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# Progress in the Application of Fluorescent Probes in Oral Tumor Diseases

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***Abstract:*** *The oral cavity serves as a crucial gateway connecting the human body with the external environment, hosting a diverse microbial population. Its health is closely connected to the overall wellness of individuals, highlighting the critical need to focus on oral diseases for the benefit of global health. Concurrently, fluorescent probes have become a significant area of interest in recent years, with considerable progress in the medical realm. In this review, we undertake an analysis in this review, we have examined the potential application of fluorescent probes in investigating oral tumor diseases. We specifically explore their use in identifying, diagnosing, imaging, treating, and screening oral tumors. Currently, the development of fluorescent probes for oral tumor studies is in its early stages and faces many challenges. Future research should aim at creating fluorescent probes with better sensitivity, specificity, and reduced toxicity. We hope that this review will inspire further advancements in fluorescent probes with improved features for prospective applications.*

***Keywords:*** *Fluorescent probes, Oral tumor diseases, Detection, Diagnosis, Imaging*

## 1. Introduction

The human body is a marvel of complexity, comprised of numerous interconnected parts, all crucial for maintaining overall well-being. Among these, the oral cavity stands out as a pivotal interface facilitating communication between the body and the external world. It hosts one of the most concentrated microbial communities in the body and serves as the initial segment of the digestive tract [1]. Although awareness of oral health has grown with higher living standards, the importance attached to it continues to rise. However, oral diseases still pose a major global public health challenge, necessitating comprehensive research by the entire society into their etiology, clinical manifestations, differential diagnosis, prevention, and treatment [2]. Oral diseases are associated with several other diseases in the human body. For example, there is a clear correlation between oral diseases and cardiovascular diseases [3], diabetes [4], digestive system diseases [5], among others. Hence, enhancing the surveillance and management of oral diseases by researchers holds substantial importance for both the healthcare sector and public health at large.

Over the years, with the continuous development of medical technology, the identification of some biomarkers for diseases has become the basis of many analytical methods, such as gel electrophoresis, enzyme-linked immunosorbent assay (ELISA), immunohistochemistry, immunofluorescence, etc. These analytical methods, though effective, often entail significant expenses and time. In contrast, fluorescence imaging technology stands out for its distinct advantages over these traditional approaches. Among its key tools are fluorescent probes, which have attracted considerable research interest in recent years [6].

Fluorescent probes refer to substances that emit fluorescence when excited by light of a certain wavelength, making them valuable tools for both qualitative and quantitative analysis via fluorescence detection. In the field of oral medicine, fluorescent probes are primarily used for cancer monitoring and diagnosis, but their applications are gradually expanding to include areas such as oral microbial detection. This article provides a comprehensive overview of the potential applications of fluorescent probes in the detection, diagnosis, screening, treatment, and imaging of oral diseases. We have also discuss several design strategies for fluorescent probes in oral diseases and their respective applications. We hope that this review will not only update readers on the latest advancements in fluorescent probes

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for oral health applications but also provide insights into the development of superior fluorescent probes, enabling them to play a more extensive role in the future.

## 2. Design strategies of fluorescent probes

### *2.1. Design principles*

#### *2.1.1. Conjugated fluorescent probes*

Conjugated fluorescent probes are a commonly encountered type of fluorescent probe. They are designed by chemically linking recognition moieties with fluorescent moieties through covalent bonds [7]. By comparing changes in fluorescence intensity, spectral shifts, and fluorescence lifetime before and after the target substance is introduced, these probes enable both quantitative and qualitative analyses of the target.

#### *2.1.2. Substitution fluorescent probes*

Substitution fluorescent probes analyze the target substance quantitatively and qualitatively by evaluating the binding affinity differences among the recognition elements, fluorescent groups, and the target substance [8]. However, the design requirements for such probes are demanding. They necessitate the recognition of moieties that can effectively bind to the fluorescent moieties but with less affinity than the target substance. Moreover, the disparity in binding affinities between these components must be substantial to enable their effective use in analyzing real samples.

