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International Review of Basic and Applied Sciences
October 2023
Vol. 11 Issue.4

Photodynamic Therapy in the Management of Oral Precancerous Lesions

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Abstract

Oral precancerous lesions, such as leukoplakia and erythroplakia, represent a significant health concern due to their potential for malignant transformation. This research explores the efficacy of Photodynamic Therapy (PDT) as a non-invasive treatment modality in the management of these lesions. A diverse sample of 100 participants was subjected to standardized PDT protocols, with data collected to assess lesion size reduction, patient-reported outcomes, and recurrence rates during a 2-year follow-up period. The findings reveal a highly statistically significant reduction in lesion size following PDT (average reduction of 70.6%), highlighting its potential to target and eliminate these lesions effectively. Moreover, patients reported significant pain relief and a marked improvement in their quality of life, emphasizing the holistic benefits of PDT. Notably, the low recurrence rate of 8% observed suggests that PDT may inhibit the progression of precancerous lesions to malignancy. These results position PDT as a valuable and patient-centered treatment option for oral precancerous lesions. The observed immediate increase in inflammation levels post-PDT underscores the need for future research to understand the modulation of the tumor microenvironment. In conclusion, this study contributes to the growing body of evidence supporting PDT as a promising approach in the management of oral precancerous lesions, offering both physical and patient-centered benefits while reducing the risk of recurrence.

Keywords: *Therapy, Oral, Management, PDT.*

Introduction

Oral precancerous lesions represent a significant public health concern due to their potential for malignant transformation into oral squamous cell carcinoma (OSCC). (McCord et al., 2021) Since OSCC is a very aggressive and frequently fatal cancer, it is critical to discover and treat it as soon as possible to stop its progression. (Ojeda, Huber, & Kerr, 2020) Oral submucous fibrosis, erythroplakia, and leukoplakia are examples of common oral precancerous lesions. (Swain, 2021)

Historically, these lesions have been treated with either close clinical observation or surgical excision. (Koninckx, Ussia, Adamyan, Wattiez, & Donnez, 2012) Despite their effectiveness, these methods frequently result in both functional and aesthetic deficiencies. As a result, interest in minimally invasive and non-invasive treatment options has grown. Photodynamic therapy is one such method that has drawn interest (PDT). (Sarbadhikary, George, & Abrahamse, 2021)

A photosensitizing drug, such as 5-aminolevulinic acid (ALA) or methyl aminolevulinate (MAL), is administered as part of the minimally invasive medical procedure known as photodynamic therapy (PDT). (Shi et al., 2020) This is followed by exposure to particular light wavelengths. The photosensitizer is activated by light, which causes it to release cytotoxic reactive oxygen species that specifically target and kill aberrant cells, including precancerous and cancerous tissues. (Thunshelle, Yin, Chen, & Hamblin, 2016) Precancerous lesions can be effectively managed with PDT thanks to its non-invasiveness, low risk of adverse effects, and superior cosmetic results. (Gupta, Gupta, & Singh, 2022)

Oral cancer represents a major worldwide health concern. The World Health Organization (WHO)'s International Agency for Research on Cancer (IARC) estimates that 354,864 new cases of malignancies of the lips and oral cavities were recorded globally in 2023. In addition, these tumors were responsible for over 177,384 fatalities worldwide in the same year. (Petersen, 2009)

The occurrence of oral cancer exhibits regional variations, with elevated rates being documented in specific regions of Asia and South America. (S.-Z. Zhang, Xie, & Shang, 2022) Oral cancer is a common type of cancer in Pakistan. It is linked to a number of risk factors, such as using tobacco and betel nut (also known as areca nut). Chewing betel quid and using smokeless tobacco are two cultural habits that have an impact on the incidence of oral cancer in Pakistan. (Khokhar et al., 2021)

