



Nanophotonics: A Nascent Tool in Early Detection of Oral Cancer Using Saliva-Based Diagnostics

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Abstract

Oral squamous cell carcinoma (OSCC) stands as the sixth most prevalent malignancy globally among both sexes, with a concerning survival rate of approximately 5% over five years. The persistently high mortality rate is primarily due to the delayed diagnosis, often at advanced and less treatable stages. Early detection remains a cornerstone for improving patient prognosis and survival outcomes. In this context, there is a growing need for highly specific, sensitive, and non-invasive diagnostic tools. Nanophotonics has recently emerged as a promising imaging and diagnostic modality with the potential to revolutionize early cancer detection. Saliva,

as a diagnostic biofluid, offers several advantages over traditional invasive techniques. It is readily accessible, non-invasive, and capable of reflecting systemic physiological and pathological conditions. A wide array of cancer biomarkers, including proteins, nucleic acids, and metabolites, can be reliably measured in saliva. Among these, the epidermal growth factor receptor (EGFR) has been recognized as a significant biomarker in OSCC due to its overexpression in malignant oral tissues. Nanophotonics leverages the interaction between light and nanomaterials to enhance the sensitivity of diagnostics. In the case of oral cancer detection, nanophotonic platforms utilize antibody-conjugated gold

nanoparticles specifically designed to bind to EGFR present in saliva. When combined with surface-enhanced Raman scattering (SERS) — a powerful optical technique that amplifies molecular vibrational signals — these nanoparticles provide a highly sensitive and specific method for biomarker detection. Raman spectroscopy, facilitated by nanophotonic enhancement, enables the detection of even trace amounts of EGFR, facilitating the identification of malignancy at its inception. This paper explores the cutting-edge applications of nanophotonic in salivary diagnostics, particularly focusing on the synergy of gold nanoparticle-based biosensing and SERS in identifying EGFR. The integration of nanotechnology with optical science paves the way for a transformative approach in the early detection of oral cancer, offering a non-invasive, rapid, and accurate diagnostic alternative. As the “war with cancer” continues, such nascent technologies hold immense potential in shifting the clinical paradigm toward earlier intervention and improved survival rates.

Keywords: Nanophotonic, Nanoparticles, Oral Cancer, Saliva-Based Diagnostics, Early Detection, Non-Invasive Biomarkers.

Introduction

Oral squamous cell carcinoma is the sixth most common cancer for both sexes worldwide, with a survival rate of about 5%. Oral carcinogenesis is often due to long-term exposure to various potential risk factors, which may lead to the accumulation of multiple genetic mutations.^{1,2} The high mortality rate in oral cancer is attributed to the difficulty in detecting the disease at an early, treatable stage, and therefore detecting oral cancer at its earliest is vital for improving the survival rate.³ Efforts have been made to develop less-invasive early diagnostic modalities for oral cancer, of which the in vivo high-resolution imaging of oral epithelial tissues using novel optical

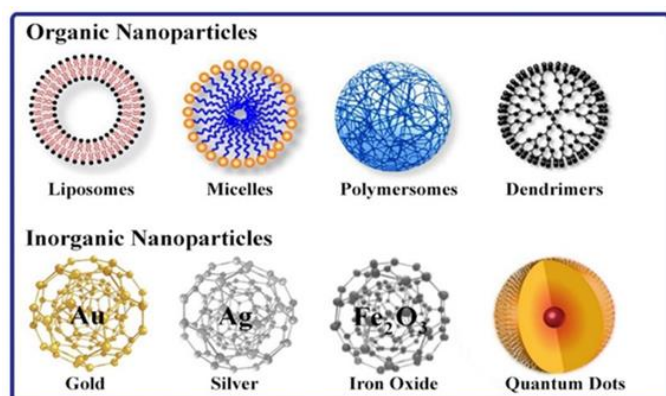
systems and the chemical analysis of saliva hold great promise as valuable tools.⁴ Other than saliva, nanophotonic can also be applied in blood samples and biopsy specimens for early detection of cancer. Thus, nanophotonic technology is a tool that can help many with its non-invasive nature and the potential to detect oral cancers early. Recent advancements have expanded nanophotonics to include hybrid nanomaterial biosensors, such as metal oxide nanoparticles integrated with optical detection methods, which further enhance salivary biomarker analysis for OSCC. These innovations allow for multiplexed detection of multiple biomarkers beyond EGFR, including interleukins and microRNAs, improving diagnostic accuracy in clinical settings.¹⁷ This evolution underscores the shift toward point-of-care devices that could integrate with smartphone-based Raman readers for real-time screening.

