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Photodynamic Therapy for Oral Squamous Cell Carcinoma: Current Status, Challenges, and Prospects

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Abstract: Oral squamous cell carcinoma (OSCC) is the most prevalent and deadly malignancy of the head and neck. The standard treatments for OSCC are surgery, radiotherapy, and chemoradiotherapy, which can cause severe cosmetic and functional damage to the oral cavity and impair the patients' quality of life. Photodynamic therapy (PDT) is a promising alternative that uses light-activated photosensitizers to induce selective phototoxicity and necrosis in the target tissues. PDT has several advantages over conventional treatments, such as minimal invasion, low side effects, high selectivity and preservation of the oral function and appearance. This review explores the principles, mechanisms, and current applications of PDT for OSCC. We address the challenges, such as the depth of light penetration and tissue hypoxia, and underscore the progressive innovations in photosensitizer enhancement, nanotechnological integration, and precision therapy. The exploration of biomarkers for refining patient selection and tailoring individualized treatment regimens is also undertaken. PDT holds promise as a secure and efficacious modality for OSCC management. Nonetheless, additional investigation is imperative to refine treatment protocols and validate sustained therapeutic success.

Keywords: oral squamous cell carcinoma, photodynamic therapy, photosensitizers, nanotechnology, biomarkers

Introduction

Oral squamous cell carcinoma (OSCC) is the most prevalent and deadly malignancy of the head and neck, associated with a significant mortality rate.[1,2] The survival rate of oral cancer is approximately 50%. OSCC commonly occurs in the tongue, gingiva and buccal mucosa.[3] OSCC is more prevalent in Asian populations, which may be due to the habit of betel nut/tobacco chewing in Asian countries. In Western populations, the most common site of oral cancer is the tongue, accounting for 40–50% of oral cancer cases.[4] Surgical treatment alone, radiotherapy and chemoradiotherapy combined with surgery are the main therapeutic options for oral cancer currently.[5] Surgical treatment is one of the most common methods for treating OSCC.[6] However, surgical removal may also impair the patient's swallowing, speech, chewing function and appearance, and even require plastic surgery.[7,8] Radiotherapy induces DNA damage, rendering cells unable to repair and leading to their destruction. The 5-year survival rate for early-stage head and neck squamous cell carcinoma patients receiving radiotherapy alone increases greatly.[9] However, non-specific radiotherapy can cause damage to normal tissues.[10] Chemotherapy can treat cancer to some extent,[11] but due to the non-specificity of chemotherapeutic drugs, severe systemic adverse reactions are common. After initiating high-dose chemotherapy, patients are at significant risk of developing ulcerative mucositis.

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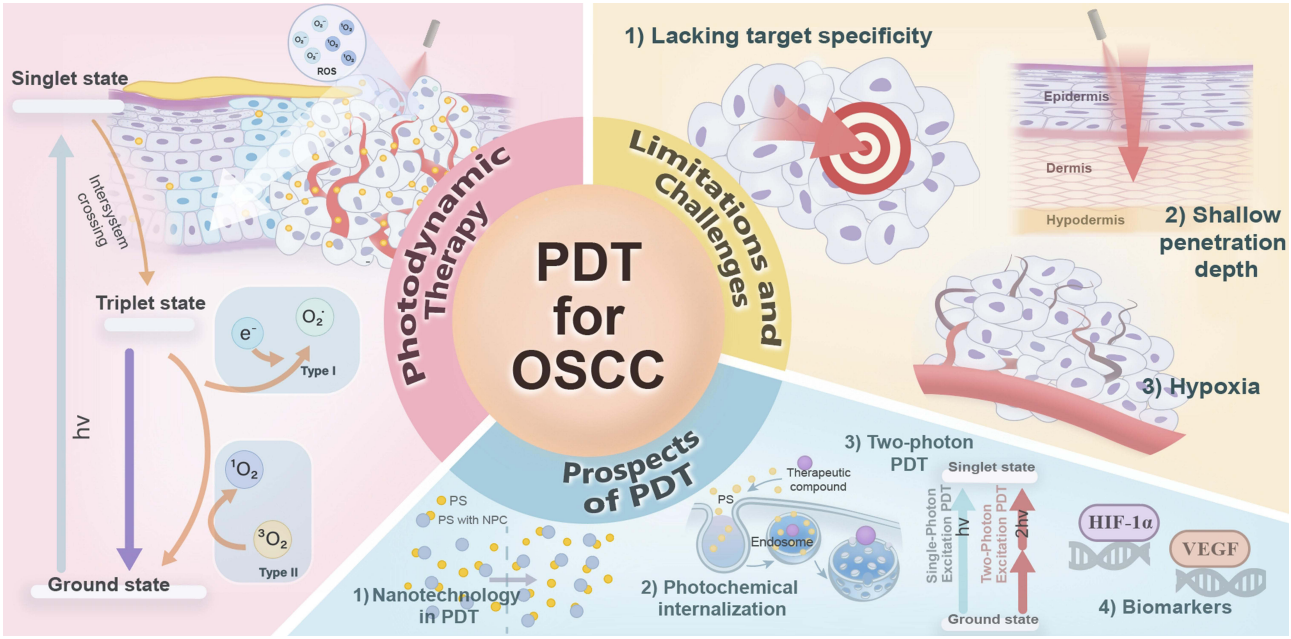
Graphical Abstract



