Highlights

- PDT for oral squamous cell carcinoma and epithelium dysplasia provides reliable short-term outcomes, but its long-term effects are limited.
- When PDT is applied to oral squamous cell carcinoma, long-term follow-up is essential because of the high risk of recurrence.
- New therapies will need to be developed to acquire the reliable outcome in the future.

Abstract

Background: Oral squamous cell carcinoma (OSCC) treatment consists mainly of surgery, chemotherapy, and radiotherapy, alone or in combination. Epithelial dysplasia (ED) is also treated with surgery. However, these treatments can induce functional and/or aesthetic disturbances. Photodynamic therapy (PDT) can preserve organs. Although short-term studies have shown good progress, long-term evaluations have not yet been conducted. This study aimed to clarify the long-term effects of PDT on OSCC and ED. *Methods:* Patients who underwent PDT with the first (porfimer sodium) or second generation photosensitizers (talaporfin sodium) for early OSCC (T1 and T2) and ED were included in this study. The long-term prognosis was assessed.

Results: Twenty-three patients were included. Complete response (CR) was observed in 19 patients (82.6%) and partial response (PR) in 4 patients (17.4%) 4 weeks after PDT. Regarding long-term progress, local region recurrence occurred in 11 of 19 CR cases (57.9%), and the term of recurrence was 27.4 ± 30.4 months. Surgical resection was performed in all local recurrence and PR cases, and 3 patients died of the underlying disease.

Conclusions: PDT provides a good outcome in the short term, but its long-term effects are limited.

Long-term effect of photodynamic therapy on oral squamous cell carcinoma and epithelial dysplasia

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Keywords: photodynamic therapy (PDT); oral squamous cell carcinoma (OSCC); epithelium dysplasia (ED)

Introduction

Oral squamous cell carcinoma (OSCC) is mainly treated with surgery, chemotherapy, and radiation therapy, alone or in combination. Additionally, molecularly targeted drugs and immune checkpoint inhibitors have been developed recently [1]. Although surgical therapy is the most reliable treatment strategy, oral dysfunction and aesthetic problems after surgical therapy often lead to a decline in the patient's quality of life (QOL), even in the early stages. Chemotherapy and radiotherapy can preserve oral and maxillofacial structures, functions, and aesthetics better than surgical procedures. However, it can induce serious adverse effects including osteonecrosis, oral mucositis, and chemotherapy-induced hematopoietic disorders [2]. Epithelial dysplasia (ED) is a common precancerous lesion. It is common for a partial biopsy to be diagnostic of ED; however, resection or total biopsy is needed to diagnose OSCC. Therefore, resection is recommended for lesions with a high risk of cancerous transformation, such as those with surface roughness [3]. Since the resection area is defined by a safety margin, the extent of the resection can be large, resulting in functional and aesthetic impairment.

Photodynamic therapy (PDT) is a minimally invasive cancer treatment strategy. It can avoid functional and aesthetic impairment and serious adverse effects observed after surgery, radiation therapy, and chemotherapy, and maintain patients' QOL [4]. Intravenously administered photosensitizers preferentially bind to low-density lipoprotein (LDL) after intravenous administration. LDL supplies the cholesterol required to create cell membranes during cell division in the tissue. Therefore, increased LDL incorporation was observed in cancer cells with intense cell division. As a result, photosensitizers accumulate significantly more in cancer cells than in normal cells [4]. When a photosensitizer is irradiated with 600–800 nm wavelengths, it binds to oxygen molecules in the cells and generates reactive oxygen species (ROS), which induces cancer cell death directly via apoptosis or necrosis.

PDT induces good outcomes in solid tumors in the whole body [5]. Several reports have shown short-term effects of PDT against T1 and T2 OSCC and ED [6,7]. However, no study has assessed the long-term prognosis after PDT. Therefore, this study aimed to evaluate the long-term effects of PDT on OSCC and ED.