Nanotechnology

According to the US National Nanotechnology Initiative, nanotechnology refers to the manipulation of matter with a length scale of 1–100 nm in at least one dimension. In the past few decades, nanotechnologies have been applied in various fields, especially in the medical field. One of the hottest subfields of nanotechnology is nanomedicine, which increases the possibility of specific targeted cancer therapy. Moreover, nanotechnology is also a useful tool for cancer detection and monitoring the disease as it metastasizes. It can detect even a single cancerous cell in vivo and deliver the highly toxic drugs to the cancerous cells. Nanoshells, carbon nanotubes, quantum dots, supermagnetic nanoparticles, nanowires, nanodiamonds, dendrimers, and recently synthesized nanosponges are some of the materials used for cancer detection. Using specific cross-linkers, such as specific antibodies against cancer cells, individual cancer cells can be located.⁵

What Are Nanoparticles?

Nanoparticles typically are smaller than several hundred nanometres in size, about one hundred ten thousand times smaller than human cells.⁶ Nanoparticles are also referred to as “zero-dimensional” nanomaterials. In recent years, these materials have emerged as important players in modern medicine, with applications ranging from contrast agents in medical imaging to carriers for gene delivery into individual cells.⁷ These nanoparticles can offer unprecedented interactions with biomolecules both on the surface of and inside the cell, which can revolutionize cancer diagnosis.⁶ Nanoparticles have made a tremendous impact in the treatment of various types of cancer, as evidenced by the numerous nanoparticle-based drugs and delivery systems that are in clinical use¹



Gold Nanoparticles

Gold nanoparticles hold favourable physiochemical properties, providing an optical contrast to differentiate malignant from normal cells. Gold nanoparticles are generally biocompatible and non-toxic to biological tissues⁶. They can improve the scattering reflection of light irradiated in their surface plasmon resonance frequency, discriminating oral cancer cells from those of normal cells.⁸ When coupled with appropriate biomarkers, these gold nanoparticle bioconjugates may provide useful optical signals for molecular-specific information to assist clinicians in the diagnosis of pre-cancers⁹. Conjugation of GNPs with UM-A9 antibodies

that home specifically to squamous cell carcinoma of the head and neck, facilitating early oral cancer detection. Gold nanoparticles with different sizes/shapes, such as nanorods, nanoshells, and nanocages, have been explored for biomedical applications⁶. They can improve the scattering reflection of light irradiated in their surface plasmon resonance frequency, discriminating oral cancer cells from those of normal cells.⁴

Nanophotonics

Nanophotonics, or nano-optics, is a part of nanotechnology that investigates the behaviour of light on nanometre scales as well as interactions of nanometre-sized objects with light. Nanophotonics is also considered a branch of electrical engineering, optics, and optical engineering, as well as a branch of nanotechnology.¹⁰ Nanophotonics often includes metallic components that can transport and focus light through surface plasmon polaritons. Surface plasmon polaritons (SPPs) are electromagnetic waves that travel along a metal-dielectric or metal-air interface, typically in the infrared or visible frequency. The term "surface plasmon polariton" explains that the wave involves both charge motion in the metal ("surface plasmon") and electromagnetic waves in the air or dielectric ("polariton")¹¹. Nanophotonics is a part of nanotechnology that investigates the behaviour of light on nanometre scales as well as interactions of nanometre-sized objects with light.³ The use of photonic nanotechnologies in medicine is a rapidly emerging and potentially powerful approach for disease protection, detection, and treatment.⁹ Emerging graphene-based nanomaterials have been incorporated into nanophotonic platforms to create electrochemical-optical hybrid biosensors, which amplify SERS signals in salivary samples for detecting OSCC biomarkers like EGFR and p53¹⁸. These hybrids offer tunable plasmonic properties,

enabling higher signal-to-noise ratios and potential integration with wearable diagnostics, thus bridging nanophotonics with personalised medicine.

