Treatment outcome of Photofrin-based photodynamic therapy for T1 and T2 oral squamous cell carcinoma and dysplasia

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Running title: Photofrin based-photodynamic therapy treatment outcome in the oral cavity

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Abstract

Background: Photodynamic therapy (PDT) is a minimally invasive treatment modality for early and superficial malignancy or premalignancy in the head and neck regions. However, few studies have examined the use of Photofrin-mediated PDT to manage early carcinoma and dysplasia in the oral cavity.

Methods: Between January 2004 and November 2008, 25 T1 to T2 patients with N0 oral squamous cell carcinoma and mucosal dysplasia in the oral cavity were treated by Porfimer sodium (Photofrin®)-mediated PDT at Nagasaki University Hospital. Clinical responses were evaluated according to the guidelines of the Response Evaluation Criteria in Solid Tumors (RECIST). After the PDT and a 2-year follow-up period, disease specific survival rates were then calculated.

Results: A total of 30 regions in 25 patients (18 with squamous cell carcinoma and 7 with epithelial dysplasia with hyperkeratosis in the oral cavity) were treated by PDT. Complete response was achieved in 24 of the 25 patients (96%), with a partial response found in the remaining patient. For the three patients who exhibited recurrence at 4, 5, and 15 months after PDT, salvage surgery or a second PDT was performed. Of these three patients, one died due to another disease, while one died due to local lymphatic metastasis that occurred during the follow-up period. Overall, the disease specific survival rate was 95.8%. Treatment-related
edema and pain emerged within 24 hours after irradiation. Pain control using non-steroid anti-inflammatory drugs and opiates was required for 3 to 4 weeks in all patients. Complete healing was attained at 4 to 6 weeks after the treatment. No persistent problems related to functional or esthetic outcomes were noted.

Conclusion: Current results demonstrate the efficacy of Photofrin-mediated PDT on early superficial squamous cell carcinoma and epithelial dysplasia in the oral cavity.
Introduction

The preferred treatment modalities for early-stage carcinomas and mucosal dysplasia in the oral cavity are surgery and radiotherapy. While both treatment modalities have good cure rates during the early stages\textsuperscript{1,2}, these treatments can lead to functional impairments. Radiotherapy often has irreversible side effects such as endarteritis, xerostomia, and mucositis, along with an added risk for osteoradionecrosis. Similarly, surgery can also have unintended side effects, with both functional and esthetic losses occurring to some degree in other healthy tissues. When present in the oral cavity, there is a potential for mucosal dysplasia to progress to cancer. A previous study has reported that the risk of progression to cancer varies from 6\% to 36\%.\textsuperscript{3} The management of patients with oral dysplasia presents a considerable problem for surgeons, as radiotherapy is not always feasible since it can only be administered once. In addition, this therapy is associated with significant local morbidity. Thus, an optimal treatment for moderate to severe dysplasia of the oral cavity needs to be safe, effective, repeatable, minimally invasive, and devoid of permanent sequelae. Photodynamic therapy (PDT) is a photochemical reaction that is based on the use of a drug, light, and oxygen, with the photochemical reaction leading to a selective destruction of tumor cells. As compared to the other conventional modalities, there are several advantages associated with using the PDT methodology. These include: (1) the treatment is a minimally invasive technique that lacks systemic toxicity; (2) there is selective
tumor destruction along with normal tissue preservation; (3) the treatment can be repeated without any cumulative tissue toxicity; (4) there is little effect on the underlying functional structures and there is an excellent esthetic outcome; and (5) the treatment can be applied before or after any conventional treatment modality. PDT has been approved worldwide for use as a clinical treatment with various photosensitizers.\(^4,5\) Porfimer sodium (Photofrin\textsuperscript{®})\(^6\) is a first generation photosensitizer with a long history of use that has shown it to be both reliable and safe.\(^7\) Photofrin has been licensed for use in esophageal, lung, stomach, and cervix cancer in the United States, Canada, European Union, Russia, and Japan.\(^8\) However, Photofrin-based PDT for carcinoma and dysplasia in the oral cavity has yet to be approved in Japan. Photofrin is activated at 630 nm, which is a wavelength that can penetrate tissues to a depth of 10 mm.\(^9\) Even though Photofrin-based PDT has been shown to be ineffective against deeper tumors, it is effective for the treatment of superficial malignancies. Since almost all lesions in the oral cavity can be observed macroscopically, light irradiation treatments can be carried out without having to use special devices such as endoscopes. Thus, superficial malignancies and mucosal dysplasia in the oral cavity are good targets for Photofrin-mediated PDT. However, few studies have specifically examined using Photofrin-mediated PDT to manage carcinoma and dysplasia in the oral cavity. In this study, we report the clinical outcomes and complications for 25 cases at 30 sites of oral squamous cell carcinoma and epithelial dysplasia after treatment with
Photofrin-mediated PDT in the Department of Oral and Maxillofacial Surgery, Nagasaki University Hospital from 2004 to 2008.