Materials and Methods

Ethics statements

This cohort study was approved by the Clinical Research Ethics Committee of Nagasaki University Hospital (number: 22091213) and was initiated after UMIN registration (UMIN000048941).

Patients

Inclusion criteria were as follows: (1) patients who underwent PDT with porfimer sodium (PS) or talaporfin sodium (TS) as photosensitizers for early OSCC (T1 and T2) or ED according to the 2005 World Health Organization criteria [8,9] at Nagasaki University Hospital between 2008 and 2013; (2) those with a depth of tumor invasion <5 mm; (3) patients with no cervical lymph node metastasis or distant metastasis according to various imaging modalities (including computed tomography, magnetic resonance imaging, ultrasound imaging, and positron-emission tomography-computed tomography); (4) those who were followed for >5 years after PDT; and (5) patients who died during the observation period.

Exclusion criterion was patients who were treated with PDT for recurrent disease.

The included T2 cases were such that if surgical management was considered, primary closure would be required after tumor resection.

PDT

PS (Photofrin®, Wyeth-Takeda, Tokyo, Japan) was dissolved in a 5% glucose solution and administered intravenously at a dose of 2 mg/kg, 48 hours before laser irradiation. The excitation light source used in this study was an excimer dye laser (PDT-EDL1®: Hama-matsu Photonics K.K., Hamamatsu, Japan). The wavelength was 630 nm, irradiation output was 4 mJ/pulse/cm^2, and repetition rate was 40 Hz. Light was delivered to the tumor via a 400-μm flat-tipped quartz fiber. Irradiation was performed with the tip of the fiber placed approximately 1.0 cm above the lesion to make a 1-cm^2 irradiation spot.

TS (Laserphrin®; Meiji Seika Pharma, Tokyo, Japan) was administered intravenously at a dose of 40 mg/m^2 4 hours before laser irradiation. The region was irradiated using a semiconductor laser (PD Laser®, Panasonic Healthcare, Tokyo, Japan) with a wavelength of 664 nm. The irradiation method was the same as that used for PDT with PS.

The light dose was 100 J/cm^2 for both PS and TS. All patients were instructed to avoided direct sunlight and were not allowed to go outside the day after photosensitizer administration.

Outcome and follow-up

All data were collected from the medical records. Recurrent lesions were resected.

Clinical response was evaluated using the Response Evaluation Criteria for Solid Tumors. Recurrence, cervical lymph node metastasis, and distant metastasis were investigated during a follow-up period of >5 years.

Results

Demographic and clinical characteristics

Twenty-three patients (10 men and 13 women) were included in this study. Their ages ranged from 55 to 90 years (mean: 71.2 years) when they underwent PDT. The mean follow-up duration was 106 ± 43.4 months. There were 15 OSCC cases (T1, 6; T2, 9) and 8 ED cases (Table 1).

Long-term prognosis after PDT

Nineteen patients had complete response (CR) and 4 patients had partial response (PR) (CR rate, 82.6%; PR rate, 100%) 4 weeks after PDT. Eight of the 19 patients had local recurrence after CR (recurrence rate, 42%) during the long-term period. The term until recurrence was 27.4 ± 30.3 months (Table 2).

T1: All 6 patients (PS, 4; TS, 2) had CR (CR rate: 100%) in the short term, and 2 of 6 patients (PS, 1; TS, 1) had recurrence (recurrence rate [RR]: 33.3%) in the long term.

T2: Seven of 9 patients (PS, 7; TS, 2) had CR (CR rate: 77.8%) and 2 had PR in the short term. Five of 7 CR cases showed recurrence (RR: 71.4%) in the long term. Five patients showed CR and 2 had PR in the short term, and 4 of 5 CR cases showed

recurrence (RR: 80%) in the long term after PDT with PS. Two patients had CR in the short term, and recurrence was found in 1 patient (RR: 50%) in the long term after PDT with TS.