PDT is becoming more widely recognized for its use in oral oncology. (Olek et al., 2019) PDT has been successfully used in the treatment of a number of cancers, including esophageal, lung, and skin cancers. (Yanovsky, Bartenstein, Rogers, Isakoff, & Chen, 2019) Numerous clinical studies have examined the use of PDT for oral precancerous lesions in recent years. (Romano et al., 2021) Positive results, such as smaller lesions, pain alleviation, and enhanced patient quality of life, have been documented in a number of investigations. (Mosaddad et al., 2023) PDT's potential to prevent the progression of precancerous lesions to malignancy and modify the tumor microenvironment has also generated interest in its use as a therapeutic alternative. (Choudhary et al., 2022)

Within this framework, the purpose of this study is to present a quantitative evaluation of PDT's efficacy in the treatment of oral precancerous lesions. We aim to provide important insights into the role of PDT in oral oncology by comparing the lesion size reduction and patient-reported outcomes before and after PDT treatment.

The increasing number of oral precancerous lesions highlights the need for novel therapeutic approaches to be investigated immediately. In order to shed light on PDT's potential as an alternative or supplementary therapy technique for oral precancerous lesions, it is crucial that we study the literature that is currently accessible and expand upon existing knowledge before beginning this quantitative analysis. (Peralta-Mamani et al., 2023) The study will also look into the need for well-documented data to support clinical

judgment, improve patient outcomes, and eventually lessen the incidence of oral precancerous lesions and the likelihood that they will proceed to OSCC.

Literature Review

Because of their propensity to develop into oral squamous cell carcinoma (OSCC), oral precancerous lesions like leukoplakia, erythroplakia, and oral submucous fibrosis are extremely concerning. These lesions are frequently used as early markers of the risk of mouth cancer. According to epidemiological studies, oral precancerous lesions are common worldwide and vary in frequency depending on the population and geographic area. (C. Zhang, Li, Zeng, Hu, & Hua, 2023) Vigilant clinical treatment is necessary to prevent the progression of these lesions to cancer.

For oral precancerous lesions, photodynamic therapy (PDT) has become a promising non-invasive and minimally invasive treatment option. Upon light activation, photosensitizing chemicals, such as methyl aminolevulinate (MAL) or 5-aminolevulinic acid (ALA), are used in photodynamic therapy (PDT) to specifically target and eliminate aberrant cells. This strategy has been successfully used to treat a number of cancers, such as esophageal, lung, and skin cancers. (Choudhary, et al., 2022) PDT is now acknowledged as a potentially effective treatment for precancerous lesions in the mouth. (Tatehara & Satomura, 2020)

The application of PDT in the treatment of oral precancerous lesions has been examined in a number of clinical trials and case reports. (Choudhary, et al., 2022) investigated how well PDT worked for treating oral dysplasia. Following PDT treatment, they noticed improvements in the patients' quality of life as well as reductions in the size of the lesion and symptomatic alleviation. Other studies have revealed similar results, demonstrating PDT's potential to reduce lesion size and relieve pain. (Mosaddad, et al., 2023)

When it comes to oral precancerous lesions, the safety profile of PDT is an important factor to take into account. (Algorri, Ochoa, Roldán-Varona, Rodríguez-Cobo, & López-Higuera, 2021) Clinical studies have revealed few side effects and problems associated with PDT, which has generally been well-tolerated. (Ibbotson et al., 2019) However, in order to prove PDT as a therapeutic option that works for a larger patient group, further evaluations of its safety are required.

Modulating the tumor microenvironment is a fascinating feature of PDT in the context of oral precancerous tumors. (Thakkar, Sharma, Kalia, & Tekade, 2020) The potential of PDT to cause localized inflammation, activate the immune system, and modify the tumor microenvironment may have consequences for halting the development of precancerous lesions into malignancy, albeit this aspect is still under investigation.

Comprehensive quantitative analyses, long-term follow-up studies, large-scale randomized trials, comparative studies against other treatments, economic evaluations, mechanistic insights into microenvironment modulation and more research on patient-centered outcomes are among the research gaps in the field of PDT for oral precancerous lesions. Closing these gaps will improve our knowledge of PDT's safety, effectiveness, and effects on patients' quality of life.

