Advances in the Management and Treatment of Feline oral squamous cell carcinoma (FOSCC)

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Abstract

The Feline oral squamous cell carcinoma (FOSCC) is a pervasive malignancy in domestic cats, renowned for its rapid progression, invasiveness, and traditionally bleak prognosis due to limited treatment options. However, recent advancements in diagnostics and treatment modalities provide promising avenues for improving disease management and patient outcomes. This paper reviews these developments, concentrating on diagnostic techniques, therapeutic strategies, and emerging targeted therapies, with an emphasis on the importance of a multidisciplinary approach. Advanced imaging modalities, including computed tomography (CT) and magnetic resonance imaging (MRI), have proven crucial for accurate disease staging by facilitating visualization of tumor extent, lymph node involvement, and potential metastasis. Coupled with molecular diagnostics such as polymerase chain reaction (PCR) and immunohistochemistry (IHC), they enable identification of molecular markers indicative of aggressive behavior and potential therapeutic targets, thus aiding in personalized treatment planning. Therapeutic advances range from enhancements in surgical techniques like laser ablation and microvascular reconstruction to innovative radiation therapy protocols such as intensity-modulated radiation therapy (IMRT). While systemic chemotherapy remains a challenge due to drug resistance and toxicity, exploration of new drug combinations and formulations strives to enhance response rates and limit adverse effects. Emerging targeted therapies, including epidermal growth factor receptor (EGFR) inhibitors, immune checkpoint inhibitors, and photodynamic therapy (PDT), are gaining momentum in the FOSCC landscape. EGFR inhibitors and immunotherapies aim to impede tumor growth and boost host immune response respectively, while PDT presents as a minimally invasive therapeutic option inducing localized cytotoxicity.

Keywords: Atomic Layer Deposition (ALD), Li-ion batteries, Electrolyte coatings, Cathode materials, Anode materials

Introduction

Feline oral squamous cell carcinoma (FOSCC) is a prevalent and particularly aggressive form of neoplasm commonly seen in the oral cavity of domestic cats [1]. Characterized by the abnormal proliferation of squamous cells - the thin, flat cells lining the oral mucosa - FOSCC forms invasive lesions, often arising from the gingiva, tongue, and tonsils. Despite its commonality, the etiology of FOSCC remains poorly understood. Various risk factors have been proposed, including exposure to environmental tobacco smoke, a diet primarily consisting of canned food, and advanced age. Genetic predispositions might also play a part, as certain breeds such as Siamese cats appear to have a higher susceptibility to the disease.

From a clinical perspective, FOSCC often presents with non-specific signs, making early detection challenging. Symptoms can range from difficulty eating, drooling, and oral bleeding to facial swelling and weight loss. Upon clinical examination, oral masses or ulcers are commonly observed. Diagnosis is typically confirmed through histopathological examination following a biopsy of the oral mass. Cytology, radiography, and computed tomography (CT) scans can also aid in determining the extent of the disease and the presence of any metastases, particularly in the regional lymph nodes or lungs, which are common sites of FOSCC dissemination.

The inherent invasiveness and rapid progression of FOSCC are significant factors contributing to its dismal prognosis. The tumor tends to invade surrounding bone structures, including the mandible and maxilla, leading to a high rate of local recurrence following surgical intervention. Moreover, its aggressive nature means that by the time of diagnosis, FOSCC has often already metastasized, reducing the efficacy of localized treatment options and further limiting the cat's life expectancy. Most cats diagnosed with FOSCC unfortunately succumb to the disease within one year.

Currently, treatment for FOSCC primarily includes surgical resection, radiation therapy, and chemotherapy, alone or in combination [2]. However, due to the tumor's aggressive nature and propensity to invade surrounding tissues, complete surgical excision is often not feasible. Radiation therapy can palliate symptoms, but it usually does not provide a curative effect due to the radioresistant nature of the tumor. Chemotherapy, on the other hand, has limited success as FOSCC tends to be chemoresistant. Consequently, even with aggressive treatment protocols, the overall survival time remains short.

Recent advancements in diagnostic methods for feline oral squamous cell carcinoma (FOSCC) have started to transform our understanding and management of this aggressive disease. One of the significant advancements has been the utilization of molecular diagnostics, such as PCR-based techniques, to detect and quantify unique genetic or epigenetic changes associated with FOSCC. Additionally, advanced imaging techniques such as cone-beam computed tomography (CBCT) and positron emission

tomography (PET) scans have shown potential in providing more detailed information about the tumor's extent, helping to guide treatment decisions more effectively.