ED: Six of 8 patients (PS, 7; TS, 1) had CR (CR rate: 75.0%) in the short term, and 1 patient (RR: 16.7%) had recurrence in the long term. Recurrence was observed in 1 of the 5 CR cases (RR; 20%) in the long term after PDT with PS.

Comparison of the effectiveness of PDT on ED, T1 OSCC, and T2 OSCC

Long-term CR rates with PDT were 66.7%, 22.2%, and 62.5%, and their follow-up term was 99.8 ± 37.0, 77.5 ± 13.4, and 131.8 ± 26.2 months for T1, T2, and ED, respectively, indicating maintenance of long-term CR (Table 3). Fisher's exact test showed no significant difference in the CR rates between the groups.

Patients who were diagnosed with PR in the short-term and had long-term recurrence underwent surgical treatment. Two patients with PR and 1 patient with recurrence died of the existing disease. In 2 cases of PR after PDT irradiation for ED, a short-term pathological diagnosis of OSCC was obtained after subsequent surgical treatment. The 5-year survival rate excluding deaths from other diseases was 86.9% (23/29), and including deaths from other diseases was 76.9% (20/26), of which the disease-specific survival rate was 50% (3/6). There were no cases of late cervical metastases in patients who were diagnosed with CR in the short term.

Discussion

The CR rate of PDT for OSCC and ED was 82.6% in the short term, but the long-term RR was 42%, suggesting that PDT has a short-term effect and that the long-term effect is limited. PDT should be used only for QOL maintenance in inoperable patients or in patients with short-term prognosis due to other diseases.

Surgery is the main treatment for OSCC, and radiotherapy, chemotherapy, and chemoradiotherapy are used as adjuvant therapies after surgery. The local RR was reported to be 15% in T1 OSCC and 26% in T2 OSCC after surgery [10]. The RR was reported to be 20–34.7% after surgery in ED [11–13]. This study’s results showed that the RRs were 33.3% for T1 OSCC, 71.4% for T2 OSCC, and 16.7% for ED after PDT during the long-term follow-up. Compared with surgery, PDT showed a lower RR in patients with ED but a higher RR in those with OSCC. Furthermore, the long-term CR

rates were 67% for T1, 22% for T2, and 62% for ED. These results suggest that PDT is less reliable than surgery for long-term outcomes, especially in stage II cancer. Moreover, PDT is not indicated for OSCC with metastases and thereby in stages III and IV cancer.

The effectiveness of PDT is determined by the depth of light delivery and is not effective for cancers with depths >10 mm [14]. Herein, the depth of the tumor was <5 mm; therefore, we considered that the light completely reached and covered the entire region of the tumor. However, a T2 OSCC case clearly showed a high RR. PDT directly kills cancer cells by generating ROS and changes the environment around the tumor by affecting vascular endothelial cells in the tissue surrounding the tumor. The coagulation process is activated by ROS damage to vascular endothelial cells. This induces platelet aggregation and thrombus formation, which result in vascular obstruction. Consequently, the tumor tissue becomes hypoxic, causing the death of cancer cells that escape the direct effects of PDT [4]. The larger the irradiated field, the more difficult ischemia of the peritumoral tissue becomes, which may have led to a higher RR in the case of T2 OSCC.

This is the first report to assess the long-term effects of PDT for OSCC and ED. Santeerapharp et al. [15] studied the long-term period of PDT for precancerous lesions of the larynx and reported recurrence in 61.5% of patients. The median follow-up duration was 4 years. Moghissi et al. [16] reported a 5-year survival rate of 53.8% after PDT for esophageal cancer. However, PDT was used in perilaryngeal surgery because of serious functional impairment in the former study, and all patients with esophageal cancer were inoperable in the latter study. These results suggest that surgery is more predictive than PDT for OSCC if surgery is possible.