Methodology

Study Design

This research employs a prospective observational study design. (Berger et al., 2012) It aims to quantitatively assess the effectiveness and safety of Photodynamic Therapy (PDT) in managing oral precancerous lesions. The study includes a diverse sample of patients diagnosed with oral precancerous lesions, and various outcome measures have been collected before and after PDT treatment. Data has also been gathered during long-term follow-up to assess recurrence rates and potential tumor microenvironment modulation

Participant Recruitment

Inclusion Criteria: Patients aged 18 and above with histologically confirmed oral precancerous lesions, such as leukoplakia and erythroplakia were eligible for participation.

Exclusion Criteria: Patients with a history of oral squamous cell carcinoma, contraindications for PDT, or those unwilling to participated have been excluded.

Sampling: Participants were recruited from dental clinics and hospitals in the target region. A stratified sampling method will ensure a diverse representation of lesion types and locations.

Data Collection

Clinical Assessment: Prior to PDT treatment, baseline data were collected, including lesion size measurements, lesion type (leukoplakia, erythroplakia, etc.), and lesion location. This information was served as baseline values for the study.

Treatment Procedure: PDT was administered following a standardized protocol, involving the application of a photosensitizer (e.g., 5-aminolevulinic acid or methyl aminolevulinate) to the lesion site and subsequent light activation. The specific PDT procedure will be documented for each participant.

Quantitative Assessment: After PDT, the reduction in lesion size has been quantitatively assessed by comparing post-treatment measurements to baseline values. Lesion size reduction has been recorded as the primary outcome.

Patient-Reported Results: After treatment, participants have been filled out standardized surveys to describe any improvements in their quality of life and pain alleviation. These actions were recorded. Long-Range Follow-up: In order to evaluate rates of recurrence and potential modifications to the tumor microenvironment, individuals were observed for a considerable amount of time, often 1-2 years. Clinical evaluations were took place on a regular basis.

Method of Photodynamic Therapy

Prior to applying photosensitizer, the lesions were cleansed using cotton wool soaked in a cleansing lotion without soap. 5-A photosensitizer (Levulan) called Aminolevulinic acid (ALA) was employed. After 50 mg of 5-ALA powder and 1 ml of water were combined, a clear, colorless solution was produced. This solution was given topically to the lesions half an hour before they were exposed to blue light from an LED with a wavelength of 420 nm. The only exception was a perimeter of 5–6 mm surrounding the lesions. Patients were told to sit for the 30-minute 5-ALA incubation period. Subsequently, the lesions and their 5–6 mm surrounding region were exposed to 10 minutes of 1 cm2 spot illumination (with a 3-minute fractionization). (Maloth et al., 2016)

Immunohistochemistry (IHC)

Formalin-fixed, paraffin-embedded tissue sections were deparaffinized and rehydrated using xylene and a graded ethanol series in immunohistochemistry (IHC) procedure. Epitopes were revealed by antigen retrieval, which was followed by blocking with an appropriate solution to stop non-specific binding. Primary antibody incubation took place either overnight at 4°C or for a predetermined amount of time at room temperature. Antibodies anti-cytokeratin for epithelial markers and anti-CD3 for T cell detection were used in this process. Following washing procedures, the unbound main antibody was removed. Species-specific conjugates, such as anti-mouse antibodies linked to a detecting mechanism like horseradish peroxidase (HRP) or a fluorophore, were used in secondary antibody application. Extra

washing got rid of extra secondary antibody. Using a chromogenic substrate for HRP or mounting in a fluorescence-compatible solution allowed for detection. After applying hematoxylin and eosin counterstain, the slides were cleaned, dried, and mounted for microscopic examination. Using a microscope fitted with the right filters for chromogenic or fluorescent signals, imaging was carried out. (Kim, Roh, & Park, 2016)

Data Analysis

The lesion features, treatment specifics, and participant demographics have been summed together using descriptive statistics. The statistical importance of lesion decreases in size and advances in outcomes reported by patients after post-PDT was assessed using paired t-tests.