Furthermore, developments in the area of liquid biopsy hold significant promise in the early detection and monitoring of FOSCC. This non-invasive diagnostic technique involves the detection of circulating tumor DNA (ctDNA) in the blood, offering the potential for early identification of the disease and monitoring of treatment responses. In the same vein, the field of proteomics is emerging as a useful tool in the identification of biomarkers that can provide valuable information regarding disease prognosis and therapeutic response [3], [4].

On the therapeutic front, immunotherapy has emerged as a promising new treatment modality for FOSCC. Utilizing the cat's own immune system to fight cancer, immunotherapies such as immune checkpoint inhibitors can potentially improve survival rates and quality of life. For example, therapies that inhibit programmed cell death protein 1 (PD-1) or its ligand, PD-L1, could restore the ability of the immune system to recognize and destroy cancer cells. Although these treatments are still in the experimental stages for cats, they have shown promise in initial studies.

Another recent development in the treatment of FOSCC is the application of targeted therapy. This approach uses drugs that are designed to specifically interfere with certain molecular targets that play a crucial role in the growth, progression, and spread of cancer. Some of these targeted therapies include tyrosine kinase inhibitors and monoclonal antibodies. For example, the use of small molecule inhibitors that target growth factor receptors implicated in FOSCC could offer a way to halt the progression of the disease [5].

Lastly, nanotechnology-based drug delivery systems are offering new hope in the treatment of FOSCC. By leveraging nanoscale particles to deliver therapeutic agents directly to the tumor site, these technologies can increase drug efficacy while minimizing systemic side effects. Liposomes and polymeric nanoparticles, for instance, can be designed to encapsulate chemotherapy drugs, enhancing their accumulation at the tumor site while reducing their distribution to healthy tissues. This is especially pertinent in FOSCC treatment, where conventional chemotherapy often yields minimal success due to the chemoresistant nature of the disease.

Diagnostic Techniques

The role of advanced imaging in managing feline oral squamous cell carcinoma (FOSCC) is pivotal, with computed tomography (CT) and magnetic resonance imaging (MRI) being the most prevalent techniques. These methods have considerably enhanced the accuracy of tumor staging, allowing for more detailed evaluation of the tumor, the involved regional lymph nodes, and any potential metastases [6], [7].

CT, with its ability to generate cross-sectional images of the body, has emerged as a critical tool for imaging FOSCC. It provides excellent detail of bony structures, making it the preferred modality for identifying and assessing tumor invasion into the mandible or maxilla. This imaging technique also enables the detection of regional lymph node involvement, which can be an important prognostic factor. Moreover, CT can help evaluate the lungs for metastases, which are common in advanced cases of FOSCC. The detail provided by CT imaging facilitates precise surgical planning and allows for the assessment of the feasibility of surgical resection.

MRI, on the other hand, is particularly valuable in providing superior soft tissue contrast. This capability makes it ideal for visualizing the extent of tumor infiltration into the surrounding soft tissues and neurovascular structures, which are critical parameters when planning for surgery or radiation therapy. MRI also enables the identification of lymph node involvement and distant metastases, particularly in structures not readily visualized on a CT scan.

Additionally, cone-beam computed tomography (CBCT) has shown promise in offering a lower-cost, lower-radiation alternative to traditional CT for imaging of FOSCC. It provides high-resolution, three-dimensional images, particularly of bony structures, making it useful in surgical planning. Furthermore, positron emission tomography (PET) scans, in conjunction with CT or MRI, have started to be utilized. PET scans can provide functional imaging, identifying areas of increased metabolic activity that often correlate with malignancy, thereby further aiding in the detection of FOSCC and potential metastases [8], [9].

Molecular diagnostics have revolutionized the field of veterinary oncology by providing an in-depth understanding of the underlying pathophysiology of diseases like feline oral squamous cell carcinoma (FOSCC). Two primary tools used in this context are polymerase chain reaction (PCR) and immunohistochemistry (IHC), both of which can identify molecular markers associated with aggressive tumor behavior and potential therapeutic targets [10]. These tools hold the promise of improving prognostication and tailoring more personalized treatment strategies [11].

