Lasers in Surgery and Medicine 38:349–355 (2006)

Advances in Photodynamic Therapy for the Treatment of Head and Neck Cancers

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Photodynamic therapy (PDT) is an FDA-approved minimally invasive medical treatment modality that utilizes light in the presence of oxygen to activate photosensitizing agents that are relatively selectively concentrated in abnormal or neoplastic cells resulting in cell death. At the present time, PDT has been approved for clinical treatment in the United States, European Union, Canada, Russia, and Japan. In the United States, US Food and Drug administration approval has been given for the use of PDT in the treatment of Barrett's esophagus, obstructing esophageal carcinoma and early and obstructing tracheobronchial carcinoma using the photosensitizer Photofrin; actinic keratosis using the photosensitizer Levulan (aminolevulinic acid); and macular degeneration using the photosensitizer BPD. In the EU the above noted indications have also been approved in addition to the treatment of early head and neck cancers and palliative treatment of head and neck cancer using the photosensitizer Foscan; and treatment of basal and squamous cell skin cancers using the photosensitizer Metvix. Lasers Surg. Med. 38:349–355, 2006.

Key words: cancer; photodynamic therapy; head and neck

INTRODUCTION

The method of photodynamic therapy (PDT) involves the use of a photosensitizing agent that is relatively selectively concentrated in abnormal or neoplastic cells. Depending on the type of photosensitizer, it may be injected intravenously, ingested orally, or applied topically. After application of the photosensitizer, it is relatively selectively retained by tumor cells so that after several hours to days, determined by the kinetics of the compound's distribution, there is more sensitizer in the neoplastic tissue than in the normal tissue. The photosensitizer is then activated with a specific wavelength of light matching the absorption characteristics that are unique to that specific photosensitizer, usually using a laser. This results in tumor necrosis via several mechanisms including oxygen radical production as well as vascular shutdown to the tumor [1]. Because there is less sensitizer in the adjacent normal tissue, only the neoplastic tissue necroses and the normal tissue are preserved. The advantage of PDT over the other conventional modalities of surgery, radiation, and chemotherapy is that it is a minimally invasive treatment technique that lacks systemic toxicity yet results in selective tumor destruction with normal tissue preservation. This advantage is of particular importance for cancers of the head and neck, where excessive tissue loss results in significant functional debilities. In addition, since this is an entirely different process, the use of chemotherapy, ionizing radiation, or surgery does not preclude the use of PDT. Also, unlike ionizing radiation, repeated applications of the photosensitizer and activating light treatments can be performed indefinitely. The following is a retrospective review of the author's 336 patients treated with PDT for head and neck neoplasia between 1990 and 2005.

MATERIALS AND METHODS

The author's clinical experience with PDT for the treatment of the head and neck spans 15 years. Three hundred thirty-six patients with various processes of the upper aerodigestive tract were treated with PDT from February 1990 to November 2005 (Table 1). Patients were divided into eight groups: those with advanced cancer where the intent of therapy was purely palliative; those with clinically focal early cancers (CIS, T1, and T2) with or without previous radiotherapy; those with T2 and T3 superficial oral cavity cancers; those with T2 and T3 invasive cancers that failed or refused conventional therapy; those with Kaposi's sarcoma; those with recurrent juvenile laryngotracheal papillomatosis that were uncontrolled with conventional therapies; and those with recurrent infiltrating carcinomas of the head and neck treated with adjuvant intra-operative PDT at the time of surgical resection. This present review will only discuss the treatment and outcome of 297 patients from the following three treatment groups: those with clinically focal early primary cancers with N0 necks (CIS, T1, and T2) with or without previous radiotherapy; those with T2 and T3 superficial oral cavity cancers; and those with recurrent infiltrating carcinomas of the head and neck treated with adjuvant intra-operative PDT at the time of surgical resection.

All patients were treated according to specific protocol in accordance with FDA and local IRB approvals. Pre-treatment evaluation included a history and physical examination, endoscopic examination with tumor mapping and biopsy, routine laboratory evaluation, and photographic documentation. All treatments were performed using the photosensitizer Photofrin (Axcan Pharma, Montreal, Canada) as an off label use indication. The male-to-female ratio was 211:86, with an age range of 24–90 years. The tumors were located in various head and neck sites (Table 1).

