Journal of Chemical Health Risks

www.jchr.org

JCHR (2026) 16(2), 2244-2259 | ISSN:2251-6727

Laser-Assisted Photodynamic Therapy in the Management of Oral Leukoplakia: A Systematic Review

Pavithra G[1], Zameera Naik [1*], Vasanti Jirge[1], Vaishali Keluskar[1], Arvind Shetti[1], Harishithaa Kuttuva[1]

[1]Department of Oral Medicine and Radiology, KAHER's KLE VK Institute of Dental Sciences, Belagavi, Karnataka, India.

Corresponding author contacts

Zameera Naik, Department of Oral Medicine and Radiology, KAHER's KLE Vishwanath Katti Institute of Dental Sciences, Nehru Nagar, Belagavi, Karnataka, 590010, India.

(Received: 28 January 2026 Revised: 16 March 2026 Accepted: 09 April 2026)

KEYWORDS
Oral Leukoplakia; Oral potentially malignant disorders; Photodynamic therapy; Lasers

ABSTRACT:
Background: Oral leukoplakia is the most common oral potentially malignant disorder with a variable risk of malignant transformation. Conventional treatments are associated with morbidity and recurrence. Laser-assisted photodynamic therapy (L-PDT) has emerged as a minimally invasive alternative.
Objective: To systematically evaluate the efficacy, safety, and clinical outcomes of laser-assisted photodynamic therapy in the management of oral leukoplakia.
Methods: Electronic searches of PubMed, Scopus, ProQuest, Google Scholar, and ClinicalKey were conducted from 1998 to 2024. Clinical studies assessing L-PDT for oral leukoplakia were included. Data on lesion response, recurrence, and adverse effects were extracted. Methodological quality was assessed using MINORS and the Joanna Briggs Institute tools. Certainty of evidence was evaluated using GRADE.
Results: Fourteen studies meeting the inclusion criteria which were conducted in clinical settings were included. Various photosensitizers (e.g., ALA, methylene blue) and LASER parameters were utilized. The overall treatment response rate was 76.1%, with recurrence ranging from 0% to 60%. Common adverse effects were transient pain, ulcers, and swelling. Risk of bias assessments revealed that most of the studies were of moderate quality, with five studies having low risk. According to the GRADE assessment, the certainty of evidence was moderate in one study (an RCT), low in eleven studies, and very low in two studies, primarily due to high risk of bias, small sample sizes, and lack of randomization in most of the studies.

Conclusion: L-PDT demonstrates significant potential as an effective and well-tolerated treatment modality for Oral leukoplakia. While preliminary outcomes are encouraging, the current body of evidence is limited by low methodological quality. High-quality randomized controlled trials with standardized protocols are needed to confirm its long-term efficacy and optimize treatment guidelines. With ongoing advancements in LASER technology, photosensitizer formulations, and treatment protocols, it is expected that the therapeutic outcomes will continue to improve, providing better clinical benefits for patients.

1. Introduction

Oral Leukoplakia (OLK) is defined as a white patch or plaque that cannot be characterized clinically or pathologically as any other disease and which is not associated with any other physical or chemical causative agent except the use of tobacco [1]. Oral Leukoplakia is a common potentially malignant oral disorder with a high risk of progressing to squamous cell carcinoma. The global incidence of Oral leukoplakia is 4.11% [2]. The morbidity rate, as reported in the literature, ranges from 0.2% to 4.3% [3]. It is a common precancerous oral lesion with a 7.7% to 38.1% malignant transformation rate, influenced by factors like geographic location, gender, tobacco use, lesion size, pathological type, and grading of dysplasia. [4,5,6].

Each year around 3,00,400 new cases of oral squamous cell carcinoma (OSCC) and 1,45,300 cancer-related deaths occur, with an average 5-year survival rate below 60% [7]. Oral cancer is a multifactorial process, preceded in most cases by precancerous lesions which are currently termed as potentially malignant disorders.[8]. Oral Leukoplakia is one such precancerous lesion which can cause systemic health effects if left untreated and literature has documented its associations with an increased risk of upper gastrointestinal cancers [9,10]. Therefore, prompt treatment of Oral leukoplakia is vital. Traditional methods for treating Oral Leukoplakia include local drug application and local surgical excision. However, these therapies have significant drawbacks, including adverse drug effects and tissue defects post-surgery. Therefore, cryotherapy, LASER and photodynamic therapy (PDT)are emerging as preferred treatment modalities gaining importance in clinical practice [11,12].

Photodynamic therapy (PDT) is a non-surgical tool that uses photosensitizing agents which accumulate selectively in target tissue before the delivery of light [13]. PDT involves 3-components such as light source, photosensitizers, and tissue oxygen [14]. In the presence of oxygen, interaction between a light source and photosensitizer (PS) is stimulated, which produces reactive oxygen species (ROS) [15]. The intracellular cytotoxic ROS results in oxidative damage to microbial cell walls along with pre-malignant and malignant cells [16,17].

PDT offers several advantages over traditional treatments like being less invasive, causing fewer side effects than systemic medication, and more precise in targeting the lesion thus preserving normal tissues. Currently, PDT therapy has been widely used to treat oral diseases, including leukoplakia [18-21]. This systematic review synthesized the available evidence regarding the efficacy, safety, and outcomes of LASER-assisted photodynamic therapy (L-PDT) in the management of Oral Leukoplakia.

This systematic review has addressed the following question:
Is Laser assisted photodynamic therapy an effective therapeutic alternative in the management of Oral Leukoplakia in terms of clinical resolution, histopathological improvement, recurrence rates, and adverse effects?

2. Objectives

To systematically evaluate the efficacy, safety, and clinical outcomes of laser-assisted photodynamic therapy in the management of Oral Leukoplakia.

3. Methods

Protocol and registration: The protocol was registered in the International Prospective Register of Systematic (PROSPERO) under CRD42024537944

Eligibility criteria: All Randomized, non-randomized controlled trials and observational studies wherein PDT was used to treat Oral Leukoplakia were included provided they were fulfilling the inclusion criteria. During the data search, no restriction was set to the study setting and the time period of the studies.

Inclusion criteria:

1. Studies which included patients above the age of 18 years, diagnosed with Oral Leukoplakia confirmed by clinical examination and/or histopathological diagnosis
2. Studies using all wavelengths of LASER-assisted photodynamic therapy for the management of oral Leukoplakia.
3. All photosensitizers, regardless of type or dose or incubation time, or route of administration.
4. Articles published from 1998 to April 2024 in the English language.
5. Original articles with one of the above-mentioned designs that had been published in scientific journals or included in grey literature repositories

Exclusion criteria:

1. Studies conducted on animal subjects or in-vitro studies.
2. All studies that utilized high-energy wavelengths for photothermal and photocoagulation effects.
3. Studies where Therapia extracorporeal (PUVA, UVB) was used.
4. Studies which included potentially malignant lesions including the oropharynx, skin, face, scalp, or extremities (extra-oral mucosal lesions);
5. Studies which included PDT and antibacterial action in patients with peri-implantitis;
6. Studies with PDT cost analysis vs other therapies;
7. Studies with molecular and genetic changes.
8. Case reports, letters to the editor, review articles, systematic reviews, literature reviews, analytical studies, experimental studies, articles that do not focus on the topic, and scientific articles with incomplete or inaccessible text,

Journal of Chemical Health Risks
www.jchr.org
JCHR (2026) 16(2), 2244-2259 | ISSN:2251-6727

studies that did not involve the use of PDT and those without valid data.

PICOS for the study was defined and is described in Table 1

Table 1: PICOS

Population	This systematic review includes studies with patients above the age of 18 years, diagnosed with Oral Leukoplakia confirmed by clinical examination and/or histopathological diagnosis.
Intervention	LASER-assisted photodynamic therapy for the management of oral Leukoplakia.
Comparison	Not applicable.
Outcomes	Efficacy of clinical response, such as complete response (CR), partial response (PR), no response (NR), and recurrence rate (RR).
Study design	All randomized, non-randomized controlled trials, observational studies, case series involving patients diagnosed with Oral Leukoplakia, evaluating clinical efficacy of photodynamic therapy and under low-level LASER therapy (LLLT), published in scientific journals and grey literature were included.