Saliva As A Diagnostic Medium

Saliva is a dynamic fluid that reflects the physiological and pathological state of the body and bears functional equality of composition with serum. Saliva is a perfect medium to be explored for health and disease surveillance. Saliva is increasingly used in the qualitative and quantitative analysis of biologically active components and as an alternative to traditional blood and urine sampling. A wide range of biomarkers is measurable in saliva, as it contains a wide array of constituents. In humans, the saliva is secreted by three pairs of major (larger) salivary glands and some minor (small) salivary glands. Parotid gland secretions are purely serous; the submandibular and sublingual glands have a mixture of mucous and serous secretions. The constituents of saliva include water (99.5%) and solids (0.5%). Solid constituents contain organic compounds (enzymes, proteins, and vitamins) and inorganic compounds (sodium, calcium, potassium, chloride, fluoride, iodide, and magnesium), cellular components, and gases. Functions of saliva include mastication and deglutition, a role in speech, appreciation of taste, antibacterial property, protective and cleansing action, and buffering. Obtaining saliva is easy; self-collection after instruction is possible, and expertise is not required.¹²

Raman Spectroscopy

Raman spectroscopy is a vibrational spectroscopic technique based on inelastic interactions between light and matter. It is a promising imaging technique for gold nanoparticle-based contrast agents.³ The normal, premalignant, or malignant lesions are distinguished by inelastic scattering of light, which can be a laser in the

visible, near-infrared, or near-ultraviolet range. The signals in normal tissues are homogeneous but heterogeneous in malignant cells, reflecting the changes in chemical characterization and molecular structure of the lesions. Raman spectroscopy is a near-field effect and has a low penetration depth. Its clinical application has been limited by the weak Raman signal intensity and the slow speed of spectrum acquisitions. Nanoparticles have been applied as exogenous contrast agents to acquire the Raman signal with high speed and resolution. After being directly adsorbed on the nanoparticle surface, the molecules emit an amplified Raman scattering intensity, known as surface-enhanced Raman scattering (SERS)¹³. This observed property of gold nanorods can be used as diagnostic signatures for cancer cells.³

Basic Principle of Raman Spectroscopy

Raman spectroscopy is a powerful optical technique that utilizes inelastic scattering of light to analyse the molecular composition of tissues and cells. It provides a biochemical fingerprint of biological samples, making it especially valuable in oncology for the detection, characterization, and monitoring of cancer.

1. Light interaction:

- The sample is focused on with a monochromatic laser (which is usually in the visible or near-infrared range).

2. Scattering events:

- Most of the photons undergo Rayleigh scattering (this process is elastic – there is no energy change).
- A small fraction of the photons (~ 1 in 10^7 photons) undergo Raman scattering (this is inelastic – energy is shifted).

3. Raman shift

- The vibrational energy levels of the molecular bonds correspond to the difference in energy between the incident and the scattered light.

- This shift will form a Raman spectrum, which is unique to the molecular composition

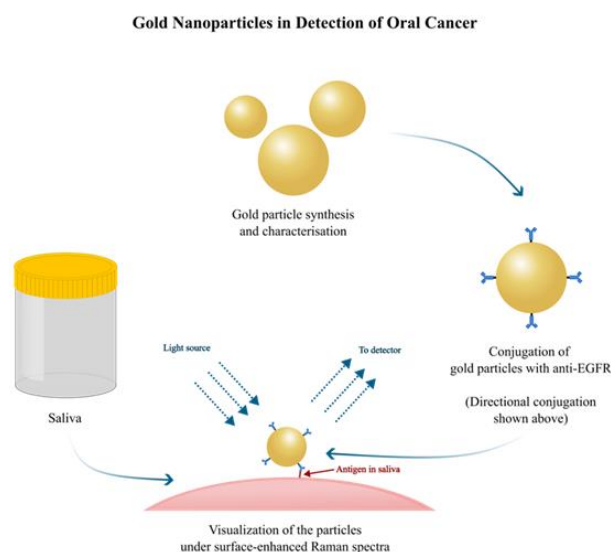
Applications in Oncology

Application	Description
Early Cancer Detection	Detects molecular changes before morphological symptoms appear
Tissue Margin Assessment	Helps surgeons distinguish tumours from normal tissue in real time
Cancer Grading and Staging	Differentiates low-grade vs. high-grade malignancies
Monitoring Treatment Response	Detects biochemical shifts post-therapy
Liquid Biopsy	Analyses cancer markers in saliva, blood, or urine via SERS enhancement

