Hindawi
International Journal of Photoenergy
Volume 2021, Article ID 6641358, 14 pages
https://doi.org/10.1155/2021/6641358

Review Article

Photodynamic Therapy for Oral Squamous Cell Carcinoma: A Systematic Review and Meta-Analysis

Jiao Lin, Guangcheng Ni, Tingting Ding, Shangxue Lei, Liang Zhong, Na Liu, Keran Pan, Ting Chen, Xin Zeng, Hao Xu, Taiwen Li, and Hongxia Dan

State Key Laboratory of Oral Diseases, National Clinical Research Center for Oral Diseases, Chinese Academy of Medical Sciences Research Unit of Oral Carcinogenesis and Management, West China Hospital of Stomatology, Sichuan University, Chengdu, Sichuan 610041, China

Correspondence should be addressed to Taiwen Li; litaiwen@scu.edu.cn and Hongxia Dan; hxdan@foxmail.com

Received 22 October 2020; Revised 14 January 2021; Accepted 28 January 2021; Published 16 February 2021

Academic Editor: Rodrigo Alvaro Lopes-Martins

To assess the efficacy of photodynamic therapy (PDT) for oral squamous cell carcinoma (OSCC), literature on this topic from Embase, PubMed, and Web of Science were obtained and analyzed. The response and recurrence rates with 95% confidence intervals (CI) were calculated using the DerSimonia–Laird method. The pooled complete response (CR) rate from the included studies was 0.799 (95% CI: 0.708–0.867), while the overall response (OR) rate was 0.967 (95% CI: 0.902–0.989). The recurrence rate (RR) was 0.158 (95% CI: 0.090–0.264). A subgroup analysis of lesion site, photosensitizer, laser type, radiant exposure, and power density revealed no statistically significant differences. In general, PDT is effective for the treatment of early OSCC. Investigations on the influence of PDT on the survival of OSCC patients, optimization of the treatment regimen, and evaluation of response after treatment are still needed.

1. Introduction

Oral squamous cell carcinoma (OSCC) is the main type of oral cancer and accounts for more than 90% of all malignant tumors in the oral cavity. At present, its main treatment is surgical treatment, supported by radiotherapy and chemotherapy; however, the efficacy is still unsatisfactory, and adverse reactions are quite common owing to the low selectivity of these treatment options [1–3]. Photodynamic therapy (PDT) is a minimally invasive treatment with high efficacy and selectivity, and it has a low risk of systemic side effects and deformities [4]. The basic elements of PDT are oxygen, photosensitizer, and visible light at specific wavelengths [5]. Photosensitizers are often given locally or intravenously, which subsequently are preferentially concentrated in overproliferative cells with membrane structural defects, such as cancer cells. In the presence of oxygen, a light source of an appropriate wavelength is applied to the target tissue to activate the excited state of the photosensitizer and produce oxygen reactive species with cytotoxic activities [6]. At present, one of the most important clinical applications of PDT is as second-line therapy for primary cancers or recurrent early and superficial cancers of the oral cavity, pharynx, and larynx [7].

In 2015, Cerrati et al. [8] conducted a meta-analysis on the efficacy between PDT and surgical treatment, which included studies published before 2010. In the last 10 years, more studies on this subject have been published. Therefore, to gain a better understanding of the outcome of PDT in the treatment of OSCC, we conducted this meta-analysis to update the cure rate and RR of PDT for OSCC treatment and to explore their relationship with lesion site, photosensitizer, laser type, radiant exposure, and power density and other related factors.

2. Materials and Methods

A systematic review and meta-analysis were performed according to the PRISMA statement [9]. The review protocol was registered on PROSPERO (CRD42020190166).

2.1. Study Identification and Selection. PubMed, Embase, and Web of Science databases were systematically searched until August 1, 2019, to identify all relevant studies using different combinations of the following keywords: "photodynamic therapy" or "photodynamic chemotherapy" and "oral cancer," "oral squamous cell carcinoma," "oral neoplasms," "head and neck tumors," and "head and neck squamous cell carcinoma."

Studies enrolled in the meta-analysis met the following criteria: (A) original study; (B) clinical study; (C) published in English; (D) articles meeting the standard of PICO, in short, all patients were diagnosed with OSCC through clinical manifestations and histological examination (P); the lesions were treated by PDT (I); comparison of lesions of patients before and after treatment (C), response was used as the primary outcome, and recurrence was used as a secondary outcome (O).

The exclusion criteria were as follows: (A) reviews, conference summaries, case reports, and commentaries; (B) animal experiments; (C) efficacy evaluation criteria were inconsistent; (D) publications of nonoriginal studies or based on the same cohort; (E) studies in which the specific sites of the lesion were not recorded.

2.2. Data Extraction. Two investigators (J. Lin and G.C. Ni) independently assessed the titles and abstracts initially to determine whether they met the inclusion criteria and then read the full text of the study. The following information was collected from all studies: first author's name, year of publication, mean age of patients, sample size, lesion locations, female-to-male ratio, light source, type and application method of photosensitizer, laser parameters (wavelength, radiant exposure, and power density), exposure time, number of sessions, follow-up time, adverse reactions, and recurrence status. If two reviewers disagreed on whether a study met the inclusion and exclusion criteria, a third reviewer would join the discussion and resolve discrepancies.

2.3. Statistical Analysis. All statistical analyses were performed using the Meta-Analyst [10] and STATA statistical software 15.1. The response rate with 95% confidence intervals (CI) for PDT in the treatment of OSCC was calculated.

Heterogeneity of meta-analysis ($I^2$and Q test): the heterogeneity of studies was assessed using I^2 and Q tests; if the heterogeneity was statistically significant (I^2 >50% or P value of Q test was <0.05), then a random effect model was used for the data analysis.

Pooled estimates calculation: for discrete variables, the proportion was calculated, and logit transformation was carried out. The inverse variance method was used in the fixed effect model, while the DerSimonia–Laird method was used in the random effect model.

Publication bias: a funnel chart was drawn to evaluate publication bias; publication bias was considered when the funnel chart was asymmetrical or the P value of Egger's test was <0.05.

Quality assessment: nonrandomized studies were assessed by using the Downs–Black Checklist with 26 items [11]. A quality assessment was independently performed by two authors (J. Lin and G.C. Ni), and a full discussion was undertaken when conflicts existed. The corresponding author (Prof. Dan) made the final decision.

Sensitivity analysis: subgroup analyses were performed, and the influence of a single study on the overall result was analyzed by omitting them one by one.

3. Results

3.1. Search Results and Study Selection. Figure 1 shows the selection process; 69 articles were included through a preestablished literature retrieval strategy. First, 10 articles were excluded because of repetition. The titles and abstracts were screened, and 29 articles of reviews, case reports, animal experiments, or basic experiments were excluded. In the subsequent full-text screening, 9 articles were excluded because of inconsistencies in the efficacy evaluation criteria. The remaining 21 articles were used for data extraction. Two studies [12, 13] were excluded because squamous cell carcinoma and dysplasia were not distinguished. One study [14] was excluded because it was based on the same cohort as another study [15]. Finally, a total of 18 studies [15–32] with 900 OSCC patients were included in the meta-analysis. The basic characteristics of the included studies are listed in Table 1.

3.2. Quality Assessment of Included Studies. The results of the Downs–Black Checklist are listed in Table 2. The majority of the non-RCT studies showed high quality in five fields: study quality, external validity, study bias, confounding, and power of study.

3.3. Meta-Analysis Results

3.3.1. Complete Response Rate of OSCC to PDT. A total of 18 articles involving 900 lesions were included in this study. Detailed information of the studies is provided in Table 1. The response rate with 95% CIs was used to evaluate the lesion complete response (CR) after PDT. The P value of the Q test was <0.001, I^2 was 80.03%, a random effect model was recommended, and the DerSimonia–Laird method was used. The pooled CR was 0.799 (95% CI:0.708–0.867), indicating that 79.9% of the lesions achieved a CR (Figure 2).

The funnel plot (Supplementary Figure 1A) and Egger's test indicated no publication bias ($P = 0.345$, 95% CI = -2.932–1.091; $P > 0.05$).

Moreover, a sensitivity analysis (Supplementary Figure 2A) showed that the results were robust.

3.3.2. Overall Response of OSCC to PDT. Seven articles involving 507 cases were included in the analysis. The OR result is shown in Figure 3, where the P value of the Q test was 0.035 and $I^2 = 55.69\%$. A random effects model was adopted, and the pooled OR was 0.967 (95% CI:0.902–0.989), indicating that 96.7% of the lesions achieved an overall response (OR).

The funnel plot (Supplementary Figure 1B) and Egger's test indicated no publication bias ($P = 0.813$, 95% CI = -17.969–17.131; $P > 0.05$).