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Accepted 24 April 2006
Published online 11 June 2006 in Wiley InterScience (www.interscience.wiley.com).
DOI 10.1002/lsm.20368

TABLE 1. Site and Pathology of PDT Treatments

Site	Pathology	Number
Larynx	Squamous Ca	117
Oral cavity, pharynx	Squamous Ca	183
Nasal cavity, sinus	Squamous Ca	2
Palate	Kaposi's sarcoma	2
Nasopharynx	Mucosal melanoma	3
Larynx-trachea	Papillomas	5
Skin carcinoma	Squamous Ca	3
	Metastatic breast	1
	Melanoma	1
Recurrent infiltrating Ca	Squamous Ca	18
Lung	Squamous Ca	1

Photofrin was injected intravenously at a dose of 2.0 mg/kg over a 5 minutes period as an outpatient procedure. Forty-eight hours after the injection, the patients underwent treatment with light from an Nd:Yag pumped-dye laser (Laserscope) at 630-nm wavelength. Light was delivered to the tissue bed with a 400-μm fused silica optical fiber (Laserguide, Inc., Buelton, CA). A microlens treatment was used for all tumors with a depth of less than 3 mm. These treatments were performed at a dose rate of 50–75 J/cm^2 and 150 mw/cm^2 in the oral cavity, nasopharynx, and skin, and 80 J/cm^2 and 150 mw/cm^2 in the larynx. For non-laryngeal tumors greater than 3 mm in depth on clinical exam or T2 laryngeal tumors, cylindrical diffusers 0.5–2.5 cm in length were placed in the tumor bed using an 18-gauge catheter under local or general anesthesia. These treatments were performed at a dose rate of 100 J/cm fiber length and 400 mw/cm fiber length. Adjuvant intra-operative PDT was performed following tumor resection covering the entire surgical resection site with a microlens fiber at 50 J/cm^2 and 150 mw/cm^2. All treatments were performed on an outpatient basis under local or general anesthesia except for those patients with intra-operative adjuvant PDT. Those treatments were performed at the time of surgical resections under general anesthesia and the patients were hospitalized for their usual post-operative course.

On completion of treatment, each patient received Decadron 10 mg intravenously for one dose to reduce tissue edema and was discharged on oral pain medications. All patients were instructed to avoid daylight for 30 days. Tumor response was evaluated at 1 week, 1 month and then monthly thereafter for 1 year and every 3 months thereafter. Multiple biopsy specimens of the treated area were obtained for most patients 1 month after treatment to evaluate a complete histopathologic response.

RESULTS

One hundred ten patients with recurrent or primary CIS, T1N0, and T2N0 laryngeal tumors were treated with PDT for cure. Three patients had recurrent CIS, 92 patients had T1N0 carcinomas of the true vocal cord of which 25 were radiation failures, and 15 patients had T2N0 carcinomas of the true vocal cord of which 8 were radiation failures. All patients underwent a single microlens light treatment and most T2 tumors also underwent cylindrical diffuser implants into the paraglottic space. All treatments were performed under general anesthesia with standard laryngoscopy and all patients were discharged to home the same day of PDT treatment. All patients obtained a complete histopathologic response after a single light treatment. With follow-up to 189 months (mean 84 months) there were 10 recurrences for a 5-year cure rate of 90%. Importantly, all the recurrences were salvaged using either PDT, surgery, or radiation for a total 5-year cure rate of 100%. In the entire treatment group, there were no episodes of airway compromise and the degree of post-operative pain was minimal and easily controlled with oral analgesics. All patients after treatment developed an immediate breathy voice that persisted for 2–3 weeks. At 4–6 weeks after treatment, the quality of voice was universally much improved over the pre-treatment state. In addition, videostroboscopy 6 weeks post-PDT treatment performed on 10 patients demonstrated a normal vocal cord mucosal fluid wave on the treated vocal cord.

One hundred twelve patients with recurrent or primary CIS and T1N0 squamous cell carcinomas of the oral cavity were treated. Two patients had recurrent CIS and 110 patients had T1N0 lesions. All patients were treated with a microlens and if the tumors clinically were invasive greater than 3 mm, they were also treated with cylindrical diffuser implantation to distribute the light deeper into the tissues. The diffusers were spaced 1-cm apart from each other. All patients obtained a complete pathologic and clinical response after a single PDT treatment. With follow-up to 190 months (mean 80 months), there were six local recurrences within 8 months of PDT treatment. These were all salvaged with either repeat PDT treatment or surgical resection. Two patients with T1 tongue tumors developed regional lymph nodes within 3 months of PDT treatment and went on to conventional neck dissection and have remained free of disease for at least 5 years. Five-year cure rates for these patients therefore remain at 100%. Unfortunately, there was one peri-PDT treatment death unrelated to PDT due to a drug overdose.

