tumours that might otherwise be missed <sup>(20)</sup>. Sharma et al. (2023) demonstrated the use of targeted AuNPs to enhance the detection of oral squamous cell carcinoma cells *in vitro* via SERS imaging, achieving high sensitivity and specificity for early molecular changes <sup>(21)</sup>.

Biosensors incorporating nanomaterials offer highly sensitive and rapid detection of oral cancer biomarkers from biological fluids like saliva, blood, or urine. These nano biosensors can detect low concentrations of circulating tumor DNA (ctDNA), microRNAs (miRNAs), proteins, or exosomes associated with oral cancer progression. Kumar et al. (2022) developed a graphene-based field-effect transistor biosensor for the detection of specific salivary miRNAs, showing promising results for non-invasive early diagnosis of OSCC <sup>(22)</sup>. Such platforms have the potential to facilitate point-of-care diagnostics, enabling widespread screening and monitoring.

### **Molecular Profiling and Liquid Biopsy**

Nanotechnology plays a crucial role in advancing molecular profiling and liquid biopsy techniques for oral cancer. Exosomes, small extracellular vesicles released by cells, carry a cargo of proteins, lipids, and nucleic acids that reflect the physiological state of their parent cells. In cancer, tumour-derived exosomes contain specific biomarkers that can be used for diagnosis and prognosis. Nanoparticle-based platforms can efficiently isolate and analyse these exosomes from patient biofluids. Patel et al. (2024) utilized magnetic nanoparticles functionalized with exosome-specific antibodies to capture and analyse tumour-derived exosomes from the saliva of oral cancer patients, identifying unique protein signatures

indicative of disease presence and stage <sup>(23)</sup>. This approach offers a non-invasive method for monitoring disease progression and treatment response, potentially guiding personalized therapy.