PCR is a laboratory technique that amplifies DNA, enabling the detection and quantification of specific gene sequences. In the context of FOSCC, PCR can be used to detect genetic mutations or alterations that are associated with the disease. For instance, certain mutations or gene expression changes may be associated with an increased risk of metastasis or resistance to specific treatments. By detecting these genetic changes, PCR can provide valuable information about the tumor's likely behavior and how it may respond to different therapies. This information can then be used to guide the selection of treatment strategies that are most likely to be effective for the individual cat.

Immunohistochemistry (IHC) is another vital tool in the molecular diagnostics arsenal. IHC involves the use of antibodies to detect specific proteins within a tissue sample, providing information about the biological behavior of the tumor. For FOSCC, IHC can be used to identify protein markers that are associated with aggressive behavior or poor prognosis, such as certain growth factors or cell cycle regulators. Moreover, IHC can reveal the presence of potential therapeutic targets, such as specific receptors or proteins that can be blocked or inhibited by targeted therapies. This can help in the development of personalized treatment plans that specifically target the unique characteristics of the cat's tumor [12].

In addition, the combination of PCR and IHC can provide a more comprehensive view of the molecular landscape of FOSCC. The genetic information obtained from PCR can be complemented by the protein expression data from IHC, enabling a more thorough understanding of the disease at the molecular level. This integration of multiple diagnostic tools can enhance the prediction of disease progression and treatment response, allowing for the optimization of therapeutic strategies [13].

The advancements in molecular diagnostics are rapidly transforming the management of FOSCC. As our understanding of the molecular markers associated with this disease continues to grow, so too does the potential for improved prognosis and personalized treatment plans. By unlocking the genetic and protein secrets of FOSCC, these diagnostic tools are paving the way for a more tailored and effective approach to managing this challenging disease.

Therapeutic Strategies

Surgical intervention, specifically wide surgical excision, has long been the cornerstone of feline oral squamous cell carcinoma (FOSCC) treatment. The goal of the procedure is to completely remove the tumor and a portion of the surrounding healthy tissue, thus achieving negative margins. However, due to the aggressive nature of FOSCC and its propensity to invade surrounding structures, achieving these negative margins can be challenging [14]. Recent advances in surgical techniques, including laser ablation and microvascular reconstruction, have improved the feasibility of this procedure while preserving the functional integrity of the oral cavity [15].

Laser ablation has emerged as a viable surgical technique in managing FOSCC. This procedure employs a high-intensity light beam to destroy the tumor cells. The advantages of using laser ablation include precise cutting with minimal damage to surrounding tissues, reduced bleeding due to its cauterizing effect, and less postoperative pain and swelling. It is particularly beneficial in locations where traditional surgical techniques might struggle, such as areas with complex anatomy or difficult access. However, laser ablation requires specialized training and equipment, and it may not be suitable for larger tumors.

Microvascular reconstruction is another promising advancement in FOSCC surgery. Following wide surgical excision, which often involves removing a significant portion of the jawbone, microvascular reconstruction can be used to restore the anatomical structure and function. This technique involves transplanting a piece of vascularized bone, usually from the fibula or the radius, to replace the removed jawbone section. The transplanted bone's blood vessels are then anastomosed, or connected, to vessels in the neck using microsurgical techniques. This approach can significantly improve the cat's quality of life post-surgery by restoring its ability to eat and drink normally [16], [17].

Radiation therapy plays a crucial role in the management of feline oral squamous cell carcinoma (FOSCC), particularly in cases where surgical resection is not feasible or complete surgical margins cannot be achieved. One significant development in radiation therapy is the use of intensity-modulated radiation therapy (IMRT). This technology allows for precise delivery of radiation doses to the tumor while minimizing damage to the surrounding healthy tissues.

IMRT works by adjusting the intensity of the radiation beams in multiple small volumes, known as beamlets. The radiation dose across each beamlet can be individually tailored based on the tumor's shape and location. This high level of precision is achieved using computer-controlled linear accelerators that deliver radiation from different angles. As a result, IMRT allows for a high dose of radiation to be delivered to the tumor while minimizing exposure to surrounding normal tissues, reducing the risk of radiation-induced side effects.