Information sources:

A comprehensive search of the scientific literature was conducted without any restrictions for the study setting and time period till September 31, 2024, in the following databases and repositories: PubMed, Google Scholar, ProQuest, Scopus, Clinical Key, and Research repository. The literature search was performed by two independent researchers, with studies limited to patients diagnosed with Oral Leukoplakia who underwent laser-assisted photodynamic therapy. To ensure the saturation of literature, the reference lists of included studies identified through the search were also searched. The author's personal files were also explored to make sure that all relevant data pertaining to the study was captured.

Search strategy:

The literature search strategy was developed using medical subject headings (MeSH) and text words related to Oral Leukoplakia, Photodynamic therapy, and Low-level laser therapy. This involved a combination of the following keywords adapted to each database with "AND", "OR", or a combination of these Boolean operators wherever applicable. The following filters were used only in their respective databases-Human – PubMed; All text-Google scholar; Full text – Scopus; All text –Clinical Key; Full text– ProQuest. (Table 2)

Table 2: Search string

1	"Photodynamic therapy" AND "Oral leukoplakia"
2	"Photodynamic therapy" AND "Oral dysplasia"
3	"Photodynamic therapy" AND "Leukoplakia"
4	"Photodynamic therapy" AND "Oral potentially malignant disorder"
5	"Photodynamic therapy" AND "Oral erythro-leukoplakia"
6	"Laser therapy" AND "Oral leukoplakia"
7	"Laser therapy" AND "Oral dysplasia"
8	"Laser therapy" AND "Leukoplakia"
9	"Laser therapy" AND "Oral potentially malignant disorder"
10	"Laser therapy" AND "Oral erythron-leukoplakia"
11	"Photodynamic therapy" AND "Laser therapy" AND "Oral leukoplakia"
12	"Photodynamic therapy" AND "Laser therapy" AND "Oral dysplasia"
13	"Photodynamic therapy" AND "Laser therapy" AND "Leukoplakia"
14	"Photodynamic therapy" AND "Laser therapy" AND "Oral potentially malignant disorder"
15	"Photodynamic therapy" AND "Laser therapy" AND "Oral erythro-leukoplakia"

Selection process:

The included studies were assessed by two observers, to determine whether they met the eligibility criteria. The full-text articles were read thoroughly, and any disputes were resolved by a third reviewer, VJ. In order to remove duplicates and manage references and bibliographies, the Mendeley desktop application version 1.19.8 was used.

Data collection process and data items:

The review team developed a standardized data extraction sheet in Microsoft Excel (2007) format that was used independently by 2 authors to collect data from each study, which was combined later, and any disagreement was resolved by discussion with a third reviewer. Items included for extracting the data were: - Author's name, Geographic area, year of publication, study design, sample size, age group, clinical type, pathological classification, site of the lesion, treatment/interventional group, comparison group,

Journal of Chemical Health Risks
www.jchr.org
JCHR (2026) 16(2), 2244-2259 | ISSN:2251-6727

follow up period, study outcome- Resolution of lesion, adverse effects, recurrence rate and parameters used.

Study risk of bias assessment:

Risk of bias assessment for included studies was done by 2 authors. Non-Randomized control trials with the help of the Methodological Index for Non-Randomized Studies (MINORS) that utilized the risk of bias (ROB) assessment tool [22]. The Joanna Briggs Institute (JBI) critical appraisal checklist, developed by the Faculty of Health Sciences at the University of Adelaide, was used to assess bias in observational studies, case series [24], and Randomized controlled trials [23]. To resolve any disagreement, a third reviewer was consulted.

Certainty assessment:

To determine whether the true effect of photodynamic therapy (PDT) for oral leukoplakia lies within a clinically meaningful range or exceeds relevant clinical thresholds, the Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) [25] approach was employed. This structured framework ensured transparent and consistent appraisal of each study's methodological rigor, risk of bias, directness, consistency, precision, and publication bias, thereby supporting the development of informed clinical recommendations in the context of evidence-based medicine.

4. Results

The search strategy yielded a total of 29,963 results from 5 databases. All titles were screened, excluding those that were out of the scope of review and those not written in the English Language, 179 articles were selected after title screening. After eliminating duplicates and screening abstracts, 28 articles were selected for full-text screening, out of which 14 were eligible for full-text review and analysis. Fourteen studies were excluded, including 2 in vitro studies, 3 review articles, and 9 studies not involving lasers, of which 7 used LED and 2 used cryotherapy. (Figure 1)

Study Characteristics

Based on the search strategy, 14 eligible articles were included in this review [26–39]. The characteristics of these studies are summarized in Table 3.

Study Design & Setting: All studies included were clinical investigations conducted across eight different countries. The included studies comprised of randomized controlled trials (n = 2) [28], retrospective studies (n = 2) [26,27], prospective nonrandomized studies (n = 9) [29,30,33–39], and two case series [31,32].

Participants: A total of 760 patients were included in the review, comprising 481 men and 279 women; the gender of participants in one study was not reported. The age of participants ranged from 20 to 98 years. Based on the geographic location of the studies, two each were conducted in Russia [26,30], China [27,29], India [28,32], and Taiwan [36,37]; one study each was conducted in the United Kingdom [35], Germany [39], and Italy [31]; and three studies were conducted in various European countries [33,34,38].

Site of Lesions: Fourteen studies reported the sites of lesions, which included the buccal and labial mucosa, tongue, palate, gingiva, floor of the mouth, buccolingual sulcus, retromolar area, and alveolar ridge.

Diagnosis: Nine studies [27,29,32,34-39] included histopathologically confirmed cases of Oral Leukoplakia, which were categorized under no dysplasia, mild dysplasia, moderate dysplasia, moderate to severe dysplasia, and severe dysplasia.

Characteristics of interventions

The primary intervention assessed was Laser-assisted photodynamic therapy (PDT). Four studies used additional modalities such as Vitamin A [28], argon-pumped dye laser [34], and light-emitting diode (LED) therapy [36,37]. (Table 4)

Lasers:

Of the 14 intervention studies evaluated, laser radiation was used as a light source with different active ingredients (argon, diode, xenon, helium/neon). The wavelengths ranged between 628 nm and 940 nm, with the majority between 630 nm and 635 nm. Energy fluence, power density, and duration of irradiation ranged between 20 and 200 joules per square centimeter (J/cm^2), 7 and 500 milliwatts per square centimeter (mW/cm^2), and 120 and 1000 seconds (s), respectively. Most researchers selected 100 J/cm^2, 100 mW/cm^2, and 1000 seconds as their parameters. Two studies reported laser power output as 300 mW[33] and 0–1200 mW[36] (milliwatts). (Table 4)

Photosensitizers:

Among 14 studies, 10 studies [27, 29, 31, 32, 34, 35, 36, 37, 38, 39], aminolevulinic acid (ALA) (10-20%) was used as a photosensitizer (PS), while another study used methylene blue [28] and three studies used chlorin-e6 [26, 30, 33]. Eleven studies reported the frequency of PDT application. The frequency of application was onetime, once every two weeks, once a week, and twice a week [26-28,30-34,36-38]. In studies using topical application of PS, pre-activation time ranged from 5 minutes to 5 hours, while it was 48 hours in one study using intravenous administration. (Table 4)

Treatment regimens: Outcomes

Lesion response was the primary outcome variable assessed across all studies. The outcomes were categorized into complete response (CR), partial response (PR), and no response (NR). Outcome assessment methods varied slightly but were predominantly based on clinical evaluation and histopathological examination [26-39]. Complete response was reported in a range of 7.7%–90.9% of lesions [26,29-32,34-39], partial response in 0%–66.7% [26-39], and no response in 0% [30,31,36,37]. Overall, the combined rates of complete and partial response across all studies were 32.9% and 43.2%, respectively, amounting to a total response rate of 76.1%. The follow-up duration ranged from 5 weeks to 7.3 years.

