Review Article

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

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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 photosensitiser, 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 DerSimonian–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 pre-established 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 DerSimonian–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; $P > 0.05$).
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 DerSimonian–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

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Figure 1: Flow diagram of literature search and study selection process.
| Author       | Year | Mean age (year) | Female/male | Types of PS | Laser type | Radiant exposure (J/cm²) | Power density (mW/cm²) | Wavelength (nm) | Method of administration | Sample size | CR OR RR | Lesion locations | Mean follow-up (months) | Exposure time (min) | Number of sessions | Adverse site                                      |
|--------------|------|-----------------|-------------|--------------|------------|--------------------------|------------------------|----------------|--------------------------|--------------|---------|-----------------|---------------------|-------------------|--------------------|-------------------------------------------------|
| Ikeda H      | 2018 | 75.2 (55-94)    | 6/2         | Taxol sodium | Diode laser | 100                      | 150                    | 664            | Intravenous             | 8            | 6       | N/A             | 1                   | G/P               | 1                  | N/A                |
| Toratani S   | 2016 | 70.8            | 22/12       | Porflamer sodium | Dye laser | 100-150                  | 160                    | 630            | Intravenous             | 34           | 30      | 33              | 9                   | N/A               | N/A                | 105                |
| Righi N      | 2013 | N/A             | N/A         | HPPH4        | Dye laser   | N/A                      | N/A                    | 665            | Intravenous             | 20           | 16      | N/A             | 5-40                | N/A               | ≥1                 | Expected pain and edema |
| Karakulhuscu B | 2013 | 60 (38-92)      | 22/33       | mTHPC5       | N/A         | N/A                      | N/A                    | 630            | Intravenous             | 55           | 49      | N/A             | N/A                 | 2                 | N/A                | N/A                |
| Ikeda H      | 2013 | 73.7            | N/A         | Porflamer sodium | Diode laser | 100                      | 150                    | 630            | Intravenous             | 18           | 17      | N/A             | 2                   | N/A               | 2                 | N/A                |
| deVascher S A | 2013 | 61.1            | N/A         | mTHPC5       | Diode laser | 100                      | 150                    | 630            | Intravenous             | 156          | 127     | N/A             | 11                  | N/A               | N/A                | N/A                |
| Karakulhuscu B | 2011 | 60.5            | N/A         | mTHPC5       | N/A         | 100                      | 652                    | 126            | Intravenous             | 126          | 86      | 114             | N/A                 | 2                 | N/A                | N/A                |
| Jerje W      | 2011 | 58              | 12/26       | mTHPC5       | N/A         | 10-20                    | 100                    | 652            | Intravenous             | 38           | 12      | 6               | N/A                 | 3                 | N/A                | N/A                |
| Merrill A, B | 2010 | N/A             | N/A         | Porflamer sodium | Dye laser   | 150                      | 630                    | Intravenous             | 190          | 190     | 190             | 13                  | N/A               | N/A                | N/A                |
| Venessa Gayl | 2010 | N/A             | N/A         | Porflamer sodium | Dye laser | 150                      | 630                    | Intravenous             | 26           | 26      | 26              | 4                   | N/A               | N/A                | N/A                |
| KAI Johannes | 2009 | 58.8 (48-62)    | N/A         | mTHPC5       | N/A         | 20                      | 100                    | 652            | Intravenous             | 8            | 4       | N/A             | 2                   | N/A               | N/A                | ≥1                 |
| Righi N R    | 2009 | 61.2 (36-85)    | N/A         | Porflamer sodium | Argon pumped dye laser or a diode laser | 50-75                  | N/A                    | 630            | Intravenous             | 11           | 10      | 11              | N/A                 | 2                 | N/A                | N/A                |
| Hopper C     | 2004 | 64 (33-99)      | N/A         | mTHPC5       | Diode laser | 20                      | 100                    | 652            | Intravenous             | 114          | 97      | 114             | N/A                 | 7                 | 6                 | N/A                |
| Copper M P   | 2003 | N/A             | N/A         | mTHPC5       | Diode laser | 20                      | 100                    | 652            | Intravenous             | 26           | 22      | N/A             | 4                   | G/P               | 1                 | N/A                |
| Kubler A C   | 2001 | 64 (44-99)      | 6/19        | mTHPC5       | N/A         | 20                      | 100                    | 652            | Intravenous             | 25           | 24      | N/A             | 2                   | G/P               | 3                 | N/A                |
| Kathleen F M | 1997 | 66.5 (30-80)    | N/A         | Porflamer sodium | Dye laser | 5-20                     | 250                    | 630            | Intravenous             | 25           | 14      | N/A             | 2                   | G/P               | 2                 | N/A                |
| Yokuda T     | 1996 | 60.2 (51-67)    | 1/4         | HPPD5        | Argon or excimer dye laser | 200                   | 200-500                 | 630            | Intravenous             | 6            | 2       | 5               | N/A                 | 1                 | ≥1                 | Pain edema itching, weight loss transient, painlessness |
| Grant W E    | 1993 | N/A             | N/A         | Porflamer sodium | Dye laser | 50-100                  | 150                    | 630            | Intravenous             | 14           | 13      | N/A             | 3                   | G/P               | 3                 | N/A                |