Additionally, prolonged medication use can lead to cancer cell resistance, affecting the efficacy of chemotherapy. Studies have shown that despite improvements in cancer survival rates, people with head and neck cancer are almost twice as likely to commit suicide compared to people with other cancers, which has increased in recent years.[12] Therefore, finding more effective and personalized OSCC treatment methods to improving the quality of life of patients, is an urgent problem that needs to be solved. Some emerging methods are being explored and developed.

Photodynamic therapy (PDT) uses light of a specific wavelength to irradiate photosensitizers (PSs) which accumulate and produce photochemical reactions in the target tissues, causing irreversible damage or necrosis.[13] Photosensitizers, light sources and oxygen are the three essential elements of photodynamic therapy. The photodynamic reaction begins when the PS absorbs light and transfers energy to oxygen molecules, resulting in the formation of ROS. The mechanisms underlying the generation of ROS can be categorized into two pathways: type I. The PS in the excited triplet state T1 ($^3PS\cdot$) reacts directly with a substrate and transfers an electron or a proton, leading to the formation of organic radicals; type II: $^3PS\cdot$ undergo triplet−triplet energy transfer to molecular oxygen (triplet in the ground state) to form excited-state singlet oxygen ($^1O_2$), an extremely strong oxidizing agent with a lifetime in biologic media from a few to hundreds of nanoseconds and it is considered to be the main factor for the therapeutic effect of PDT.[14]

PDT is considered to have good application prospects because of its advantages such as minimally invasive, low side effects and high selectivity.[15] When PDT is used as an adjuvant therapy, it has been demonstrated to yield better cancer treatment outcomes. PDT has been successfully used to treat various lesions in the head and neck region, especially oral potentially malignant disorders (OPMDs) or oral cancer, effectively eliminate cancer cells and improve the quality of life and prognosis of patients.[16,17] In this review, we aim to provide an overview of the current evidence and challenges of PDT for OSCC. This paper retrieved literature related to PDT and OSCC from the PubMed and Web of Science databases etc., with a focus on analyzing studies from the past five years. We will first summarize the clinical trials and studies on PDT for OSCC and discuss the limitations and future directions of PDT for OSCC, such as the development of novel PSs, nanotechnology, biomarkers, and combination therapies. We hope that this review will help researchers to better understand and utilize PDT for OSCC.

Studies and Clinical Trials on PDT for OSCC

PDT has demonstrated effectiveness in treating OSCC across various study types. In vitro studies allow for controlled experiments to elucidate the mechanisms of action and optimize treatment parameters. These studies have shown that PDT inhibits OSCC cell proliferation in a dose-dependent manner and can induce apoptosis (programmed cell death).[18,19] In vivo models, often utilizing animal models with induced OSCC, further evaluate the efficacy and safety of PDT in a more complex environment that mimics the human body. Here, researchers can observe the impact of PDT on factors like tumor blood flow, the immune system, and surrounding healthy tissues.[20] Finally, human clinical trials provide the most crucial evidence for the clinical application of PDT. These trials assess the safety, efficacy, and optimal treatment regimens for patients with OSCC.[21–23]

In vitro Studies on PDT for OSCC

In recent years, many studies have investigated the effects of PDT on OSCC cells in vitro, aiming to elucidate the optimal conditions, mechanisms, and outcomes of this therapy. PDT inhibited OSCC cell proliferation in a dose- and time-dependent manner, and cell viability decreased with increasing 5-aminolevulinic acid (ALA) concentration and irradiation time.[24] The focus is on the uptake and accumulation of protoporphyrin IX in OSCC cells, and the phototoxicity and apoptosis induced by PDT in OSCC cells.[25] Research by Pinto et al[26] has found that PDT significantly reduces the viability and migratory ability of OSCC cells, demonstrating its potential application in eradicating OSCC stem cells and inducing their differentiation. Further studies by Olek et al[27,28] suggest that PDT may also influence cancer treatment efficacy by modulating the expression of pro-inflammatory cytokines and the tumor microenvironment. PDT has been shown to increase the secretion of certain cytokines, such as IL-6 and IL-20, which contribute to long-term tumor control and the activation of anti-tumor immunity. Currently, with the emergence of various novel PSs, PDT has exhibited promising therapeutic effects in vitro,[29] demonstrating good biocompatibility without causing significant inflammation or pathological damage to normal tissues, thus offering new insights into the development of more effective treatment strategies.[30]

