Photodiagnosis and Photodynamic Therapy 28 (2019) 146–152

Contents lists available at ScienceDirect

Photodiagnosis and Photodynamic Therapy

journal homepage: www.elsevier.com/locate/pdpdt

Review

Photodynamic therapy for oral potentially malignant disorders

Xin Jin[a,b], Hao Xu[c], Jing Deng[c], Hongxia Dan[c], Ping Ji[a,b,d], Qianming Chen[c], Xin Zeng[c,*]

[a] College of Stomatology, Chongqing Medical University, Chongqing 401147, China
[b] Chongqing Key Laboratory of Oral Diseases and Biomedical Sciences, Chongqing 401147, China
[c] State Key Laboratory of Oral Diseases, National Clinical Research Center for Oral Diseases, West China Hospital of Stomatology, Sichuan University, Chengdu 610041, China
[d] Chongqing Municipal Key Laboratory of Oral Biomedical Engineering of Higher Education, Chongqing 401147, China

ARTICLE INFO

Keywords:
Photodynamic therapy
Oral potentially malignant disorders
Meta-analysis
Systematic review

ABSTRACT

To assess the impact of photodynamic therapy (PDT) parameters in the management of oral potentially malignant disorders (OPMDs). We conducted a systematic review and meta-analysis of studies that assessed the curative effect of PDT published in PubMed and Embase until Dec 2018. Random or fixed effects models for pooled estimates calculation were used. A pooled estimate calculation revealed that lesion size decreased by 1.38 cm^2 (95% CI: 0.39–2.36) after PDT, and the overall complete response (CR) was 0.52 (95% CI: 0.36–0.68), while partial response (PR) reached 0.82 (95% CI: 0.74–0.88). Subgroup analyses revealed that the lesion response (CR: 0.21 [95% CI: 0.12–0.33]) of oral lichen planus was worse than that of other disease entities. 20% aminolevulinic acid was more effective than other photosensitizers, with the overall CR was 0.68 (95% CI: 0.42–0.86), while the PR was 0.88 (95% CI: 0.76–0.94). Topical use of photosensitizers can yield desirable results, while gargling methylene blue yields poor response (0.82 [95% CI: 0.75–0.88] vs. 0.59 [95% CI: 0.44–0.72], respectively). PDT is an effective treatment modality in the management of OPMDs, the overall efficacy of which is influenced by several factors.

1. Introduction

The World Health Organization Working Group defines oral potentially malignant disorders (OPMDs) as all clinical features with a risk of oral cancer formation. Not all OPMDs, including oral leukoplakia (OLK), oral lichen planus (OLP), erythroleukoplakia, and oral verrucous hyperplasia (OVH), will transform to invasive cancer [1]. They significantly impact the quality of life; aside from the pain and dysfunction, the depression or anxiety from their potentially malignant transformation is also a heavy burden [2].

Identifying the proper management of the OPMDs is urgently needed. Surgical excision causes scar tissue formation that impairs eating and talking abilities. After surgical intervention, recurrencies and cancer development in areas of excised lesions have been reported in as much as 10–20% and 3–9%, respectively [3]. According to the published Cochrane database of systematic reviews, no evidence shows that nonsurgical intervention modalities, such as topical and oral drugs, are effective for preventing oral cancer [4,5]. Other therapies include laser ablation or cryotherapy, but they cannot optionally target abnormally proliferating cells.

Photodynamic therapy (PDT) is an alternative treatment option for OPMD [6]. It involves an interaction between a light source and the administration of a chemical dye or a photosensitizer (PS) in the presence of oxygen. This interaction produces singlet oxygen and free radicals, causing localized oxidative damage and cell death [7]. Findings from reviews suggested that PDT is a potential treatment for OPMDs with high efficacy and minimal side effects. However, the disease categories, sites, degree of dysplasia, type of PS, and administration methods varied in the published studies. The present study aimed to conduct a meta-analysis and systematically review the efficacy and evaluate the impact of different related factors of PDT in the management of OPMDs to develop specific recommendations on the usage of PDT for OPMDs.

2. Materials and methods

2.1. Study identification and selection

PubMed, Embase, and ISI Web of Knowledge databases were searched until Dec 2018. Different combinations of the following keywords were used: photodynamic therapy, oral premalignant lesions, oral potentially malignant disorders, oral leukoplakia, oral lichen planus,

* Corresponding author at: 14 RenMinNanLu, Section 3, Chengdu, Sichuan 610041, China.
E-mail address: zengxin22@163.com (X. Zeng).

https://doi.org/10.1016/j.pdpdt.2019.08.005
Received 14 December 2018; Received in revised form 30 June 2019; Accepted 2 August 2019
Available online 05 August 2019
1572-1000/ © 2019 Elsevier B.V. All rights reserved.

erythroplakia, erythroleukoplakia, verrucous hyperplasia, oral dysplasia, and submucous fibrosis. The inclusion criteria were: (a) original studies; (b) clinical studies; (c) intervention aims to evaluate the efficacy of PDT in the management of OPMDs; (d) lesion response was assessed and recorded; (e) articles published only in English language. The exclusion criteria were: (a) reviews, abstracts, and commentaries; (b) pre-clinical studies; (c) inconsistent efficacy evaluation standard such that subsequent analysis cannot be performed. If several articles were published by the same authors using the same patient data, only the most recent study or the one with the largest size was included.

2.2. Data extraction

Two investigators independently assessed the titles and abstracts of all eligible publications. The following details were collected from each study: first author's name, PubMed ID, publication year, type of PS, disease types, method of administration, disease location (buccogingival sulcus, retromolar trigone, alveolar ridge, and vestibulum were grouped into one as gingival mucosa for analytical purposes), number of lesions, changes in lesion size, and lesion responses after treatment. Complete response (CR) was defined as no visible lesion confirmed via clinical evaluation. Meanwhile, partial response (PR) was defined as at least 20% reduction in lesion size, including the lesions with CR.