G/P, gingiva and/or palate; L/BM/T/TFM: lips and/or buccal mucosa and/or tongue and/or floor of the mouth. m-THPC: m-Tetra(hydroxyphenyl) chlorin; HPPH2: chlorin-based compound, 3-(1'-hexyloxyethyl) pyropheophorbide; HPPD: hematoporphyrin derivative. N/A: not applicable.
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
## Table 1: Estimate (95% CI) and Ev/Trt for OR Rate

| Studies                  | Estimate (95% CI) | Ev/Trt |
|--------------------------|-------------------|--------|
| Toratani S 2016          | 0.971 (0.819, 0.996) | 33/34  |
| Karakullukcu B 2011      | 0.905 (0.840, 0.945) | 114/126|
| Merrill A. Biel 2010     | 0.997 (0.960, 1.000) | 190/190|
| Vanessa Gayl 2010        | 0.981 (0.764, 0.999) | 26/26  |
| Rigual N R 2009          | 0.958 (0.575, 0.997) | 11/11  |
| Hopper C 2004            | 0.996 (0.934, 1.000) | 114/114|
| Yoshida T 1996           | 0.833 (0.369, 0.977) | 5/6    |
| Overall ($I^2 = 55.69\%, P = 0.035$) | 0.967 (0.902, 0.989) | 493/507|

## Figure 3: Forest plots of OR rate after PDT.

## Table 2: Estimate (95% CI) and Ev/Trt for Proportions of RR

| Studies                  | Estimate (95% CI) | Ev/Trt |
|--------------------------|-------------------|--------|
| Ikeda H 2018             | 0.125 (0.017, 0.537) | 1/8    |
| Toratani S 2016          | 0.265 (0.144, 0.435) | 9/34   |
| Ikeda H 2013             | 0.111 (0.028, 0.352) | 2/18   |
| Jerjes W 2011            | 0.158 (0.073, 0.310) | 6/38   |
| Merrill A. Biel 2010     | 0.068 (0.040, 0.114) | 13/190 |
| Vanessa Gayl 2010        | 0.154 (0.059, 0.345) | 4/26   |
| Rigual N R 2009          | 0.958 (0.575, 0.997) | 11/11  |
| Copper M P 2003          | 0.154 (0.059, 0.345) | 4/26   |
| Kuhler A C 2001          | 0.080 (0.020, 0.269) | 2/25   |
| Overall ($I^2 = 67.32\%, P = 0.002$) | 0.158 (0.090, 0.264) | 52/376 |

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

## Table 3: Estimate (95% CI) and Ev/Trt for Complete Rate

| Studies                  | Estimate (95% CI) | Ev/Trt |
|--------------------------|-------------------|--------|
| Ikeda H 2018             | 0.250 (0.013, 0.891) | 0/1    |
| Ikeda H 2013             | 0.857 (0.419, 0.980) | 6/7    |
| Karakullukcu B 2011      | 0.654 (0.457, 0.809) | 17/26  |
| KAI Johannes 2009        | 0.500 (0.123, 0.877) | 2/4    |
| Hopper C 2004            | 0.857 (0.419, 0.980) | 6/7    |
| Copper M P 2003          | 0.600 (0.200, 0.900) | 3/5    |
| Grant W E 1993           | 0.875 (0.266, 0.993) | 3/3    |
| Subgroup G/P ($I^2 = 0\%, P = 0.603$) | 0.675 (0.532, 0.791) | 37/53  |
| Ikeda H 2016             | 0.857 (0.419, 0.980) | 6/7    |
| Ikeda H 2013             | 0.958 (0.575, 0.997) | 11/11  |
| Karakullukcu B 2011      | 0.690 (0.593, 0.773) | 69/100 |
| Grant W E 1993           | 0.889 (0.500, 0.985) | 8/9    |
| KAI Johannes 2009        | 0.500 (0.123, 0.877) | 2/4    |
| Hopper C 2004            | 0.845 (0.761, 0.903) | 87/103 |
| Copper M P 2003          | 0.905 (0.689, 0.976) | 19/21  |
| Kuhler A C 2001          | 0.960 (0.765, 0.994) | 24/25  |
| Subgroup L/BM/T/FM ($I^2 = 57.52\%, P = 0.021$) | 0.833 (0.720, 0.906) | 226/280|
| Overall ($I^2 = 40.43\%, P = 0.053$) | 0.781 (0.690, 0.851) | 263/333|