Despite these encouraging research findings, the clinical efficacy of PDT may be influenced by various factors, including the distribution of PSs within the body, the penetration depth of light, and the complexity of the tumor microenvironment.[31,32] Additionally, while PDT-induced cytokine secretion can enhance anti-tumor immunity,[33,34] it may also trigger adverse inflammatory responses, impacting the safety and efficacy of the treatment. Therefore, rigorous and systematic in vivo studies are needed to validate the efficacy and safety of PDT as research progresses and its application advances.

In vivo Studies on PDT for OSCC

In addition to in vitro studies, animal models are also important means to evaluate the efficacy of PDT in the treatment of OSCC. Animal models can simulate the tumor microenvironment in humans and observe the impact of PDT on tumor blood vessels, immune system and normal tissues, as well as possible adverse effect.[35,36] Research by Zhang et al[37] has demonstrated that during the PDT process, the PS under in vitro laser irradiation enhances the cytotoxicity of T-cells and inflammatory factors. This not only aids in preventing tumor development but also strengthens the tumor immune microenvironment, which is consistent with the conclusions of previous in vitro experiments. In vivo experiments further illustrate the points above. PDT can achieve complete or partial remission of OSCC in animal models, extend the survival period of animals, reduce the recurrence rate of tumors, induce apoptosis and autophagy of tumor cells, activate the immune system, and inhibit proliferation and metastasis of tumor cells.[38] However, animal models still have shortcomings. For the commonly used animal model, hamster cheek pouch model,[39] there is no corresponding organ in humans, which cannot reflect the situation of cancer in humans well; mice have low immune function, and the interaction between host immune cells and cancer cells is difficult to observe. Despite this, PDT has been proven to be useful in the treatment of OSCC in animal models, but further clinical trial results are needed to confirm that PDT has an efficacy in OSCC that can be used for clinical treatment.

Animal models have provided valuable insights into the efficacy of PDT, but there are still significant limitations that cannot be ignored. Firstly, the tumor growth rate and immune response in animal models differ significantly from those in humans, which may lead to lower reproducibility of experimental results in clinical applications. Secondly, the tumor

microenvironment in animal models differs from that in humans, which may affect the actual efficacy of PDT in clinical trials.[40]

Human Clinical Trials on PDT for OSCC

Since the 1980s, PDT has been used as treatment for malignant tumors. Early oral cancer is limited in scope and shallow in depth of invasion, which is conducive to irradiation. The meta-analysis by Jiao Lin et al[41] evaluated the efficacy and safety of PDT for OSCC. The results showed that the CR of PDT for OSCC was 79.9% and the OR was 96.7%, and PDT had a high short-term efficacy for early OSCC. However, the RR of OSCC after PDT was 15.8%, suggesting that close follow-up after PDT treatment is needed for timely detection and treatment of recurrent lesions. In addition, researchers performed a subgroup analysis to investigate the effects of lesion site, PS, light source, radiation exposure and power density on the efficacy of PDT and found that none of these factors had a significant effect on the CR and OR of PDT (Table 1), but did have an effect on the RR. The researchers concluded that PDT is an effective and safe treatment for OSCC, especially for early and small lesions, but it is necessary to select the appropriate PS, light source and dose according to different clinical conditions to achieve the best therapeutic effect. It is also important to be aware of the limitations of PDT, such as the poorer effect on deep and metastatic lesions, and the possible publication bias.

Photodynamic therapy (PDT) not only serves as an independent local therapeutic approach but also can be used in conjunction with surgical interventions and radiotherapy, these combined treatments have demonstrated improved effects against cancer.[60] Vander Poorten et al[61] applied PDT to treat two patients with residual tumor after surgery for squamous cell carcinoma at the base of tongue. Both two patients were disease-free at 42 and 24 months of follow-up respectively, achieved locoregional tumor control, while preserving speech, respiration, and swallowing. PDT can be used as a palliative treatment option when patients refuse or are not suitable for conventional treatments after extensive prior