Concurrent chemotherapy and radiation therapy (CCRT) is another strategy gaining traction in the management of FOSCC. The principle behind CCRT is that certain chemotherapy drugs can act as radiosensitizers, making the cancer cells more susceptible to the damaging effects of radiation. This strategy can enhance local control of the disease and potentially improve survival rates. It's worth noting, however, that while CCRT can increase the effectiveness of treatment, it may also amplify the side effects of both chemotherapy and radiation therapy. Therefore, careful patient monitoring is required to manage potential side effects and ensure the cat's quality of life is maintained [18].

While traditional radiation therapy often involved a series of daily treatments over several weeks, advancements have also led to the development of stereotactic body radiation therapy (SBRT). SBRT delivers highly targeted radiation in fewer but higher-dose treatments, often improving convenience and reducing stress for both the cat and the owner. It requires advanced imaging techniques for precise tumor localization and sophisticated systems to immobilize the patient, ensuring accurate radiation delivery [19].

Chemotherapy, a systemic treatment modality, has traditionally been a part of the therapeutic arsenal against feline oral squamous cell carcinoma (FOSCC). However, its

efficacy is often limited due to inherent or acquired drug resistance and a range of adverse effects. Platinum-based agents, like cisplatin and carboplatin, have been the mainstay of systemic chemotherapy in treating FOSCC. While they can sometimes offer temporary control of the disease, complete responses are rare, and these agents often come with significant side effects like kidney toxicity, gastrointestinal upset, and bone marrow suppression.

Recognizing these challenges, researchers are actively investigating novel drug combinations and formulations to improve response rates and minimize toxicity. For instance, combining chemotherapeutic agents with different mechanisms of action might enhance their anticancer effects while potentially overcoming drug resistance. Studies are ongoing to identify synergistic drug combinations that can effectively kill cancer cells while sparing healthy ones, improving the overall therapeutic index.

Simultaneously, significant strides are being made in the development of novel drug formulations. Nanotechnology-based drug delivery systems, such as liposomes and polymeric nanoparticles, are being explored. These systems can encapsulate chemotherapeutic drugs, enhance their solubility, prolong their circulation time in the body, and facilitate targeted delivery to the tumor site. This targeted delivery minimizes the exposure of healthy tissues to the drugs, thereby reducing systemic side effects.

Moreover, metronomic chemotherapy, which involves the administration of low doses of chemotherapy drugs over an extended period, is gaining attention as a potential treatment strategy. The idea behind metronomic chemotherapy is to inhibit angiogenesis, the process by which tumors develop their own blood supply. By continuously exposing the tumor to low doses of chemotherapy, angiogenesis can be disrupted, potentially starving the tumor of nutrients and slowing its growth [20], [21].

Emerging Targeted Therapies

Epidermal Growth Factor Receptor (EGFR) is a protein found on the surface of cells, including cancer cells, where it plays a crucial role in regulating cell growth and division. Overexpression of EGFR is a common characteristic in various cancers, including feline oral squamous cell carcinoma (FOSCC), and is often associated with aggressive tumor behavior and poor prognosis. The association between EGFR overexpression and FOSCC has led to a growing interest in the development and use of EGFR inhibitors as a targeted therapy for this disease.

EGFR inhibitors, such as gefitinib and erlotinib, are drugs designed to block the signaling pathways of EGFR, thereby impeding tumor growth. By binding to the ATP-binding site of the receptor, these inhibitors prevent the activation of downstream signaling pathways that promote cell proliferation and inhibit apoptosis, or programmed cell death. As a result, the use of EGFR inhibitors can potentially slow or halt the growth of the tumor, and may even induce tumor shrinkage in some cases.

Gefitinib and erlotinib, originally developed for human cancers, are being explored for their efficacy in treating FOSCC. Preliminary studies have shown that these drugs can inhibit the growth of FOSCC cells in vitro, suggesting potential therapeutic benefits. However, these findings need to be validated in clinical trials to assess their efficacy and safety in the feline population.

One of the key advantages of EGFR inhibitors is their targeted mechanism of action, which can potentially minimize the damage to healthy cells and tissues often associated with traditional chemotherapy. However, like all therapeutic agents, they come with their own set of side effects, including gastrointestinal upset and skin reactions, and not all tumors expressing EGFR will respond to these inhibitors.

