Review Article

Role of Photodynamic Therapy in the Treatment of Oral Cancer: A Review

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ABSTRACT

Oral cancer is a major public health problem worldwide and is among the ten most common cancers. Despite the advances in research and treatment, oral cancer is still one of the major challenges in medical science. Common treatments for this cancer include surgery, radiotherapy, and chemotherapy, as well as adjuvant photodynamic therapy (PDT). The aim of this study was to evaluate oral cancer and its treatment methods with an emphasis on the use of adjuvant PDT. The present study is a review performed by searching the articles published in the past 20 years (2000-2020) in Elsevier, PubMed, Springer, and Wiley databases with "oral cancer", "photodynamic therapy", and "treatment modalities" keywords. Research shows that PDT can be an effective way to treat oral cancer due to its few side effects and minimal invasion. However, accurate evaluation of the efficacy of PDT requires further studies.

Keywords: Oral Cancer, Tumor, Photodynamic Therapy, Surgery and Radiotherapy

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Introduction:

Oral cancer develops as a result of malignant cell growth in the oral cavity; the affected areas are the lips, tongue, cheeks, floor of the mouth, hard palate, soft palate, and gums.[1] Oral cancer is one of the ten most common cancers in the world with delayed clinical diagnosis, poor prognosis, no specific symptoms, and expensive treatments. This disease is defined as oral squamous cell carcinoma (OSCC). Histologically, in 90% of cases, the source of cancer cells is the squamous tissue of oral cavity surfaces with different levels of differentiation and a tendency for lymph node metastasis.[2] The most important predisposing factors are tobacco, alcohol, diet and nutrition, viruses, ethnicity and race, genetics, thrush, suppression of the immune system, syphilis, and occupational hazards.[3] Common treatments for oral cancer include surgery, radiation therapy, or a combination of radiation therapy, chemotherapy, and surgery. These therapies are effective in treating primary tumors. They are used in advanced cases in the metastatic stage to relieve the patient's pain. These treatments are associated with numerous and significant side effects that affect patients' health and quality of life.[4]The average survival rate for oral cancer is five years. Of course, it is different for patients with different clinical stages. The average survival rate is 81%, 42%, and 17% in regional, zonal, and distant metastatic stages, respectively.[5] Due to its anatomical position, progression, and treatment stages, oral cancer significantly affects the quality of life and causes major functional disorders in swallowing, speech, taste, and appearance.[6] Photodynamic therapy (PDT) is one of the treatment methods for the management of benign tumors. Although PDT may be emerging

and evolving, it is currently a successful, effective, and clinically proven method. PDT consists of three basic components: a light-sensitive composition (PS), a light source, and oxygen. None of these components is toxic alone, but together, they initiate a photochemical reaction and eventually lead to the production of a highly reactive product of single oxygen, leading to selective destruction of tumor cells.[7] PDT promotes successful treatment of oral and laryngeal cancers by preserving normal tissue and vital functions such as speech and swallowing.[8] Studies on the role of PDT in oral cancer treatment showed that PDT could be successful and acceptable in the treatment of primary and superficial carcinomas.[9-13] The aim of this study was to evaluate PDT and its effect on the treatment of oral cancer.

Epidemiology of oral cancer

Oral cancer is a public health problem and is the sixth most malignant neoplasm. About 300,000 cases of oral cancer are reported worldwide each year, with the prevalence in developing countries being higher compared to developed countries. The highest prevalence of oral cancer in men has been recorded in northern India, several regions of Central and Eastern Europe, and Latin America. Women in South and Southeast Asia show the highest prevalence. India, South America, and Oceania have the highest mortality rates. Men are 2 to 3 times more likely to get oral cancer compared to women because of more alcohol and tobacco use and poor oral health. Although the disease has been reported in different age groups, it most often occurs in patients over 60 years of age.[14]