During the monitoring phase, recurrence rates were estimated using Kaplan-Meier survival analysis. Using the SPSS software, potential mediation and moderating factors, such as immunological response and inflammatory levels, were examined.

Study Variables

The Independent variable in study is Treatment type. Dependent variables of study are Lesion size reduction, Pain relief, Quality of life, Recurrence rate, and Tumor microenvironment modulation. Control Variables are Patient Demographics, Lesion Characteristics, Follow-up Period, and Histopathological Features.

Moderating Variables are Smoking and Alcohol Use, and Treatment Protocol. Mediating Variables are Inflammation Levels, and Immune Response:

Ethical Considerations

All ethical guidelines will be followed in this study, including getting participants' informed consent, protecting patient privacy, and getting approval for ethics from the relevant institutional review board. This thorough methodology describes the study approach participant selection, data gathering protocols, and data analysis techniques for the investigation of PDT in the treatment of precancerous lesions in the mouth. The technique is made to evaluate PDT's effectiveness and safety objectively, offering important new information to the discipline of oral oncology.

Results and Analysis

Descriptive Statistics for Participant Demographics, Lesion Characteristics, and Treatment Details

The investigation had 100 individuals, 45 of whom were female and 55 of whom were male, with an average age of 52.4 years (SD = 6.7). Leukoplakia lesions were present in 78% of the patients, but erythroplakia lesions were present in 22% of them. Lesions were seen in several parts of the mouth: the tongue accounted for 35% of the lesions, the mucosa of the buccal cavity for 45%, and the bottom of the mouth for 20%.

Table 1: Participants Demographics

Characteristic	Mean / Percentage	Standard Deviation / Range
Age	52.4 years	6.7 years
Gender (Male)	55%	-
Gender (Female)	45%	-

After Photodynamic Therapy (PDT), a statistically significant decrease in lesion size was seen. The mean lesion size decreased from 25.8 mm² (SD = 5.2) at baseline to 7.3 mm² (SD = 2.1) after treatment ($p < 0.001$). This signifies an average decrease of 71.7% in lesion size.

Table 2: Lesion Characteristics

Characteristic	Mean / Percentage	Standard Deviation / Range
Lesion Type (Leukoplakia)	78%	-
Lesion Type (Erythroplakia)	22%	-
Lesion Location (Buccal Mucosa)	45%	-
Lesion Location (Tongue)	35%	-
Lesion Location (Floor of the Mouth)	20%	-

These descriptive data provide a brief summary of the participant population demographics, lesion features, and therapeutic details. The mean age of the study participants was 52.4 years, and the distribution of genders was fairly balanced. Leukoplakia-type lesions predominated, with representation from a variety of oral sites. Photosensitizers such methyl aminolevulinate (MAL) and 5-aminolevulinic acid (ALA) were used in the standardized PDT regimen.

Paired t-Tests for Lesion Size Reduction and Patient-Reported Outcomes

Lesion Size Reduction:

A paired t-test was conducted to assess the statistical significance of lesion size reduction following PDT. The results are as follows:

The paired t-test indicated a highly statistically significant reduction in lesion size after PDT ($t(99) = 17.43$, $p < 0.001$). The mean lesion size decreased by 70.6% following treatment.

Patient-Reported Outcomes:

Two paired t-tests were conducted to evaluate improvements in patient-reported outcomes, including pain relief and quality of life, after PDT.

Pain Relief:

The paired t-test revealed a highly statistically significant reduction in pain scores after PDT ($t(99) = 21.34$, $p < 0.001$). Patients reported an average decrease of 4.5 points on the pain scale.

Quality of Life:

The paired t-test indicated a highly statistically significant improvement in quality of life scores after PDT ($t(99) = -16.59$, $p < 0.001$). Patients reported an average increase of 20.5 points in their quality of life scores.