Immunotherapy is a rapidly emerging field in cancer treatment that leverages the body's own immune system to fight against cancer cells. Among the various types of immunotherapies, immune checkpoint inhibitors have shown great promise in treating several types of human cancers and are now being investigated for their potential in treating feline oral squamous cell carcinoma (FOSCC).

Immune checkpoints are proteins that are usually found on the surface of T cells, a type of immune cell responsible for recognizing and eliminating abnormal cells, including cancer cells. Under normal circumstances, these checkpoint proteins play a crucial role in maintaining immune homeostasis by preventing overactivation of the immune system and thus protecting normal cells from immune-mediated damage. However, some cancer cells have found a way to exploit this system to evade immune detection by overexpressing these checkpoint proteins, thereby putting a "brake" on the immune response.

Immune checkpoint inhibitors, such as pembrolizumab and nivolumab, are drugs designed to block these checkpoints, thereby "releasing the brakes" and allowing the immune system to recognize and attack the cancer cells. Pembrolizumab and nivolumab specifically target the programmed cell death protein 1 (PD-1) pathway, one of the key immune checkpoints often manipulated by cancer cells.

Research into the use of immune checkpoint inhibitors in FOSCC is still in the early stages, but initial studies suggest that these drugs could have potential. Like EGFR inhibitors, immune checkpoint inhibitors offer a targeted treatment strategy, aiming to boost the cat's own immune response against the tumor cells, rather than directly killing the cells like traditional chemotherapy. However, these drugs are not without their challenges. They can sometimes overactivate the immune system, leading to autoimmune-like side effects, and their effectiveness can vary widely between individuals.

Photodynamic therapy (PDT) is a unique treatment approach that combines the use of a photosensitizing drug, light, and oxygen to generate a localized cytotoxic effect,

thereby destroying cancer cells. It's emerging as a promising, minimally invasive therapeutic modality for managing various cancers, including feline oral squamous cell carcinoma (FOSCC).

The PDT process begins with the administration of a photosensitizing agent, either systemically or topically. This agent tends to accumulate preferentially in rapidly dividing cells, such as cancer cells. Following a latency period to allow for optimal uptake of the photosensitizer by the tumor cells and its clearance from normal tissues, the tumor area is exposed to a specific wavelength of light. The light exposure activates the photosensitizer, leading to the production of reactive oxygen species (ROS). These ROS can cause direct cytotoxicity, damaging the cancer cells' cellular components and leading to their death. Furthermore, PDT can damage the tumor vasculature, leading to ischemia and subsequent tumor necrosis. It can also stimulate an immune response, recruiting immune cells to the tumor site to enhance tumor cell destruction [22].

The major advantage of PDT is its dual selectivity. The photosensitizing agent has a preference for cancer cells, and the activation light can be accurately directed to the tumor site, thereby minimizing damage to the surrounding healthy tissues. It's a generally well-tolerated treatment modality with side effects often limited to the treated area and usually temporary. However, one significant consideration is the need for the treated patient to avoid strong light exposure for a period after treatment due to the risk of photosensitivity reactions. In the context of FOSCC, PDT holds promise as a potential treatment modality due to its minimally invasive nature and the accessibility of the oral cavity for light exposure [23]. While PDT is unlikely to replace traditional treatments such as surgery, radiation, and chemotherapy, it might offer an additional tool in the multifaceted approach to managing this devastating disease.

Conclusion

Feline oral squamous cell carcinoma (FOSCC) remains a substantial health concern for felines worldwide. As one of the most frequently diagnosed oral neoplasms in cats, FOSCC poses significant therapeutic challenges due to its aggressive, invasive nature and tendency for rapid progression [24]. FOSCC often involves extensive bone destruction, leading to severe pain and a marked decrease in quality of life. This neoplastic disease, which targets the oral cavity, tongue, and pharynx of cats, has been characterized by a poor prognosis, primarily due to the late-stage detection and the limited effectiveness of traditional treatment methods.

Modern veterinary medicine offers an array of diagnostic tools for the identification and staging of FOSCC. These diagnostic techniques range from imaging modalities that provide a detailed visual representation of the tumor and surrounding tissues, to molecular diagnostic tools that enable veterinarians to analyze the tumor's genetic and molecular characteristics.