Other parameters collected in the course of the treatment included wavelength and energy density of the laser, duration of irradiation and lesion dressing, treatment interval, and relapse during follow-up. Additionally, adverse reactions during or after PDT were also recorded.

2.3. Statistical analysis

Heterogeneity of meta-analysis (the I^2 and Q): heterogeneity statistic Q and the I-squared statistics were calculated. If the I^2 statistic was > 50% or the p value of Q test was < 0.05, then the results of random effect model were recommended.

Pooled estimates calculation: for the continuous variable, the mean difference was chosen as the summary measure. Meanwhile, inverse variance method was employed for the fixed effects model, and the restricted maximum-likelihood was used for the random effects model. For the discrete variable, the proportion was calculated, and logit transformation was implemented. Inverse variance method was applied for the fixed effects model, while the DerSimonian-Laird method was used for the random effects model.

Meta bias: the funnel plot was plotted to evaluate the publication bias, and a weighted linear regression was used to test the funnel plot asymmetry. When the p value was > 0.05, the publication bias can be ignored.

Sensitivity analysis: the subgroup and influence analyses were performed for sensitivity analysis. The influence analysis is the pooled estimates calculated by omitting one study at a time.

3. Results

3.1. Demographic characteristics of included studies

Fig. 1 shows the selection process. A total of 79 publications were identified after an initial search of the PubMed, Embase, and ISI Web of Knowledge databases. Among these, 40 were excluded for being irrelevant to OPMDs and PDT or being pre-clinical studies. After reading 39 potential articles, 11 reviews and letters were excluded. Thus, 28 articles were left for data extraction. One study was excluded because treatment was a combination of PDT and cryotherapy [8], and three studies were excluded for unavailability of efficacy evaluation data [9–11]. Two studies were excluded for data duplication [12,13]. Finally, a total of 22 publications were included for meta-analysis [14–35].

The total numbers of subjects ranged 5–147, with ages ranging from 21 to 89 years. Eighteen studies reported the gender of subjects, in which the number of male participants ranged 0–90 individuals. Overall, 874 OPMD lesions exposed to PDT were included.

3.2. Impact of PDT on the lesion size of OPMDs

Four publications recorded the changes in lesion size before and after PDT, and 136 lesions in eight trials were identified for meta-analysis. Table S1 shows the details.

The forest plot (Fig. 2) shows the lesion size decreased by 1.38 cm^2 (95% CI: 0.39–2.36) after treatment. The I-squared statistic was 73% ($p < 0.01$), suggesting heterogeneity in the eight trials. The p value of the funnel plot asymmetry was 0.1369, indicating no publication bias existed (Appendix Fig. 1). The result of sensitivity analysis suggests the stability of this meta-analysis (Appendix Fig. 2). Subgroup analyses were performed for different disease types, and lesion locations, but the mean differences of lesion size changes have no statistical significance based on t test (see supplemental appendices).

3.3. Impact of PDT on the lesion response of OPMDs

The present study included 22 publications involving 874 lesions that assessed the lesion response (complete or partial) after PDT. Table 1 shows the details.

As shown in Appendix Fig. 7, heterogeneity exists in the meta-analysis. The p value of Q test was < 0.01, and the I^2 was 91%; thus, the result of the random effects model was recommended. The overall CR was 0.52 (95% CI: 0.36–0.68), which indicated that nearly 50% of the lesions reached complete remission. The funnel plot showed no publication bias existed (Appendix Fig. 8). Moreover, the sensitivity analysis (Appendix Fig. 9) showed that the study conducted by Chen (2007) played an important role on the heterogeneity.

The results of PR are displayed in Fig. 3. I^2 statistic (72%) and p value of Q test (< 0.01) indicated heterogeneity. The pooled PR was 0.82 (95% CI: 0.74–0.88). The funnel plot indicated no publication bias existed ($p > 0.05$, Appendix Fig. 10), and the sensitivity analysis showed that the results were robust (Appendix Fig. 11).

3.3.1. Subgroup analysis of disease types

Ten studies were analyzed for OLK lesions, five for erythroleukoplakia, four for verrucous hyperplasia, five for OLP, and three for epithelial dysplasia. Appendix Fig. 12 shows the forest plot of subgroup analysis for CR, while Appendix Fig. 13 shows that for PR. The pooled CR of OLK, erythroleukoplakia, verrucous hyperplasia, OLP, and epithelial dysplasia was 0.31 (95% CI: 0.15–0.53), 0.85 (95% CI: 0.73–0.93), 0.94 (95% CI: 0.52–1.00), 0.21 (95% CI: 0.12–0.33), and 0.94 (95% CI: 0.76–0.99), respectively. This indicated that most lesions of erythroleukoplakia, verrucous hyperplasia, and epithelial dysplasia lesions can achieve CR, while only a small percentage of OLK and OLP lesions may achieve CR, and the difference is statistically significant based on t test. When the overall PR of the above diseases was calculated, the proportion of OLK and OLP lesions increased to 0.76 (95% CI: 0.63–0.85) and 0.70 (95% CI: 0.57–0.80), but was still significantly different compared with that of verrucous hyperplasia (Fig. 4A and F).