Principle of Nanophotonics Used for Cancer Detection

Head and neck squamous cell carcinoma has been reported to show a relatively higher expression of epidermal growth factor receptor (EGFR) with a stepwise increment in the EGFR with an increase in the degree of dysplasia and ultimately higher oral cancer risk.¹⁴ Gold nanoparticles can be conjugated with anti-EGFR antibodies to map the expression of the biomarker for molecular imaging and early diagnosis of oral cancer. For bioconjugation, to prevent aggregation, a shielding coating of polyethylene glycol is absorbed on the gold nanorod. The use of gold nanoparticles in surface-enhanced Raman scattering (SERS) to enhance the Raman spectroscopy signal for the analysis of cancer-related chemical changes in saliva (using cancer biomarkers present in saliva).¹⁵

How Gold Nanoparticles Are Used in The Detection of Oral Cancer



Schematic representation for saliva-based diagnostics for oral cancer

1. Synthesis and Characterization of Gold Nanoparticles

Gold nanospheres (gold colloids) of 2 nm to over 100 nm in diameter can be synthesized by controlled reduction of an aqueous HAuCl_4 (hydro tetrachloride aurate) solution at a temperature of 90°C .³

2. Collection of Saliva

About 10 ml of whole saliva from the patient with oral cancer is obtained and then transferred into a 1.5 ml centrifuge tube and spun. Using the centrifuge at 14,000 rpm for 5 min, small particulates and exfoliated cells are removed. The supernatant is then extracted and stored in a new centrifuge tube at -20°C .⁴

3. Conjugation of Gold Nanoparticles with Anti-Egfr

The epidermal growth factor receptor is a cell surface receptor biomarker (present in saliva) that is overexpressed in epithelial cancer but not in normal cells. The anti-epidermal growth factor receptor (EGFR) antibody-conjugated nanoparticles specifically and

homogeneously bind to the surface of the gold. The conjugation is performed by incubating the gold nanoparticles with anti-EGFR for about 10 minutes at room temperature. The successful conjugation of antibodies on gold nanoparticles was ascertained by the addition of 10% common salt solution and observing a visible colour change in the colloidal solution³ or bioconjugation. To prevent aggregation, a shielding coating of polyethylene glycol is absorbed on gold nanorods. One of the in vitro studies reports conjugation of GNPs with UM-A9 antibodies that home specifically to squamous cell carcinoma of the head and neck, facilitating early oral cancer detection

4. Visualization of The Particles Under Surface-Enhanced Raman Spectra

The polarized Raman spectra of the samples are visualized. The strong, sharpened polarized Raman spectra of the anti-epidermal growth factor receptor antibody conjugated particles are observed in the cancer cell samples, but not in the healthy cell samples.

- In bright field mode, gold nanorods can be identified by the weak red colour images due to the binding of the antibodies onto the gold surface.
- In dark field mode, gold nanorods strongly scatter the enhanced red light because the surface plasmon oscillation has a frequency in the near-infrared region⁶
- The absorption spectrum of gold nanorods in the sample incubated with the normal cells is broader than that of the cancer cells, which suggests that the environments of the different rods in the two samples are different and the absorption maxima of their surface plasmon oscillations are at different wavelengths.

- The sharper absorption spectrum of the cancer samples suggests that the gold nanorods are more homogeneously dispersed on the cancer cell surface.
- The differences in the absorption spectra of gold nanorods arise because the gold nanorods bind to the overexpressed EGFR present on the surface of cancer cells.¹⁶

Why Is A Strong Raman Spectrum Observed In The Cancer Cells?

A fraction of the rods on the cancer cell surface has a very strong surface plasmon field overlapping and rod alignment, which results from the binding of the antibodies to its overexpressed EGFR, which allows them to have overlapping surface plasmon fields, giving them strong and sharp Raman spectra.¹⁶ Cancer cells display a stronger Raman spectrum because of their biochemically altered composition, increased nuclear material, high metabolic activity, and sometimes enhanced optical interactions (e.g., resonance or SERS). These unique spectral features are what make Raman spectroscopy a powerful tool in cancer diagnosis and tissue discrimination. Cancer cells undergo profound biochemical and structural changes, which are readily detected in their Raman spectra. Compared to normal cells, the following key differences are often observed:

1. Increased nucleic acid content:

- The cancer cells show stronger peaks at $\sim 785\text{ cm}^{-1}$ and $\sim 1095\text{ cm}^{-1}$, which indicates elevated DNA and RNA due to increased transcriptional activity and higher proliferation rates.

2. Altered protein structure:

- The amide I ($\sim 1655\text{ cm}^{-1}$) and amide III ($\sim 1240\text{--}1300\text{ cm}^{-1}$) bands often exhibit shifts or intensity changes, reflecting alterations in protein conformation, overexpression of the oncogenic proteins, or degradation of structural proteins.