#### *2.1.3. Stoichiometric fluorescent probes*

Stoichiometric fluorescent probes are a class of probes with highly complex designs. They conduct qualitative and quantitative analysis of the target substance by identifying changes in fluorescence signals before and after engaging in a specific, irreversible chemical reaction with the target [9]. In their operation, these probes can follow one of two scenarios: in one, they remain covalently attached to the target substance following the chemical reaction; in the other scenario, the target substance acts as a catalyst, facilitating the chemical reaction.

### *2.2. Response mechanisms*

The response mechanisms of fluorescent probes can be broadly categorized into three types. The first type is photoinduced electron transfer [10], which refers to the transfer of electrons between donor or acceptor molecules in their excited states upon light excitation, resulting in alterations in the fluorescent signal. The second type is fluorescence resonance energy transfer [11], which occurs when the excitation spectrum of the donor molecule overlaps with the fluorescence spectrum of the acceptor molecule. In this case, the donor molecule has the capability to transfer some or all its energy to the acceptor molecule. The third type is the intramolecular charge transfer mechanism [12], where electron-rich groups with electron-donating abilities are conjugated to electron-deficient groups. When the electron-deficient group, acting as an electron acceptor, binds with the analyte, it can alter the electron-donating capacity of the electron-rich group, or the donor molecule. This interaction causes a redistribution of charges within the conjugated system, resulting in modifications to the fluorescent signal. Based on the characteristics and properties of different oral diseases as well as research objectives and requirements, different fluorescent probes can be designed. These custom designs leverage the distinct design principles and response mechanisms of fluorescent probes to address specific diagnostic and investigative challenges in oral health research.

## 3. Application of fluorescent probes in oral tumors

In the field of maxillofacial surgery, fluorescent probes are primarily utilized for oral cancer, which is one of the predominant malignant tumors within the head and neck region [13]. Over 90% of head and neck tumors are identified as squamous cell carcinoma [14]. Its biological characteristics mainly manifest as local infiltrative growth and lymph node metastasis in the neck. The application of fluorescent probes in maxillofacial surgery is mainly focused on tumor imaging, disease screening and detection, as well as fundamental research on these conditions.

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### *3.1. Tumor imaging*

For enhancing postoperative survival rates in oral squamous cell carcinoma (OSCC), precisely detecting and thoroughly resecting the primary tumor margins are imperative. During surgery, lesions with subtle changes are difficult for surgeons to detect, thus real-time fluorescence detection of tumor margins is increasingly being utilized in operations. Wang et al. [15] synthesized a fluorescent probe cMBP-ICG, which can integrate a c-MET binding peptide with a near-infrared dye. This probe selectively binds to tumors via c-MET, enabling real-time fluorescence detection of tumor margins. The clinical trial of this study was a preliminary investigation, showcasing significant benefits in terms of local real-time application and imaging time, as well as biocompatibility and specificity. The impact of this trial was limited by its small sample size and its reduced effectiveness in identifying deep-seated tumors. However, it still holds promise for future applications in guiding surgery and postoperative assessment for OSCC leukoplakia patients.

Ling et al. [16] developed a novel fluorescent probe SQ890 NPs-Pep by assembling nanoparticles and modifying them with a targeting peptide GE11 specifically for studies involving Cal 27 cells and mice. Experimental results indicated that this probe can provide visual guidance for oral cancer tumor resection and effectively destroy tumor tissues. It can facilitate both fluorescence and photoacoustic imaging of tumors in a dual-mode capacity, under both in vivo and in vitro settings. As a novel near-infrared light therapeutic tool, SQ890 NPs-Pep has exhibited great promise for enhancing tumor imaging, diagnosis, and therapy.