Recurrence

Thirteen studies [26-32, 34-39] reported the recurrence rate in oral leukoplakia patients treated with PDT, ranging between 0 and 60%, and mostly below 20%, One study did not report on recurrence [33].

Adverse effects

All the included studies reported local adverse effects. Pain [26,27,29,30,34,35,38], ulcers [27, 29], swelling [30], burning sensation [39], erythema [34,38], edema [34,38], photosensitivity reaction [35] and secondary infection [38] were reported in a few studies.

Risk of bias in studies:

The assessment of the quality of included studies was performed independently by 2 authors. In case of disagreement, among which one author acted as a moderator to achieve a consensus.

Quality assessment of Non-Randomized Controlled trials:

Of the 14 studies that were included, 11 were categorized using the Methodological Index for Non-Randomized Studies (MINORS) [26,27,29,30, 33-39]. The risk of bias assessment within each study is mentioned in the form of tables subsequently. The single-arm interventional studies were given a score for 8 items, and the maximum score that could be given was 16. The studies which have a comparative group were given a score for 12 items, and the maximum score that can be given is 24. Quality assessment: A score of less than 8 is considered poor quality, 9–14 is moderate quality, and 15–16 is good quality in the case of non-comparative studies. Studies are graded as very low quality (0–6), low quality (7–10), fair quality (11–15), good quality (16–20), and high quality (≥20) in case of comparative studies.

Overall risk of Bias:

Out of the 11 studies, eight were single-arm interventional studies [26,27,29,30,33-39] and three studies were comparative studies [34,36,37]. 5 studies were at an overall low risk of bias (High quality) [30,33,35,38,39] and the remaining 6 studies were at an overall moderate risk of bias (moderate quality) [26,27,29,34,36,37]. Risk of bias as seen in Figure 2.

Quality assessment of Randomized Controlled trials and Case series:

Joanna Briggs Institute (JBI) Critical Appraisal was used for included Randomized controlled trials [24] and Observational studies [23]. A high risk of bias was adjudged when a positive response was ≤ 49%, a moderate risk of bias was adjudged when a positive response was between 50% and 69%, and a low risk of bias was adjudged when a positive response was above 80%. Based on the above-mentioned criteria, one randomized controlled trial [28] and two case series [31,32] were of moderate quality and high quality as depicted in Figures 3 and 4, respectively.

Certainty Of Evidence (According to GRADE Method)

According to the GRADE framework, the overall certainty of evidence for photodynamic therapy (PDT) in the treatment of Oral Leukoplakia ranges from very low to moderate, depending on study design, risk of bias, and reporting quality. (Table 5) Based on the quality appraisal, one study (Bhandari et al., 2023) was rated as having moderate certainty of evidence. Ten of the remaining studies were non-randomized, observational, or single-arm and suffered from limitations such as lack of randomization, no blinding, small sample sizes, and unclear publication bias. Low certainty of evidence was found in: Jerjes et al. [35], Kawczyk-Krupka et al. [34], Artsemyeva&Tzerkovsky [26], Wang et al. [27], Lin et al. [36], Yu et al. [37], Sieron et al. [38], Kübler et al. [39], Han et al. [29], Istomin et al. [30], Pietruska et al. [33]. These studies were relegated due to high risk of bias (lack of control group, randomization, or blinding), serious imprecision, and unclear publication bias.Very low certainty of evidence was noted in: Gaimari et al. [31], Selvam et al. [32]. These were case series or poorly reported observational studies with very small sample

Journal of Chemical Health Risks
www.jchr.org
JCHR (2026) 16(2), 2244-2259 | ISSN:2251-6727

sizes, no control group, and high risk of bias, resulting in the lowest level of certainty according to GRADE.