Materials and Methods

This retrospective study attempted to determine the effects of Photofrin-mediated PDT on oral squamous cell carcinoma (SCC) and dysplasia. Between January 2004 and November 2008, this 48-month study examined patients seen at the Oral and Maxillofacial Surgery Unit of Nagasaki University Hospital. All procedures were performed according to the specific protocol approved by the Institutional Review Board of Nagasaki University Hospital (Approval No. 17). Informed consent was obtained from all patients prior to their enrollment in the study. To prevent any photosensitivity side effects, all patients were hospitalized during their treatments. Inclusion criteria for this study were as follows: (1) biopsy-proven SCC in the oral cavity; (2) biopsy-proven moderate to severe oral mucosal dysplasia, as per the WHO classification criteria; (3) tumor diameter less than 4 cm (T1 to T2) without any lymph-node or distant metastases (N0, M0); (4) tumor depth less than 5 mm, as measured by magnetic resonance imaging and ultrasound imaging; (5) patients with severe complications who could not tolerate conventional therapy; and (6) patients who refused conventional therapy or who had previous failed treatments. Patients were excluded if they had Porphyria or exhibited hypersensitivity for
porphyrin. Photofrin (Wyeth-Takeda, Tokyo, Japan) was dissolved in a 5% glucose solution and
administered intravenously 48 hours prior to laser irradiation at a dose of 2 mg/Kg within
10-minute. After PDT administration, all patients avoided direct sunlight. The excitation light
source used in the study was an Excimer dye laser (PDT-EDL1: Hamamatsu Photonics K.K.,
Hamamatsu, Japan). The wavelength was 630 nm, irradiation output was 4 mJ/pulse/cm², and
the 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 from the
lesion to make 1cm² irradiation spot. Light doses consisted of 100 J/cm² \(^{11}\). Irradiation times
needed about 11 minutes for 100 J/cm². The lesion plus an additional 5 mm margin of the
normal mucosa were illuminated. Surrounding normal tissues were covered by wet gauze in
order to protect them from the laser light. Topical or local anesthesia was not required during
any of the treatments in all patients. Treatment times varied from 30 to 150 minutes in
accordance with the lesion size. Postoperative care included an intravenous Betamethasone
4mg/body administration once a day for 3 days in order to relieve any swelling. Intravenous or
orally administered antibiotics were then administered for 1 week to prevent infection. Oral
non-steroid anti-inflammatory drugs (NSAIDs) and opiates were used as needed to control any
postoperative pain. Biopsies were performed 4 to 6 weeks after the PDT. Clinical responses
were evaluated as a complete response (CR), partial response (PR), stable disease, or
progressive disease in accordance with the guidelines for the Response Evaluation Criteria in Solid Tumors (RECIST)\textsuperscript{(12)}. Follow-ups were performed at 1, 2, 4, 8, 16, 24, 36, 52 weeks and 2 years after the PDT. After completion of 2 years of follow-up, we have continued to follow the patients where possible.

Results

Patients

Twenty-five patients were treated by Photofrin-mediated PDT from January 2004 to December 2008. Table 1 lists the demographic and histopathological characteristics of the lesions in 25 patients who were treated by Photofrin-mediated PDT. The group included 12 males and 13 females, ranging in age from 29 to 85, with an average age of 70.8 years. A total of 18 had SCC while 7 were diagnosed as epithelial dysplasia with hyperkeratosis. Out of the 25 patients, 5 had recurrent disease (with 4 undergoing surgery and 1 receiving radiation therapy), while 20 had primary disease.