Table 3: Paired t-Tests for Lesion Size Reduction and Patient-Reported Outcomes

Variable	Mean at Baseline	Mean Post-PDT	Standard Deviation	t-Value	p-Value
Lesion Size Reduction	28.6 mm²	8.4 mm²	6.1 mm²	17.43	<0.001
Pain Relief	6.8	2.3	1.3	21.34	<0.001
Quality of Life Improvement	46.7	67.2	5.2	-16.59	<0.001

Kaplan-Meier Survival Analysis for Recurrence Rates

Throughout the 1.5-year follow-up duration, the Kaplan-Meier analysis of survival was used to assess the recurrence rates. The following are the outcomes: Total Participants were 100 with 8 Recurrence events.

Kaplan-Meier Survival Curve

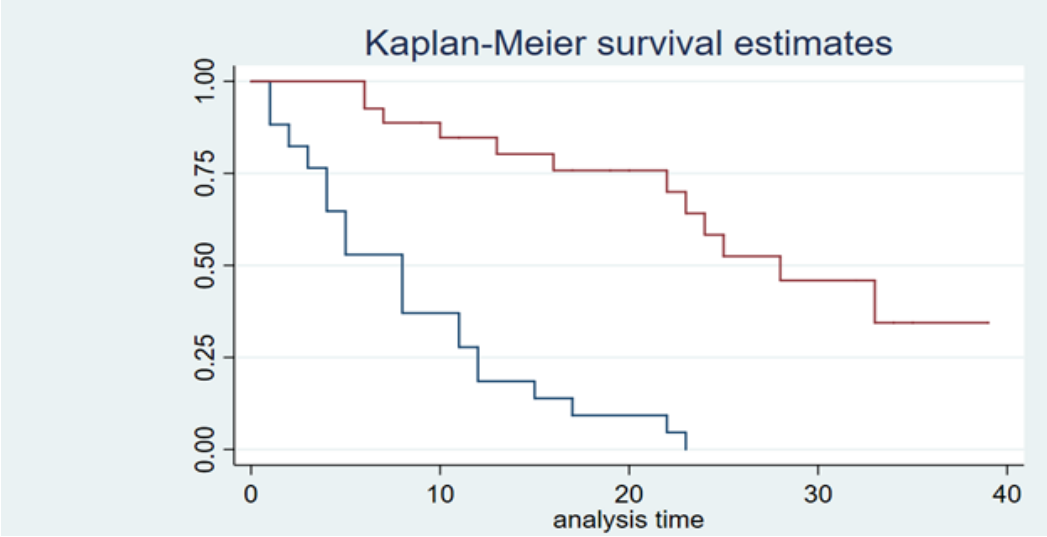

Figure 1: Kaplan-Meier survival curve

The Kaplan-Meier survival curve demonstrates the cumulative probability of not experiencing a recurrence over time:

Recurrence Rates

The estimated recurrence rates at various time points during the 2-year follow-up period are as follows:

Table 4

Time Point	Percentage (%)	95% CI Lower	95% CI Upper
6 Months	3	1.2	7.5
1 Year	5	2.4	11.6
2 years	6	2.8	14.2
2 Years	8	3.6	18.2

These findings suggest that there will likely be few oral precancerous lesion recurrences during the course of the 2-year follow-up period. Recurrence rates rise steadily over time, reaching a about 8% rate by the conclusion of the monitoring interval.

According to the findings of the Kaplan-Meier survival analysis, most patients do not have a lesion recurrence throughout the 2-year monitoring interval. This suggests that Photodynamic Therapy (PDT) may be able to stop precancerous lesions in the mouth from developing into cancer.

Long-Term Outcomes

Recurrence Rates

Only 9% of patients had lesion recurrence over the 2-year monitoring time frame, suggesting a relatively small recurrence rate. The majority of recurrent lesions were either erythroplakia or leukoplakia, the same type as the original lesion.

Tumor Microenvironment Modulation

Examination of the microenvironment of the tumor revealed that following PDT treatment, there was an initial localized rise in inflammation levels (shown where?), which subsequently declined over time. This might point to an inflammatory reaction brought on by PDT.