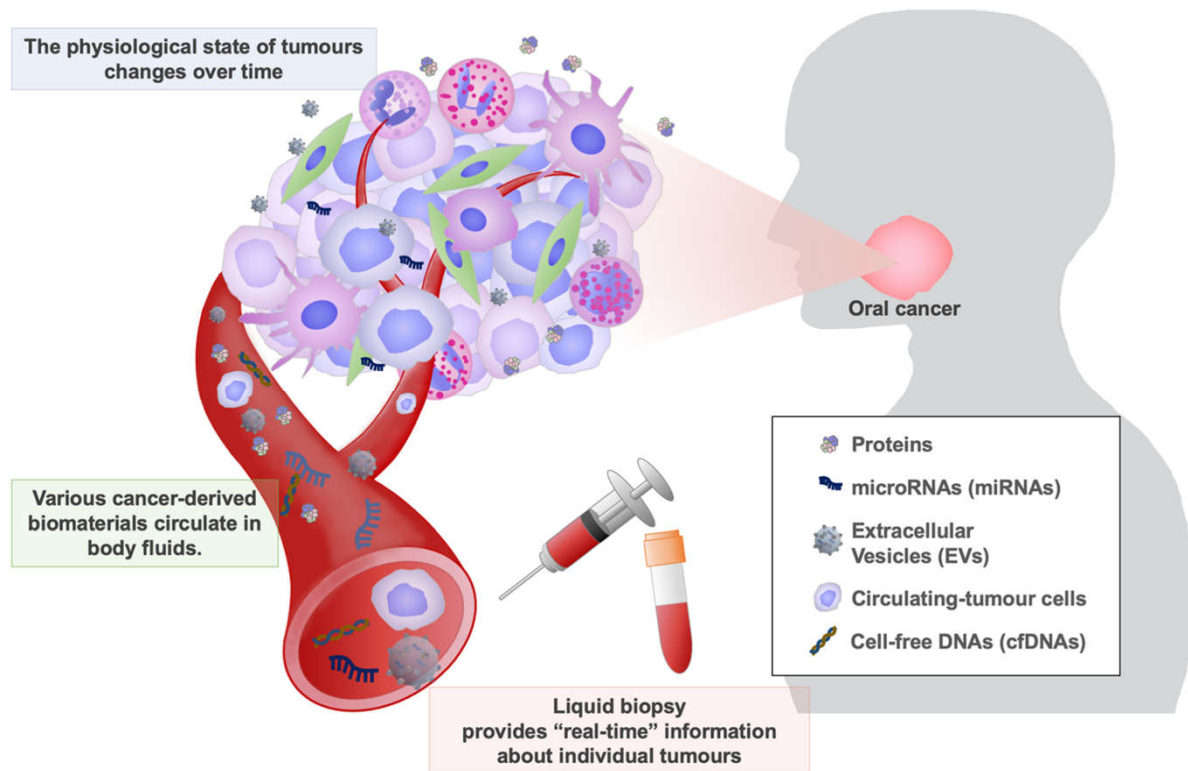


Figure 1- Liquid Biopsy for Oral Cancer Diagnosis

## Nanotechnology in Oral Cancer Therapy

The therapeutic applications of nanotechnology in oral cancer are vast, primarily focusing on enhancing drug delivery, enabling novel treatment modalities, and overcoming drug resistance.

### Targeted Drug Delivery

One of the most significant advantages of nanocarriers is their ability to deliver therapeutic agents specifically to tumour cells while sparing healthy tissues. This "passive targeting" relies on the enhanced permeability and retention (EPR) effect, where nanoparticles

preferentially accumulate in tumour tissues due to their leaky vasculature and impaired lymphatic drainage <sup>(24)</sup>. "Active targeting" involves functionalizing the nanoparticle surface with ligands (e.g., antibodies, peptides, aptamers) that bind specifically to receptors overexpressed on oral cancer cells <sup>(25)</sup>. For example, liposomes conjugated with anti-EGFR antibodies can specifically deliver chemotherapeutic agents like doxorubicin to EGFR-positive oral cancer cells, as shown by Singh et al. (2023) in preclinical models, resulting in enhanced tumour regression and reduced systemic toxicity compared to free doxorubicin <sup>(26)</sup>. Nanoparticles can encapsulate various therapeutic agents, including conventional chemotherapeutics (e.g., cisplatin, paclitaxel), gene therapy agents (e.g., siRNA, plasmid DNA), and immunomodulators. This encapsulation protects the drug from degradation, improves its solubility, and allows for controlled release at the tumour site, optimizing therapeutic windows and minimizing off-target effects <sup>(27)</sup>.

### **Photodynamic and Photothermal Therapy**

Photodynamic therapy (PDT) and photothermal therapy (PTT) are promising minimally invasive treatment modalities that can be significantly enhanced by nanotechnology. In PDT, photosensitizers are activated by light of a specific wavelength, generating reactive oxygen species (ROS) that induce cancer cell death. Nanocarriers can deliver photosensitizers more efficiently and specifically to tumour cells, improving their accumulation and reducing skin photosensitivity, a common side effect of conventional PDT <sup>(28)</sup>. Lee et al. (2021) demonstrated that polymeric nanoparticles loaded with a photosensitizer and targeted to oral cancer cells exhibited superior photodynamic efficacy *in vitro* and *in vivo* compared to the free photosensitizer <sup>(29)</sup>.

PTT utilizes light-absorbing nanoparticles (e.g., AuNPs, carbon nanotubes) that convert absorbed light energy into heat, leading to localized thermal ablation of tumour cells. This

approach offers precise spatial control and minimal damage to surrounding healthy tissues. Wang et al. (2022) reported the successful use of PEGylated gold nanorods for PTT in an oral cancer xenograft model, achieving significant tumour growth inhibition with minimal systemic toxicity <sup>(30)</sup>. The combination of PDT and PTT using multifunctional nanoparticles is also being explored to achieve synergistic therapeutic effects <sup>(31)</sup>.

### **Immunotherapy Enhancement**

Nanotechnology can also augment the efficacy of immunotherapy for oral cancer. Nanoparticles can serve as carriers for immune checkpoint inhibitors, tumour antigens, or adjuvants, delivering them directly to immune cells or tumour microenvironment components to stimulate an anti-tumour immune response <sup>(32)</sup>. For instance, polymeric nanoparticles encapsulating immune checkpoint inhibitors (e.g., anti-PD-L1 antibodies) can improve their pharmacokinetics and biodistribution, leading to enhanced therapeutic outcomes and reduced systemic side effects <sup>(33)</sup>. Furthermore, nanoparticles can be designed to reprogram tumour-associated macrophages or modulate the activity of T-cells, thereby overcoming immunosuppression within the oral cancer microenvironment <sup>(34)</sup>.