Table 1 Summary of Clinical Trials on PDT for OSCC

Year	PS	Stage	Patients/Lesion Sites (n)	Complete Response (n, %)	References
2023	Photofrin/ Talaporfin sodium	T1/T2	23	19 (83)	[42]
2022	ALA	T1	34	26 (76)	[22]
2018	Talaporfin sodium	T2/T3/T4	8	6 (75)	[43]
2016	Photofrin	Tis/T1/T2/T3	34	30 (88)	[44]
2016	ALA	–	20	29 (69)	[45]
2013	mTHPC	T1	126	108 (86)	[23]
		T2	30	19 (63)	
2013	Photofrin	T1/T2	18	17 (94)	[46]
2013	mTHPC	T1/T2	4	3 (75)	[47]
		T3/T4	7	2 (29)	
2012	mTHPC	–	20	9 (45)	[48]
2011	mTHPC	T1/T2	145	99 (68)	[49]
2011	Foscan	T1/T2	38	26 (68)	[21]
2011	Foscan	T3/T4	21	1 (5)	[50]
2010	Photofrin	T1/T2	135	129 (96)	[51]
2009	Photofrin	T1	11	10 (91)	[52]
2007	Foscan	T1/T2	20	12 (60)	[53]
2004	mTHPC	–	114	97 (85)	[54]
2003	Foscan	T1/T2	7	7 (100)	[55]
		T3/T4	2	1 (50)	
2001	Photofrin	T1/T2	10	8 (80)	[56]
1997	Foscan	T1/T2	13	6 (46)	[57]
		T3/T4	7	4 (57)	
1991	Photofrin	T1	23	20 (87)	[58]
1987	Photofrin II	T1/T2	8	7 (88)	[59]

treatments have rendered salvage surgery or re-irradiation not feasible. In the study by Lambert et al,[62] 76.9% of patients achieved complete response and 42.3% of patients achieved local control. PDT is a valuable treatment modality that induces durable local control in an important proportion of treated patients. In the palliative treatment, PDT can improve the quality of life of patients with limited remaining treatment options.

Despite showing significant efficacy in the treatment of early and localized OSCC, PDT remains limited in its effectiveness for deep-seated and metastatic lesions.[63] This limitation may be due to insufficient penetration of PSs into deep tissues and the inability of light to effectively reach deep tumor areas. Additionally, tumor angiogenesis and immune evasion mechanisms may also affect the efficacy of PDT.[64] Furthermore, the selection and dosage of PSs need to be individualized based on specific clinical situations to avoid unnecessary damage to normal tissues. Photodynamic therapy will increasingly rely on personalized treatment plans, tailored to the patient's genetic characteristics and the molecular subtype of the tumor, to achieve the best therapeutic outcomes. Meanwhile, the high recurrence rate after PDT suggests the need for close follow-up and possible adjuvant therapies to improve long-term efficacy.

Challenges and Future Directions of PDT for OSCC

Despite the promising results of PDT for OSCC, several challenges limit its widespread application. These challenges can be broadly categorized into limitations of the PSs themselves and difficulties associated with treatment delivery. Additionally, there's a need for further research to optimize treatment protocols and personalize them for individual patients.

The Limitations and Challenges of PDT for OSCC

PDT still faces challenges, which related to the performance of PS, such as the lack of specific targeting of tumors and poor stability.[65,66] The first-generation PS is Hematoporphyrin Derivative, which has achieved certain clinical efficacy, but still has shortcomings such as insufficient targeting accuracy, weak penetration ability, and large toxic side effects. The second-generation PS overcomes many of the shortcomings. The third-generation PS combines a PS with a carrier which acts as a targeted localization and alters the properties of the PS to facilitate the PS to reach the target tissue for more precise PDT therapy.[67] Light with a wavelength of about 635 nm is now widely used in clinical practice. Due to the shallow tissue penetration depth, the PDT treatment depth is limited, which is only effective for superficial lesions.[68] The efficacy of PDT is also affected by the oxygen concentration in the tumor tissue. OSCC is usually in a hypoxic state, which means that the oxygen concentration in the tumor tissue is lower than that in normal tissue.[69] This is caused by factors such as the rapid growth of the tumor, imperfections in the vascular system, and so on. In addition, PDT itself also consumes oxygen in the tumor tissue, further aggravating the hypoxia problem. Therefore, how to increase the oxygen concentration in the tumor tissue is the key to improve the PDT effect.

Unlike other parts of the body, photodynamic therapy (PDT) in the oral cavity is affected by the oral environmental factors. There are many important, sensitive and vulnerable structures in the oral cavity. PDT usually requires attention to protect normal tissues and organs, to avoid unnecessary damage or complications. Some adverse reactions may occur after PDT treatment in the oral cavity, such as burns, edema, ulcers, bleeding, dysfunction, etc. Damage of the oral anatomical structure may easily affect the patient's oral function and quality of life. Saliva in the mouth may cause the reduction of PS concentration, low efficiency of PDT, and also affect the irradiation of light source.