3.3.2. Subgroup analysis of light sources

Five types of light source were used in 16 studies, namely, dye laser (n = 3), LED (n = 6), diode laser (n = 3), semiconductor laser (n = 3), and xenon lamp (n = 1). Appendix Fig. 14 (CR) and Appendix Fig. 15 (PR) show the forest plots of this subgroup analysis. The results of random effects model for the pooled CR and PR indicated that the efficacy of diode laser was better than others, as the overall CR from the diode laser was 0.89 (95% CI: 0.55–0.98) while other light sources resulted in full remission in only approximately half of the lesions (Fig. 4B and G). However, the difference had no statistical significance based on the t test. The overall PR of LED and semiconductor laser

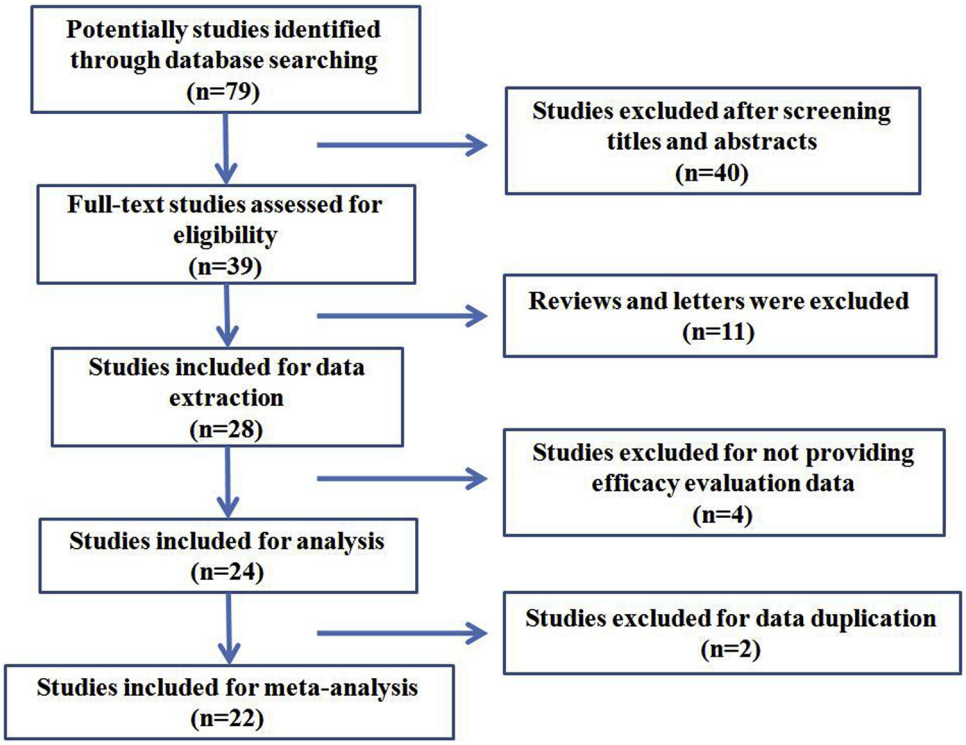

Fig. 1. Flow diagram of included/excluded studies.

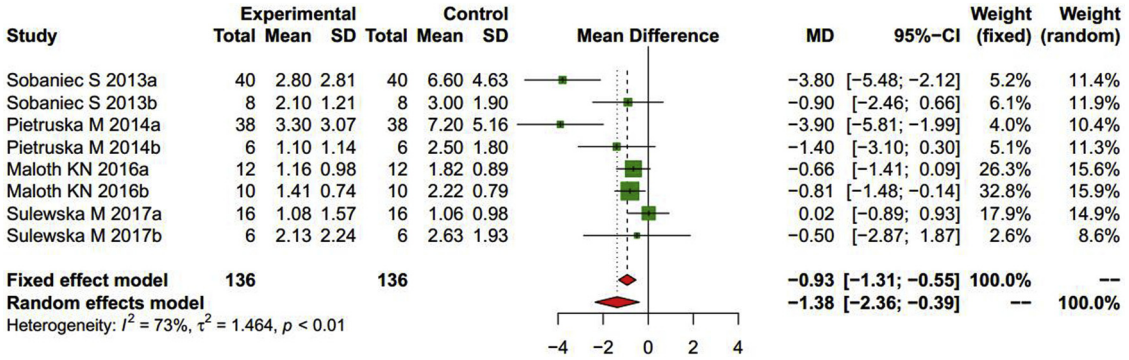

Fig. 2. Forest plots of mean difference of lesion size changes before and after PDT. The solid circles indicate estimates of lesion size changes for each trial, and the size of each solid circle represents the sample size of each trial. The negative symbol of the mean differences indicates the lesion size was decreased. The error bars are 95% confidence intervals.

increased to 0.78 (95% CI: 0.66–0.86) and 0.84 (95% CI: 0.73–0.91), but they had significant differences compared to diode laser at 0.95 (95% CI: 0.79–0.99).

3.3.3. Subgroup analysis of lesion locations

Two types of lesion locations were detailed in 20 studies. Appendix Fig. 16 (CR) and Appendix Fig. 17 (PR) show the forest plots. The overall CR and PR of the BM/L and T/FM/G groups were on an average level, with no statistically significant differences (Fig. 4C and H).

3.3.4. Subgroup analysis of administration methods

Among the 21 trials for PDT, 15 used topical application, two used MB gargle, three used intravenous administration, and only one used injection. Appendix Fig. 18 (CR) and Appendix Fig. 19 (PR) show the forest plots. Intravenous administration was more effective than other administrations methods (overall CR: 0.94 [95% CI: 0.76–0.99]. When the analysis included pooled PR, the percentage of topical use increased to 0.82 (95% CI: 0.75–0.88), but the difference was not statistically significant compared to intravenous use. However, MB gargle still yielded poor response (Fig. 4D and I).