3. Changes in lipid profile:

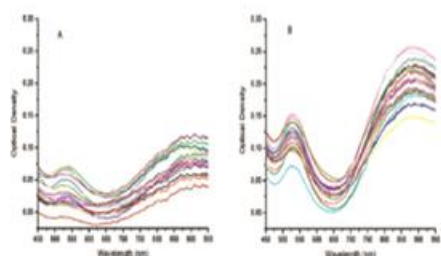
- The decreased intensity of lipid-associated bands ($\sim 1440\text{ cm}^{-1}$ and $\sim 1745\text{ cm}^{-1}$) suggests the loss of membrane integrity or lipid depletion, which is a hallmark of membrane fluidity changes seen in malignant transformation.
- Cancer cells often exhibit reduced lipid-to-protein ratios, which is indicative of increased cellular activity and reduced energy storage.

4. Increased metabolic activity:

- The elevated peaks corresponding to cytochromes and other mitochondrial components ($\sim 750\text{ cm}^{-1}$, $\sim 1580\text{ cm}^{-1}$) reflect changes in oxidative metabolism and mitochondrial dysfunction.

5. Presence of abnormal metabolites:

- The unique peaks or shifts in Raman spectra may represent abnormal metabolites like lactate or glutathione, associated with the Warburg effect and oxidative stress in cancer cells.



Surface plasmon absorption spectra of (a) Normal cells (b) Cancer cells

What Is Observed with The Normal Cells In Raman Spectra?

Normal cells exhibit well-organised and predictable Raman spectra that reflect their stable biochemical composition. The main components contributing to the Raman signature of normal cells include:

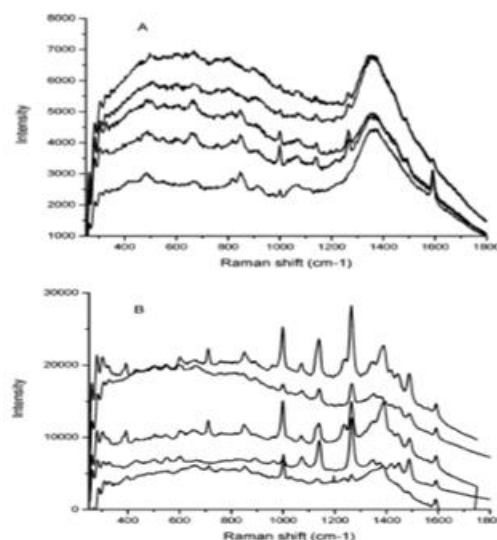
- **Proteins:** The Raman peaks at $\sim 1004\text{ cm}^{-1}$ (phenylalanine), $\sim 1655\text{ cm}^{-1}$ (amide I – C=O

stretching), and $\sim 1445\text{ cm}^{-1}$ (CH_2/CH_3 deformation) represent protein content and secondary structure.

- **Nucleic acids:** The peaks at $\sim 785\text{ cm}^{-1}$ (DNA/RNA backbone O–P–O stretching) and $\sim 1095\text{ cm}^{-1}$ (PO_2^- symmetric stretch) correspond to DNA and RNA content.
- **Lipids:** The strong signals at $\sim 1300\text{ cm}^{-1}$ (CH_2 twisting), $\sim 1440\text{ cm}^{-1}$ (CH_2 scissoring), and $\sim 1745\text{ cm}^{-1}$ (C=O stretching of lipids) indicate membrane integrity and lipid composition.
- **Carbohydrates:** The Raman bands at $\sim 1125\text{ cm}^{-1}$ and $\sim 1045\text{ cm}^{-1}$ may reflect glycosidic bonds in the carbohydrates.

These spectral features are relatively consistent across healthy cells and tissues, reflecting their normal metabolic and structural balance. The nonspecific binding of gold nanorods to normal cells results in randomly distributed nanorods on the cell surface and on the substrate. This makes the nanorod density level and the overlapping surface plasmon fields in the normal cell sample much lower and more heterogeneous than in the cancer cell sample.¹⁶

- These spectral fingerprint differences can very well be used as molecular diagnostics for cancer cells.¹⁶



SERS of anti-EGFR antibody conjugated gold nanorods with A. normal cells and B. cancer cells. The bottom spectra from the cancer cell samples are stronger,

sharper, and better resolved, suggesting the potential of using surface-enhanced Raman spectroscopy as a molecular type of imaging for the diagnostics of cancer.