Currently, there is no unified standard or guideline to guide the PDT treatment process for OSCC. The efficiency of PDT is affected by various factors, such as the choice and dosage of PS, the nature and intensity of the light source, and the duration of irradiation. Different research centers and clinical institutions may adopt different PDT protocols, resulting in less comparable and reproducible results. In addition, the lack of standard procedure may leave patients feeling uncertain and anxious, which may affect their decision-making and acceptance.

Possible Solutions to Overcome These Challenges

Some strategies have been proposed to improve the efficiency of PDT (Figure 1). Nanotechnology-related PDT enhancement strategies are currently a hotspot. For instance, the design and preparation of PS can be modified by utilizing nanomaterials as carriers or enhancers,[70] aims to enhance the properties and targeting of PSs,[71] and make it more suitable for oral cavity. Additionally, several strategies have been proposed to resolve the issue of inadequate light

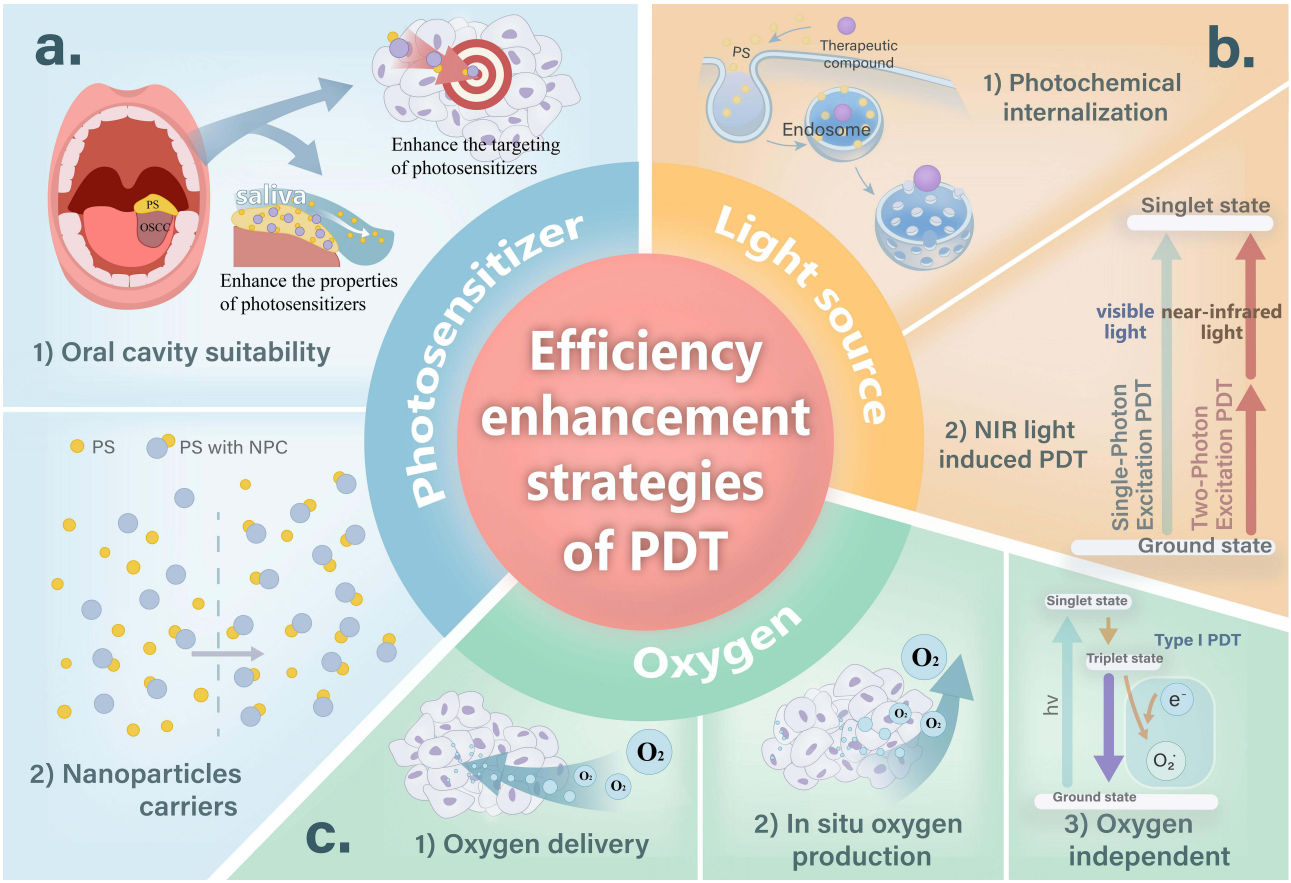


Figure 1 Efficiency enhancement strategies of PDT for OSCC. (**a**) PS. (1) enhance the oral cavity suitability: On the one hand, by improving the PS properties such as persistence, so that it can resist the washing effect of saliva or prevent being swallowed. On the other hand, by improving the targeting of PSs, the side effects of PS on healthy tissue can be reduced, thus improving the efficacy of PDT. (2) Nanotechnology in PDT: multifunctional nanoparticles with PSs. (**b**) Light source. (1) PCI: based on the PS distributed in phagosomes, the compartmentalized macromolecules within the phagosomes are released under light-induced sensitization, allowing various biological macromolecules that are not easily permeable across the plasma membrane to enter the cytoplasm from the phagosomes. (2) NIR light induced PDT: the PS simultaneously absorbs two low-energy photons, transitioning to singlet state, which then generates a PS in the excited triplet state. This molecule undergoes energy transfer with ground-state oxygen to produce $^1O_2$. (**c**) Oxygen. Three main strategies of oxygen enhancement in PDT: (1) exogenous oxygen delivery: using hyperbaric oxygen chamber or carrier systems to deliver oxygen directly to the tumor to increase the local oxygen concentration and enhance the effect of PDT. (2) in situ oxygen production: using PS or catalyst capable of decomposing peroxides or water to produce oxygen under light irradiation. (3) oxygen-independent treatment: adopting the Type I photosensitization mechanism to avoid oxygen restriction.

Abbreviations: PDT, photodynamic therapy; PS, photosensitizer; NIR, near Infrared.