**Table 2. Illustrative comparison of conventional vs. nano-enabled approaches in oral cancer management.**

Feature	Conventional Approaches	Nano-enabled Approaches	Advantages of Nano-enabled Approaches
<b>Diagnosis</b>	Visual inspection, biopsy, histopathology, imaging (CT, MRI)	Targeted imaging with nano contrast agents, nano biosensors, liquid biopsy with nanoplatforms	Earlier detection, higher sensitivity/specificity, non-invasive, multiplexed biomarker detection
<b>Drug Delivery</b>	Systemic chemotherapy, radiotherapy	Targeted drug delivery via nanoparticles (EPR effect, active targeting)	Reduced systemic toxicity, increased drug concentration at tumor site, improved drug solubility
<b>Therapy</b>	Surgery, radiotherapy, chemotherapy	Photodynamic/photothermal therapy, gene therapy, immunotherapy enhancement	Minimally invasive, localized treatment, reduced side effects, overcoming drug resistance
<b>Monitoring</b>	Follow-up imaging, clinical examination	Nanoparticle-based liquid biopsy for circulating biomarkers	Real-time monitoring of disease progression, recurrence, and treatment response
<b>Side Effects</b>	Significant systemic toxicity, damage to healthy tissues	Reduced off-target effects, localized treatment	Improved patient quality of life, fewer complications

## Challenges and Future Perspectives

Despite the immense promise of nanotechnology in oral cancer, several significant challenges must be addressed before widespread clinical translation. Biocompatibility and long-term toxicity remain primary concerns. While many nanomaterials are designed to be biocompatible, their degradation products, accumulation in organs, and potential for chronic toxicity need rigorous evaluation <sup>(35)</sup>. Standardized protocols for *in vitro* and *in vivo* toxicity assessments are crucial.

Regulatory hurdles also pose a substantial challenge. The unique properties of nanomaterials necessitate new regulatory frameworks for their approval, distinct from those for

conventional drugs or medical devices <sup>(36)</sup>. Comprehensive guidelines for manufacturing, quality control, and clinical trials are essential to ensure the safety and efficacy of nanomedicines.

The complexity of the tumour microenvironment in oral cancer, including its heterogeneity, dense extracellular matrix, and immunosuppressive nature, can limit nanoparticle penetration and efficacy <sup>(37)</sup>. Future research needs to focus on designing "smart" nanoparticles that can actively overcome these biological barriers and respond dynamically to the changing tumour environment.

Despite these challenges, the future of nanotechnology in oral cancer management is bright. Integration of artificial intelligence (AI) and machine learning with nano diagnostics can lead to more accurate and rapid interpretation of complex biomarker data <sup>(38)</sup>. The development of theragnostic nanoparticles, which combine diagnostic and therapeutic functionalities into a single platform, holds particular promise for personalized medicine, allowing for real-time monitoring of treatment response and adjustment of therapy <sup>(39)</sup>. Furthermore, the combination of nanotechnology with emerging fields like CRISPR-Cas9 gene editing or CAR T-cell therapy could unlock novel, highly effective treatment strategies for oral cancer <sup>(40)</sup>. Continued interdisciplinary collaboration among material scientists, oncologists, biologists, and engineers will be critical to translate these innovative nanotechnologies from bench to bedside, ultimately improving the lives of oral cancer patients.

## **Summary / Conclusion**

Oral cancer continues to pose a formidable challenge in oncology, necessitating innovative approaches for improved diagnosis and therapy. Nanotechnology has emerged as a transformative field, offering unprecedented opportunities to overcome the limitations of conventional methods. By leveraging the unique physicochemical properties of

nanomaterials, researchers are developing highly sensitive diagnostic tools for early detection and molecular profiling, as well as sophisticated therapeutic platforms for targeted drug delivery, phototherapy, and immunotherapy enhancement. These advancements promise to reduce systemic toxicity, improve treatment efficacy, and enable personalized medicine for oral cancer patients. While challenges related to biocompatibility, regulatory pathways, and complex tumour biology persist, ongoing research and interdisciplinary efforts are steadily paving the way for the clinical translation of nanomedicine. The integration of nanotechnology into oral cancer management holds the potential to revolutionize patient care, leading to earlier diagnoses, more effective treatments, and ultimately, better survival outcomes and quality of life.

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