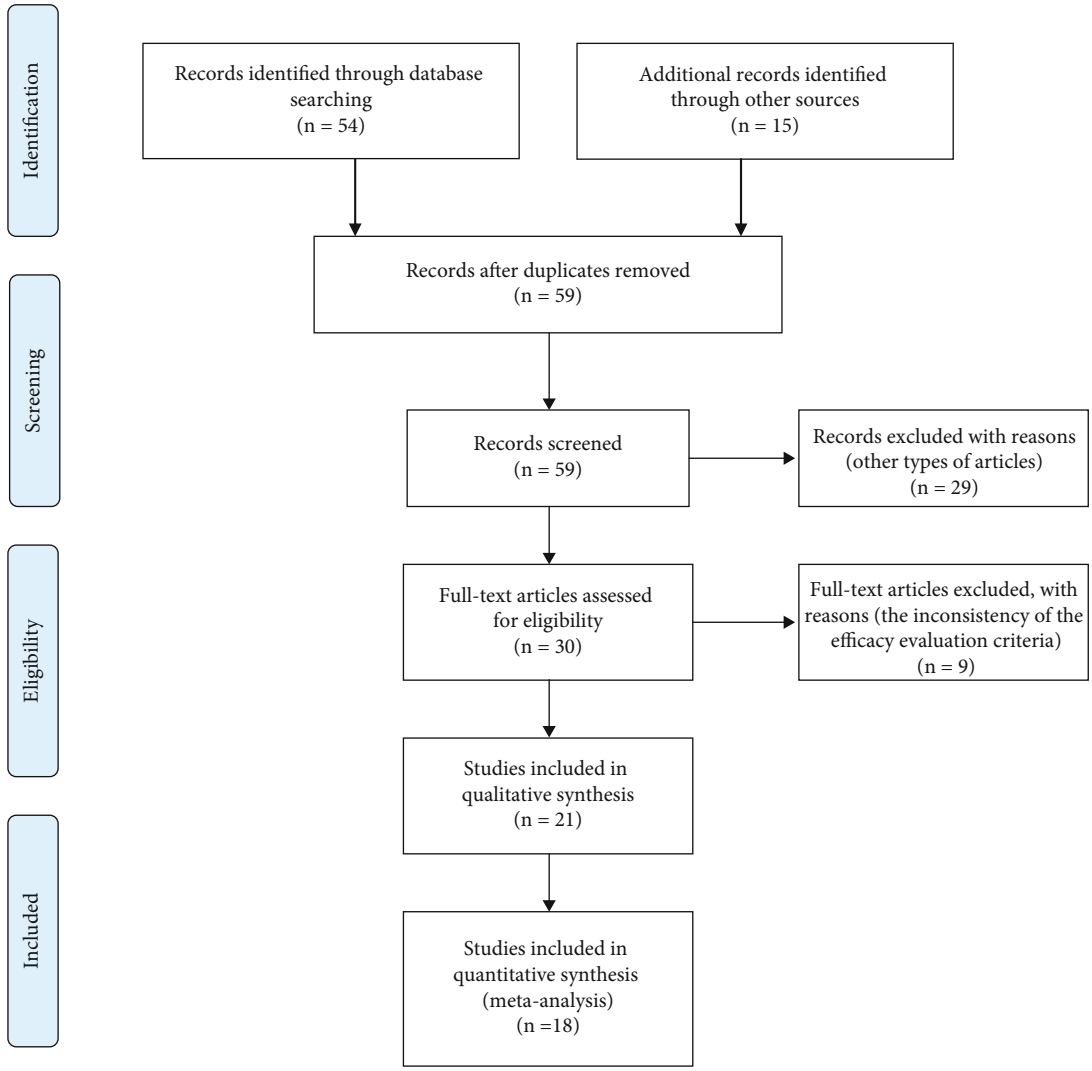


Figure 1: Flow diagram of literature search and study selection process.

Moreover, a sensitivity analysis (Supplementary Figure 2B) showed that the results were robust.

3.3.3. Impact of PDT on the Recurrence Rate of OSCC. Nine articles reported the RR, involving 376 cases. The RR results are shown in Figure 4. Heterogeneity among studies was significant ($I^2 = 67.32\%$, P of Q test = 0.002), and the random effect model and DerSimonia–Laird method were used. The pooled RR was 0.158 (95% CI:0.090–0.264), indicating that 15.8% of the lesions relapsed.

A funnel plot (Supplementary Figure 1C) and Egger's test indicated no publication bias ($P = 0.621$, 95% CI = -4.049 - 2.627; $P > 0.05$).

Moreover, a sensitivity analysis (Supplementary Figure 2C) showed that the results were robust.

3.4. Subgroup Analysis

3.4.1. Lesion Sites. Eight studies were included in the subgroup analysis of the influence of lesion location on the CR of OSCC. They were divided into two groups: the lips and/or buccal mucosa and/or tongue and/or floor of the mouth (BM/L/T/FM) group and gingiva and/or palate (G/P) group. There was no statistically significant difference between the groups (Figure 5).

3.4.2. Photosensitizers. Eighteen studies were included in the subgroup analysis of the influence of the photosensitizer types on the CR of OSCC, including five types of photosensitizers: m-Tetra(hydroxyphenyl) chlorin (m-THPC), chlorin-based compound, 3-(1'-hexyloxyethyl) pyropheophorbide (HPPH), hematoporphyrin derivative (HPD), talaporfin sodium, and porfimer sodium. They were administered intravenously. The results are shown in Figure 6(a). The curative effects were all at the average level, and the differences between the different types of photosensitizers were not statistically significant.

Seven studies were included in the subgroup analysis of the influence of photosensitizer type on the OR of OSCC, including three types of photosensitizers. The results are

Table 1: Parameters of the studies included.

Author	Year	Mean age (year)	Female/male	Types of PS	Laser type	Radiant exposure (J/cm^2)	Power density (mW/cm^2)	Wavelength (nm)	Method of administration	Sample size	CR	OR	RR	Lesion locations	Sample size	CR	OR	Mean follow-up(month)	Exposure time(min)	Number of sessions	Adverse site
Ikeda H	2018	75.2 (55-94)	6/2	Talaporfin sodium	Diode laser	100	150	664	Intravenous	8	6	N/A	1	G/P[a] L/BM/T/FM[b]	1 7	0 6	N/A N/A	48	55-176	1	N/A
Toratani S	2016	70.8	22/12	Porfimer sodium	Dye laser	100-150	160	630	Intravenous	34	30	33	9	N/A	N/A	N/A	N/A	105	N/A	1	Sunburn and sequestrum formation of alveolar bone
Rigual N	2013	N/A	N/A	HPPH[d]	Dye laser	Firstly:50-75/100-125. Then:100-125/140	N/A	665	Intravenous	20	16	N/A	N/A	N/A	N/A	N/A	N/A	5-40	N/A	≥1	Expected pain and edema
Karakullukcu B	2013	60 (38-92)	22/33	mTHPC[c]	N/A	N/A	N/A	630	N/A	55	49	N/A	N/A	N/A	N/A	N/A	N/A	24	N/A	1	N/A
Ikeda H	2013	73.7	N/A	Porfimer sodium	N/A	N/A	N/A	N/A	Intravenous	18	17	N/A	2	G/P L/BM/T/FM	7 11	6 11	N/A N/A	48	30-150	N/A	Swelling and edema
deVisscher S A	2013	61.1	N/A	mTHPC	Diode laser	N/A	100	630	Intravenous	156	127	N/A	N/A	N/A	N/A	N/A	N/A	33	N/A	1	N/A
Karakullukcu B	2011	60.5	N/A	mTHPC	N/A	N/A	100	652	Intravenous	126	86	114	N/A	G/P L/BM/T/FM	26 100	17 69	23 91	60	N/A	N/A	Scar formation
Jerjes W	2011	58	12/26	mTHPC	N/A	10-20	100	652	Intravenous	38	12	N/A	6	N/A	N/A	N/A	N/A	60	N/A	1	Pain and swelling
Merrill A. Biel	2010	N/A	N/A	Porfimer sodium	Dye laser	N/A	150	630	Intravenous	190	190	190	13	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Vanessa Gayl	2010	N/A	N/A	Porfimer sodium	Pumped laser or a diode laser	50-100	100-200	630	Intravenous	26	22	26	4	N/A	N/A	N/A	N/A	N/A	N/A	≥1	N/A
KAI Johannes	2009	58.8 (48-62)	N/A	mTHPC	N/A	20	100	652	Intravenous	8	4	N/A	N/A	G/P L/BM/T/FM	4 4	2 2	N/A N/A	N/A	N/A	N/A	N/A
Rigual N R	2009	61.2 (36-85)	N/A	Porfimer sodium	Argon pumped dye laser or a diode laser	50-75	N/A	630	Intravenous	11	10	11	11	N/A	N/A	N/A	N/A	15	N/A	≥1	Pain edema itching, weight loss transient hoarseness
Hopper C	2004	64 (33-99)	N/A	mTHPC	Diode laser	20	100	652	Intravenous	114	97	114	N/A	G/P L/BM/T/FM Others	7 103 4	6 87 4	N/A N/A N/A	N/A	N/A	N/A	N/A
Copper M P	2003	N/A	N/A	mTHPC	Diode laser	20	100	652	Intravenous	26	22	N/A	4	G/P L/BM/T/FM	5 21	3 19	N/A N/A	37	N/A	N/A	N/A
Kubler A C	2001	64 (44-99)	6/19	mTHPC	N/A	20	100	652	Intravenous	25	24	N/A	2	G/P L/BM/T/FM	N/A 25	N/A 24	N/A N/A	14	N/A	N/A	Swelling and local pain
Kathleen F M	1997	66.5 (30-80)	N/A	Porfimer sodium	Dye laser	5-20	250	652	Intravenous	25	14	N/A	N/A	G/P	N/A	N/A	N/A	N/A	N/A	≥1	N/A
Yoshida T	1996	60.2 (51-67)	1/4	HPD[e]	Argon or excimer dye laser	200	200-500	630	Intravenous	6	2	5	N/A	L/BM/T/FM	N/A	N/A	N/A	153	N/A	1	Inflammation swelling
Grant W E	1993	N/A	N/A	Porfimer sodium	Dye laser	50-100	150	630	Intravenous	14	13	N/A	N/A	G/P L/BM/T/FM	3 9	3 8	N/A N/A	10.63	N/A	N/A	N/A

G/P[a]: gingiva and/or palate; L/BM/T/FM[b]: lips and/or buccal mucosa and/or tongue and/or floor of the mouth. m-THPC[c]: m-Tetra(hydroxyphenyl) chlorin; HPPH[d]: chlorin-based compound, 3-(1'-hexyloxyethyl) pyropheophorbide; HPD[e]: hematoporphyrin derivative. N/A: not applicable.