source penetration. Combining PS with two-photon absorbing materials allows for two-photon excitation in the near-infrared (NIR) range and facilitates deep tissue penetration. Photochemical Internalization (PCI) facilitates the surmounting of a principal obstacle to the efficacious delivery of therapeutic molecules: the membrane barrier of the endocytic vesicles. The PSs, which localize within these vesicles, initiate photochemical reactions upon light activation, resulting in the destruction of the endocytic membranes via ROS, and the liberation of the entrapped drugs into the cytoplasmic matrix. To solve the problem of hypoxia, one method is to directly deliver exogenous oxygen directly to the tumor, such as by hyperbaric oxygen therapy or by applying carrier systems to carry oxygen to the tissue. Another method is to generate oxygen in situ, such as by using PSs or catalysts that have the ability to decompose peroxides or water. Besides, using oxygen-independent type I photosensitization mechanism can avoid oxygen limitation.[72] These strategies provide new ideas and methods to improve the efficiency of PDT and expand its application range.

There are unique structures in the oral cavity, PDT should be performed with protection for normal tissues. Additionally, the administration method should have high localization and persistence, which can keep the PS at the lesion site for a long time, and avoid being washed by saliva or swallowed.[73,74] Lastly, a standard PDT procedure for OSCC needs to be developed to ensure the quality and efficacy of the treatment. This requires based on a large number of clinical trials and evidence-based medicine to formulate reasonable PDT parameters and steps, and take into account the

individual differences of different patients and tumors. The long-term efficacy and complications of PDT for OSCC also need to be monitored and evaluated to improve the safety and efficacy of PDT for OSCC.

In the future, standardized guidelines for PDT in OSCC should be established to provide clinicians with uniform treatment standards. These standardized guidelines will facilitate the widespread clinical application of PDT in OSCC, helping doctors choose the most appropriate PDT protocols and thereby improving efficacy. Additionally, the introduction of guidelines will help reduce potential side effects, enhancing patients' quality of life. Furthermore, standardized guidelines across countries will promote international collaboration, enabling researchers to compare different protocols and advance the clinical application and innovation of PDT technology. The formulation of standardized guidelines requires the collaboration of clinicians, researchers, medical organizations. By developing and implementing standardized guidelines for PDT in OSCC, we can anticipate more effective and safer treatments in the future, benefiting more patients.

Recent Advances of PDT for OSCC

The development of novel PSs may contribute to the application of photodynamic therapy in oral cancer.[75] PDT in the oral cavity is mainly used for local lesions. The tissues in the oral cavity are more accessible, and PSs are usually administered by local application or injection, thereby lowering the systemic side effects. Saliva in the mouth may cause the reduction of PS concentration, low efficiency of PDT, and also affect the irradiation of light source. Therefore, PSs should possess high localization and persistence, which can keep their concentration at the lesion site for a long time, and are resistant to being washed by saliva or swallowed. On the other hand, appropriate PS, light source, and irradiation time also should be chosen to improve the efficiency of PDT.