Comparative Raman Spectral Features: Normal Vs. Cancer Cells

Raman Shift (cm ⁻¹)	Molecular Assignment	Normal Cells	Cancer Cells
720 – 785	DNA/RNA bases	Moderate intensity – reflects normal nucleic acid levels	High intensity – due to increased DNA/RNA synthesis and replication
1003	Phenylalanine (protein marker)	Sharp, strong peak – consistent protein synthesis	Sometimes, intensified, altered or overexpressed proteins
1095	Phosphate (DNA backbone)	Stable – normal nuclear structure	Increased – enlarged nucleus, higher mitotic activity
1250 – 1300	Amide III (protein structure)	Consistent – mainly α -helix	May shift or broaden – conformational protein changes
1445	CH ₂ bending (lipids/proteins)	Balanced – stable membrane composition	Altered – reflects membrane remodelling, lipid metabolism changes
1655	Amide I (protein secondary structure)	Prominent α -helix peak – normal protein folding	Shifted or less defined – β -sheet prevalence, misfolding in tumour cells
1740	C=O stretching (lipids)	Low or absent – minimal lipid peroxidation	Elevated – due to oxidative stress and altered lipid metabolism
2850 – 2930	CH stretching (lipids/proteins)	Normal cellular density and composition	Broad/intense bands – increased cellular mass, altered membrane and cytoplasmic components

Advantages and Disadvantages of Nanophotonics in Early Detection Of Oral Cancer Using Saliva-Based Diagnostics

Advantages	Disadvantages
Non-invasive: Utilises saliva, avoiding the need for biopsies or blood draws.	High initial cost for equipment and research infrastructure.
Enables early-stage detection, improving prognosis.	Technically complex, it requires skilled personnel and sophisticated tools.
High sensitivity and specificity via SERS and nanoparticle targeting.	Lack of standardised protocols for saliva collection and analysis.

Rapid analysis compared to conventional diagnostics.	Regulatory hurdles for clinical approval of nanophotonic devices.
Real-time monitoring of disease biomarkers is possible.	Salivary biomarker variability due to physiological and environmental factors.
Portable and scalable technology for point-of-care testing.	Stability issues with nanoparticles (e.g., aggregation, shelf life).
Cost-effective in long-term cancer management.	Ethical and safety concerns regarding nanoparticle use in biological systems.
Allows multiplex detection of multiple biomarkers simultaneously.	Still largely under research, with limited large-scale clinical validation.
Facilitates integration with AI-driven analysis for automated biomarker interpretation, accelerating clinical decision-making ¹⁹	Potential interference from salivary matrix components requires advanced preprocessing techniques for consistent results

Conclusion

The application of nanophotonics in the early detection of oral cancer, particularly through saliva-based diagnostics, represents a significant breakthrough in the pursuit of non-invasive, accurate, and rapid cancer screening tools. Oral squamous cell carcinoma continues to pose a global health burden due to its late-stage detection and low survival rates. The integration of nanotechnology with optical techniques, such as surface-enhanced Raman scattering (SERS), enables the ultrasensitive identification of biomarkers like the epidermal growth factor receptor (EGFR) in salivary samples. This innovative approach addresses key limitations of traditional diagnostic methods by offering enhanced sensitivity, specificity, and patient compliance. The use of antibody-conjugated gold nanoparticles facilitates targeted biomarker detection, while Raman spectroscopy provides the necessary precision in signal enhancement. Together, they allow for the detection of minute biomolecular changes associated with malignant transformation, often before clinical symptoms appear. The accessibility of saliva as a diagnostic medium further promotes mass screening, especially in resource-limited

settings. Future perspectives include the development of nanomaterial-enhanced biosensors for real-time monitoring of salivary biomarkers, potentially incorporating machine learning algorithms to predict OSCC progression based on dynamic biomarker profiles¹⁹. Such advancements could enable longitudinal tracking in high-risk populations, further reducing mortality through proactive interventions. However, while the potential is immense, challenges such as standardisation, cost, regulatory approval, and nanoparticle safety must be addressed to ensure clinical translation. Despite these hurdles, the current trajectory of research indicates that nanophotonic-based salivary diagnostics may soon become a cornerstone in routine oral cancer screening programs. In conclusion, nanophotonic stands at the forefront of a new era in oncological diagnostics, with the promise to not only detect cancer earlier but to do so in a manner that is patient-friendly, cost-effective, and scalable—paving the way for improved outcomes and reduced cancer mortality.

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