Table 2: Results of bias risk assessment for each included non-RCT (score).

Included studies	Reporting	External validity	Bias	Confounding	Power	Overall score
Ikeda H 2018	7	2	3	2	5	19
Toratani S 2016	8	1	3	2	5	19
Rigual N 2013	7	1	3	2	5	18
Karakullukcu B2013	8	1	2	2	5	18
Ikeda H 2013	9	2	3	2	5	21
deVisscher S A2013	8	1	4	3	5	21
Karakullukcu B 2011	8	3	4	2	5	22
Jerjes W2011	9	2	4	2	5	22
Vanessa G S2010	6	1	3	2	5	17
KAI Johannes2009	7	1	4	2	5	19
Merrill A. Biel2010	8	1	4	2	5	20
Rigual N R2009	9	1	3	2	5	20
Hopper C2004	8	1	4	2	5	20
Copper M P2003	7	1	4	2	5	19
Kubler A C2001	8	1	4	2	5	20
Kathleen FM 1997	7	1	3	2	5	18
Yoshida T1996	9	1	4	2	5	21
Grant W E1993	8	1	4	2	5	20

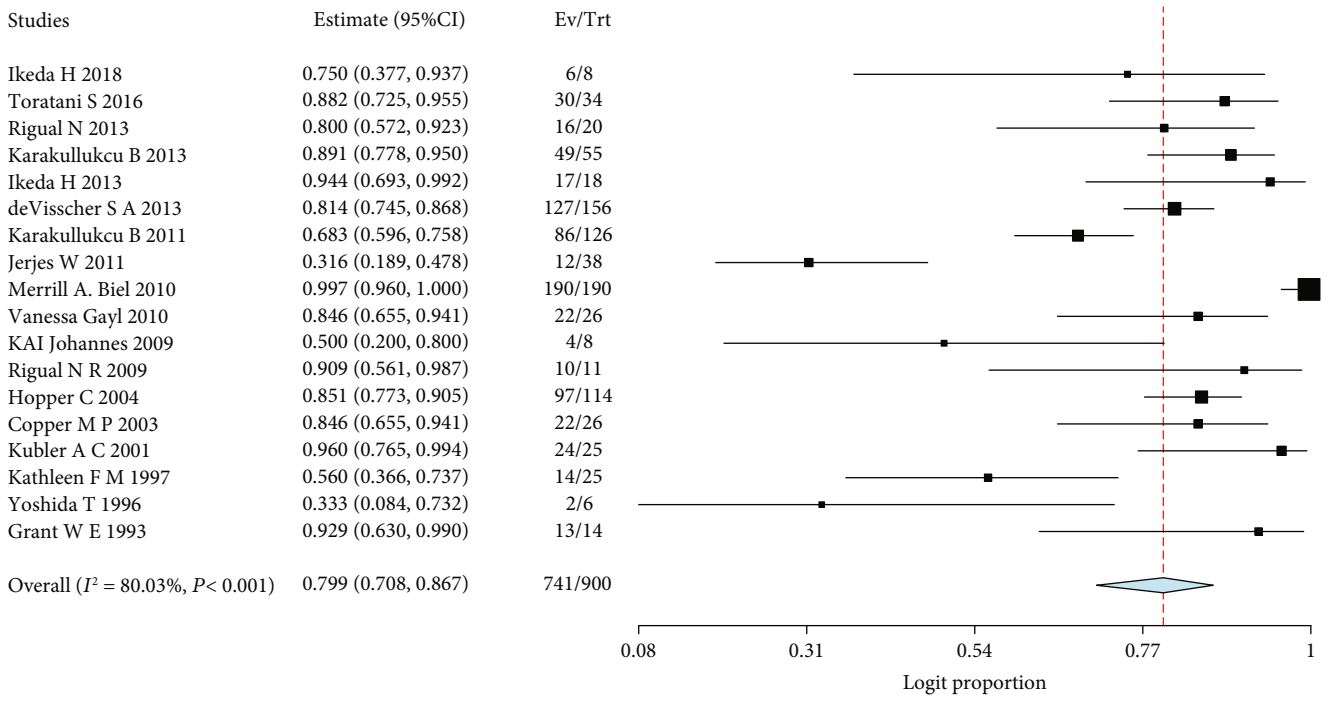


Figure 2: Forest plots of proportions of CR after PDT.

shown in Figure 6(b). There was no statistically significant difference between the different types of photosensitizers.

Nine studies were included in the subgroup analysis of the influence of photosensitizer types on the RR of OSCC, and the results are shown in Figure 6(c). The differences between the different types of photosensitizers were not statistically significant.

3.4.3. Laser Types. Eleven studies were included in the subgroup analysis of the influence of laser type on the CR of OSCC. They were divided into two groups: diode laser and dye laser. As shown in Figure 7(a), there was no significant statistical difference between the different laser types.

Five studies were included in the subgroup analysis of the influence of laser type on the OR of OSCC. The results are

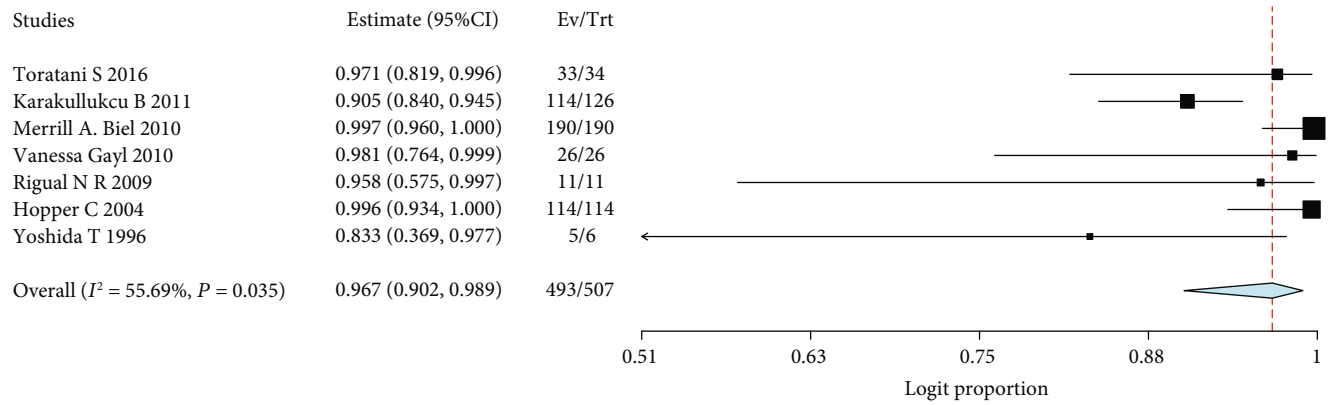


Figure 3: Forest plots of OR rate after PDT.

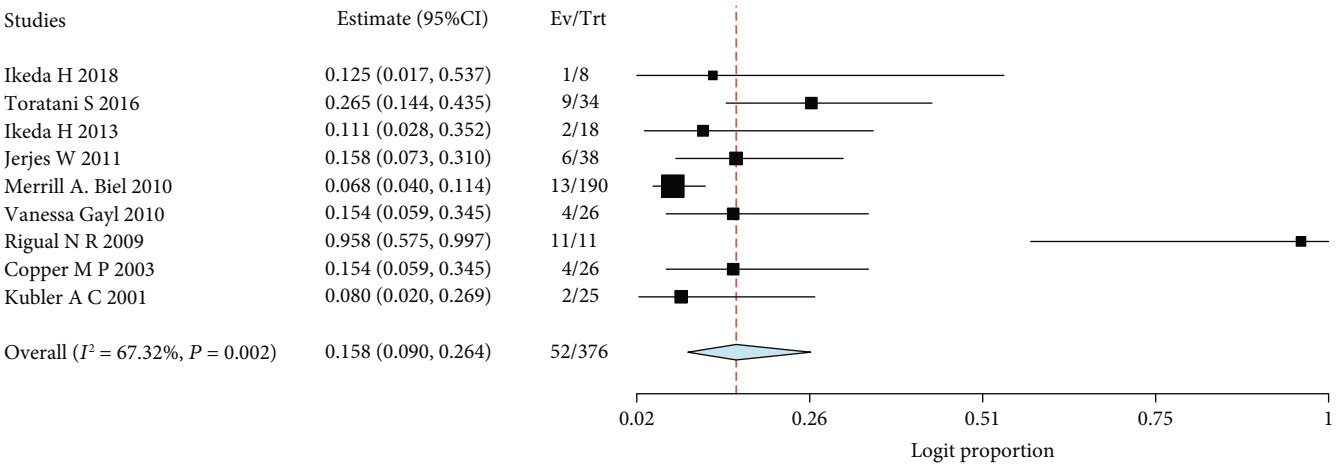


Figure 4: Forest plots of proportions of RR after PDT.