The application of nanotechnology in PDT is currently a research focus. Nanomaterials, due to their excellent properties, have been extensively studied for use in targeted delivery systems.[76,77] These systems can increase the local drug concentration at tumor sites, reduce toxicity to normal tissues, minimize side effects, and amplify the efficacy of PDT.[69] Nanoparticles have demonstrated great potential to address the major challenges of PDT through enhancing targeted delivery into specific tissues and reach into deeper regions, or ameliorating hypoxic conditions.[78,79] This new technology has great potential to revolutionize PDT and bring it to the forefront of cancer treatment in the near future. NPs can have two main functions in PDT: 1) active participants that stimulate PSs, and 2) passive carriers that deliver PSs. An example of the former is self-lighting photodynamic therapy, a technique combines nanoparticles that exhibit luminescence and scintillation properties when they are subjected to ionizing radiation with PDT, the scintillation luminescence of the nanoparticles activates the PS. Ionizing radiation penetrates deeper than visible light, providing a possible way to treat deep tumors more effectively. Zhang et al[80] loaded salvianolic acid B (Sal B) and 5-ALA on a nano-PS, which performed better in generating singlet oxygen than nano-Sal B and nano-ALA. As an illustration of a secondary function, the research by Tao Y[81] constructed dandelion-like size-shrinkable nanoparticles, serving as carriers for the targeted tumor delivery of the hypoxia-regulating agent resveratrol and the photodynamic therapy agent chlorin e6. These nanoparticles are capable of targeted accumulation within tumors. Resveratrol inhibited cellular oxygen consumption, thereby providing ample oxygen to activate the production of ROS, which augments the effect of photodynamic therapy, demonstrating promising prospects for the treatment of oral squamous cell carcinoma.

Passive targeting drug delivery systems are more commonly studied, and various nanoparticles encapsulating PSs have been synthesized and proven to have good therapeutic effects. Liao et al[82] synthesized Lipo-ICG particles using membrane filtration technology, achieving an ICG encapsulation efficiency of 81.74%. The results showed that SAS-LN cells effectively internalized Lipo-ICG, and significant apoptosis was observed after PDT. This demonstrates the broad prospects of nanoparticles as carriers. An example of passive targeting drug delivery systems is the use of the enhanced permeability and retention (EPR) effect to promote the specific accumulation of PSs in tumors. The EPR effect refers to the phenomenon that large molecules or particles in circulation accumulate in tumor tissues due to the high permeability of tumor vessels and the low reflux of the lymphatic system. Although the EPR effect has been shown to have expected outcomes in preclinical in vitro studies, some issues are still need to be addressed. Some early tumors may not have a significant EPR effects, because their vascular systems are relatively normal. The EPR effect relies on blood perfusion and vascular permeability, while these factors are influenced by various tumor growth, treatment, hypoxia, etc., which

may lead to uneven distribution of nanomedicines in tumors. In addition, the advantages of the EPR effect showed in animal models have not been fully validated in human clinical trials, which may cause by the significant differences between animal models and human tumors.

The rapid proliferation of tumors results in higher concentrations of H_2O_2 in tumor cells compared to normal tissues,[83] making it a potential substrate for oxygen production within tumors. Lots of studies have focused on utilizing catalyst-loaded nanocarriers to decompose H_2O_2, thereby enhancing the oxygen supply required for PDT, leading to the development of in situ oxygen generation strategies. Upon delivery to the tumor site, these drugs react with oxygen-containing compounds such as H_2O_2 or H_2O in the tumor microenvironment to produce oxygen. Zhu et al[84] synthesized fluorinated chitosan-chlorin e6 (FC-Ce6) and combined it with catalase to form stable nanoparticles. These nanoparticles effectively delivered catalase to tumor cells, significantly increasing intracellular oxygen levels and mitigating tumor hypoxia. Both in vitro and in vivo experiments demonstrated their high anticancer efficacy and low toxicity.

PCI is a novel intervention derived from PDT, which enables the release of endocytosed macromolecules into the cytoplasmic matrix. Both in vitro and in vivo models have demonstrated that PCI can enhance the effect of various types of macromolecules and some small molecule anticancer drugs.[85] In a study by Ahmed A Sultan et al.[86] University College London Hospital performed a first-in-human trial, enrolling 22 patients with advanced malignancies. The study was designed and conducted as an open, Phase I dose escalation study to assess the safety and tolerance of disulfonated tetraphenyl chlorin (TPCS2a - PS) mediated photochemical internalization with bleomycin as the chemotherapeutic agent. The results indicated that TPCS2a was a safe and tolerable PS for all patients. TPCS2a-mediated bleomycin PCI may provide an effective and localized anticancer therapy, as it combines the synergistic action of photodynamic and chemotherapeutic treatments. Significant antitumor effects were observed with all doses tested on several different types of tumors in patients with a life expectancy of no more than a few months, but some of them still survived four years after the end of the trial.