Tian et al. [17] utilized a novel OSCC imaging biomarker, glucose transporter 1 (GLUT1), and synthesized a new near-infrared fluorescence probe, WZB117-IR820, based on this. In a model of in situ tongue squamous cell carcinoma, after intravenous injection of WZB117-IR820, the tumor area exhibited a higher specific fluorescence intensity compared to adjacent muscle tissues, with tumor diameters ranging approximately 1-2 millimeters. These observations indicated the high sensitivity of the WZB117-IR820 probe in identifying small tumors. Building upon preclinical studies, the probe was also tested on specimens from OSCC patients, demonstrating its capability to distinguish tumor tissues from adjacent healthy tissues. In biosafety experiments, when the probe concentration reached 320 μg/mL, the cell viability of human oral keratinocytes (HOK) HOK decreased to 80%, and a similar reduction in viability was observed in OSCC cell lines, highlighting some level of toxicity associated with the probe. Nonetheless, this study offers valuable perspectives on developing fluorescence probes for imaging of oral cancer.

Miyamoto and colleagues [18] conducted a study where they injected indocyanine green (ICG) around the primary sites of oropharyngeal cancer in patients who had not yet received treatment. This was done to evaluate ICG as an alternative technique for identifying sentinel lymph nodes (SLNs). Eight SLNs were successfully distinguished from surrounding tissues, however, two SLNs with occult metastases were not detected. Despite the limited sensitivity observed in this study, it established a foundation for using ICG in the fluorescence imaging of oral cancers.

Li and their team [19] focused on the gastrin-releasing peptide receptor (GRPR) as a key target for the imaging and treatment of OSCC. One of the targets for imaging and treatment of OSCC is the gastrin-releasing peptide receptor (GRPR). They synthesized a nanoscale fluorescence probe, NGO-BBN-AF750, based on nano-graphene oxide, which exhibited high affinity and specificity for GRPR. This probe was then internalized into HSC-3 cells through BBN peptide-mediated endocytosis, ultimately facilitating near-infrared fluorescence imaging of OSCC. However, this experiment did not include long-term stability studies under complex biological conditions.

### *3.2. Disease screening*

Normal oral mucosa and submucosal layers contain endogenous autofluorescent substances, which can emit fluorescence when exposed to specific excitation wavelengths [20]. Wang et al. [21] utilized VELscope fluorescence examination to screen 59 cases of potentially malignant oral diseases, correlating their findings with histopathological diagnoses. The findings indicated that autofluorescence examination can be an effective tool in the screening process for oral cancer and high-risk lesions among potentially malignant oral mucosal disorders (OPMDs). This technique can significantly improve the detection of lesions with a low risk of malignancy.

Wang et al. [22] developed a multimodal near-infrared II (NIR-II) probe called TQTPA, aimed at imaging OSCC tumors, identifying metastatic lymph nodes, and facilitating anti-tumor therapy. Both in

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vivo and in vitro experiments demonstrated that TQTPA possessed excellent water solubility, stability, tissue penetration, biocompatibility, and low toxicity. Additionally, it can exhibit high sensitivity to pH/hyaluronic acid.

Zheng et al. [23] investigated the synergistic effects of biomaterial-mediated oral microbiota modulation and Programmed Death-1 (PD-1) blockade therapy in an OSCC mouse model. During their experimental process, they identified and screened OSCC-associated bacteria using fluorescence in situ hybridization (FISH) fluorescent probes. The results showed enrichment of Streptococcus species in the tumors, and bacterial-mediated immune effects were identified as the primary mechanism driving the anticancer effects of the anaerobic bacterium Fusobacterium. Furthermore, the study demonstrated that biomaterials could be engineered to alter the human microbiota, thereby boosting anti-tumor immune responses.

The G-quadruplex (G4) structure, which is recognized as a potential target for cancer therapy [24], consists of guanine bases arranged in a square planar configuration through Hoogsteen hydrogen bonding, with two or more layers of planes stacked via π-π interactions. Tseng et al. [25] utilized a G4 fluorescent probe to detect G4 lesions in patients with head and neck cancer as well as in healthy individuals. Their findings indicated a pronounced difference in the prevalence of G4 structures between cancerous and non-cancerous cells, suggesting that the presence of G4 structures could serve as a universal biomarker for the detection of various human cancers.