Figure 1: PRISMA flowchart depicting study selection

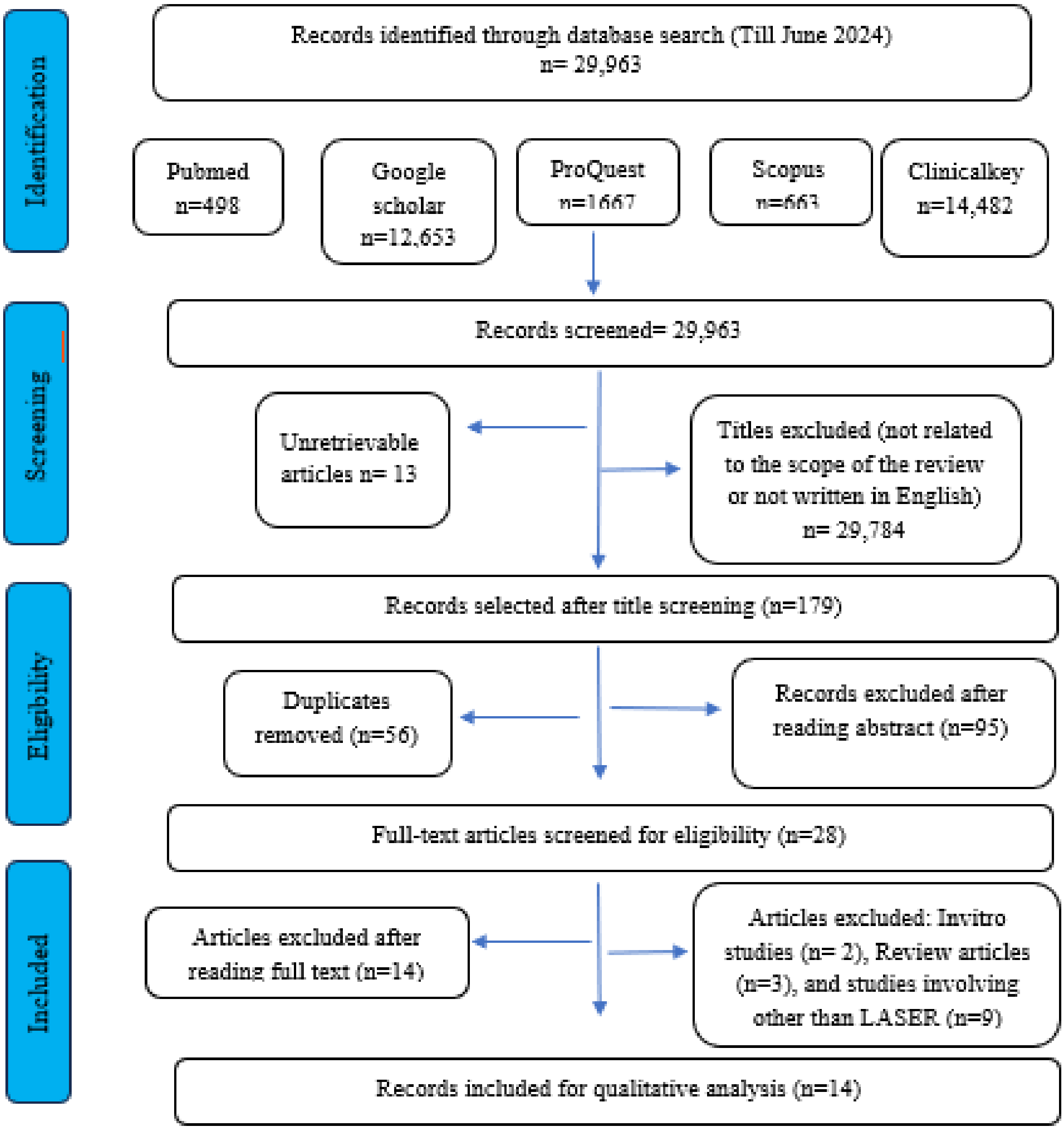


Table 3: Study characteristics

Authors	Country	Year of publication	Study design	Patients	Age range	Gender M/F	Clinical type	Pathological classification	Site of the lesion	Intervention	Comparison	Follow up	Study outcome	Adverse effects	Recurrence(%)
Artsemyeva et al	Russia	2024	Non randomized Retrospective	223	28-76	151/72	H-211, NH-12	NA	BM,P,T	Diode laser	Nil	6 years	CR:212,PR:9,NR:2	Pain	9%
Wang et al	China	2024	Non randomized Retrospective	50	18-75	26/24	H-34, NH-16	ND-17,MD-20,MSD-13	FM,BM,T,L,DT,G,P	He-Ne laser	Nil	2 years	CR:6,PR:28,NR:16	Pain, ulcers	32%
Bhandari et al	India	2023	RCT	40	NA	36/4	OL	NA	BM,T	Diode laser	Vitamin A	1 year	CR:3,PR:14,NR:23	Nil	0%
Han et al	China	2019	Non randomized Prospective	29	18-80	11--18	H-20, NH-9	ND-10,MD-12,MSD-7	BM, G, DT,VT	He-Ne laser	Nil	3 months	CR:16 ,PR:9, NR:4	Pain, ulcers	12%
Istomin et al	Russia	2016	Non randomized Prospective	40	30-79	7--33	H-36, NH-4	NA	BM,T,FM,G	Diode laser	Nil	1-30 months	CR:38,PR:2,NR:0	Swelling, Pain	3%
Gaimari	Italy	2016	Case series	5	45-84	4--1	OL	NA	BM,LM,L,RMA	Diode laser	Nil	3 months	CR:3,PR:2,NR:0	Nil	60%
Selvam et al	India	2015	Case series	5	35-49	5---NA	H-3,NH-2	ND-0,MD-1,MSD-4	BM,G,VT	Xenon laser	Nil	24 months	CR:2,PR:2,NR:1	Nil	0%
Pietruska et al	Europe	2014	Non randomized Prospective	23	21-79	7--16	H-23	NA	BM,G,T,LM	Diode laser	Nil	5 weeks	CR:6,PR:11,NR:5	Nil	NA
Kawczyk et al	Europe	2012	Non randomized Prospective	48	32-75	20--28	H, NH	ND-43,MD-5	BM, L, FM, P, T and B-G sulcus	Diomed Laser	Argon pumped dye laser	34 months	CR:35,PR:7,NR:6	Erythema, edema, pain	27%
Jerjes et al	UK	2011	Non randomized Prospective	147	41-98	82--65	H-55, NH-92	ND-0,MD-19,MOD-33,SD-63,CIS-32	T, BM, P,FM, RMA, TB, UA, LA	Diode laser	Nil	Up to 7.3 years	CR:119,PR:12,NR:16	Pain, photosensitivity reaction	19%
Lin et al	Taiwan	2010	Non randomized Prospective	80	34-89	77--3	NH-40, VH-40	ND-0,MD-12,MOD-18,SD-7,CIS-3	BM,P,T,LM,A,FM	Diode laser	LED	6-37 months	CR:78,PR:2,NR:0	Nil	21%

Journal of Chemical Health Risks
www.jchr.org
JCHR (2026) 16(2), 2244-2259 | ISSN:2251-6727

Yu et al	**Taiwan**	**2009**	**Non randomized Prospective**	**46**	**34-89**	**44--2**	**NH-46**	**ND-0,MD-11,MOD-24,SD-7,CIS-3**	**BM,T,LM,AM,G,P,FM**	**Diode laser**	**LED**	**16-76 months**	**CR:42,PR,4,NR:0**	**Nil**	**29%**
Sieron et al	**Europe**	**2003**	**Non randomized Prospective**	**12**	**32-72**	**NA**	**OL**	**ND-10,MD-2**	**BM,FM,G,L,B-G sulcus**	**Argon dye laser**	**Nil**	**4-34 months**	**CR:10,PR:0,NR:2**	**Erythema, edema, pain, secondary infection**	**8.30%**
Kubler et al	**Germany**	**1998**	**Non randomized Prospective**	**12**	**NA**	**11--1**	**H-9,NH-3**	**ND-6,MD-4,MOD-1,SD-1**	**BM,FM,B-G sulcus**	**Argon dye laser**	**Nil**	**6-16 months**	**CR:5,PR:4,NR:3**	**Burning sensation**	**0%**

H: Homogenous; NH: Non Homogenous; VH: Verrucous Hyperplasia; ND: No Dysplasia; MD: Mild Dysplasia; MOD: Moderate Dysplasia; SD: Severe Dysplasia; CIS: Carcinoma in situ; T: tongue; DT: dorsal surface of tongue; VT: ventral surface of tongue; L: lips; BM: buccal mucosa; LM: labial mucosa; G: gingiva; B-G sulcus: Bucco-gingival sulcus; P: palate; FM: floor of the mouth; RMA: retro molar area; NR: no response; PR: partial response; CR: complete response; LED: Light Emitting Diode

Table 4: Characteristics of interventions

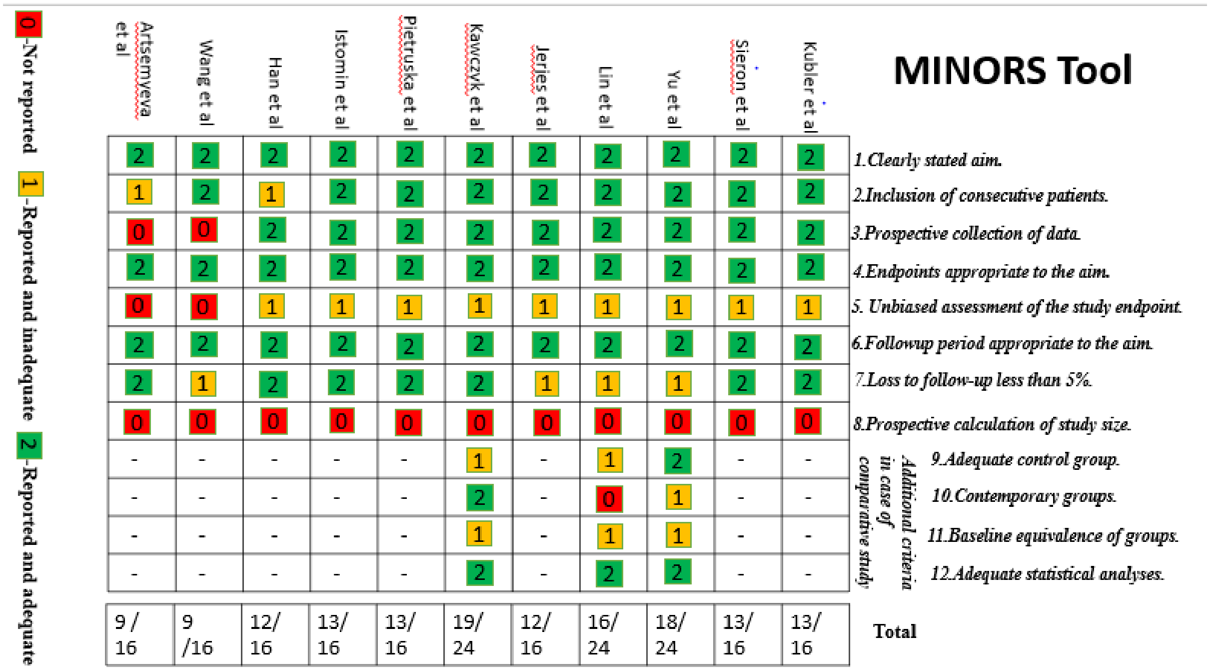
Si no	**Authors**	**Type of laser sources**	**Photosensitizers**	**Wavelength(nm)**	**Power density (mW / cm2)**	**Energy fluence (J/cm2)**	**Power output (mW)**	**Duration of irradiation (seconds)**	**Frequency**
1.	Artsemyeva et al	Diode laser	Chlorin-e6	665	7—32	25-100	NA	120-780	1-6 sessions
2.	Wang et al	He-Ne laser	20% ALA	635	150-300	NA	NA	300	3-4 sessions
3.	Bhandari et al	Diode laser/Vitamin A	Methylene blue	940	NA	NA	NA	NA	6-9 sessions
4.	Han et al	He-Ne laser	20% ALA	632	500	90-180	NA	180	NA
5.	Istomin et al	Diode laser	Chlorin-e6	660	7—32	25-100	NA	120-780	1-3 sessions
6.	Gaimari	Diode laser	20% ALA	635	100	100	NA	1000	2-5 sessions
7.	Selvam et al	Xenon laser	10% ALA	630	100	100	NA	1000	6-8 sessions
8.	Pietruska et al	Diode laser	Chlorin-e6	660	NA	90	300	NA	10 sessions