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

| Studies            | Estimate (95%CI) | Ev/Trt |
|--------------------|------------------|--------|
| Toratani S         | 0.882 (0.725, 0.955) | 30/34  |
| Ikeda H            | 0.944 (0.693, 0.992)  | 17/18  |
| Merrill A. Biel    | 0.997 (0.960, 1.000)  | 190/190|
| Vanessa Gayl       | 0.846 (0.655, 0.941)  | 22/26  |
| Rigual N R         | 0.909 (0.561, 0.987)  | 10/11  |
| Kathleen F M       | 0.560 (0.366, 0.737)  | 14/25  |
| Grant W E          | 0.929 (0.630, 0.990)  | 13/14  |
| Subgroup Porfimer sodium ($I^2 = 75\%, P = 0.001$) | 0.898 (0.748, 0.963)  | 296/318|
| Rigual N           | 0.800 (0.572, 0.923)  | 16/20  |
| Subgroup HPPH ($I^2 = NA, P = NA$) | 0.800 (0.572, 0.923)  | 16/20  |
| Karakullukcu B     | 0.891 (0.778, 0.950)  | 49/55  |
| deVisscher S A     | 0.814 (0.745, 0.868)  | 127/156|
| Karakullukcu B     | 0.683 (0.596, 0.758)  | 86/126 |
| Jerjes W           | 0.316 (0.189, 0.478)  | 12/38  |
| KAI Johannes       | 0.500 (0.200, 0.800)  | 4/8    |
| Hopper C           | 0.851 (0.773, 0.905)  | 97/114 |
| Copper M P         | 0.846 (0.655, 0.941)  | 22/26  |
| Kubler A C         | 0.960 (0.765, 0.994)  | 24/25  |
| Subgroup mTHPC ($I^2 = 87.11\%, P = 0.000$) | 0.763 (0.623, 0.863)  | 421/548|
| Yoshi da T         | 0.333 (0.084, 0.732)  | 2/6    |
| Subgroup HPD ($I^2 = NA, P = NA$) | 0.333 (0.084, 0.732)  | 2/6    |
| Overall ($I^2 = 80.03\%, P = 0.000$) | 0.799 (0.708, 0.867)  | 741/900|

### Figure 6: Continued.
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 each 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/cm²), 50–100 J/cm², and 100–200 J/cm². 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/cm²), 150–200 mW/cm², and ≥200 mW/cm². 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 chemotherpay. 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,
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
Studies | Estimate (95%CI) | Ev/Trt
---|---|---
Ikeda H | 0.750 (0.377, 0.937) | 6/8
Vanessa Gayl | 0.846 (0.655, 0.941) | 22/26
Rigual N R | 0.909 (0.561, 0.987) | 10/11
Grant W E | 0.929 (0.630, 0.990) | 13/14
Subgroup 50−100 ($I^2 = 0\%$, $P = 0.674$) | 0.854 (0.734, 0.926) | 51/59
Toratani S | 0.882 (0.725, 0.955) | 30/34
Yoshida T | 0.333 (0.084, 0.732) | 2/6
Subgroup 100−200 ($I^2 = 85.91\%$, $P = 0.008$) | 0.679 (0.130, 0.968) | 32/40
Jerjes W | 0.316 (0.189, 0.478) | 12/38
KAI Johannes | 0.500 (0.200, 0.800) | 4/8
Hopper C | 0.851 (0.773, 0.905) | 97/114
Copper M P | 0.846 (0.655, 0.941) | 22/26
Kubler A C | 0.960 (0.765, 0.994) | 24/25
Kathleen F M | 0.560 (0.366, 0.737) | 14/25
Subgroup 0−50 ($I^2 = 88.77\%$, $P = 0.000$) | 0.711 (0.454, 0.880) | 173/236
Overall ($I^2 = 81.2\%$, $P = 0.000$) | 0.761 (0.605, 0.869) | 256/335

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{forest_plot}
\caption{Forest plot of subgroup analysis of (a) CR, (b) OR, and (c) RR in cases about different radiant exposures.}
\end{figure}
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/cm² 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/cm² 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.

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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.

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