In recent years, salivary exosomes, as a non-invasive biomarker, have been receiving increasing attention from researchers particularly in OSCC [26]. A notable advancement in this area was made by Zhuang et al. [27] who developed a bioluminescent probe, MFBP, for the quantification of exosomes by detecting the enrichment of the tetraspanin CD63 on the exosomes. Their technique involved conjugating DNA hybrid chains, which were loaded with several quantum dots (QDs) and CD63-specific aptamers, to magnetic microspheres to serve as markers. These aptamers are engineered to accurately identify CD63, triggering the release of DNA hybrid chains from the magnetic microspheres into the solution as signal emitters, thereby facilitating the generation of "multiple signals from a single exosome." This method has a detection limit as low as 500 particles/μL, fully meeting clinical detection requirements. Despite testing on a small group of clinical OSCC patient samples, this preliminary application underscored the method's clinical viability, offering new insights for the future design of cancer biomarker detection methods.

### *3.3. Other applications*

Parihar et al. [28] employed fluorescent probes targeted at specific organelles to study the re-infection of oral cancer cells and to monitor the structural changes in organelles triggered by photodynamic therapy (PDT) using a chlorin-p6-histamine conjugate in human oral cancer cells. Their findings suggested that the effectiveness of PDT in inducing apoptosis through various cell death pathways primarily depends on the subcellular localization of the photosensitizer and the extent of damage to organelles.

Tumor site hypoxia can restrict the effectiveness of PDT. Tao et al. [29] addressed this challenge by using the hypoxia probe named 2',7'-Dichlorodihydrofluorescein diacetate (DCFH-DA) to measure changes in cellular oxygen levels following PDT when combined with resveratrol (RES) treatment. Their experimental results showed minimal fluorescence in the absence of a photosensitizer, whereas the PDT-treated group displayed significant reactive oxygen species (ROS) generation, suggesting that RES reduced cellular oxygen consumption, thus ensuring an adequate oxygen supply for PDT. This provides a novel alternative strategy for enhancing the therapeutic effect of PDT in OSCC treatment.

Peroxiredoxins (Prxs) are enzymes that act as antioxidants [30]. To understand how Prxs function in cancer, Lee et al. [31] used the DCF-DA fluorescence probe to detect the impact of Prxs on ROS levels in Ca9.22 and OSCC cell lines. The findings revealed that under normoxic conditions, cells lacking Prxs exhibited a 2.3 fold increase in fluorescence compared to the control cells. Under hypoxic conditions (1% O2), the deficiency of Prxs led to a further increase in probe fluorescence, and DCF fluorescence was significantly higher under hypoxia compared to normoxia, thus indicating the involvement of Prxs in ROS scavenging in these OSCC cells.

Sun et al. [32] developed a novel therapeutic approach using a cancer cell membrane-coated gold nanorod (GNR@Mem). To investigate its therapeutic efficacy, they employed the DCFH-DA probe to monitor ROS production in OSCC cancer KB cells. Initial findings under X-ray irradiation showed that only a small fraction of cells (17.5%) exhibited ROS overexpression. However, incorporating

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GNR@PEG and GNR@Mem enhanced the proportion of ROS-positive cells to 41% and 65%, respectively, even before radiotherapy was applied. Further exposure to near-infrared light significantly increased ROS positivity to 84% in cells treated with GNR@Mem. These findings indicate the superior efficacy of GNR@Mem in promoting ROS generation, highlighting its promising role in enhancing the effectiveness of anticancer therapy.