Journal of Chemical Health Risks
www.jchr.org
JCHR (2026) 16(2), 2244-2259 | ISSN:2251-6727

9.	Kawczyk et al	Group 1 (Diomed Laser) Group 2 (Argon pumped dye laser)	Group 1 (20%ALA) Group 2 (10%ALA)	Group 1:630,Group 2 :635	NA	100	NA	900	6-8 sessions
10.	Jerjes et al	Diode laser	ALA ,mTHPC	628, 652	NA	100—200, 20	NA	NA	NA
11.	Lin et al	Diode laser/LED	20% ALA	635	100	100	0-1200	1000	6 sessions
12.	Yu et al	LED/ Diode laser	20% ALA	635	100	100	NA	1000	5 sessions
13.	Sieron et al	Argon dye laser	10% ALA	635	150	100	NA	900	6-8 sessions
14.	Kubler et al	Argon dye laser	20% ALA	630	100	100	NA	1000	NA

PS: photosensitizer; ALA: aminolevulinic acid; LED: Light Emitting Diode.

Figure 2: Quality assessment (Risk of bias within studies) using Methodological Index for Non-Randomized Studies (MINORS) [22]



Journal of Chemical Health Risks

www.jchr.org

JCHR (2026) 16(2), 2244-2259 | ISSN:2251-6727

Figure 3: Assessment of risk of bias of included studies utilizing the Joanna Briggs Institute (JBI) critical appraisal tool for randomized controlled trials [24]

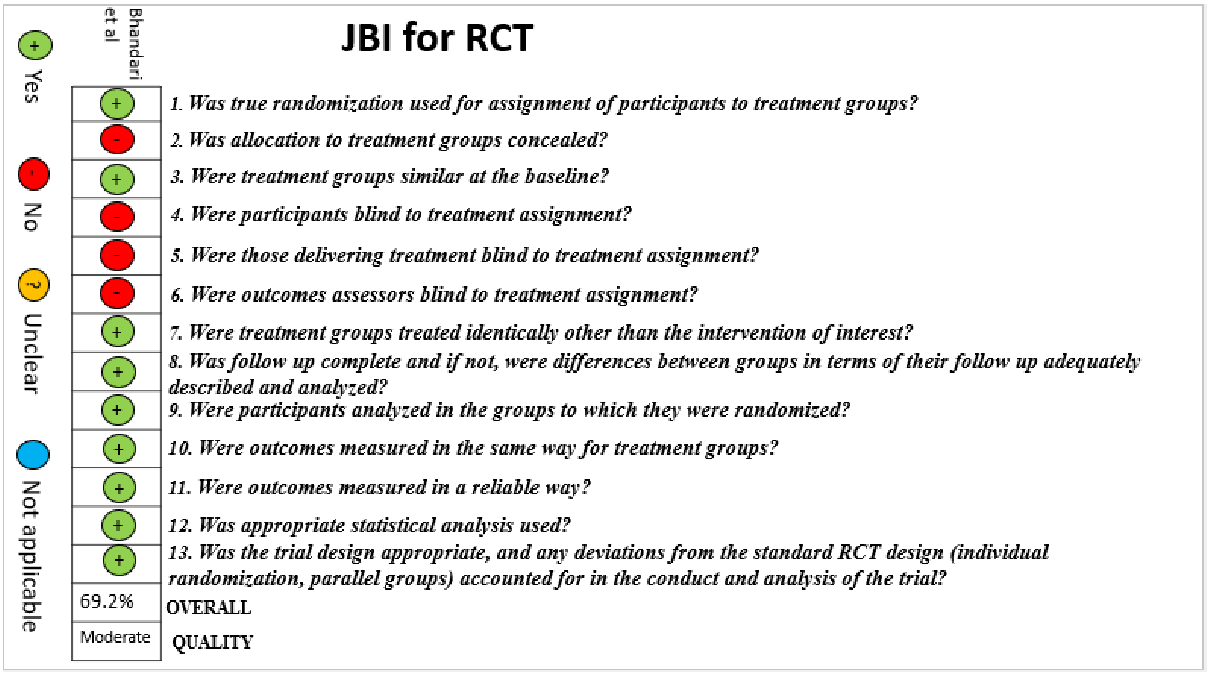
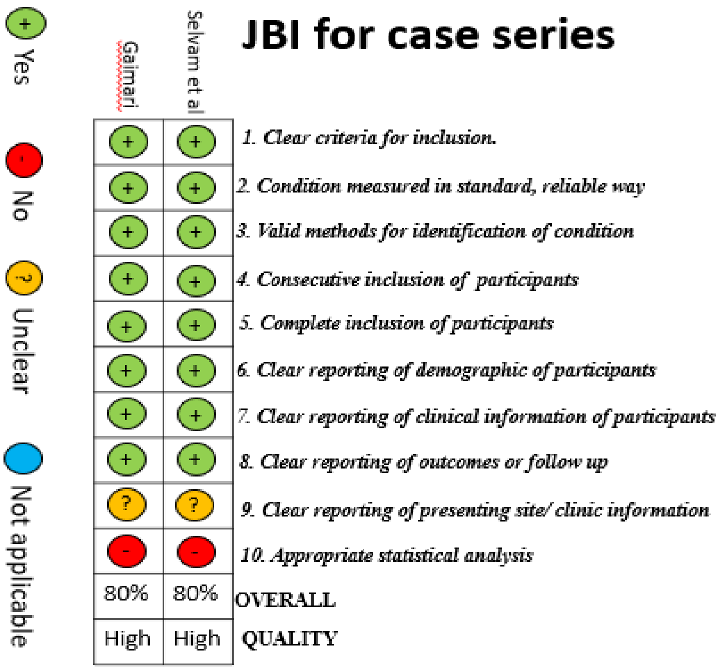


Figure 4 Assessment of risk of bias of included studies utilizing the Joanna Briggs Institute (JBI) critical appraisal tool for case series [23]



Journal of Chemical Health Risks

www.jchr.org

JCHR (2026) 16(2), 2244-2259 | ISSN:2251-6727

Table 5: GRADE evidence profile (EP) for the 14 studies included in the systematic review

Study	Outcome	Study design	Limitation (Risk of Bias)	Inconsistency	Indirectness	Imprecision	Publication Bias	Relative Effect	Absolute Effect	Overall Quality
Artsemyeva Tzerkovsky (2024) [26]	Lesion resolution	Non-randomized retrospective (n = 223)	Serious (High risk; retrospective, no control/blinding)	Not serious	Moderate	Serious	Unclear	Not reported	CR:81.6%	⊕⊕◯◯ Low
Wang et a (2024) [27]	Lesion response	Non-randomized retrospective observational (n = 50)	Serious (High – single arm, small sample)	Not serious	Moderate	Serious	Unclear	Not reported	CR: 70%	⊕⊕◯◯ Low
Bhandari et a (2023) [28]	Lesion resolution, recurrence	RCT (n = 40)	Moderate (Unclear randomization/ blinding)	Not serious	Not serious	Serious (small sample, no CI)	Unclear	Not reported	MB-PDT: 95% vs. Vit A: 75%	⊕⊕⊕◯ Moderate
Han et a (2019) [29]	Lesion response	Non-randomized Uncontrolled clinical study (n = 29)	Serious (non-randomized, small sample)	Not applicable	Moderate	Serious	Unclear	Not reported	CR: 65.5%	⊕⊕◯◯ Low
Istomin et a (2016) [30]	Lesion response (complete/partial)	Non-randomized Uncontrolled clinical study (n = 40)	Serious (No control/ blinding)	Not serious	Moderate	Serious	Unclear	Not reported	CR: 86.7%	⊕⊕◯◯ Low
Gaimari et a (2016) [31]	Treatment response	case series (n = 5)	Serious (small sample)	Not serious	Moderate	Serious	Unclear	Not reported	CR in 3/5 patients	⊕◯◯◯ Very Low
Selvam et a (2015) [32]	Treatment response	case series (n = 5)	Serious (small sample)	Not serious	Moderate	Serious	Unclear	Not reported	All lesions responded	⊕◯◯◯ Very Low
Pietruska et a (2014) [33]	Response rate	Non-randomized Uncontrolled clinical study (n = 23)	Serious (non-randomized, uncontrolled, no blinding)	Not serious	Moderate	Serious	Unclear	Not reported	CR: 65.2%, PR: 34.8%	⊕⊕◯◯ Low
Kawczyk-Krupka et a (2012) [34]	Comparison PDT vs. Cryotherapy	Non-randomized controlled (n = 48)	Serious (non-randomized, no blinding)	Not serious	Moderate	Serious	Unclear	PDT provides better lesion clearance	CR-PDT: 68% vs. Cryo: 45%	⊕⊕◯◯ Low
Jerjes et a (2011) [35]	Recurrence	Non-randomized clinical trial, prospective (n = 147)	Serious (no control, no blinding)	Not serious	Moderate	Serious	Unclear	Not reported	Recurrence: 16%	⊕⊕◯◯ Low