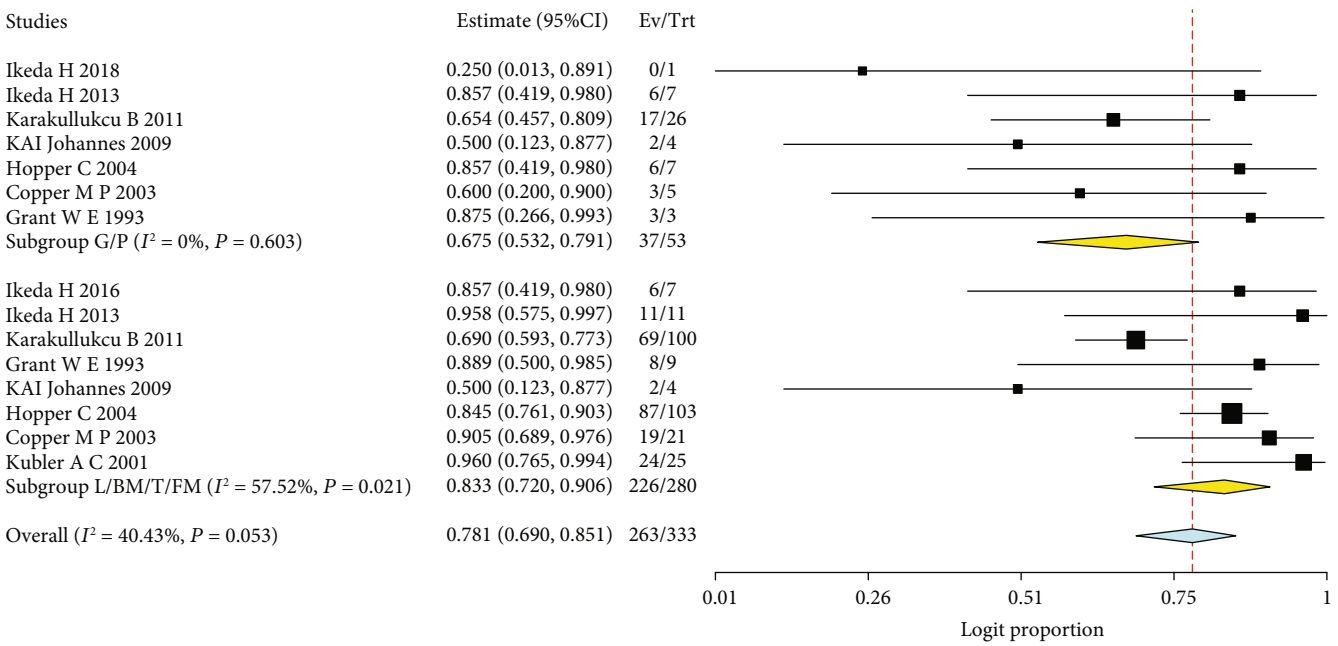
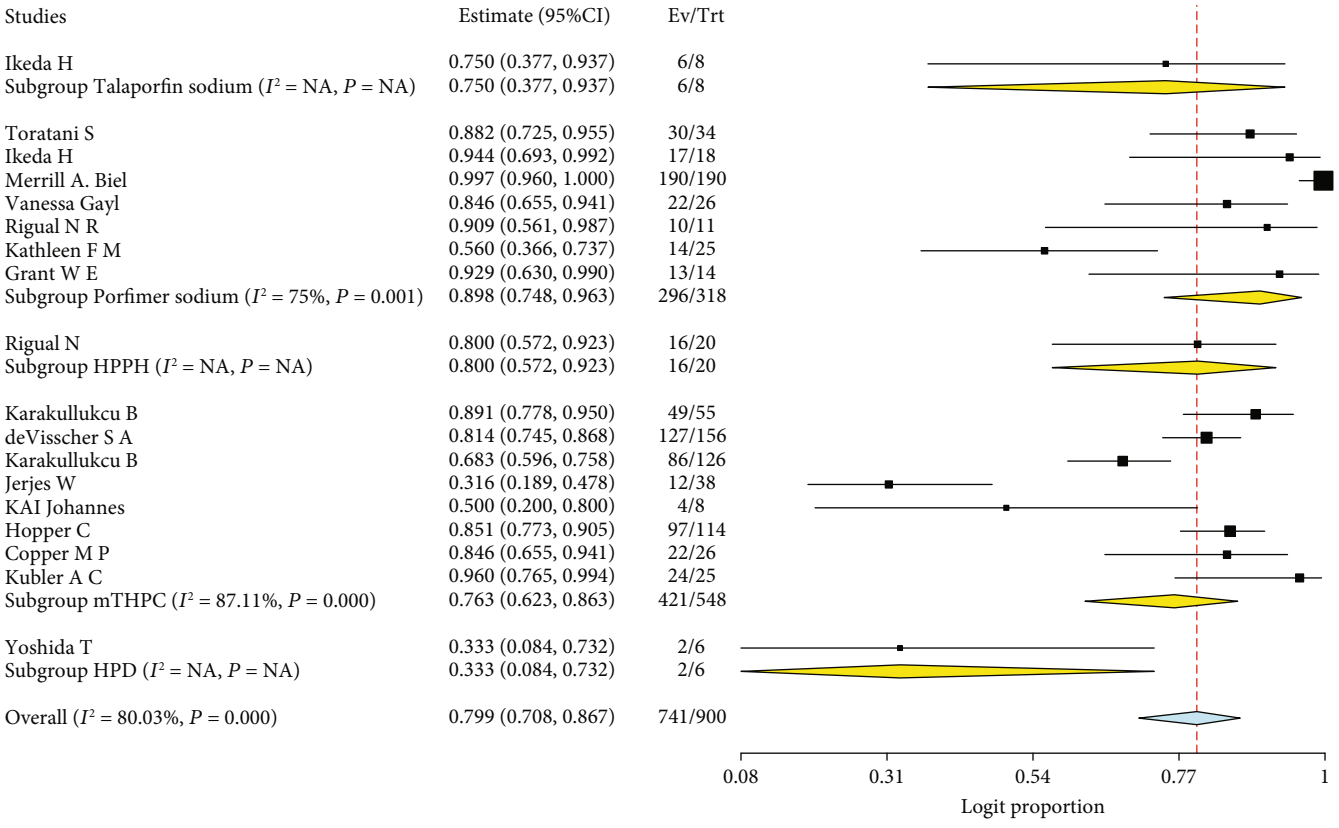
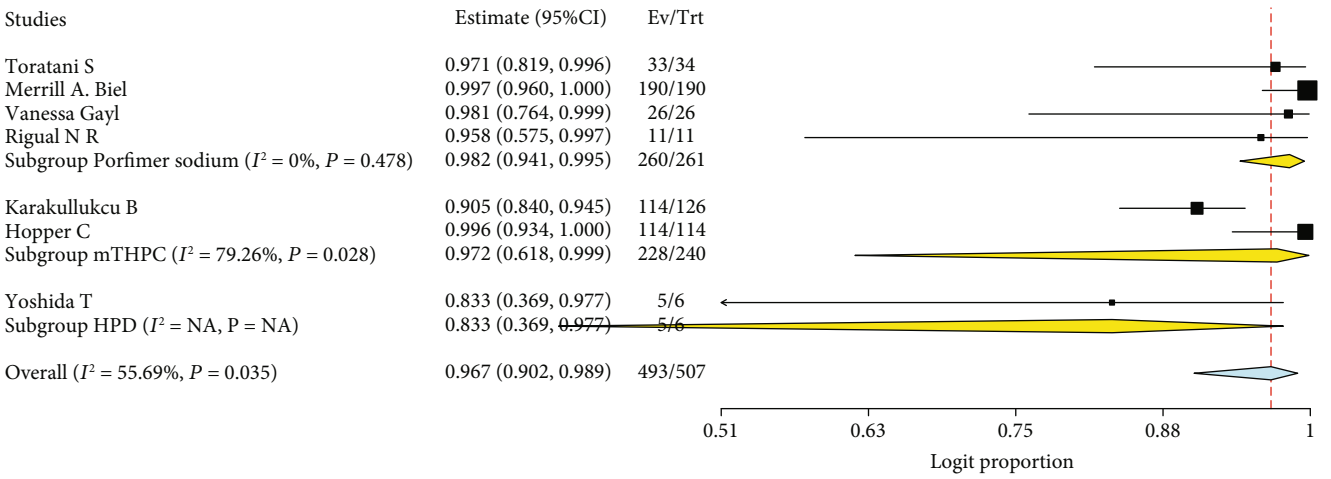


Figure 5: Forest plot of subgroup analysis of complete rate in cases at different lesion sites.