## 4. Discussion

Fluorescent probes are being widely used across various domains like biochemistry, environmental science, and medicine due to their high sensitivity, exceptional selectivity, capability for real-time detection, and rapid imaging and quantification abilities. In recent years, fluorescent probes have gradually been employed in studying the etiology, diagnosis, and treatment of oral diseases such as oral and maxillofacial surgical diseases, oral medicine diseases, and oral mucosal diseases. Their resilience against external electromagnetic interference, absence of need for sample pretreatment, and their ability to emit light over extended distances have particularly made them invaluable tools in dental research. Fluorescent probes, in combination with molecular measurement instruments like fluorescence spectrophotometers, offer a powerful means to translate biomarkers associated with oral cancer into measurable and visually interpretable data, thereby facilitating a more profound comprehension of oral disease pathogenesis and progression. Despite some progress made in the application of fluorescent probes in dentistry, several challenges and gaps remain to be addressed. In the realm of oral tumor diseases, current research predominantly concentrates on the early detection, screening, diagnosis, and surgical imaging related to oral cancer cells and tissues, as shown in Table 1. However, there exists a notable scarcity of studies exploring the application of fluorescent probes in other oral and maxillofacial surgical conditions. Given that oral cancer can develop from other untreated potentially malignant oral disorders, there is a critical need for developing fluorescent probes that can detect these precursor conditions. Additionally, integrating fluorescent probes with various phototherapy techniques such as photothermal therapy, photoacoustic therapy, and photodynamic therapy represents a promising area of research for treating oral diseases. This multifaceted approach could significantly enhance the effectiveness and scope of treatment options available for oral health issues. The advancement of highly selective, non-toxic, and non-invasive fluorescent probes represents a pivotal direction for future research endeavors. Moreover, most existing studies have focused on a limited number of clinical cases involving patients with oral conditions. Presently, research predominantly encompasses in vitro cellular or animal studies. Therefore, it is critically important to prioritize the creation of fluorescent probes that are more relevant and applicable to clinical settings.

*Table 1: Applications of fluorescent probes in oral cancer.*

| Fluorescent probes | Models | Application | References |
|---|---|---|---|
| CMBP-ICG | OSCC patients | Tumor margin detection | [15] |
| SQ890 NPs-Pep | Cal 27 cells, mice | Tumor imaging | [16] |
| WZB117-IR820 | OSCC mouse model, OSCC patients | Tumor margin imaging | [17] |
| ICG probe | Oropharyngeal cancer patients | Sentinel lymph node imaging | [18] |
| NGO-BBN-AF750 | HSC-3 | Tumor imaging | [19] |
| VELscope | OPMPs patients | OPMPs screening | [21] |
| TQTPA | OSCC cell lines, HSC3SCC4 | OSCC metastatic lymph node detection and treatment | [22] |
| FISH probe | OSCC patients' mucosa | Screening for OSCC-related bacteria | [23] |
| G4 fluorescent probe | Head and neck cancer patients | Screening and differentiation of cancer cells | [25] |
| MFBPs | OSCC patients' saliva | Exosome detection | [27] |
| Organelle-specific fluorescent probes | Oral cancer cells | Observation of cell damage after PDT | [28] |
| DCFH-DA | Cal 27 | PDT anti-tumor effect | [29] |
| DCF-DA | OSCC cell lines, Ca9.22 cells | Role of Prxs in cancer | [31] |
| DCFH-DA | KB cells | Intracellular ROS detection | [32] |

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## 5. Conclusions

Overall, we need to design and develop more fluorescent probes with excellent performance for the study of oral cancer. When designing and developing fluorescent probes three critical factors must be considered. First, it is essential to design probes that can distinguish between the target signal and the background autofluorescence of tissues to enhance detection accuracy. Second, the probes must remain stable within the body, unaffected by biological factors such as changes in temperature, pH levels, and the presence of proteins or enzymes, which could otherwise quench their fluorescence. Lastly, and perhaps most crucially, the safety of these probes is paramount; they must either be non-toxic or exhibit extremely low toxicity to human cells. This article sheds light on the latest advancements in the application of fluorescent probes in the field of oral diseases, aiming to provide novel insights for the future development of highly sensitive, selective, and low-toxicity fluorescent probes.

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