3.3.5. Subgroup analysis of photosensitizers

Four types of PS were discussed in 15 trials; 9 of them were 20% ALA, two were 10% ALA, two were CDS, and two were 5% ALA. Appendix Fig. 20 (CR) and Appendix Fig. 21 (PR) show the forest plots of subgroup analysis. The 20% ALA was more effective than 5% ALA and CDS and the difference as was statistically significant. The overall CR of 20% ALA was 0.68 (95% CI: 0.42–0.86), while that for the other two was 0.16 (95% CI: 0.07–0.35) and 0.28 (95% CI: 0.20–0.38). As to the pooled PR, the ratios of 5% ALA and CDS increased to 0.77 (95% CI: 0.62–0.87) and 0.79 (95% CI: 0.70–0.86) (Fig. 4E and *J)*.

3.4. Other factors in the course of PDT

In all studies, lasers with wavelength ranging from 630 to 635 nm, and energy density of 100–200 joules per square centimeters (J/cm^2) were commonly used. Duration of irradiation ranged between 120 s and 1200s, with or without intervals of 3-minute rests. In studies using

Table 1
Characteristics of the studies with lesion response after PDT.

Author	Year	Light sources	Types of PS	Disease types	Administration method	Lesion locations	Sample size	CR	PR (only)	NR
Sulewska M	2017	LED	5% ALA	OLP	topical	BM/L	16	4	7	5
						T/FM/G	6	1	4	1
Maloth KN	2016	LED	5% ALA	OLK	topical	mixed	12	2	8	2
				OLP			10	0	8	2
Selvam NP	2015	xenon lamp	10% ALA	OLK	topical	BM/L	1	0	1	0
				erythroleukoplakia		BM/L	1	1	0	0
				OLK		T/FM/G	1	1	0	0
				OLK		T/FM/G	1	0	1	0
				OLK		T/FM/G	1	0	0	1
Romeo U	2014	diode laser	20% ALA	OLK	topical	BM/L	1	1	0	0
Pietruska M	2014	Semiconductor laser	CDS	OLK	topical	BM/L	38	9	21	8
						T/FM/G	6	3	1	2
Ikeda H	2013	excimer laser	Porfimer	epithelial dysplasia	intravenous	mixed	7	7	0	0
Sobaniec S	2013	Semiconductor laser	CDS	OLP	topical	BM/L	40	13	22	5
						mixed	8	1	3	4
Wong SJ	2013	dye laser	30 mg/kg ALA	OLK	oral administration	T/FM/G	7	0	0	7
Sadaksharam J	2012	xenon lamp	MB	OLP	gargle MB	BM/L	20	0	10	10
Kawczyk- Krupka A	2012	Semiconductor laser	20% ALA	OLK	topical	BM/L	29	23	5	1
						T/FM/G	12	9	1	2
						BM/L	5	4	1	0
						mixed	1	1	0	0
						T/FM/G	2	1	1	0
						T/FM/G	2	1	0	1
		dye laser	10% ALA			BM/L	14	11	1	2
						T/FM/G	9	8	0	1
						BM/L	2	2	0	0
						mixed	1	0	1	0
						T/FM/G	3	3	0	0
Uehara M	2011	excimer laser	Porfimer	epithelial dysplasia	intravenous	T/FM/G	4	4	0	0
						mixed	2	2	0	0
						BM/L	1	1	0	0
Shafirstein G	2011	dye laser	20% ALA	OLK	topical	BM/L	5	3	2	0
						T/FM/G	4	1	3	0
						T/FM/G	1	0	1	0
						T/FM/G	5	2	3	0
					injected	BM/L	2	0	1	1
						T/FM/G	2	2	0	0
						mixed	1	0	1	0
						T/FM/G	1	1	0	0
Jerjes W	2011	diode laser	mixed	mixed	mixed	mixed	147	114	24	9
Lin HP	2010	diode laser	20% ALA	OVH	topical	mixed	40	40	0	0
				erythroleukoplakia			40	38	2	0
Yu CH	2009	LED	20% ALA	erythroleukoplakia	topical	mixed	20	17	3	0
Rigual NR	2009	mixed	Porfimer	epithelial dysplasia	intravenous	mixed	9	9	0	0
Yu CH	2008	LED	20% ALA	OVH	topical	mixed	36	36	0	0
Chen HM	2007	LED	20% ALA	OVH	topical	mixed	24	24	0	0
				OLK		T/FM/G	21	5	11	5
				OLK		mixed	76	11	43	22
				OLK		mixed	22	6	14	2
				OLK		mixed	75	10	40	25
				erythroleukoplakia		mixed	6	4	2	0
Aghahosseini F	2006	diode laser	MB	OLP	gargle MB	mixed	5	2	2	1
Aghahosseini F	2006	diode laser	MB	OLP	gargle MB	mixed	26	4	12	10
Tsai JC	2004	LED	20% ALA	OLK	topical	mixed	24	3	9	12
				OVH			2	0	2	0
				erythroleukoplakia			5	4	1	0
KYbler A	1998	dye laser	20% ALA	OLK	topical	BM/L	1	1	0	0
						BM/L	2	1	1	0
						T/FM/G	2	0	2	0
						T/FM/G	4	1	1	2
						T/FM/G	3	2	0	1

LED: light emitting diode; PS: photosensitizer; ALA: 5-Aminolevulinic acid; CDS: chlorine-e6 and dimethyl sulfoxide; MB: methylene blue;
OLP: oral lichen planus; OLK: oral leukoplakia; OVH: oral verrucous hyperplasia;
BM/L: buccal mucosa and/or lips; T/FM/G: tongue and/or floor of the mouth and/or gingival mucosa;
CR: complete response; PR: partial response; NR: no response;
mixed: with different required information or information were not mentioned.

topical application of PS, the lesion dressing time ranged 30–240 min. The frequency of PDT application ranged from 1 to 12 times throughout the study period at one- to two-week intervals (Table 2).