Journal of Chemical Health Risks
www.jchr.org
JCHR (2026) 16(2), 2244-2259 | ISSN:2251-6727

Lin et a (2010) [36]	Lesion response (OVH & OEL)	Non-randomized uncontrolled study (n = 80)	Serious (single-arm, no blinding or comparator)	Not serious	Moderate	Serious	Unclear	Not reported	CR: 93.75%	⊕⊕◯ ◯ Low
Yu et al. (200 [37]	Lesion response	Non-randomized controlled study (n = 46 lesions)	Serious (no blinding, small groups)	Not serious	Moderate	Serious	Unclear	No significant difference	LED: 85%, Laser: 84.6%	⊕⊕◯ ◯ Low
Sieron et a (2003) [38]	Lesion response	Non-randomized single-arm (n = 12)	Serious (small sample)	Not serious	Moderate	Serious	Unclear	Not reported	CR: 63.3%	⊕⊕◯ ◯ Low
Kübler et a (1998) [39]	Lesion response	Non-randomized single-arm (n = 12)	Serious (Very small sample)	Not serious	Moderate	Serious	Unclear	Not reported	CR: 58%	⊕⊕◯ ◯ Low

5. Discussion

Oral cancer is among the most common malignancies in India, accounting for nearly one-third of global cases.[40] Most are preceded by oral potentially malignant disorders (OPMDs), with leukoplakia being the most prevalent, largely linked to tobacco use, alcohol, and HPV.[41] The global prevalence of oral leukoplakia ranges from 1% to 5%, while in India, it is higher (2%–7%) due to widespread tobacco use.[42,43] Malignant transformation occurs in 1%–20% of cases, especially in dysplastic lesions.[44] Despite various treatments, strong evidence for preventing transformation or recurrence is lacking.[45] Early detection is vital, driving interest in newer, minimally invasive treatments like laser-assisted photodynamic therapy (L-PDT), which show promising results with lower morbidity.[46,47]

The potentially malignant nature of oral Leukoplakia necessitates effective therapeutic interventions to prevent malignant transformation.[47] Conventional treatment modalities, including surgical excision and cryotherapy, have shown variable success rates and are often associated with recurrence and morbidity.[48] L-PDT emerges as a promising non-invasive alternative, offering targeted treatment with minimal adverse effects.

The findings from various studies on laser-assisted photodynamic therapy (L-PDT) highlight its promising potential in the management of oral leukoplakia, particularly in dysplastic lesions. Across the 14 included studies, complete response (CR) rates ranged from 7.7% to 95%, with an overall pooled clinical response rate of 76.1%. High CR rates were particularly noted in studies using diode and He-Ne lasers in combination with photosensitizers such as Chlorin-e6, 20% ALA, and Methylene Blue. For example, Artsemyeva et al. [26] and Bhandari et al. [28] reported outstanding CR rates of 95%, suggesting excellent efficacy under optimal parameters.

In contrast, lower CR outcomes, such as the 12% reported by Wang et al., [27] underscore the variability in treatment effectiveness, which can be attributed to differences in lesion characteristics, study design, photosensitizer type, wavelength, power density, and irradiation duration. These treatment variables likely affect tissue penetration and photosensitizer activation, ultimately influencing clinical outcomes. Despite this variability, the overall data support L-PDT as a potentially effective first-line or adjunctive therapy, especially when tailored to individual lesion profiles and optimized treatment protocols.

Recurrence rates following PDT ranged from 0% to 60%, though most studies reported rates below 20%. This variability is likely due to differences in lesion severity, photosensitizers used, treatment protocols, patient factors, and follow-up duration. Notably, Bhandari et al. [28] reported 0% recurrence, while Wang et al. [27] observed 32%. Most studies also reported minimal, self-limiting adverse effects, supporting the favorable safety profile of PDT compared to invasive treatments. Extended follow-up is essential to better understand long-term efficacy and recurrence risk.

Laser parameters, especially wavelength, energy fluence, and power density, played a critical role in determining the success of L-PDT. Wavelengths ranging from 632 nm to 940 nm were employed across studies, with the majority favoring the lower end of the spectrum. The shorter wavelengths, such as 632 nm, offer better tissue

Journal of Chemical Health Risks

www.jchr.org

JCHR (2026) 16(2), 2244-2259 | ISSN:2251-6727

penetration and are more effective in selectively targeting photosensitizers, which can improve therapeutic outcomes. However, the optimal combination of wavelength, energy fluence, and power density remains unclear, emphasizing the need for standardized protocols to guide clinicians in achieving the best results.

An analysis of the methodological quality of the included studies revealed varying levels of rigor. While studies like those of Artsemyeva et al.,[26] Wang et al.,[27] and Han et al. [29] although were adhering to well-established guidelines for reporting study endpoints, inclusion criteria, and follow-up periods, certain methodological inconsistencies were evident in aspects such as randomization, blinding, and statistical analysis. Particularly in retrospective studies, there were issues with biases that could have impacted the interpretation of results. Conversely, randomized controlled trials (RCTs), such as the one by Bhandari et al.,[28] showed clearer evidence of minimized bias through transparent randomization processes and statistical analyses.

While the clinical outcomes are promising, the certainty of evidence, assessed using the GRADE approach—ranged from very low to moderate. Many were limited by small sample sizes, lack of control groups, absence of blinding, and unclear or missing reporting on study protocols or registration. These factors contributed to a downgrading of the certainty of evidence due to a serious risk of bias, imprecision, and suspected publication bias.

Despite the positive outcomes demonstrated in most studies, some limitations remain. These include small sample sizes, heterogeneity in study designs, and the absence of long-term follow-up in some cases. Additionally, the variation in treatment protocols and outcome assessment methods across studies adds a layer of complexity when comparing results and drawing definitive conclusions.

Limitations

While Laser-assisted Photodynamic Therapy (L-PDT) shows promise in treating oral lesions, its effectiveness varies due to differences in laser type, photosensitizer, and lesion characteristics. Studies report inconsistent complete response rates, reflecting data heterogeneity. Methodological limitations, such as small sample sizes, varied study designs, lack of blinding, and inconsistent protocols, undermine the reliability of findings. These heterogeneities also hinder meta-analysis and the development of standardized clinical recommendations.