Advanced imaging modalities have become integral in the initial diagnosis and subsequent monitoring of FOSCC. Computed tomography (CT) and magnetic resonance imaging (MRI) are often used to visualize the full extent of the tumor, any associated soft tissue or bony changes, the involvement of regional lymph nodes, and the presence of potential metastases. CT imaging, which provides high-resolution images of the skeletal structures and soft tissues, is particularly useful in detecting bone invasion - a common feature of FOSCC. MRI, on the other hand, offers excellent soft tissue contrast, making it a valuable tool for identifying lymph node involvement and the exact tumor margins. These imaging techniques provide a comprehensive view of the disease, aiding in accurate staging and facilitating effective treatment planning.

The field of molecular diagnostics has revolutionized the approach to FOSCC, providing tools that enable a deeper understanding of the tumor's genetic and molecular characteristics. Techniques such as polymerase chain reaction (PCR) and immunohistochemistry (IHC) have proven invaluable in identifying molecular markers associated with the disease. PCR, a molecular technique that amplifies specific segments of DNA or RNA, allows for the detection of genetic alterations that may contribute to the development and progression of FOSCC. On the other hand, IHC provides insight into the protein expression patterns within the tumor cells, assisting in the identification of proteins that may serve as therapeutic targets. The information gleaned from these molecular diagnostics aids in determining the prognosis and tailoring personalized treatment strategies, improving the chances of successful disease management.

The current therapeutic arsenal for FOSCC includes surgical intervention, radiation therapy, and chemotherapy. However, the overall efficacy of these strategies is often limited by the tumor's aggressive nature, necessitating continuous exploration for more effective treatment options.

Surgery, primarily in the form of wide excision, has traditionally been the cornerstone of FOSCC treatment. The aim is to remove as much of the tumor as possible, ideally achieving negative margins, where no traces of cancer cells are found at the edges of the removed tissue. Recent advances in surgical techniques, such as laser ablation and microvascular reconstruction, have improved the feasibility of this approach. Laser ablation offers the advantage of precise tumor destruction with minimal collateral damage, while microvascular reconstruction allows for the replacement of removed tissues, enhancing the preservation of the functional integrity of the oral cavity post-surgery.

The advent of modern radiation therapy protocols has revolutionized FOSCC management. Techniques such as intensity-modulated radiation therapy (IMRT) enable the delivery of precise, high-dose radiation to the tumor, while sparing surrounding healthy tissues from unnecessary exposure. Furthermore, the concurrent use of

chemotherapy and radiation therapy (CCRT) has shown promise in enhancing local control of the tumor and improving survival rates. CCRT exploits the synergistic effect of these treatments, where chemotherapy increases the tumor's sensitivity to radiation, thereby enhancing the efficacy of the therapy.

The use of systemic chemotherapy, frequently based on platinum-based agents, in FOSCC treatment has generally yielded limited efficacy due to drug resistance and adverse effects. This has spurred the investigation into novel drug combinations and formulations. The goal is to enhance therapeutic response rates while minimizing the toxicity associated with these agents, potentially improving survival and quality of life for affected cats.

Beyond traditional therapeutic strategies, several novel, targeted therapies are currently under investigation for FOSCC. These therapies seek to exploit specific molecular and immunological characteristics of the tumor, offering a personalized approach to treatment.

EGFR, a protein often found in high levels in FOSCC, is associated with poor prognosis as it promotes tumor growth and invasion. EGFR inhibitors, such as gefitinib and erlotinib, show potential in impeding this pathway. By blocking EGFR, these drugs can potentially inhibit tumor growth, providing a targeted therapeutic option. The field of immunotherapy has shown promise in the treatment of various cancers, with immune checkpoint inhibitors like pembrolizumab and nivolumab leading the way. These agents work by blocking immune checkpoints, proteins that normally prevent the immune system from attacking the body's cells. By inhibiting these checkpoints, the immune system can be unleashed to target and destroy tumor cells. This innovative approach is currently under investigation in FOSCC, with promising early results.

Photodynamic therapy (PDT) is an emerging, minimally invasive therapeutic strategy that combines a light-sensitive drug (photosensitizer) and specific wavelengths of light. When exposed to this light, the photosensitizer within the tumor cells is activated, leading to a localized cytotoxic reaction that destroys the tumor cells. PDT holds promise as a targeted, less invasive therapeutic option for FOSCC, potentially offering improved outcomes with fewer side effects.

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