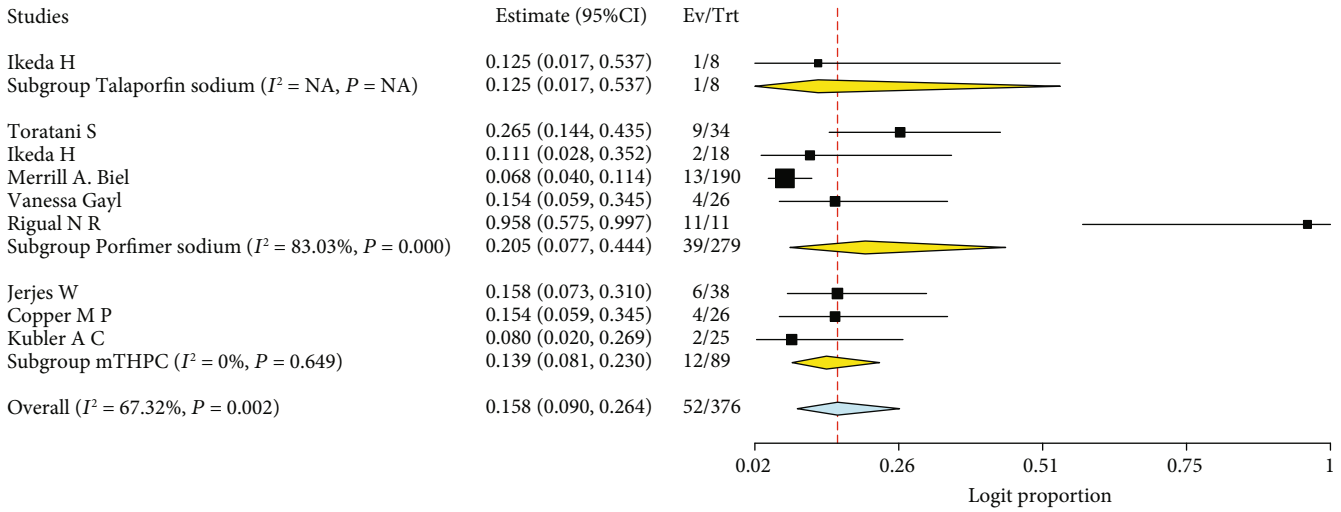


(a)



(b)

Figure 6: Continued.



(c)

Figure 6: Forest plot of subgroup analysis of (a) CR, (b) OR, and (c) RR in cases using different types of photosensitizers.

shown in Figure 7(b); there was no significant statistical difference between the different laser types.

Five studies were included in the subgroup analysis of the influence of laser type on the RR of OSCC. The results are shown in Figure 7(c), and the difference between the different laser types was not statistically significant.

3.4.4. Radiant Exposure. Twelve studies were included in the subgroup analysis of the influence of radiant exposure on the CR of OSCC. They were divided into three groups: 0–50 joules per square centimeters (J/cm^2), 50–100 J/cm^2, and 100–200 J/cm^2. The results are shown in Figure 8(a); there was no significant statistical difference between the different groups.

Five studies were included in the subgroup analysis of the influence of radiant exposure on the OR of OSCC. The results are shown in Figure 8(b), and there was no statistically significant difference between the groups.

Seven studies were included in the subgroup analysis of the influence of radiant exposure on the RR of OSCC. The results are shown in Figure 8(c), and there was no statistically significant difference between the groups.

3.4.5. Power Density. Thirteen studies were included in the subgroup analysis of the influence of power density on the CR of OSCC. They were divided into three groups: 100–150 milliwatt per square centimeters (mW/cm^2), 150–200 mW/cm^2, and ≥200 mW/cm^2. The results are shown in Figure 9(a); there was no statistically significant difference between the groups.

Five studies were included in the subgroup analysis of the influence of power density on the OR of OSCC. The results are shown in Figure 9(b); there was no statistically significant difference between the groups.

Six studies were included in the subgroup analysis of the influence of power density on the RR of OSCC. The results are shown in Figure 9(c), and there was no statistically significant difference between the groups.

3.5. Other Factors in PDT Process in all Studies (Table 1). In all studies included, wavelengths of 630–665 nm were used. Most of the patients had no obvious discomfort or only mild discomfort (local pain and inflammatory edema); some patients had scar formation, itching, and weight loss. A small number of patients had alveolar bone sunburns and dead bone formation.

4. Discussion

OSCC is a common type of cancer in the head and neck region [33]. The annual incidence rate is 3.90/100,000, and the mortality rate is 1.94/100,000 [34]. Owing to the high mortality rate and potential damage to the appearance and function of the oral and maxillofacial region caused by the cancer itself as well as the treatment, OSCC has a very negative influence on the physical and mental health of patients [35]. Currently, surgery is still the first-line treatment for OSCC [36] and is supported by radiotherapy and chemotherapy. The advantage of surgery is that the lesion can be removed completely, and neck dissection can be performed at the same time; however, delayed wound healing is commonly seen, and scar formation is almost inevitable. When the lesion is large or located at a special anatomic site (such as the angle of the mouth, frenum linguae, or pterygomandibular fold), surgery often results in impairment of the mouth opening, mastication, language, and appearance. If recurrence occurs, repeated surgery will further exacerbate the situation [8].

PDT has been used for managing many malignant tumors including OSCC. Compared with surgical treatment, it is highly selective, minimally invasive, and easily accepted by patients, with mild adverse reactions and no cumulative toxicity [37]. Unlike radiotherapy and surgery, treatment can be repeated at the same site as needed [5]. According to a previous meta-analysis, PDT can achieve a response rate similar to that of surgical treatment. In that study,

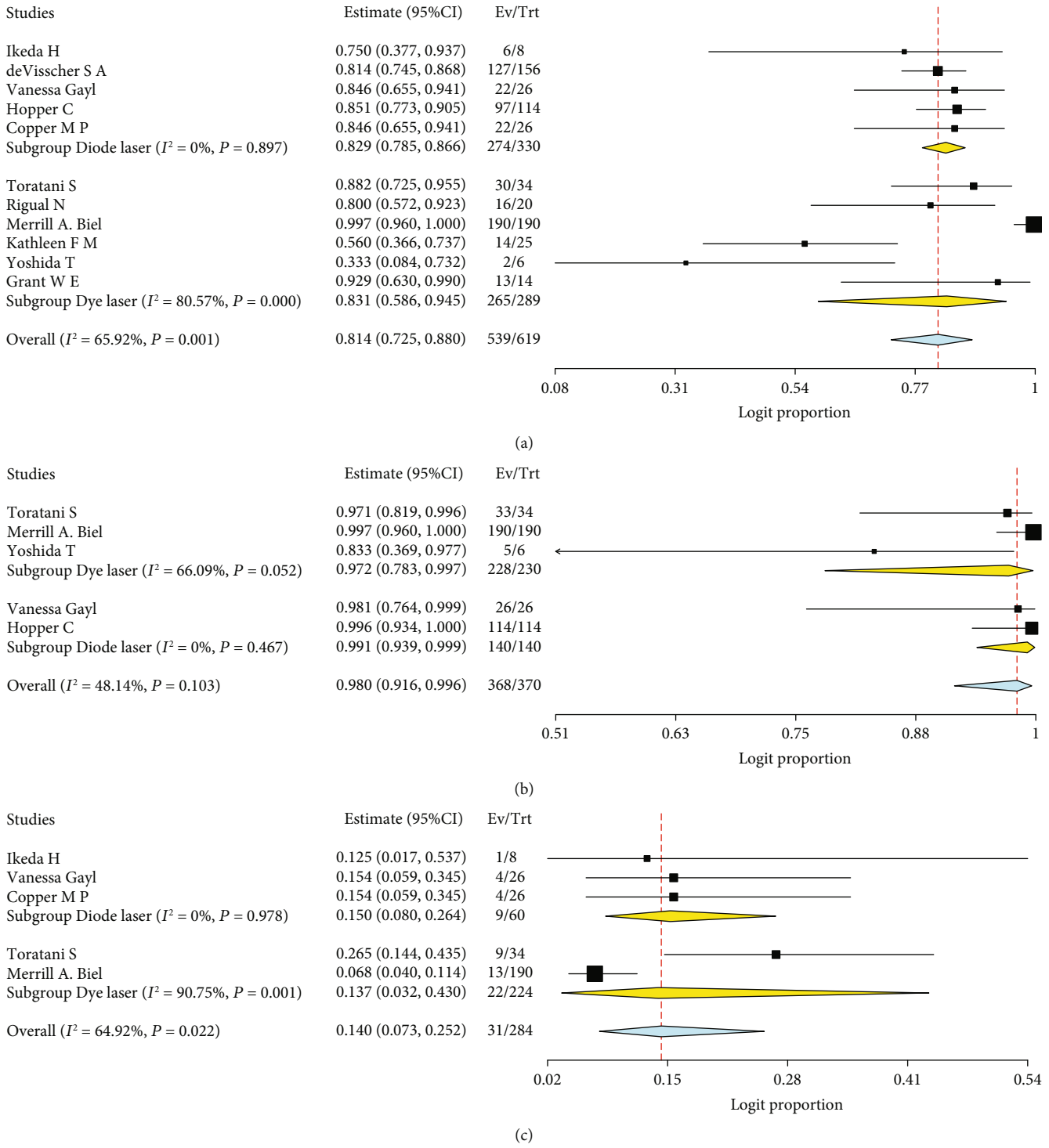


Figure 7: Forest plot of subgroup analysis of (a) CR, (b) OR, and (c) RR in cases using different laser types.

leukoplakia and dysplasia were also included in the calculation of oral cancer, which might have affected the final results.