PDT involving the PSs which can absorb either one photon in the UV-Vis range or two photons in the NIR range,[87] which offers a new opportunity for PDT to treat lesions that are otherwise inaccessible.[88] Liu et al[89] synthesized four types of ruthenium (II) polypyridyl complexes as two-photon absorption PSs. These complexes showed negligible toxicity in the absence of light, but they were highly effective in killing cancer cells under near-infrared TPE.

Biomarkers are substances or signals that can reflect the biological state or disease process of an organism. In order to optimize and personalize PDT protocols, finding and utilizing biomarkers can be an important step. For example, vascular endothelial growth factor (VEGF) and hypoxia-inducible factor-1α (HIF-1α) are biomarkers related to tumor angiogenesis and hypoxia in oral cancer tissues, and their expression levels in oral cancer tissues can predict the cytotoxicity of PDT to tumors.[90] By detecting these biomarkers, we can stratify patients according to the risk of disease recurrence or progression, and provide them with more personalized PDT treatment. At the same time, we can also identify patients who may benefit from PDT or have adverse reaction risks, and guide the selection of appropriate PDT protocols, avoiding unnecessary damage or waste. However, due to the complexity of tumor development and patient heterogeneity,[91] a single diagnostic biomarker has limited effectiveness in cancer diagnosis.[92] In fact, a comprehensive patient assessment may require the integration of multiple omics approaches to enhance its reliability and specificity.

Conclusions

PDT presents a promising minimally invasive and safe alternative or adjunctive treatment modality for treating OSCC. Clinical trials and studies have shown its effectiveness in achieving local tumor control and potentially improving patient quality of life. However, limitations such as PS performance, light penetration depth, tumor hypoxia, and challenges specific to the oral cavity require further optimization. Currently, research in the field of PDT for OSCC has shifted towards investigating the mechanisms of photodynamic therapy and exploring strategies to enhance its efficacy. Ongoing research in PS development, nanotechnology, combination therapies, and biomarker identification offers exciting possibilities to overcome these limitations. Nanotechnology enhances the performance of PSs, reducing damage to healthy tissues. However, the mechanisms by which they enter tumors and exert their effects remain unclear.[93,94] Understanding these mechanisms is crucial for optimizing the design of nanomedicines, ensuring targeting accuracy, and improving safety. Nanoparticles may accumulate in the body over time, necessitating further pharmacokinetic and toxicological studies to confirm their safety.[95] The identification and application of biomarkers can aid in real-time monitoring of therapeutic responses, optimizing treatment

plans, and achieving personalized precision medicine.[96] Advances in genomics, proteomics, metabolomics, immunomics, and microbiomics have expanded our understanding of OSCC progression, further facilitating biomarker discovery. Photodynamic therapy is expected to become a more effective and widely used cancer treatment method in the future. Standardization of PDT protocols will also be crucial for ensuring consistent and optimal treatment delivery.

Overall, although PDT shows great potential in the treatment of OSCC, its clinical application still requires further optimization and validation. Further high-quality clinical trials are needed to confirm the long-term efficacy of PDT for OSCC. Currently, the clinical guidelines for oral cancer treatment primarily recommend surgery combined with radiotherapy and chemotherapy as the mainstream treatment methods.[97–99] However, it is noteworthy that PDT has been approved by the FDA for the treatment of diseases[100,101] such as esophageal cancer and lung cancer. Subsequently, many countries have approved PDT for various indications,[102] laying the foundation for its application in OSCC treatment. With continuous technological advancements and in-depth clinical research, the potential of PDT in oral cancer treatment will be further explored and validated. We have reason to believe that in the future, PDT will become an important modality in the treatment of oral cancer, bringing more hope and better therapeutic outcomes for patients. By addressing these challenges and capitalizing on advancements, PDT has the potential to become a valuable tool in the fight against OSCC, improving patient outcomes and quality of life.

Abbreviations

OSCC, oral squamous cell carcinoma; PDT, photodynamic therapy; ROS, reactive oxygen species; OPMD, oral potentially malignant disorder; 5-ALA, 5-aminolevulinic acid hydrochloride; CR, complete response; RR, recurrence rate; OR, overall response; PS, photosensitizer; NIR, near Infrared; PCI, photochemical internalization; NP, nanoparticle; EPR, enhanced permeability and retention effect; TPE, two-photon excitation; VEGF, vascular endothelial growth factor; HIF-1α, hypoxia inducible factor-1α.

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Disclosure

The authors declare that they have no competing interests.

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