Treatment of oral cancer

In approximately two-thirds of patients, oral cancer is diagnosed in the late stages, leading to extensive treatment and low survival rates. In the early stages of cancer, surgery and radiation therapy are used separately. However, if the disease is in advanced stages, a combination of treatment methods, including surgery, radiation therapy, and chemotherapy, is used.[15]

Surgery

Surgery is the first and most common option for treating oral cancer. Surgery consists of two components: resection and reconstruction. Resection involves the removal of primary tumors and, if necessary, removal of lymph nodes in the neck plus tracheostomy. Reconstructive surgery aims at minimizing the complications of resection through tissue replacement and minimizing swallowing and speech disorders. The goal of surgery is to remove the tumor and a microscopic margin of 5 mm from the normal, healthy tissue around the tumor.[16]

Radiation therapy (radiotherapy)

Radiation therapy alone is not usually the treatment of choice for oral cancers and is only used when the tumor site is inoperable or the patient is reluctant to have surgery. Nevertheless, postoperative radiation therapy is an adjunct therapy in the treatment of oral and head and neck cancers. It is used for the treatment of large primary tumors and symptoms such as vascular and peripheral nerve invasion. This technique is also used to treat neck cancers and prevent metastasis, especially when there is no extracellular spread from the lymph nodes. The purpose of this procedure is to clear the margin of the surgery or to remove the remnants of the tumor. The radiation dose can vary, but typically, the total dose is approximately 60g, and the radiotherapy course is 6 weeks.[17] The basis of radiation therapy is the use of ionizing radiation to kill or damage cancer cells. The most common method used to manage oral cancer is external beam radiation therapy, in which the patient is exposed to high-energy x-rays. These rays target specific locations, and the tumor is treated with minimal damage to surrounding tissues.[16]

Chemotherapy

Chemotherapy has been used to relieve the pain caused by oral cancer. However, with the discovery of new drugs, this method became known as an important treatment method to cure advanced oral cancer. The goal of chemotherapy is to prevent the rapid division of cancer cells to manage tumor spread and metastasis. Chemotherapy can be divided into three categories of induction chemotherapy (before surgery), concomitant chemotherapy (with radiation therapy), and adjuvant chemotherapy (after surgery or radiation therapy).[18] Common drug protocols include cisplatin (cispl atin) and epidermal growth factor inhibitors, such as cetuximab.[16]

Common treatments and their side effects Short-term side effects include pain and difficulty in swallowing and speaking.

Long-term side effects include problems and changes in the patient's appearance, tissue and bone lesions, functional problems, and difficulty in swallowing and speaking.[18]

Short-term side effects of radiation therapy include decreased saliva, mucositis, dysgeusia, increased risk of infections, such as Candida albicans, and trismus. Xerostomia, increased risk of periodontal disease, tooth decay, and osteonecrosis after irradiation are among the long-term side effects of radiation therapy.[18]

Short-term side effects of chemotherapy include nausea, vomiting, and subsequent enamel erosion, mucositis, skin rashes, and increased bleeding. Long-term side effects of chemotherapy include an increased risk of infection, neuropathy, loss of appetite, pulmonary, renal and auditory disorders, and bone marrow failure or suppression.[18]

Photodynamic therapy

Overall, despite the advances in surgery and radiotherapy, the mortality rate and complications of oral cancer have not decreased. Low quality of life, psychosocial effects, and functional disabilities such as tissue complications, dry mouth, mucositis, and fibrosis that occur after conventional oral cancer treatments indicate the need for better treatment options such as PDT.[19] These methods work by inactivating cells, microorganisms, or molecules by the light. This treatment activates a light-sensitive compound (PS) by a light source to produce reactive oxygen species (ROS) and free radicals that selectively destroy rapidly growing cells.[20] PDT is a minimally invasive treatment. Unlike radiation therapy, PDT can be applied repeatedly to the same site. This technique is widely accepted in medicine and is extensively used in the treatment of cancer. Chemotherapy, radiation therapy, and surgery do not avert the use of PDT, and all of these can be used in patients that have been treated with this method. Although PDT is not an alternative to conventional cancer therapy, it is used as a successful and clinically approved treatment for the management and treatment of benign tumors.[21] Some examples of experiments performed on PDT and the results are given in Table 1.The antitumor effects of PDT may be directly due to the death of tumor cells or indirectly due to damage of tumor vessels and activation of specific and nonspecific immune responses against tumor cells. Precancerous lesions affecting the oral mucosa are ideal candidates for PDT because wide areas of the disease can be treated with minimal complications. In this treatment, the collagen and elastin that are required for healthy regeneration are maintained, resulting in patient recovery with minimal damage and excellent functional and aesthetic results.[19]