In this study, only patients diagnosed with OSCC were included. The standards for calculating response rates were set. OR means tumor size reduction of 50% or more after PDT; CR refers to no evidence of tumor both clinically or pathologically. According to these standards, the CR of OSCC treated with PDT was 79.9%. The OR rate, which was the sum of the CR and partial response, was 96.7%. These results indicated that the efficiency, especially the short-term efficiency of PDT in the treatment of early OSCC, was high. At the same time, PDT was highly selective with mild adverse reactions, which made it preferable to surgery when the protection of appearance and function of the target site was needed. However, it should also be noted that PDT had little

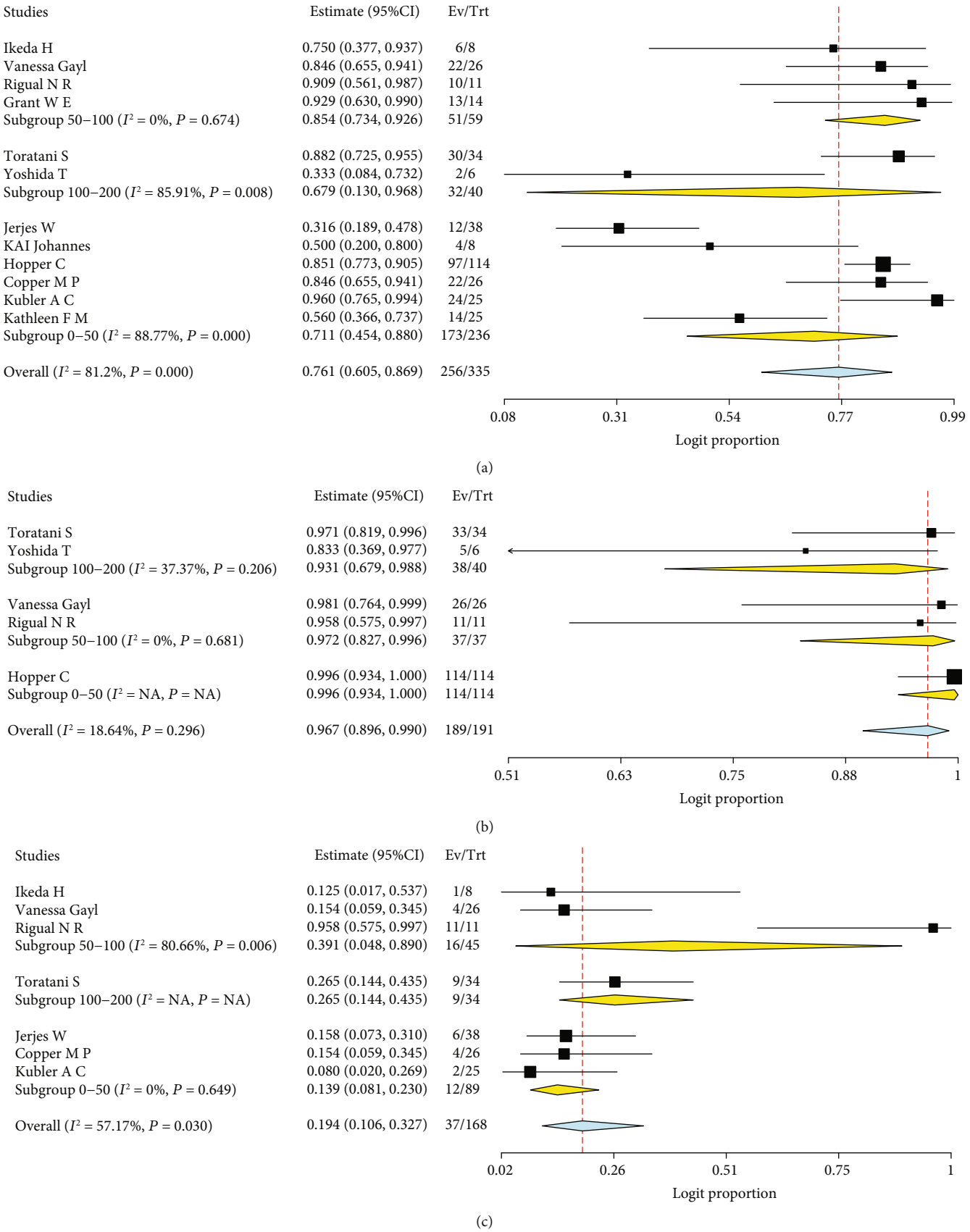


Figure 8: Forest plot of subgroup analysis of (a) CR, (b) OR, and (c) RR in cases about different radiant exposures.

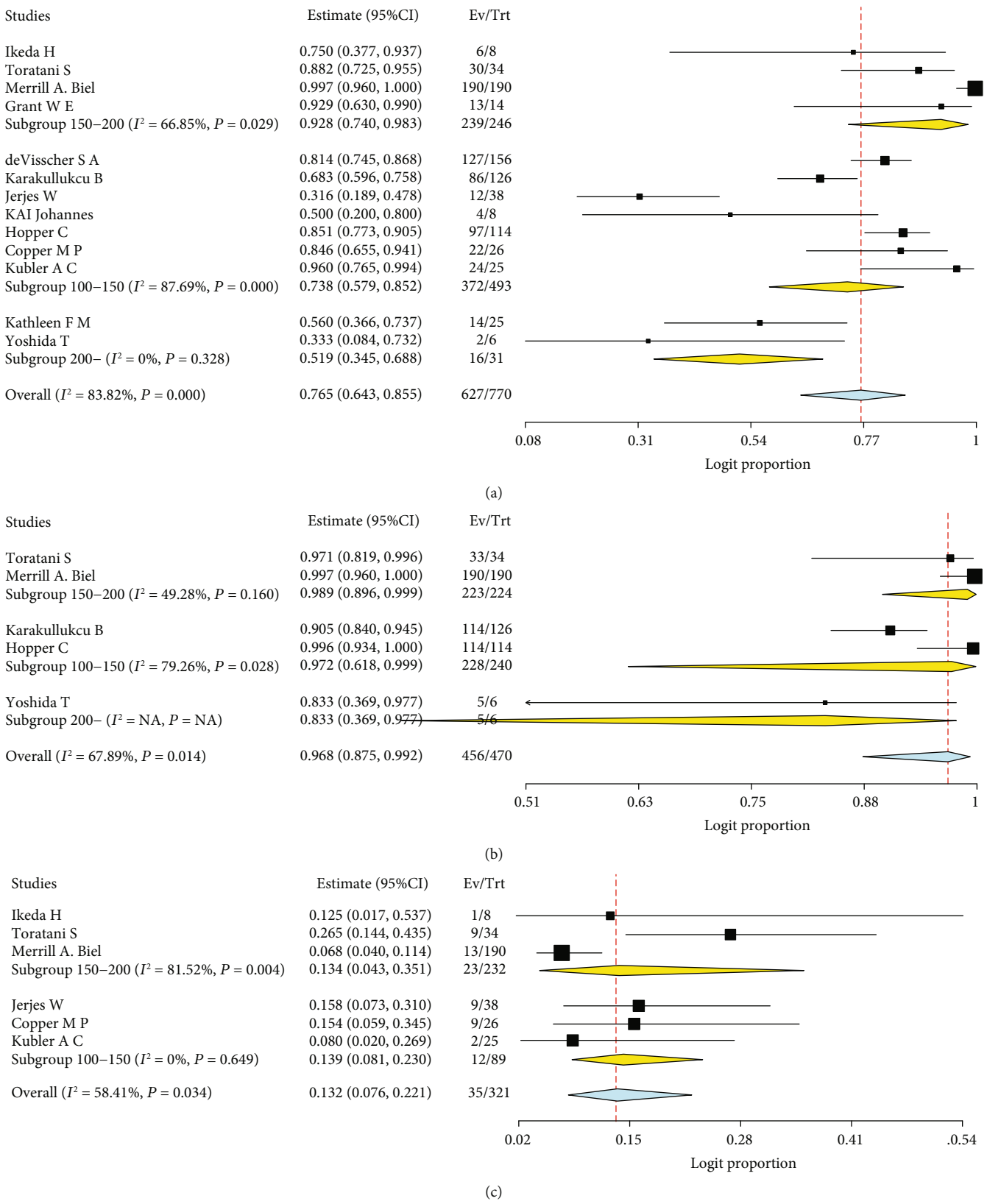


Figure 9: Forest plot of subgroup analysis of (a) CR, (b) OR, and (c) RR in cases using different power densities.

effect on metastatic lesions; therefore, patients with OSCC should be carefully selected (patients at the T1N0M0/T2N0M0 stage in most cases) before PDT treatment. Optional treatment plans should be suggested when a CR could not be achieved. In the current study, the pooled RR of OSCC after PDT was 15.8%, indicating that even when CR was achieved, frequent follow-up should be applied to monitor recurrence.

To determine whether the effect of PDT was affected by different factors, several subgroup analyses were performed, including sites of the lesion, photosensitizers, light sources, radiant exposure, and power density.

As for the sites of lesions, the effect of PDT on OSCC lesions on lining mucosa and masticatory mucosa was compared. The lining mucosa is different from the masticatory mucosa in structure; the latter bears greater masticatory forces and has a keratinized layer that is thicker than the former. In the lining mucosa, less keratin, less fiber, and more vascular connective tissue is formed, while the masticatory mucosa contains connective tissue components with higher density and fewer blood vessels [38]. The subgroup analysis showed that the CR rate of lesions on the lining mucosa was slightly higher than that of the masticatory mucosa, probably owing to the higher infiltration of photosensitizers in lesions on the lining mucosa; however, there was no significant statistical difference.