Majority of patients experienced no discomfort or only minor adverse effects (pain, swelling, burning sensation, and taste alteration) during treatments and disappeared immediately. Patients with moderate to severe pain received local anesthesia and/or were given oral analgesic drugs.

Nineteen studies reported the recurrence rate, and it ranged between 0% and 34.5%, with a usual follow-up time of 1–12 months.

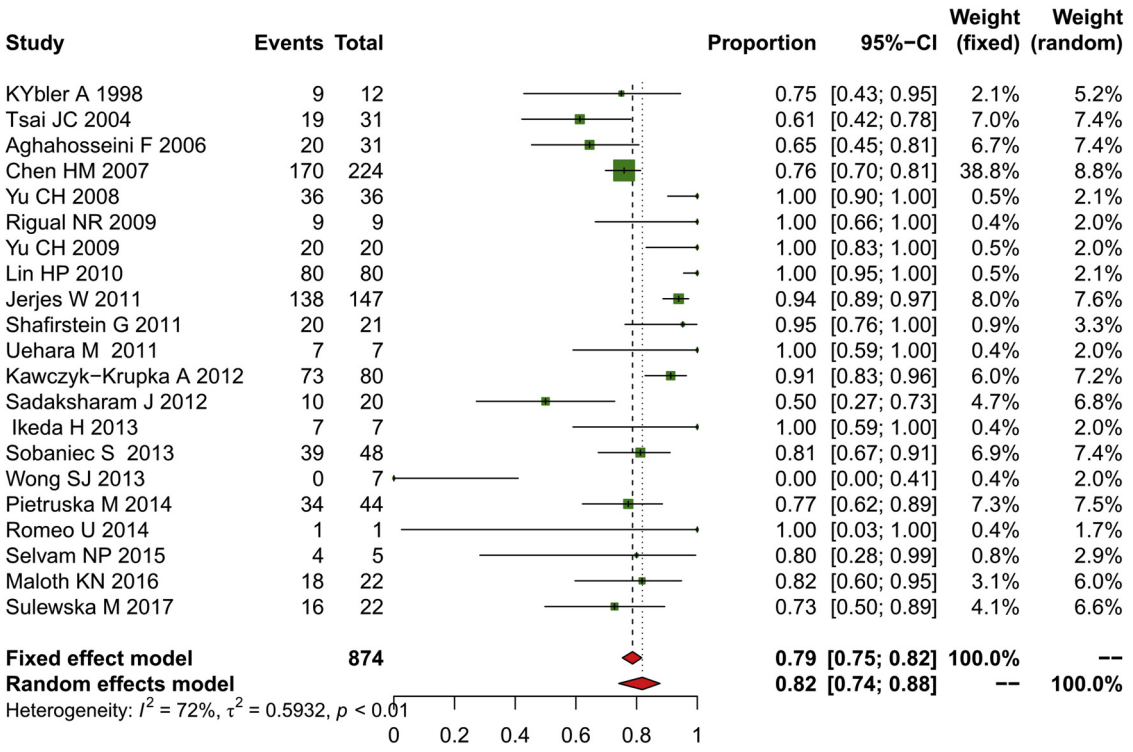

Fig. 3. Forest plots of proportions of PR after PDT. The solid circles indicate proportions of PR for each study, and the size of each solid circle represents the sample size of each study.

4. Discussion

PDT offers a new approach in treating several early lesions [6], but a standard application has not been established. Our meta-analysis focused on the association between the curative effect and possible factors that affect the efficacy of PDT to establish optimal protocols.

We found that topical use of 20% ALA had a significantly higher efficacy compared to 5% ALA or CDS in terms of CR and PR. Constant saliva secretion and frequent tissue movement may impair drug absorption; thus, high local concentration of PS may achieve better potency. Therefore, the topical use of 20% ALA may be recommended as the optimal modality. With time and practice, new promising products will be found with higher efficacy and shorter dressing time.

The most widely employed method of administration among the included studies was topical. In terms of CR, intravenous administration had a significantly better efficacy compared to topical use and gargle.