Recommendation

To address these limitations, future research in L-PDT should focus on several key areas:

1. **Larger, Multicenter Randomized Controlled Trials (RCTs):** Large-scale trials with diverse patient populations and consistent protocols would provide more reliable and generalizable findings.
2. **Standardization of Treatment Parameters:** A clearer understanding of optimal laser parameters (wavelength, energy fluence, and power density) is essential. Standardized protocols will help reduce variability in clinical outcomes.
3. **Long-term Follow-up:** Incorporating longer follow-up periods into studies would help assess the sustainability of L-PDT's effects and recurrence rates over time.
4. **Improved Methodological Rigor:** More rigorous study designs, such as transparent randomization and comprehensive statistical analysis, would minimize biases and enhance the robustness of the results.

Implications for Practice and Research

Photodynamic therapy (PDT) appears to be a promising treatment modality for oral leukoplakia, demonstrating favorable lesion resolution rates across most studies. Based on the findings from the included studies, PDT may offer a non-invasive, safe, and effective alternative to conventional treatments such as surgery or cryotherapy, particularly in early-stage lesions.

Despite encouraging preliminary results, the majority of the evidence is derived from non-randomized, observational studies, with only one randomized controlled trial identified. This limits the certainty and generalizability of the current evidence. Nevertheless, reported outcomes—including high lesion clearance rates, low recurrence in some studies, and minimal adverse events—suggest the potential clinical utility of PDT in managing oral leukoplakia.

The certainty of evidence, as assessed using the GRADE approach, ranged from very low to moderate, indicating a need for caution in clinical decision-making. However, these findings provide valuable insights and form a basis for further investigation.

Such studies would enhance the quality of evidence and help establish PDT as a standard therapeutic option in clinical practice for Oral leukoplakia and potentially other oral premalignant disorders.

Conclusion

L-PDT holds considerable promise as a safe and effective treatment for oral lesions, showing particularly favorable outcomes in specific settings, such as when using diode and He-Ne lasers combined with certain photosensitizers like Chlorin-e6 or ALA. Although variability in treatment success and recurrence rates remains a concern, the overall safety profile, with only transient side effects like pain and ulcers, supports its continued use. With ongoing advancements, the treatment's effectiveness is likely to improve, offering better outcomes for individuals with oral lesions.

References

1. Bewley, A.F. and D.G. Farwell, Oral leukoplakia and oral cavity squamous cell carcinoma. Clinics in Dermatology, 2017. 35(5): p. 461-467. [doi: 10.1016/j.clindermatol.2017.06.008]
2. Mello FW, Miguel AFP, Dutra KL, Porporatti AL, Warnakulasuriya S, Guerra ENS. Rivero. Prevalence of oral potentially malignant disorders: a systematic review and meta-analysis. J Oral Pathol Med. 2018;47:633–40 [doi: 10.1111/jop.12726]
3. Guan JY, Luo YH, Lin YY, et al. Malignant transformation rate of oral leukoplakia in the past 20 years: A systematic review and meta-analysis. *J Oral Pathol Med*. 2023;52(8):691-700. [doi:10.1111/jop.13440]
4. Arnaoutakis, D., et al., Recurrence patterns and management of oral cavity premalignant lesions. Oral Oncol, 2013. 49(8): p. 814-7.[doi: 10.1016/j.oraloncology.2013.04.008].
5. Liu, W., et al., Malignant transformation of oral leukoplakia: a retrospective cohort study of 218 Chinese patients. BMC Cancer, 2010. 10: p. 685. [doi: 10.1186/1471-2407-10-685].
6. van der Waal, I., Potentially malignant disorders of the oral and oropharyngeal mucosa; terminology, classification and present concepts of management. Oral Oncol, 2009. 45(4- 5): p. 317-23. [doi: 10.1016/j.oraloncology.2008.05.016]
7. Saini, R., et al., Prospects in the application of photodynamic therapy in oral cancer and premalignant lesions. Cancers, 2016. 8(9). [doi: 10.3390/cancers8090083]
8. Warnakulasuriya S. Clinical features and presentation of oral potentially malignant disorders. Oral Surgery, Oral Medicine, Oral Pathology and Oral Radiology. 2018 Jun;125(6):582–90. [doi: 10.1016/j.oooo.2018.03.011]
9. Maymone MBC, Greer RO, Kesecker J, Sahitya PC, Burdine LK, Cheng AD, Maymone AC. Vashi. Premalignant and malignant oral mucosal lesions: clinical and pathological findings. J Am Acad Dermatol. 2019;81:59–71. [doi: 10.1016/j.jaad.2018.09.060]
10. Fan JH, Wang JB, Qu CX, et al. Association between oral leukoplakia and upper gastrointestinal cancers: a 28-year follow-up study in the Linxian General Population Trial. *Oral Oncol*. 2014;50(10):971-975. [doi:10.1016/j.oraloncology.2014.07.009]
11. Holmstrup P, Dabelsteen E. Oral leukoplakia-to treat or not to treat. Oral Dis. 2016;22:494–7. [doi:10.1111/odi.12443]
12. Chau L, Jabara JT, Lai W, Svider PF, Warner BM, Lin HS, et al. Topical agents for oral cancer chemoprevention: a systematic review of the literature. Oral Oncol. 2017;67:153–9. [doi:10.1016/j.oraloncology.2017.02.014]
13. Yu, C.H., et al., Photodynamic therapy outcome for oral verrucous hyperplasia depends on the clinical appearance, size, color, epithelial dysplasia, and surface keratin thickness of the lesion. Oral Oncol, 2008. 44(6): p. 595-600. [doi: 10.1016/j.oraloncology.2007.08.016].
14. Konopka K, G.T., Photodynamic Therapy in Dentistry. J Dent Res., 2007. 86(8): p. 694- 707. [doi: 10.1177/154405910708600803].
15. Buytaert, E., M. Dewaele, and P. Agostinis, Molecular effectors of multiple cell death pathways initiated by photodynamic therapy. BiochimBiophys Acta, 2007. 1776(1): p. 86-107. [doi: 10.1016/j.bbcan.2007.07.001].
16. Javed, F., L.P. Samaranayake, and G.E. Romanos, Treatment of oral fungal infections using antimicrobial photodynamic therapy: a systematic review of currently available evidence. PhotochemPhotobiol Sci, 2014. 13(5): p. 726-34. [doi: 10.1039/c3pp50426c].
17. Siddiqui, S.H., K.H. Awan, and F. Javed, Bactericidal efficacy of photodynamic therapy against Enterococcus faecalis in infected root canals: a systematic literature review. PhotodiagnosisPhotodyn Ther, 2013. 10(4): p. 632-43. [doi: 10.1016/j.pdpdt.2013.07.006]