Site and classification

A total of 30 regions were treated by PDT in the 25 patients. Locations treated included the tongue (n=14), gingiva (n=6), palate (n=5), buccal mucosa (n=4) and the floor of the mouth
In accordance with the WHO histological grading guidelines, 5 out of 7 of the epithelial dysplasia patients were moderate, while 2 were classified as severe dysplasia with hyperkeratosis. For the histological grading of the SCC, 17 were classified as well differentiated while 1 was moderately differentiated. According to the T size classification, 9 were T1 and 10 were T2 (Table 1).

Treatment responses

Follow-up information was available for all patients. Based on the physical and histological examinations, 24 out of 25 patients (96%) achieved CR, with the remaining patient classified as PR. A CR was achieved by 17 out of 18 patients (94.4%) in the SCC group and in 7 out of 7 patients (100%) in the epithelial dysplasia group. As seen in Table 1, the T1 palatal SCC patient who only achieved PR subsequently underwent surgical resection. As of 2010, this patient has remained disease-free.

Disease-free interval and disease-specific survival rate

Recurrences occurred in 3 patients (3/25: 12%) after PDT. In the SCC group, 2 out of the 18 patients had recurrences at 4 and 15 months. Both of these patients underwent surgical resection and have remained disease-free during the subsequent follow-up periods. In the epithelial dysplasia group, 1 out of 7 patients had a recurrence at 5 months after the PDT. This patient has
been disease-free after undergoing a second Photofrin-mediated PDT procedure. Two SCC patients died during the follow-up period even though they initially achieved CR. A T2 palate SCC patient died 4 months after the PDT due to neck metastasis, while a T2 buccal mucosa SCC patient died at 24 months after PDT due to hepatic cirrhosis. Overall, the total disease specific survival rate in this study was 95.8%.

Postoperative courses

Within 24 hours after the irradiation, swelling and edema were observed at the site and continued for approximately 1 week. Severe swelling was noted more often in patients who had irradiation of the tongue or buccal mucosa versus the gingiva or palate. While slight dyspnea that lasted 2 to 3 days was observed in some patients who had irradiation of their tongue, none of these patients required airway intervention as a result of the treatment. Postoperative pain occurred 1 to 2 days after PDT, with contact and swallowing pain being the major symptom seen in all patients. Systemic intraoral administration of NSAIDs was required for 3 to 4 weeks post-irradiation. Some patients needed oral administration of opiates in addition to the NSAIDs. Transient odynophagia made it necessary for all patients to continue on a liquid diet for 7 to 10 days after the treatment. Treated areas underwent surface necrosis 2 to 3 days after the irradiation, with the necrosis lasting for 10 to 14 days. Complete healing occurred 4 to 6 weeks
after PDT with little scar formation (Fig 1~4). Direct sunlight caused a phototoxic reaction of
the facial edema in 2 patients. After oral administration of steroids, this reaction resolved within
1 week. All patients had slight skin coloration changes, although no symptoms were noted on
either the face or hands. This change completely disappeared within 1 year in all patients. There
were no persistent problems related to functional or esthetic outcomes in any of the patients.
Discussion

The main advantage of PDT for oral early carcinoma and dysplasia is the ability to preserve normal tissue and the oral function. In the oral cavity, almost all of the lesions can be observed macroscopically. Since light irradiation can be performed without the need for special devices such as endoscopes, the oral cavity may be an appropriate region for PDT. Over the past 30 years, the first generation photosensitizer, Porfimer sodium (Photofrin®), has been widely utilized and shown to have a high level of safety. However, few studies have investigated the Photofrin-mediated PDT treatment outcomes for SCC and dysplasia in just the oral cavity.

In previous studies, treatment outcomes for oral cavity carcinoma and epithelial dysplasia have been reported to vary from 83.3% to 100%. In the current study, 25 patients with SCC or epithelial dysplasia in the oral cavity were treated using Photofrin-mediated PDT. A single PDT treatment resulted in a complete response in 24 out of 25 patients (96%). During the 24-month follow-up period, recurrence occurred in 3 patients within 15 months. This result demonstrates the efficacy of Photofrin-mediated PDT for both SCC and epithelial dysplasia in the oral cavity.