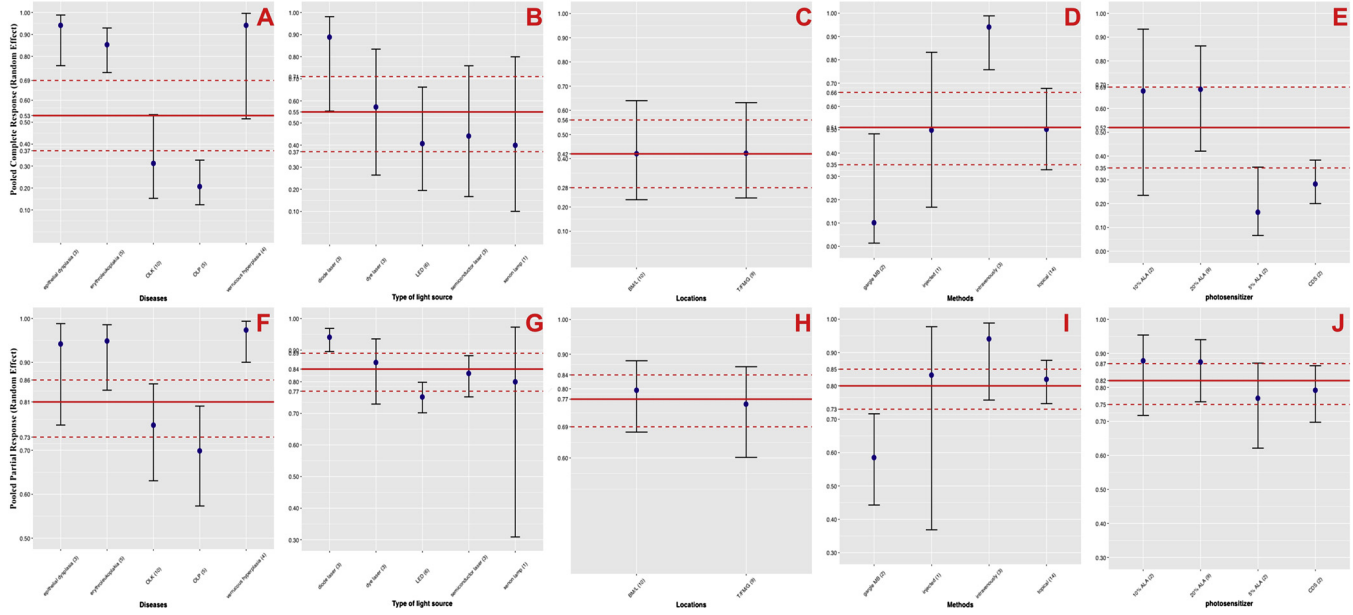

Fig. 4. A–J With random effects model, differences between the pooled lesion response after PDT: subgroups of diseases (Fig. 12A and F), light sources (Fig. 12B and G), lesion locations (Fig. 12C and H), methods (Fig. 12D and I) and PS (Fig. 12E and J), the five plots at the first column represent the results of CR, and the plots at the second column represent the results of PR, the full red lines in the plots indicate the pooled overall CR or PR and the dashed red lines indicate the lower limits and upper limits of their 95%CI.

Table 2
Parameters without meta-analysis of the studies included.

Author	Year	Wavelength (nm)	Energy density (J/cm^2)	Duration of irradiation	Dressing time	Frequency of PDT
Sulewska M	2017	630	150	500s	2h	10 weekly
Maloth KN	2016	420	210	600 s (3-min irradiations/rest)	0.5h	NA
Selvam NP	2015	630 ± 5	100	1000s (3-min irradiations/rest)	3h	8 sessions at an interval of 1 week
Romeo U	2014	635	100	1000s (3-min irradiations/rest)	1.5h	twice a week, 4 sessions
Pietruska M	2014	660	90	NA	1h	2-week intervals,10 sessions
Ikeda H	2013	630	100	660s	NA	NA
Sobaniec S	2013	660	90	NA	1h	2-week intervals,10 sessions
Wong SJ	2013	585	2-4	NA	3-4h	NA
Sadaksharam J	2012	632 ± 5	120	1200s	NA	repeated on day 3, 7 and 15
Kawczyk-Krupka A	2012	630, 635	100	900s	2h	two-week interval 2-12 sessions
Uehara M	2011	630	100-200	NA	NA	NA
Shafirstein G	2011	585	8	intervals of 1-3 s within minutes	1.5h	NA
Jerjes W	2011	628, 652	100-200, 20	NA	3-4h	NA
Lin HP	2010	635	100	1000s (3-min irradiations/rest)	1.5-2h	once a week (range, 1–6)
Yu CH	2009	635 ± 5	100	1000s (3-min irradiations/rest)	1.5h	once a week (range, 2–7)
Rigual NR	2009	630	50	NA	NA	NA
Yu CH	2008	635 ± 5	100	1000s (3-min irradiations/rest)	1.5-2h	once a week (range, 1–6)
Chen HM	2007	635 ± 5	100	1000s (3-min irradiations/rest)	1.5-2h	once a week (range, 1–6)
Aghahosseini F	2006	632	100	NA	NA	1 session
Aghahosseini F	2006	632	120	120s	NA	1 session
Tsai JC	2004	635 ± 5	100	NA	2h	repeated twice on day 8 and 15
Kübler A	1998	630	100	3600s	2h	1 session

nm: nanometers; J/cm2: Joules per square centimeters; NA: not available.

As for PR, topical administration yielded the highest partial remission rate among all methods of administration, along with intravenous use, which resulted in remarkably higher PR than gargle. Gargle MB has not been commonly used recently. The relatively poor outcome from such administration method can be possibly due to the short gargle time of only five minutes and the improved effect of modern PS. Although the curative effect of topical administration is inferior to intravenous administration in terms of CR, the equivalent efficacy is similar in terms of PR. Because of the advantages of safety, minimal complications, convenience, and applicability beyond the clinical margins of the lesion to address the likely field cancerization of the oral mucosa, topical administration is recommended. Meanwhile, the small sample size of studies using injection remains a limitation for further analysis.

OLK was the most common lesion among all studies; however, the effect of PDT treatment on OLK was not very desirable. For example, the curative effect of PDT on OLK is significantly inferior to that on erythroleukoplakia and epithelial dysplasia in terms of CR, and the rate of PR was significantly lower in OLK than in verrucous hyperplasia. Due to the histological nature of hyperkeratosis and epithelial hyperplasia, penetration and absorption of PS in OLK could be difficult [1]. Topical use of retinoic acid prior to PDT to thin out the hyperplasia may be a possible solution. Notably, the curative effect of PDT in OLP was significantly inferior to that of other diseases. This might be because OLP is an inflammatory disease with basal cell degeneration, cell proliferate is less actively than other OPMDs [36], which result in the low absorption efficacy of PS.

Considering the impact of lesion sites, the BM/L and T/FM/G groups had approximately the same number of lesions and achieved similar effect from PDT. Although lesion location may influence the difficulty of PS dressing, the degree of mouth wetting and activity has no effect on the lesion response to PDT.