18. Wan W, Gao X, Song S, Peng J, Jiang C, Fang C, Li N. L. Ma. 5-aminolevulinic acid photodynamic therapy for extensive oral leukoplakia with concomitant oral submucous fibrosis: a case report, photodiagnosis and photodynamic therapy. 2022; 41: 103203. [doi: 10.1016/j.pdpdt.2022.103203]
19. Silva LAD, Pinheiro SL. Clinical evaluation of intravascular blood irradiation with laser, Photobiomodulation, and photodynamic therapy in Cancer patients with Mucositis, Photobiomodulation, photomedicine, and laser surgery. 2021; 39: 687–95. [doi:10.1089/photob.2021.0031]
20. Santos DSA, Galvão GS, Ribas PF, Peres MPSM. J. B. Franco. Photodynamic therapy in the treatment of oral lesions caused by paracoccidiomycosis, photodiagnosis and photodynamic therapy. 2022; 37: 102648. [doi: 10.1016/j.pdpdt.2021.102648]
21. Silva FCristinaD, Rosa LP, Santos GPO, Inada NM, Blanco KC, Araújo TSD. V. S. Bagnato. Total mouth photodynamic therapy mediated by blue led and curcumin in individuals with AIDS, Expert review of anti-infective therapy. 2020; 18: 689–96. [doi: 10.1080/14787210.2020.1756774]
22. Slim K, Nini E, Forestier D, Kwiatkowski F, Panis Y, Chipponi J. Methodological index for non-randomized studies (minors): development and validation of a new instrument. *ANZ J Surg*. 2003;73(9):712-716. [doi: 10.1046/j.1445-2197.2003.02748.x]
23. Moola S, Munn Z, Sears K, et al. Conducting systematic reviews of association (etiology): The Joanna Briggs Institute's approach. *Int J Evid Based Healthc*. 2015;13(3):163-169. [doi:10.1097/XEB.0000000000000064]
24. Tufanaru C, Munn Z, Aromataris E, Campbell J, Hopp L. Chapter 3: Systematic reviews of effectiveness. JBI manual for evidence synthesis. JBI. 2020 Dec;10. [doi: 10.46658/JBIMES-20-04]
25. Atkins D, Best D, Briss PA, et al. Grading quality of evidence and strength of recommendations. *BMJ*. 2004;328(7454):1490. [doi:10.1136/bmj.328.7454.1490]
26. Artsemyeva TP, Tzerkovsky DA. Photodynamic therapy of Leukoplakia of the oral mucosa: Experience of using the method in 223 Patients. Biomedical Photonics. 2024 May 13(1):39-46. [doi: 10.24931/2413-9432-2023-13-1-39-46].
27. Wang Y, Tang H, Wang K, Zhao Y, Xu J, Fan Y. Clinical evaluation of photodynamic therapy for oral leukoplakia: a retrospective study of 50 patients. BMC Oral Health. 2024 Jan 3;24(1):9. [doi:10.1186/s12903-023-03791-5]
28. Bhandari A, Budakoti A, Chaudhary M. Methylene Blue-mediated Photodynamic Therapy for the Treatment of Oral Leukoplakia. Journal of the Scientific Society. 2023 Sep 1;50(3):394-8. [doi: 10.4103/jss.jss_97_23]
29. Han Y, Xu S, Jin J, Wang X, Liu X, Hua H, Wang X, Liu H. Primary clinical evaluation of photodynamic therapy with oral leukoplakia in Chinese patients. Frontiers in physiology. 2019 Jan 22;9:1911. [doi: 10.3389/fphys.2018.01911]
30. Istomin YP, Artemyeva TP, Tzerkovsky DA. Photodynamic therapy with photosensitizer photolon for oral leukoplakia. Biomedical Photonics. 2016;5(2):13-20. [doi: 10.24931/2413-9432-2016-5-2-13-20]
31. Gaimari G, Russo C, Palaia G, Tenore G, Del Vecchio A, Romeo U. Photodynamic therapy in the treatment of epithelial potentially malignant disorders of the mouth: advantages and disadvantages. InSixth International Conference on Lasers in Medicine 2016 Mar 22 (Vol. 9670, pp. 148-154). SPIE. [doi: 10.1117/12.2192039]
32. Selvam NP, Sadaksharam J, Singaravelu G, Ramu R. Treatment of oral leukoplakia with photodynamic therapy: A pilot study. Journal of cancer research and therapeutics. 2015 Apr 1;11(2):464-7. [doi:10.4103/0973-1482.147703]
33. Pietruska M, Sobaniec S, Bernaczyk P, Cholewa M, Pietruski JK, Dolińska E, Skurska A, Duraj E, Tokajuk G. Clinical evaluation of photodynamic therapy efficacy in the treatment of oral leukoplakia. Photodiagnosis and photodynamic therapy. 2014 Mar 1;11(1):34-40. [doi:10.1016/j.pdpdt.2013.10.003]
34. Kawczyk-Krupka A, Waśkowska J, Raczkowska-Siostrzonek A, Kościarz-Grzesiok A, Kwiatek S, Straszak D, Latos W, Koszowski R, Sieroń A. Comparison of cryotherapy and photodynamic therapy in treatment of oral leukoplakia. Photodiagnosis and photodynamic

therapy. 2012 Jun 1;9(2):148-55. [doi:10.1016/j.pdpdt.2011.12.007]
35. Jerjes W, Upile T, Hamdoon Z, Mosse CA, Akram S, Hopper C. Photodynamic therapy outcome for oral dysplasia. Lasers in surgery and medicine. 2011 Mar;43(3):192-9. [doi:10.1002/lsm.21036]
36. Lin HP, Chen HM, Yu CH, Yang H, Wang YP, Chiang CP. Topical photodynamic therapy is very effective for oral verrucous hyperplasia and oral erythroleukoplakia. Journal of oral pathology & medicine. 2010 Sep;39(8):624-30. [doi:10.1111/j.1600-0714.2010.00935.x]
37. Yu CH, Lin HP, Chen HM, Yang H, Wang YP, Chiang CP. Comparison of clinical outcomes of oral erythroleukoplakia treated with photodynamic therapy using either light-emitting diode or laser light. Lasers in Surgery and Medicine: The Official Journal of the American Society for Laser Medicine and Surgery. 2009 Nov;41(9):628-33. [doi: 10.1002/lsm.20841]
38. Sieroń A, Adamek M, Kawczyk-Krupka A, Mazur S, Ilewicz L. Photodynamic therapy (PDT) using topically applied δ-aminolevulinic acid (ALA) for the treatment of oral leukoplakia. Journal of oral pathology & medicine. 2003 Jul;32(6):330-6. [doi: 10.1034/j.1600-0714.2003.00068.x]
39. Kübler A, Haase T, Rheinwald M, Barth T, Mühling J. Treatment of oral leukoplakia by topical application of 5-aminolevulinic acid. International journal of oral and maxillofacial surgery. 1998 Dec 1;27(6):466-9. [doi: 10.1016/s0901-5027(98)80040-4]
40. Subramanian S, Sankaranarayanan R, Bapat B, Somanathan T, Thomas G, Mathew B, et al. Cost-effectiveness of oral cancer screening: Results from a cluster randomized controlled trial in India. Bull World Health Organ 2009;87:200-6, [doi: 10.2471/blt.08.053231]
41. Sharma M, Bairy I, Pai K, Satyamoorthy K, Prasad S, Berkovitz B, et al. Salivary IL-6 levels in oral leukoplakia with dysplasia and its clinical relevance to tobacco habits and periodontitis. Clin Oral Investig 2011;15:705-14. [doi: 10.1007/s00784-010-0435-5]
42. Warnakulasuriya S, Kujan O, Aguirre-Urizar JM, Bagan JV, González-Moles MÁ, Kerr AR, Lodi G, Mello FW, Monteiro L, Ogden GR, Sloan P. Oral potentially malignant disorders: A consensus report from an international seminar on nomenclature and classification, convened by the WHO Collaborating Centre for Oral Cancer. Oral diseases. 2021 Nov;27(8):1862-80. [doi: 10.1111/odi.13704]
43. Gupta N, Gupta R, Acharya AK, Patthi B, Goud V, Reddy S, Garg A, Singla A. Changing Trends in oral cancer-a global scenario. Nepal journal of epidemiology. 2016 Dec;6(4):613. [doi: 10.3126/nje.v6i4.17255]
44. Napier SS, Speight PM. Natural history of potentially malignant oral lesions and conditions: an overview of the literature. Journal of Oral Pathology & Medicine. 2008 Jan;37(1):1-0. [doi: 10.1111/j.1600-0714.2007.00579.x]
45. Rhodus, N. L., Kerr, A. R., and Patel, K. (2014). Oral cancer: leukoplakia, premalignancy, and squamous cell carcinoma. Dent. Clin. North Am.58, 315–340. [doi: 10.1016/j.cden.2013.12.004]
46. Speight PM, Khurram SA, Kujan O. Oral potentially malignant disorders: risk of progression to malignancy. Oral Surg Oral Med Oral Pathol Oral Radiol. 2018;125(6):612-627. [doi:10.1016/j.oooo.2017.12.011]
47. Li Y, Wang B, Zheng S, He Y. Photodynamic therapy in the treatment of oral leukoplakia: A systematic review. *Photodiagnosis Photodyn Ther*.2019;25:17-22. [doi:10.1016/j.pdpdt.2018.10.023]
48. Saka-Herrán C, Jané-Salas E, Mari-Roig A, Estrugo-Devesa A, López-López J. Time-to-treatment in oral cancer: causes and implications for survival. Cancers. 2021 Mar 16;13(6):1321.[doi: 10.3390/cancers13061321]