The ideal photosensitizer should be easy to prepare, stable in storage, highly selective to tumor lesions, and have a significant absorbance band at longer wavelengths [39]. Different photosensitizers have different properties and characteristics. Porfimer sodium is the first-generation photosensitizer, and its depth of action is limited to 5 mm. For thicker tumors, temoporfin, which is a second-generation photosensitizer, can achieve a CR rate of up to 93% [40]. The therapeutic effect of temoporfin is similar to that of porfimer sodium, but the former has better selectivity for early cancer [41]. HPD is the first photosensitizer with water solubility, sufficient affinity for tumors, and low toxicity to normal tissues [39]. However, its metabolism in the body is slow, and patients need to be protected from bright light for weeks after intravenous administration of HPD [42]. HPPH, a compound that strongly absorbs light at 665 nm, has a higher penetration in tumor tissue and less skin photosensitivity [43]. Talaporfin sodium is a second-generation photosensitizer that can be easily eliminated from the body [16]. In the current meta-analysis, there was no significant difference in the response rate among different photosensitizers. Clinicians may consider the availability, incidence, and severity of adverse reactions, cost-performance ratio, and local medical insurance policy when choosing an appropriate photosensitizer.

Different lasers are used for different wavelengths, including diode lasers (630–1100 nm) and dye lasers (390–1000 nm) [44]. Near-infrared lasers with longer wavelengths have deeper penetration, minimal thermal effects, and spatial selectivity than visible lasers, which may be important in the treatment of brain cancer. The properties of the photosensitizer, tissue properties, and matching absorption wavelength should be considered when choosing laser types [44, 45].

In a typical clinical PDT scheme, a radiant exposure of the laser of approximately 50–100 J/cm^2 is typically used. There was no significant difference in the subgroup analysis of the radiant exposure, which might be associated with the fact that the combination of photosensitizer and light was an effective method to destroy tissue based on chemical damage caused by photosensitive reaction rather than heating [45]. Because PDT consumes oxygen, it is important to use an appropriate power density. High power density can accelerate the consumption of oxygen molecules; if oxygen cannot be transferred to the treatment area in time, the PDT efficiency can be reduced. In general, it should be maintained between 150 and 200 mW/cm^2 to avoid hypoxia in tissues [46, 47]. Adverse reactions are inevitable, but their incidence can be reduced by adjusting the light dose, interval time between photosensitizer administration and irradiation, irradiation area, administration method, etc. [48].

The current study still has several limitations. Most studies included did not count the survival time of the patients. In future studies of OSCC treated with PDT, attention should be paid to the follow-up of patients' survival time to provide more powerful evidence for the efficacy of PDT in the treatment of OSCC. Almost all studies included in this meta-analysis were retrospective studies, and there was no control group. The number of treatments and reexamination times of PDT in each study were different, and the results might be inconsistent. Through subgroup analysis, we found that there was no statistically significant difference among the different sites, photosensitizers, and therapy parameters, but this did not mean that the above factors had no influence on efficacy. A possible reason is that these factors are not consistent in different studies, and different factors may interfere with each other. Therefore, it may be necessary to further explore the effects of different factors on the efficacy of PDT through randomized controlled trials to optimize the treatment regimen of PDT for OSCC.

5. Conclusions

Although surgical treatment is still the first choice for the treatment of OSCC, PDT for OSCC has great potential as an adjuvant therapy. Investigations on the influence of PDT on the survival of OSCC patients, optimization of the treatment regimen, and evaluation of response after treatment are still needed.

Abbreviations

PDT:	Photodynamic therapy
OSCC:	Oral squamous cell carcinoma
CI:	Confidence intervals
CR:	Complete response
OR:	Overall response
RR:	Recurrence rate
G/P:	Gingiva and/or palate
L/BM/T/FM:	Lips and/or buccal mucosa and/or tongue and/or floor of the mouth
m-THPC:	m-Tetra(hydroxyphenyl) chlorin
HPPH:	Chlorin-based compound, 3-(1'-hexyloxyethyl) pyropheophorbide
HPD:	Hematoporphyrin derivative
N/A:	Not applicable.

Conflicts of Interest

The authors have no conflict of interest to declare.

Acknowledgments

This study was supported by the National Natural Science Foundation of China (grant numbers: U19A2005, 82071125, 81572663, 81972551), Sichuan Science and Technology Program (grant numbers: 2020YFS0044, 2020YFSY009), and Research and Develop Program, West China Hospital of Stomatology, Sichuan University (grant numbers: LCYJ2019-11).

Supplementary Materials

Supplementary 1. Figure 1: funnel plot of proportions of (A) CR, (B) OR, and (C) RR after PDT.

Supplementary 2. Figure 2: sensitivity analysis of proportions of (A) CR, (B) OR, and (C) RR after PDT.

References

[1] J. J. Kain, A. C. Birkeland, N. Udayakumar et al., "Surgical Margins in Oral Cavity Squamous Cell Carcinoma: Current Practices and Future Directions," *The Laryngoscope*, vol. 130, no. 1, pp. 128–138, 2019.

[2] P. J. Lamey, "Management Options in Potentially Malignant and Malignant Oral Epithelial Lesions," *Community Dental Health*, vol. 10, Supplement 1, pp. 53–62, 1993.

[3] C. Scully, "Oral precancer: preventive and medical approaches to managementOral precancer: Preventive and medical approaches to management," *European Journal of Cancer. Part B, Oral Oncology*, vol. 31, pp. 16–26, 1995.

[4] Q. Chen, H. Dan, F. Tang et al., "Photodynamic therapy guidelines for the management of oral leucoplakiaPhotodynamic Therapy Guidelines for the Management of Oral Leucoplakia," *International Journal of Oral Science*, vol. 11, 2019.

[5] C. Hopper, "Photodynamic therapy: a clinical reality in the treatment of cancerPhotodynamic Therapy: a Clinical Reality in the Treatment of Cancer," *The Lancet Oncology*, vol. 1, pp. 212–219, 2000.

[6] P. Agostinis, K. Berg, K. A. Cengel et al., "Photodynamic Therapy of Cancer: An Update," *CA: a Cancer Journal for Clinicians*, vol. 61, no. 4, pp. 250–281, 2011.

[7] J. Meulemans, P. Delaere, and V. Vander Poorten, "Photodynamic therapy in head and neck cancer: indications, outcomes, and future prospectsPhotodynamic Therapy in Head and Neck Cancer," *Current Opinion in Otolaryngology & Head and Neck Surgery*, vol. 27, no. 2, pp. 136–141, 2019.

[8] E. W. Cerrati, S. A. Nguyen, J. D. Farrar, and E. J. Lentsch, "The Efficacy of Photodynamic Therapy in the Treatment of Oral Squamous Cell Carcinoma: A Meta-Analysis," *Ear, Nose & Throat Journal*, vol. 94, pp. 72–79, 2019.

[9] PRISMA-P Group, D. Moher, L. Shamseer et al., "Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement," *Systematic Reviews*, vol. 4, no. 1, 2015.

[10] B. C. Wallace, C. H. Schmid, J. Lau, and T. A. Trikalinos, "Meta-Analyst: software for meta-analysis of binary, continuous and diagnostic data," *BMC Medical Research Methodology*, vol. 9, no. 1, 2009.

[11] S. H. Downs and N. Black, "The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions," *Journal of Epidemiology and Community Health.*, vol. 52, no. 6, pp. 377–384, 1998.

[12] P. H. Ahn, J. C. Finlay, S. M. Gallagher-Colombo et al., "Lesion oxygenation associates with clinical outcomes in premalignant and early stage head and neck tumors treated on a phase 1 trial of photodynamic therapy," *Photodiagnosis and Photodynamic Therapy*, vol. 21, pp. 28–35, 2018.

[13] P. H. Ahn, H. Quon, B. W. O'Malley et al., "Toxicities and early outcomes in a phase 1 trial of photodynamic therapy for premalignant and early stage head and neck tumorsToxicities and early outcomes in a phase 1 trial of photodynamic therapy for premalignant and early stage head and neck tumors," *Oral Oncology*, vol. 55, pp. 37–42, 2016.

[14] M. P. Copper, M. Triesscheijn, I. B. Tan, M. C. Ruevekamp, and F. A. Stewart, "Photodynamic therapy in the treatment of multiple primary tumours in the head and neck, located to the oral cavity and oropharynxPhotodynamic therapy in the treatment of multiple primary tumours in the head and neck, located to the oral cavity and oropharynx," *Clinical Otolaryngology*, vol. 32, no. 3, pp. 185–189, 2007.

[15] M. P. Copper, I. B. Tan, H. Oppelaar, M. C. Ruevekamp, and F. A. Stewart, "Meta-tetra(hydroxyphenyl)chlorin Photodynamic Therapy in Early-Stage Squamous Cell Carcinoma of the Head and NeckMeta-tetra(hydroxyphenyl)chlorin photodynamic therapy in early-stage squamous cell carcinoma of the head and neck," *Archives of Otolaryngology – Head & Neck Surgery*, vol. 129, no. 7, pp. 709–711, 2003.

[16] H. Ikeda, S. Ohba, K. Egashira, and I. Asahina, "The effect of photodynamic therapy with talaporfin sodium, a second-generation photosensitizer, on oral squamous cell carcinoma: aA series of eight casesThe effect of photodynamic therapy with talaporfin sodium, a second-generation photosensitizer, on oral squamous cell carcinoma: A series of eight cases," *Photodiagnosis and Photodynamic Therapy*, vol. 21, pp. 176–180, 2018.