Different types of photosensitizers (PS) include dyes, chlorines, porphyrins, xanthine, and monoterpene. Common PSs used in PDT include 5-aminolevulinic acid (ALA), methyl 5-aminolevulinate (MAL), methylene blue (MB), photo line, and toluidine blue.[20] Light therapy has been used for several thousand years. In the ancient civilizations of India and China, light therapy was used to treat various diseases. In 1897, the chemical sensitivity of tissues to light was first reported. Finsen, who received the Nobel Prize, used eosin and localized white light to treat skin cancer; he reported the first modern light therapy in 1903. The first PDT was tested in 1976 for bladder cancer. Another study on skin and lung tumors also proved it to be effective in controlling cancer growth. Photofrin, the first PDT reagent, was approved in 1993 for the treatment of bladder cancer. Photofrin is currently approved by the Food and Drug Administration (FDA) for various types of cancer.[22]

The only light-sensitive substance approved for the treatment of advanced SCC of the head and neck is Foscan (temoporfin, meta-tetrahydroxyphenylchlorin).[23]

On the other hand, lasers are ideal for PDT because of their monochromatic light source, and their use in soft tissue therapy is defined as low-power or low-energy laser therapy. [24]Clinical applications of PDT in malignant oral disorders and oral cancer PDT consists of two stages. The first stage involves the injection and accumulation of a light-sensitive substance in rapidly dividing cells. The second stage involves exposing these cells to radiation from a specific wavelength of light that corresponds to the peak absorption of the light-sensitive compound.[20] A summary of the mechanisms of cell death following PDT is shown in Figure 1.