The 5-year survival rate for all patients was 86.9%, and rates were 100% for T1 and 67% for T2 OSCC in this study. This result was comparable to that of Murthy et al.'s study, in which the 5-year survival rates were reported to be 87% for T1 and 67% for T2 OSCC [10]. In other words, PDT is effective in the short term for T1/T2 OSCC treatment. Even if recurrence is found, appropriate treatment can obtain a long-term period comparable to that of current methods. Therefore, PDT as an initial treatment for T1/T2 OSCC is worth considering as an effective treatment strategy if surgery must be avoided to preserve function and maintain aesthetics. Additionally, as medicines have developed, patients' lifetimes have become longer. Subsequently, the number of patients with the disease has increased. Moreover, the number of patients who are incapable of general anesthesia is

increasing [17]. Thus, PDT as an initial treatment for T1/T2 OSCC is considered an effective treatment strategy for patients who are unable to undergo general anesthesia.

PDT is a minimally invasive treatment procedure [4], and no serious adverse effects have been reported [7,8]. Moreover, widespread lesions, such as those with field change, which would require extensive resection, are considered a good indication for PDT because laser can irradiate the wide regions of field change. This was a single-arm study and the effectiveness of PDT as a primary treatment procedure was assessed. Thus, patients who were treated with PDT for recurrent disease were not included in this study. Further prospective studies should be performed in the near future.

The photosensitizers used in this study were PS, a first-generation photosensitizer, and TS, a second-generation photosensitizer. de Visscher et al. [18] performed PDT with another photosensitizer, meta-tetra(hydroxyphenyl)chlorin, for head and neck SCC and observed CR rates of 86% for T1 and 63% for T2 SCC. However, the overall survival rate of patients with T2 SCC who underwent PDT as the primary treatment procedure was comparable to that of patients who underwent surgical treatment. Further prospective studies comparing PDT and standard treatment are necessary to clarify the effectiveness of PDT in SCC. Recently, a third-generation photosensitizer was developed to further enhance tumor cell selectivity and antitumor efficacy [19]. In addition to PDT, photothermal therapy, and photoimmunotherapy, other types of nanomaterial-based phototherapies have been developed [20], and their application to head and neck tumors awaits further investigation. In addition, a combination of brachytherapy and PDT has been reported to be effective in lung cancer for prolonged regional control [21]. The usefulness of this combination for OSCC should be assessed to expand the indication of PDT.

Conclusions

PDT for OSCC and ED provides reliable short-term outcomes, but its long-term effects are limited. This implies that PDT should be used as an initial treatment and only to maintain QOL in inoperable patients or patients with short-term prognosis due to other diseases. When PDT is applied, long-term follow-up is essential because of the high risk of recurrence. Considering its safety and minimal invasiveness, further studies should be performed to expand the indications of PDT.

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Tables

Table 1.

Patient demographics and clinical data.

Table 2.

Long-term prognoses.

Table 3.

Table 3. Long-term prognoses after PS without additional treatment.

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recurrence (RR: 80%) in the long term after PDT with PS. Two patients had CR in the short term, and recurrence was found in 1 patient (RR: 50%) in the long term after PDT with TS.

ED: Six of 8 patients (PS, 7; TS, 1) had CR (CR rate: 75.0%) in the short term, and 1 patient (RR: 16.7%) had recurrence in the long term. Recurrence was observed in 1 of the 5 CR cases (RR; 20%) in the long term after PDT with PS.

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Discussion

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rates were 67% for T1, 22% for T2, and 62% for ED. These results suggest that PDT is less reliable than surgery for long-term outcomes, especially in stage II cancer. Moreover, PDT is not indicated for OSCC with metastases and thereby in stages III and IV cancer.