Wavelength of 635 ± 5 nm is recommended when 20% ALA is used, because light at 635 nm corresponds to the absorption peak of ALA. In studies involving gargling MB, the chosen wavelength of 632 nm did not reach the maximum absorption wavelength of MB (around 665 nm, from an online website of the Oregon Medical Laser Center at http://omlc.org/spectra/mb/index.html), which could explain partially why the effect of MB was less than satisfactory. This finding indicates of the importance of choosing the proper wavelength according to type of PS used. The diode laser showed better clinic response in treatment of OPMDs, perhaps because of its one wave length of light, which made it more effective. Given the lack of consensus regarding duration of irradiation and lesion incubation time as well as the frequencies of PDT, further studies are warranted according to the disease characteristics and patient tolerance. The definite recurrence rate of OPMDs remains unknown. Due to the possibility of malignancy and relapse, regular follow-up every month is recommended for patients with OPMD.

The limitations of this study need to be addressed. First, these poor-quality clinical studies lead to low statistical power to get reliable findings. Second, the heterogeneity of the treated lesions, photosensitizers, procedures, etc. reduces the significance of the results. In addition, the sample size for subgroup analysis is limited, which could increase the possibility of errors. Although this review has some disadvantages, it provides the clues for seeking more reasonable approach to PDT treatment of OPMDs. More high-quality clinical studies are required to improve the reliability of the results, in order to guide clinical practice.

5. Conclusions

PDT is an effective treatment modality in the management of OPMDs, the overall efficacy of which is influenced by several factors. Currently, topical use of 20% ALA is the primary approach for erythroleukoplakia and verrucous hyperplasia, but is not recommended as a routine treatment for OLP. And different lesion locations do not influence the response to PDT. The wavelength of 630 ± 5 nm tends to be optimal when 20% ALA is used. High-quality trials with long follow-ups are required to properly evaluate the impact of PDT-related parameters on OPMDs.

Declaration of Competing Interest

None.

Acknowledgement

This project was supported by grants from the National Natural Science Foundations of China (No. 81870775, 81500855, 81771081).

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.pdpdt.2019.08.005.