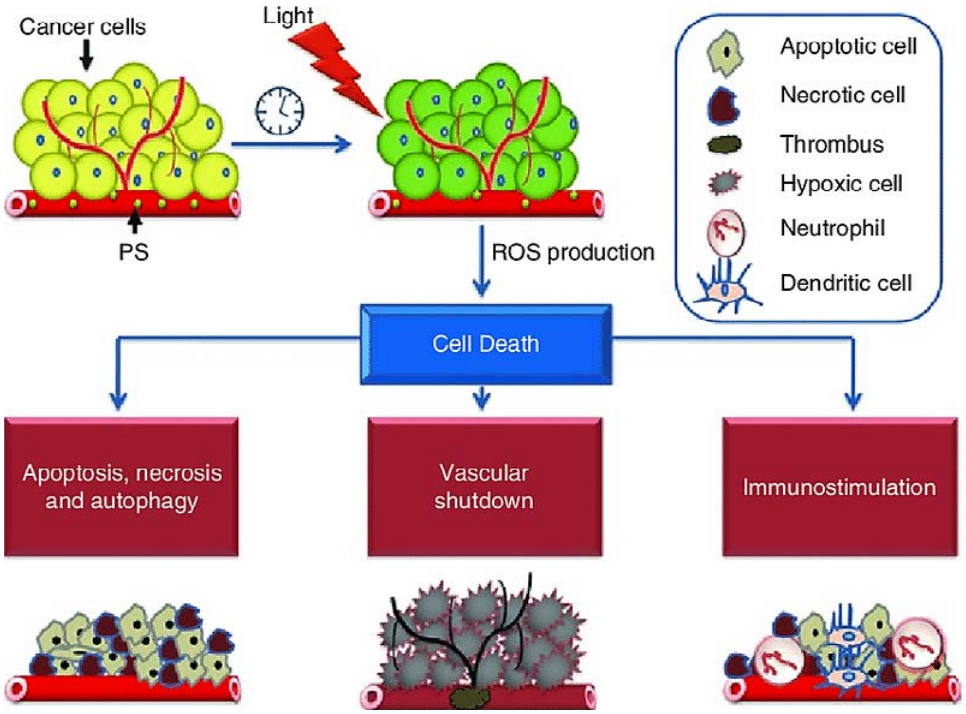

Figure 1. Summary of cell death mechanisms after photodynamic therapy (PDT).

Irradiation of cancer cells leads to the production of ROS in the tumor environment. Direct cell death occurs through apoptosis, necrosis, or sometimes, the process of autophagy. Closure of arteries and subsequent cell death due to hypoxia may also occur.[25]

Advantages of PDT

PDT has several advantages over other conventional therapies:

- It is minimally invasive.
- It does not show systemic toxicity.
- It leads to selective destruction of the tumor while preserving normal tissue.
- It can be used with other treatments without the effect of electrocution.
- Frequent use of PDT is unrestricted.
- It is associated with excellent and acceptable functional and physical results.[26]

Materials and Methods

Search strategy

Elsevier, PubMed, Springer, and Wiley databases of the past 20 years were electronically searched using various combinations of the terms "oral cancer", "photodynamic therapy", and "treatment modalities".

Publication selection

The following selection criteria were applied to all the publications returned by the electronic search to be included in the review.

Inclusion criteria

Inclusion criteria are as follows: (i) papers published after 2001, (ii) use of PDT in oral cancer, (iii) studies carried out all over the world, and (iv) the reported outcome or one of the reported outcomes being oral cancer.

Exclusion criteria

Exclusion criteria are as follows: (i) studies reporting other therapies, (ii) the base of the tongue and salivary gland cancers, (iii) and studies involving laboratory research and molecular/genetic epidemiology.

Quality assessment

All selected publications were assessed for their quality based on the "PDT in the treatment of oral cancer".[27] Studies were ranked as "strong," "moderate" and "weak after being

assessed on six parameters. The authors carried out quality assessments independently, and the results were later compared. Any differences were discussed in the presence of all three authors, and a final decision was reached by consensus.

Results:

Regarding the experiments performed on the use of PDT in the treatment of oral cancer, the research conducted by Durbec et al showed that 93% of patients responded completely to this treatment, and 7% of patients responded partially.[25]

Recurrence was observed in 46.66% of patients. In another study on 25 patients, it was shown that 96% of patients responded completely to this treatment, and 4% responded partially. Recurrence was observed in 12% of patients (Table 1).

Table 1. Some examples of the trials on the use of photodynamic therapy (PDT) in the treatment of oral cancer