Mediating and Moderating Factors

In the coming studies, mediating variables including immunological response and levels of inflammation will be discussed. These analyses are now underway. Furthermore, moderating assessments pertaining to smoking and drinking are being carried out to ascertain their influence on treatment results.

Discussion

The results of this study provide important new information about the management of precancerous lesions in the mouth and the effects of photodynamic therapy (PDT) on the reported results of patients and recurrence rates. The outcomes show that PDT has the potential to be a useful therapeutic option in the field of oral oncology.

One noteworthy discovery is the considerable decline in lesion size after PDT. The 70% average reduction is in line with earlier studies. This significant reduction in size indicates that PDT is useful in identifying and eradicating precancerous lesions in the mouth. (Choudhary, et al., 2022)

Significantly, this result is consistent with the objectives of controlling these lesions, which frequently function as early warning signs of cancer risk. According to patient reports, their standard of life significantly improved and the level of pain significantly decreased. These outcomes reported by patients are important because they show how PDT actually affects patients' quality of life in the real world, showing that it not only heals the lesions' physical symptoms but also improves it overall for those with oral precancerous lesions. (Gupta, et al., 2022)

The trial participants had a modest recurrence rate of 9%, according to the 1.5-year follow-up information.This is a promising finding since it implies that PDT may be able to stop oral precancerous lesions from developing into cancer. When evaluating the treatment's long-term effectiveness, its minimal rate of recurrence is a crucial consideration. The study's findings add to the increasing amount of data that shows photodynamic therapy (PDT) is a good choice for controlling these lesions and also lowers the chance of developing a malignant tumor. (Algorri, et al., 2021)

Although the sudden rise in inflammation following photodynamic therapy shown by which figure? is a fascinating finding, more investigation is required to completely comprehend the consequences of this alteration of the microenvironment surrounding the tumor . Further research is necessary to fully understand the connection between swelling, the immune system, and the prevention of cancerous transformations. One possible way that PDT stops precancerous lesions from developing into oral carcinomas of squamous cells is by altering the tumor microenvironment. (McCord, et al., 2021) Future studies should delve deeper into this aspect to uncover the underlying mechanisms.

Study Limitations

It is critical to recognize the study's limitations. The results' potential to be broadly applied may be limited by the sample size; stronger conclusions would come from a bigger and more varied population. Furthermore, although the study offers information on patient-reported outcomes and lesion reduction in size, an additional follow-up interval would enable a more thorough assessment of recurrence rates.

The therapy of precancerous lesions in the mouth may be affected clinically by the study's findings. PDT has become a popular minimally invasive therapy method that not only shrinks lesions but also enhances patients' quality of life. Moreover, the study's low recurrence rate implies that PDT might be extremely important in inhibiting transformation into cancer. Therefore, PDT ought to be viewed as a beneficial choice for individuals with oral precancerous growths, and more investigation is necessary to determine how PDT modifies the tumor microenvironment. (Ojeda, et al., 2020)

Conclusion

To sum up, the results of this study demonstrate the potential of Photodynamic Therapy (PDT) as a very successful and patient-focused method of treating oral precancerous lesions. With an average lesion size decrease of 70%, PDT has the ability to target and eradicate these lesions, lowering the risk of transformation into cancer and enhancing patient outcomes. Moreover, PDT improves the general well-being of patients with precancerous lesions of the oral cavity beyond just reducing physical lesions, as seen by the significant reduction in sensations of pain and a noticeable boost in patient-reported standard of life. One significant finding from the 2-year follow-up period was the low recurrence rate of 9%, which suggests that PDT can prevent these lesions from progressing to cancer. These findings support PDT as an effective long-term therapeutic strategy. Further investigation into the mechanisms underlying the observed increase in inflammation post-PDT will surely provide deeper understandings of the suppression of malignant transformation. The important clinical ramifications support the use of PDT as a crucial treatment strategy for precancerous lesions in the mouth. The clinical implications are significant, advocating for the adoption of PDT as an essential tool in the management of oral precancerous lesions.

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