[17] S. Toratani, R. Tani, T. Kanda, K. Koizumi, Y. Yoshioka, and T. Okamoto, "Photodynamic therapy using Photofrin and excimer dye laser treatment for superficial oral squamous cell carcinomas with long-term follow up," *Photodiagnosis and Photodynamic Therapy.*, vol. 14, pp. 104–110, 2016.

[18] N. Rigual, G. Shafirstein, M. T. Cooper et al., "Photodynamic therapy with 3-(1'-hexyloxyethyl) pyropheophorbide a for cancer of the oral cavity," *Clinical Cancer Research*, vol. 19, no. 23, pp. 6605–6613, 2013.

[19] B. Karakullukcu, S. D. Stoker, A. P. E. Wildeman, M. P. Copper, M. A. Wildeman, and I. B. Tan, "A matched cohort comparison of mTHPC-mediated photodynamic therapy and trans-oral surgery of early stage oral cavity squamous cell cancerA matched cohort comparison of mTHPC-mediated photodynamic therapy and trans-oral surgery of early stage oral cavity squamous cell cancer," *European Archives of Oto-Rhino-Laryngology*, vol. 270, no. 3, pp. 1093–1097, 2013.

[20] H. Ikeda, T. Tobita, S. Ohba, M. Uehara, and I. Asahina, "Treatment outcome of Photofrin-based photodynamic therapy for T1 and T2 oral squamous cell carcinoma and dysplasia," *Photodiagnosis and Photodynamic Therapy*, vol. 10, no. 3, pp. 229–235, 2013.

[21] B. Karakullukcu, K. van Oudenaarde, M. P. Copper et al., "Photodynamic therapy of early stage oral cavity and

oropharynx neoplasms: an outcome analysis of 170 patients," *European Archives of Oto-Rhino-Laryngology*, vol. 268, no. 2, pp. 281–288, 2011.

[22] N. R. Rigual, K. Thankappan, M. Cooper et al., "Photodynamic therapy for head and neck dysplasia and cancer," *Archives of Otolaryngology – Head & Neck Surgery*, vol. 135, no. 8, pp. 784–788, 2009.

[23] C. Hopper, A. Kübler, H. Lewis, I. B. Tan, G. Putnam, and the Foscan 01 Study Group, "mTHPC-mediated photodynamic therapy for early oral squamous cell carcinomamTHPC-mediated photodynamic therapy for early oral squamous cell carcinoma," *International Journal of Cancer*, vol. 111, no. 1, pp. 138–146, 2004.

[24] A. C. Kubler, J. de Carpentier, C. Hopper, A. G. Leonard, and G. Putnam, "Treatment of squamous cell carcinoma of the lip using Foscan-mediated Photodynamic TherapyTreatment of squamous cell carcinoma of the lip using Foscan-mediated photodynamic therapy," *International Journal of Oral and Maxillofacial Surgery*, vol. 30, no. 6, pp. 504–509, 2001.

[25] T. Yoshida, H. Kato, T. Okunaka et al., "Photodynamic therapy for head and neck cancer," *Diagnostic and Therapeutic Endoscopy*, vol. 3, no. 1, pp. 41–51, 1996.

[26] W. E. Grant, C. Hopper, P. M. Speight, A. J. Macrobert, and S. G. Bown, "Photodynamic therapy of malignant and premalignant lesions in patients with 'field cancerization' of the oral cavityPhotodynamic therapy of malignant and premalignant lesions in patients with 'field cancerization' of the oral cavity," *Journal of Laryngology and Otology*, vol. 107, no. 12, pp. 1140–1145, 1993.

[27] W. Jerjes, T. Upile, Z. Hamdoon, C. Alexander Mosse, M. Morcos, and C. Hopper, "Photodynamic therapy outcome for T1/T2 N0 oral squamous cell carcinoma," *Lasers in Surgery and Medicine*, vol. 43, no. 6, pp. 463–469, 2011.

[28] S. A. H. J. de Visscher, L. J. Melchers, P. U. Dijkstra et al., "mTHPC-mediated photodynamic therapy of early stage oral squamous cell carcinoma: a comparison to surgical treatment," *Annals of Surgical Oncology*, vol. 20, no. 9, pp. 3076–3082, 2013.

[29] K. F. M. Fan, C. Hopper, P. M. Speight, G. A. Buonaccorsi, and S. G. Bown, "Photodynamic therapy using mTHPC for malignant disease in the oral cavity," *International journal of cancer*, vol. 73, no. 1, pp. 25–32, 1997.

[30] M. A. Biel, "Photodynamic therapy of head and neck cancers," *Methods in molecular biology*, vol. 635, pp. 281–293, 2010.

[31] V. G. Schweitzer and M. L. Somers, "PHOTOFRIN-mediated photodynamic therapy for treatment of early stage (Tis-T2N0M0) SqCCa of oral cavity and oropharynx," *Lasers in Surgery and Medicine*, vol. 42, no. 1, pp. 1–8, 2010.

[32] K. J. Lorenz and H. Maier, "Photodynamic therapy with meta-tetrahydroxyphenylchlorin (Foscan) in the management of squamous cell carcinoma of the head and neck: experience with 35 patients," *European Archives of Oto-Rhino-Laryngology*, vol. 266, no. 12, pp. 1937–1944, 2009.

[33] P. Tandon, A. Dadhich, H. Saluja, S. Bawane, and S. Sachdeva, "The prevalence of squamous cell carcinoma in different sites of oral cavity at our Rural Health Care Centre in Loni, Maharashtra - a retrospective 10-year study," *Contemporary oncology*, vol. 2, no. 2, pp. 178–183, 2017.

[34] A. J. Cowan, C. Allen, A. Barac et al., "Global bBurden of mMultiple mMyeloma: aA sSystematic aAnalysis for the gGlobal bBurden of dDisease sStudy 2016Global Burden of Multiple Myeloma," *JAMA oncology*, vol. 4, no. 9, pp. 1221–1227, 2018.

[35] F. Bray, J. Ferlay, I. Soerjomataram, R. L. Siegel, L. A. Torre, and A. Jemal, "Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countriesGlobal cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries," *CA: a cancer journal for clinicians*, vol. 68, no. 6, pp. 394–424, 2018.

[36] A. Almangush, A. A. Mäkitie, A. Triantafyllou et al., "Staging and grading of oral squamous cell carcinoma: An update," *Oral oncology*, vol. 107, article 104799, 2020.

[37] W. Jerjes, T. Upile, Z. Hamdoon, C. A. Mosse, S. Akram, and C. Hopper, "Photodynamic therapy outcome for oral dysplasia," *Lasers in surgery and medicine*, vol. 43, no. 3, pp. 192–199, 2011.

[38] G. Taybos, "Oral changes associated with tobacco use," *The American journal of the medical sciences.*, vol. 326, no. 4, pp. 179–182, 2003.

[39] D. Kessel, "Photodynamic therapy: a brief history," *Journal of clinical medicine*, vol. 8, no. 10, p. 1581, 2019.

[40] A. Kübler, T. Haase, C. Staff, B. Kahle, M. Rheinwald, and J. Mühling, "Photodynamic therapy of primary nonmelanomatous skin tumours of the head and neck," *Lasers in surgery and medicine*, vol. 25, no. 1, pp. 60–68, 1999.

[41] J. Savary, P. Monnier, C. Fontolliet et al., "Photodynamic therapy for early squamous cell carcinomas of the esophagus, bronchi, and mouth with m-tetra (hydroxyphenyl) chlorin-Photodynamic Therapy for Early Squamous Cell Carcinomas of the Esophagus, Bronchi, and Mouth With m-Tetra(Hydroxyphenyl) Chlorin," *Archives of Otolaryngology - Head and Neck Surgery*, vol. 123, no. 2, pp. 162–168, 1997.

[42] T. J. Dougherty, G. Lawrence, J. H. Kaufman, D. Boyle, K. R. Weishaupt, and A. Goldfarb, "Photoradiation in the treatment of recurrent breast carcinoma," *Journal of the National Cancer Institute*, vol. 62, no. 2, pp. 231–237, 1979.

[43] G. Loewen, R. Pandey, D. Bellnier, B. Henderson, and T. Dougherty, "Endobronchial photodynamic therapy for lung cancerEndobronchial photodynamic therapy for lung cancer," *Lasers in surgery and medicine*, vol. 38, no. 5, pp. 364–370, 2006.

[44] J.-T. Lin, "Progress of medical lasers: fundamentals and applications," *Medical Devices and Diagnostic Engineering*, vol. 1, no. 2, pp. 36–41, 2016.

[45] X. Li, J. F. Lovell, J. Yoon, and X. Chen, "Clinical development and potential of photothermal and photodynamic therapies for cancer," *Nature Reviews Clinical Oncology*, vol. 17, no. 11, pp. 657–674, 2020.

[46] D. M. Ozog, A. M. Rkein, S. G. Fabi et al., "Photodynamic tTherapy: aA cClinical cConsensus gGuide," *Dermatologic Surgery*, vol. 42, no. 7, pp. 804–827, 2016.

[47] P. Babilas, S. Schreml, M. Landthaler, and R.-M. Szeimies, "Photodynamic therapy in dermatology: state-of-the-art," *Photodermatology Photoimmunology & Photomedicine*, vol. 26, no. 3, pp. 118–132, 2010.

[48] Y. Wang, H. Wang, L. Zhou et al., "Photodynamic therapy of pancreatic cancer: where have we come from and where are we going?," *Photodiagnosis and photodynamic therapy*, vol. 101876, 2020.