The major side effect associated with Photofrin use is its photosensitivity, which can last for up to 4 weeks. In the current study, two patients exhibited photosensitivity after discharge. Upon further examination, this photosensitivity appeared to be caused by the patients wearing improper clothing. In addition, although all of the patients exhibited slight pigmentation after the PDT
treatment, this completely disappeared without any additional persistent esthetic problems within 1 year. These findings indicate that photosensitivity was not a major complication in the current study. One other problem encountered during the treatment period was related to postoperative swelling and pain. Postoperative swelling was observed within 24 hours after the original light irradiation, with resolution occurring within 1 week. If the lesions are located at the base of the tongue or on the posterior portion of the oral floor, the airways could potentially be compromised. The possibility of airway obstruction needs to be taken into consideration prior to treatment. Post operative pain was severe and continued to be a problem for a long time. Pain relief in the current study was obtained by a 3 to 4 week systemic administration of NSAIDs along with opiates, when necessary. However, the pain duration observed in the current study was substantially longer than has been previously reported\textsuperscript{18}. Light penetration depth, tumor bed homogeneity, and the irradiation times have all been reported to have a major influence on therapeutic effects\textsuperscript{18,19}. Although human tissue transmits light most effectively in the red part of the visible spectrum, Photofrin only has moderate activity in the tissue because the excitation wavelength (630 nm) can only penetrate tissue to a depth of 10 mm.\textsuperscript{9} In the SCC group, we observed a residual tumor on the floor of the mouth in one patient, along with recurrence on the palate of another patient. The palate and the floor of the mouth have complex structures within the oral cavity, with both sites having an irregular surface that makes it difficult to accurately
illuminate nonhomogenous structures. Therefore, an insufficient light penetration depth combined with the complex structure may be responsible for the presence of residual tumor cells. One patient with dysplasia of the tongue had recurrence 5 months after PDT. In this case, the irradiation areas were 60×20 mm. the irradiation times this patient required over 120 min. When large irradiation fields require irradiation times that are longer than 120 min, this can result in a significant source of treatment error due to either patient or light source motion. Likewise, the reason for recurrence in patients may be due to an inaccurate light delivery that occurs as a direct result of the longer required treatment times. It should be noted that patients with SCC and dysplasia in the oral cavity appear to be amenable to PDT treatments. In contrast, it is difficult to treat these tumors and premalignancies when using conventional therapies. When employing PDT, the superficial affected areas can be easily treated without damaging the surrounding normal tissues. Photofrin is a useful and reliable photosensitizer that has a long history of administration worldwide. In the current study, Photofrin-mediated PDT for superficial SCC and dysplasia in the oral cavity resulted in excellent outcomes. Even so, these promising findings are somewhat tempered by the photosensitivity and weak tissue penetration problems associated with Photofrin treatments. However, second generation photosensitizers such as mTHPC and mono-L-aspartylchlorin-e6 have been shown to not only be rapidly eliminated in the body but also to have longer excitation wavelengths as compared to Photofrin.
Thus, use of these second-generation photosensitizers for PDT may very well lead to better
tresults when treating early-stage SCC and dysplasia in the oral cavity.
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New response evaluation criteria in solid tumours: revised ECIST guideline (version 1.1)


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SCC, squamous cell carcinoma; well, well differentiated; moderate, moderate differentiated or moderate dysplasia; CR, complete remission and PR, partial remission.
Figure legends

Fig 1-a. Squamous cell carcinoma at left buccal mucosa (Case No 8)
Before PDT treatment

Fig 1-b. During PDT treatment (Case No 8).

Fig 1-c. After PDT treatment. Tumor disappeared at irradiation site (Case No 8).

Fig 2-a. Squamous cell carcinoma at left buccal mucosa (Case No 9)
Before PDT treatment

Fig 2-b. During PDT treatment (Case No 9)

Fig 2-c. After PDT treatment. First, second premolar and first molar teeth dropped after treatment (Case No 9).

Fig 3-a. Moderate epithelial dysplasia both side of the palate (Case No 4)
Before During PDT treatment
Fig 3-b. Moderate epithelial dysplasia both side of the palate (Case No 4)

   During PDT treatment

Fig 3-c. After PDT treatment (Case No 4).

   Epithelial dysplasia was complete disappeared.

Fig 4-a. Moderate epithelial dysplasia both side of the palate (Case No 20)

   Before PDT treatment

Fig 4-b. During PDT treatment(Case No 20)

   Necrosis was seen at irradiation site

Fig 4-c. Five month after PDT treatment(Case No 20).

   Recurrence was noticed at irradiation site
Fig. 1

a. 

b.
Fig. 1

c.
c.
c.