Author	Number of patients	Combination of photosensitizer and light source	Number of PDT sessions	Follow-up period	Results
Durbec et al., 2013 (25)	5 patients (10 men and 5 women). Age: 52-97 years	0.15 mg/kg (mTHPC) by intravenous injection. Light source: Diode laser with a wavelength of 652nm and an energy density of 220 J/cm	Once	3-75 months	14 patients (93%) responded completely to this treatment and one (7%) patient responded partially. Recurrence was observed in 7 (46.66%) patients.
Ikeda et al., 2013 (26)	25 patients (13 females and 12 males). Age: 29-85 years	2 mg/kg of Photofrin by intravenous injection. Light source: Eximerd laser with 630nm wavelength and 2100 J/cm	Once	Maximum 24 months	24 patients (96%) responded completely to this treatment and one (4%) patient responded partially. Recurrence was observed in 3 patients (12%).
Jerjes et al., 2011(27)	38 patients (26 men and 12 women). Age: 51-69 years	0.15 mg/kg (mTHPC) by intravenous injection. Light source: Single channel diode laser with a wavelength of 652 nm and an energy density of 220 J/cm	1-3 times	Minimum 60 months	26 patients (68.42%) fully responded to this treatment. Recurrence was observed in 6 patients (15.79%).
Lorenz and Maier, 2009 (10)	35 patients (27 men and 8 women). Average age: 59 years	0.15 mg/kg (mTHPC) by intravenous injection. Light source: Ceralas laser with a wavelength of 652 nm and energy of 2100 J/cm	Once	Maximum 12 months	In 21 patients (60%) complete recovery was achieved and in 10 patients (28.5%) partial recovery was achieved. 4 patients (11.43%) did not respond to this treatment.
Rigual et al., 2009 (9)	20 patients (14 men and 6 women). Age: 36-85 years	2 mg/kg porfimer sodium or Photofrin by intravenous injection. Light source: 630 nm diode or argon laser with an energy of 275-50 J/cm	Once	7-52 months	19 patients (95%) responded completely to this treatment and one patient (5%) responded partially. Recurrence was observed in 3 patients (15%).
Tan et al., 2010 (28)	39 patients (31 men and 8 women) Average age: 60.9 years	0.15 mg/kg (mTHPC) by intravenous injection Light source: Diode laser with a wavelength of 652 nm and an energy of 220 J/cm	Once	4-44 months	19 patients (48.7%) responded completely to this treatment and 2 patients (5.1%) responded partially.18 patients (46.15%) did not respond to PDT.
Kubler et al., 2001 (29)	25 patients (17 men and 8 women). Age: 44-99 years	0.15 mg/kg (mTHPC) by intravenous injection. Light source: Diode or argon laser with a wavelength of 652 nm and an energy of 220 J/cm	Once	14 months	24 patients (96%) responded completely to this treatment and one (4%) responded partially. Recurrence was observed in 2 patients (8%).

Discussion:

The opportunity for local control and management of tumors along with side effects of treatment and its effects on the quality of life of patients should be considered in the selection of an appropriate treatment method for oral cancer. Tumor thickness is an important parameter in the success of PDT. Tumors with a maximum depth of 10 mm have been reported to respond better than tumors with a depth of more than 1010 mm. [25] On the other hand, it has been shown that the use of PDT in the clinical stage of long-term metastasis has little effect.[10]

The mTHPC is a second-generation light-sensitive substance that is very effective in treating oral cancer using PDT. Some studies have shown the complete elimination of the disease without reduced function in all patients that received this light-sensitive compound.[30-32]

These studies have shown that mTHPC can be effective even in advanced stages of the disease. It has been shown that PDT can destruct primary carcinomas and small, medium, and large tumors. With several recent technological advances, PDT has the potential to become the mainstay of cancer treatment.[33-35]

It is clear from the mentioned studies that PDT is safe in normal conditions to be used near blood vessels. It makes perfect sense to assume that in a clinical setting, where the tumor erodes the vessel wall, PDT will not be safe and may cause acute bleeding. However, treatment can be done safely as long as the tumor is close but the arterial wall is not destroyed.

As a result, although it is important to be aware of the potential problems of normal tissue healing after PDT, none of the animal work shows unfathomable problems, and because of the significant safety data, the use of PDT in clinical practice is safe.[36,37]

Conclusion:

Oral cancer is a malignant neoplasm that develops on the lips or in the oral cavity and, like most diseases, genetic and epigenetic factors play a role in it. Treatment for oral cancer depends on the location and the stage of cancer. This research has shown that PDT can be as effective as other common therapies such as surgery, radiation therapy, or chemotherapy in treating certain types of cancer, such as oral cancer, and precancerous cases. On the other hand, due to the advantages of this treatment method over other methods, the tendency to use PDT has increased in recent years. However, data on PDT,as a new adjunctive therapy, are limited, and further studies are needed to evaluate its efficacy.

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