The effectiveness of PDT is determined by the depth of light delivery and is not effective for cancers with depths >10 mm [14]. Herein, the depth of the tumor was <5 mm; therefore, we considered that the light completely reached and covered the entire region of the tumor. However, a T2 OSCC case clearly showed a high RR. PDT directly kills cancer cells by generating ROS and changes the environment around the tumor by affecting vascular endothelial cells in the tissue surrounding the tumor. The coagulation process is activated by ROS damage to vascular endothelial cells. This induces platelet aggregation and thrombus formation, which result in vascular obstruction. Consequently, the tumor tissue becomes hypoxic, causing the death of cancer cells that escape the direct effects of PDT [4]. The larger the irradiated field, the more difficult ischemia of the peritumoral tissue becomes, which may have led to a higher RR in the case of T2 OSCC.

This is the first report to assess the long-term effects of PDT for OSCC and ED. Santeerapharp et al. [15] studied the long-term period of PDT for precancerous lesions of the larynx and reported recurrence in 61.5% of patients. The median follow-up duration was 4 years. Moghissi et al. [16] reported a 5-year survival rate of 53.8% after PDT for esophageal cancer. However, PDT was used in perilaryngeal surgery because of serious functional impairment in the former study, and all patients with esophageal cancer were inoperable in the latter study. These results suggest that surgery is more predictive than PDT for OSCC if surgery is possible.

The 5-year survival rate for all patients was 86.9%, and rates were 100% for T1 and 67% for T2 OSCC in this study. This result was comparable to that of Murthy et al.'s study, in which the 5-year survival rates were reported to be 87% for T1 and 67% for T2 OSCC [10]. In other words, PDT is effective in the short term for T1/T2 OSCC treatment. Even if recurrence is found, appropriate treatment can obtain a long-term period comparable to that of current methods. Therefore, PDT as an initial treatment for T1/T2 OSCC is worth considering as an effective treatment strategy if surgery must be avoided to preserve function and maintain aesthetics. Additionally, as medicines have developed, patients' lifetimes have become longer. Subsequently, the number of patients with the disease has increased. Moreover, the number of patients who are incapable of general anesthesia is

increasing [17]. Thus, PDT as an initial treatment for T1/T2 OSCC is considered an effective treatment strategy for patients who are unable to undergo general anesthesia.

PDT is a minimally invasive treatment procedure [4], and no serious adverse effects have been reported [7,8]. Moreover, widespread lesions, such as those with field change, which would require extensive resection, are considered a good indication for PDT because laser can irradiate the wide regions of field change. This was a single-arm study and the effectiveness of PDT as a primary treatment procedure was assessed. Thus, patients who were treated with PDT for recurrent disease were not included in this study. Further prospective studies should be performed in the near future.

The photosensitizers used in this study were PS, a first-generation photosensitizer, and TS, a second-generation photosensitizer. de Visscher et al. [18] performed PDT with another photosensitizer, meta-tetra(hydroxyphenyl)chlorin, for head and neck SCC and observed CR rates of 86% for T1 and 63% for T2 SCC. However, the overall survival rate of patients with T2 SCC who underwent PDT as the primary treatment procedure was comparable to that of patients who underwent surgical treatment. Further prospective studies comparing PDT and standard treatment are necessary to clarify the effectiveness of PDT in SCC. Recently, a third-generation photosensitizer was developed to further enhance tumor cell selectivity and antitumor efficacy [19]. In addition to PDT, photothermal therapy, and photoimmunotherapy, other types of nanomaterial-based phototherapies have been developed [20], and their application to head and neck tumors awaits further investigation. In addition, a combination of brachytherapy and PDT has been reported to be effective in lung cancer for prolonged regional control [21]. The usefulness of this combination for OSCC should be assessed to expand the indication of PDT.

Conclusions

PDT for OSCC and ED provides reliable short-term outcomes, but its long-term effects are limited. This implies that PDT should be used as an initial treatment and only to maintain QOL in inoperable patients or patients with short-term prognosis due to other diseases. When PDT is applied, long-term follow-up is essential because of the high risk of recurrence. Considering its safety and minimal invasiveness, further studies should be performed to expand the indications of PDT.