References

[1] T. Amagasa, M. Yamashiro, N. Uzawa, Oral premalignant lesions: from a clinical perspective, Int. J. Clin. Oncol. 16 (1) (2011) 5–14.
[2] J. Tadakamadla, S. Kumar, R. Lalloo, G. Babu, N.W. Johnson, Impact of oral potentially malignant disorders on quality of life, J. Oral Pathol. Med. (2017).
[3] P. Vedtofte, P. Holmstrup, J. Reibel, K. Stoltze, Long-term treatment outcome of oral premalignant lesions, Oral Oncol. 42 (2006) 461–474.
[4] G. Lodi, R. Franchini, S. Warnakulasuriya, E.M. Varoni, A. Sardella, A.R. Kerr, A. Carrassi, L.C. MacDonald, H.V. Worthington, Interventions for treating oral leukoplakia to prevent oral cancer, Cochrane Database Syst. Rev. 7 (2016) CD001829.
[5] K. Thongprasom, M. Carrozzo, S. Furness, G. Lodi, Interventions for treating oral lichen planus, Cochrane Database Syst. Rev. 7 (2011) CD001168.
[6] K. Konopka, T. Goslinski, Photodynamic therapy in dentistry, J. Dent. Res. 86 (8) (2007) 694–707.
[7] L. Chau, J.T. Jabara, W. Lai, P.F. Svider, B.M. Warner, H.S. Lin, S.N. Raza, A.M. Fribley, Topical agents for oral cancer chemoprevention: a systematic review of the literature, Oral Oncol. 67 (2017) 153–159.
[8] Y.C. Chang, C.H. Yu, Successful treatment of oral verrucous hyperplasia with photodynamic therapy combined with cryotherapy–report of 3 cases, Photodiagnosis Photodyn. Ther. 11 (2) (2014) 127–129.
[9] A. Sieron, G. Namyslowski, M. Misiolek, M. Adamek, A. Kawczyk-Krupka, Photodynamic therapy of premalignant lesions and local recurrence of laryngeal and hypopharyngeal cancers, Eur. Arch. Otorhinolaryngol. 258 (7) (2001) 349–352.
[10] S.I. Kvaal, E. Angell-Petersen, T. Warloe, Photodynamic treatment of oral lichen planus, Oral Surg. Oral Med. Oral Pathol. Oral Radiol. 115 (1) (2013) 62–70.
[11] H.H. Jajarm, F. Falaki, M. Sanatkhani, M. Ahmadzadeh, F. Ahrari, H. Shafaee, A comparative study of toluidine blue-mediated photodynamic therapy versus topical corticosteroids in the treatment of erosive-atrophic oral lichen planus: a randomized clinical controlled trial, Lasers Med. Sci. 30 (5) (2015) 1475–1480.
[12] H.M. Chen, C.T. Chen, H. Yang, M.Y. Kuo, Y.S. Kuo, W.H. Lan, Y.P. Wang, T. Tsai, C.P. Chiang, Successful treatment of oral verrucous hyperplasia with topical 5-aminolevulinic acid-mediated photodynamic therapy, Oral Oncol. 40 (6) (2004) 630–637.
[13] H.M. Chen, T.P.C. Yu CH, C.Y. Yeh, T. Tsai, C.P. Chiang, Successful treatment of oral verrucous hyperplasia and oral leukoplakia with topical 5-aminolevulinic acid-mediated photodynamic therapy, Lasers Surg. Med. 37 (2) (2005) 114–122.
[14] A. Kubler, T. Haase, M. Rheinwald, T. Barth, J. Muhling, Treatment of oral leukoplakia by topical application of 5-aminolevulinic acid, Int. J. Oral Maxillofac. Surg. 27 (6) (1998) 466–469.
[15] J.C. Tsai, C.P. Chiang, H.M. Chen, S.B. Huang, C.W. Wang, M.I. Lee, Y.C. Hsu, C.T. Chen, T. Tsai, Photodynamic Therapy of oral dysplasia with topical 5-aminolevulinic acid and light-emitting diode array, Lasers Surg. Med. 34 (1) (2004) 18–24.
[16] F. Arbabi-Kalati, F. Aghahosseini, L.A. Fashtami, G.E. Djavid, M. Fateh, J.M. Beitollahi, Methylene blue-mediated photodynamic therapy: a possible alternative treatment for oral lichen planus, Lasers Surg. Med. 38 (1) (2006) 33–38.
[17] E. Djavid, Treatment of oral lichen planus with photodynamic therapy mediated methylene blue: a case report, Med Oral Patol Oral Cir Bucal. 11 (2) (2006) E126–129.
[18] H.M. Chen, C.H. Yu, T. Tsai, Y.C. Hsu, R.C. Kuo, C.P. Chiang, Topical 5-aminolevulinic acid-mediated photodynamic therapy for oral verrucous hyperplasia, oral leukoplakia and oral erythroleukoplakia, Photodiagnosis Photodyn Ther. 4 (1) (2007) 44–52.
[19] C.H. Yu, H.M. Chen, H.Y. Hung, S.J. Cheng, T. Tsai, C.P. Chiang, 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. 44 (6) (2008) 595–600.
[20] N.R. Rigual, K. Thankappan, M. Cooper, M.A. Sullivan, T. Dougherty, S.R. Popat, T.R. Loree, M.A. Biel, B. Henderson, Photodynamic therapy for head and neck dysplasia and cancer, Arch Otolaryngol Head Neck Surg. 135 (8) (2009) 784–788.
[21] C.H. Yu, H.P. Lin, H.M. Chen, H. Yang, Y.P. Wang, C.P. Chiang, Comparison of clinical outcomes of oral erythroleukoplakia treated with photodynamic therapy using either light-emitting diode or laser light, Lasers Surg Med. 41 (9) (2009) 628–633.
[22] H.P. Lin, H.M. Chen, C.H. Yu, H. Yang, Y.P. Wang, C.P. Chiang, Topical photodynamic therapy is very effective for oral verrucous hyperplasia and oral erythroleukoplakia, J Oral Pathol Med. 39 (8) (2010) 624–630.
[23] W. Jerjes, T. Upile, Z. Hamdoon, C.A. Mosse, S. Akram, C. Hopper, Photodynamic therapy outcome for oral dysplasia, Lasers Surg Med. 43 (3) (2011) 192–199.
[24] Suen, Using 5-aminolevulinic acid and pulsed dye laser for photodynamic treatment of oral leukoplakia, Arch Otolaryngol Head Neck Surg. 137 (11) (2011) 1117–1123.
[25] Nonaka, I. Asahina, Predictive factor for photodynamic therapy effects on oral squamous cell carcinoma and oral epithelial dysplasia, Arch Oral Biol. 56 (11) (2011) 1366–1372.
[26] Raczkowska-Siostrzonek, A. Kosciarz-Grzesiok, Koszowski, A. Sieron, Comparison of cryotherapy and photodynamic therapy in treatment of oral leukoplakia, Photodiagnosis Photodyn Ther. 9 (2) (2012) 148–155.
[27] P. Selvam, Treatment of oral lichen planus with methylene blue mediated photodynamic therapy–a clinical study, Photodermatol Photoimmunol Photomed. 28 (2) (2012) 97–101.
[28] Uehara, I. Asahina, Treatment outcome of Photofrin-based photodynamic therapy for T1 and T2 oral squamous cell carcinoma and dysplasia, Photodiagnosis Photodyn Ther. 10 (3) (2013) 229–235.
[29] Olszewska, et al., Clinical assessment of the efficacy of photodynamic therapy in the treatment of oral lichen planus, Lasers Med Sci. 28 (1) (2013) 311–316.
[30] Skripkauskas, et al., A phase I trial of aminolevulinic acid-photodynamic therapy for treatment of oral leukoplakia, Oral Oncol. 49 (9) (2013) 970–976.
[31] Duraj, G. Tokajuk, Clinical evaluation of photodynamic therapy efficacy in the treatment of oral leukoplakia, Photodiagnosis Photodyn Ther. 11 (1) (2014) 34–40.
[32] Del, Oral proliferative verrucous leukoplakia treated with the photodynamic therapy: a case report, Ann Stomatol (Roma). 5 (2) (2014) 77–80.
[33] N.P. Selvam, J. Sadaksharam, G. Singaravelu, R. Ramu, Treatment of oral leukoplakia with photodynamic therapy: A pilot studyJ Cancer Res, Ther. 11 (2) (2015) 464–467.
[34] Ugrappa, N. Meka, Photodynamic Therapy - A Non-invasive Treatment Modality for Precancerous LesionsJ Lasers Med, Sci. 7 (1) (2016) 30–36.
[35] Pietruski, M. Pietruska, A clinical evaluation of the efficacy of photodynamic therapy in the treatment of erosive oral lichen planus: A case series, Photodiagnosis Photodyn Ther (2017).
[36] D. Farhi, N. Dupin, Pathophysiology, etiologic factors, and clinical management of oral lichen planus, part I: facts and controversies, Clin Dermatol. 28 (1) (2010) 100–108.