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Tables

Table 1.

Patient demographics and clinical data.

Table 2.

Long-term prognoses.

Table 3.

Table 3. Long-term prognoses after PS without additional treatment.

Table 1. Patient demographics and clinical data.

Case	Sex	Age (years)	Diagnosis	T classification	Photosensitizer	Response	Outcome	Follow-up period (m)
1	F	55	OSCC	T1	PS	CR	No recurrence	71
2	F	69	OSCC	T2	PS	PR	Death due to uncontrolled disease	48
3	F	90	OSCC	T2	PS	PR	Death due to uncontrolled disease	9
4	F	66	ED	-	PS	PR	Controlled by surgical treatment	197
5	M	61	ED	-	PS	CR	No recurrence	175
6	F	79	ED	-	PS	CR	No recurrence	132
7	F	80	OSCC	T1	PS	CR	No recurrence	90
8	M	83	OSCC	T2	PS	CR	Recurrence after 30 m	101
9	M	70	OSCC	T1	PS	CR	Recurrence after 6 m	105
10	M	73	ED		PS	CR	No recurrence	108
11	F	84	OSCC	T2	PS	CR	Recurrence after 102 m	90
12	M	76	OSCC	T1	PS	CR	No recurrence	154
13	M	70	ED	-	PS	CR	Recurrence after 6 mo	167
14	F	76	OSCC	T2	PS	CR	Recurrence after 32 m; surgery was performed, but death occurred due to uncontrolled disease	85
15	M	67	ED	-	PS	PR	Controlled by surgical treatment	60
16	F	66	OSCC	T2	PS	CR	No recurrence	68
17	M	75	OSCC	T2	PS	CR	Recurrence after 29 m	164
18	M	68	ED	-	PS	CR	No recurrence	130

19	M	55	OSCC	T1	TS	CR	Recurrence after 9 m	114
20	M	55	ED	-	TS	CR	No recurrence	114
21	F	60	OSCC	T1	TS	CR	No recurrence	84
22	F	72	OSCC	T2	TS	CR	No recurrence	87
23	F	87	OSCC	T2	TS	CR	Recurrence after 6 m	95

ED, epithelial dysplasia; PS, perfumer sodium; OSCC, oral squamous cell carcinoma; TS, talaporfin sodium; CR, complete response; PR, partial response; M, male; F, female; m, months.

Rrecurrence refers to local recurrence.

Table 2. Long-term prognoses.

	Photosensitizer	Case	Response, n	Recurrence after CR determination, n	No recurrence, n	Long-term CR rate
OSCC T1	PS	4	CR: 4 PR: 0	1	3	75%
	TS	2	CR: 2 PR: 0	1	1	50%
OSCC T2	PS	7	CR: 5 PR: 2	4	3	14%
	TS	2	CR: 2 PR: 0	1	1	50%
ED	PS	7	CR: 5 PR: 2	1	4	57%
	TS	1	CR: 1 PR: 0	0	1	100%

PS, perfumer sodium; TS, talaporfin sodium; CR, complete response; PR, partial response; OSCC, oral squamous cell carcinoma; ED, epithelial dysplasia.

Table 3. Long-term prognoses after PS without additional treatment.

	Case	Short-term		Long-term		
		CR	PR	CR	Follow-up term (month)	Recurrence (month)
OSCC T1	6	6	0	4 (66.7%)	99.8 ± 37.0	2 (60.0 ± 76.4)
OSCC T2	9	7	2	2 (22.2%)	77.5 ± 13.4	4 (64.0 ± 39.9)
ED	8	6	2	5 (62.5%)	131.8 ± 26.2	1 (6)

PS, perfumer sodium; TS, talaporfin sodium; CR, complete response; PR, partial response; OSCC, oral squamous cell carcinoma; ED, epithelial dysplasia.