Forty patients with superficial T2N0 and T3N0 squamous cell carcinomas of the oral cavity were treated. All of these patients had extensive areas of tumor involvement up to 7 cm in size. The maximal depth of the tumor, however, was clinically less than 1 cm. These patients were treated with a microlens and for those areas where there was clinical invasion greater than 3 mm, cylindrical diffusers of 0.5–1.0 cm were employed to distribute the 630-nm light deeper into the tissues. All patients obtained a complete clinical and pathologic response after a single PDT treatment. With follow-up to 116 months (mean 46 months), there were three recurrences at the edge of the PDT treatment field. These were all salvaged with either repeat PDT treatment or surgical resection. No patients developed regional lymph node involvement. Three-year cure rates for these patients are 100%. Importantly, the post-PDT healing of these patients demonstrated normal mobile oral mucosa without scar formation and preservation of the patency of the submandibular and parotid salivary ducts. Histologic evaluation of the post-PDT healing process demonstrated preservation of the cellular collagen matrix with repopulation of the normal mucosal cells into the preserved collagen matrix resulting in normal mucosa and submucosa.

Intra-operative adjuvant PDT was performed in 35 patients. These patients were divided into two treatment groups: (1) PDT for curative intent following gross tumor debulking. The goal of this treatment is to achieve complete tumor eradication with preservation of normal vital structures, such as the larynx and tongue; and (2) PDT of the surgical resection bed following complete resection of T3 and T4 tumors. The goal of this treatment is to increase local regional disease control by increasing tumor-free resection margins and destroy microscopic skip lesion disease while preserving uninvolved normal structures.

In the first treatment group, PDT for curative intent following gross tumor debulking, 17 patients were treated, 11 laryngeal and 6 oral cavity. Of the 11 laryngeal, 8 were supraglottic and 3 were glottic. The oral cavity lesions were tongue and floor of mouth. The treatment consisted of the patient receiving Photofrin 2 mg/kg pre-operatively and 2 days after the injection the patient underwent general anesthesia and gross but incomplete resection of the tumor mass. Residual microscopic disease was confirmed with frozen section biopsies intra-operatively. PDT was then performed to the resection site using a microlens fiber at 75–80 J/cm^2 at 150 mw/cm^2. Cylindrical diffuser implantation 0.5 cm in length was placed wherever the location was safe to do so and illumination performed at 100 J/cm fiber length at 400 mw/cm fiber length. Most of the treatments were performed on an outpatient basis. For the laryngeal tumors treated, with follow-up to 69 months, there have been no recurrences. For the six oral cavity tumors, with follow-up to 58 months there was one recurrence that went on to conventional surgical resection and remains free of disease.

In the second treatment group, intra-operative adjuvant PDT of the surgical resection bed following complete resection of T3 and T4 tumors, 18 patients with recurrent infiltrating squamous cell carcinoma of the head and neck were treated. Each patient had undergone previous treatment of the primary lesion of the head and neck with surgical resection, radiotherapy, and chemotherapy. The initial primary carcinomas were in the larynx; tongue and floor of mouth; branchial cleft cyst; medial canthal skin and ethmoid sinus; and tonsil. The sites of recurrence included the pharyngoesophagus and anterior neck skin; mandible and neck; medial orbit, ethmoid and anterior skull base; neck skin, parotid and lateral skull base; tongue and floor of mouth; and neck. In all cases, extensive skin involvement with tumor was present with deep infiltration into the soft tissues as determined by CT, MRI, and angiographic scanning. All lesions were determined to be surgically resectable.

Intra-operative adjuvant PDT was performed as follows: Photofrin was injected intravenously at a dose of 2.0 mg/kg over a 5-minute period as an outpatient procedure 2 days prior to surgery. Forty-eight hours after injection, the patient underwent planned surgical resection of the recurrent tumor. All uninvolved skin was covered during the surgical procedures, which lasted up to 10 hours. Lighting during the surgical resection was with headlights. The resected tumor underwent frozen section pathologic evaluation of the margins in order to ensure a complete surgical resection. PDT was then performed on the entire tumor resection bed at a dose rate of 50 J/cm^2 and 150 mw/cm^2 using a microlens fiber tip (Laserguide, Inc.). The areas involved with the PDT treatment were up to 8 cm $\times$ 10 cm and included the carotid artery and internal jugular veins. Following PDT treatment, the patients underwent surgical reconstruction of the defect using microvascular free flaps in 14 of 18 patients.

The post-operative course of all of the patients was uncomplicated and each patient healed without difficulty with only one self-limited fistula. The time of hospitalization and the time to total healing were not altered with the use of PDT. There was increased facial swelling post-operatively that lasted up to 1 week post-operatively. As well, there was prolonged serous drainage from the neck drains that lasted an average of 2 days longer than an equivalent non-PDT-treated patient. There were no post-operative vascular complications.

All patients were followed post-operatively (minimum 133 months, maximum 164 months) with only six patients developing recurrent or metastatic disease, two inside the field of PDT treatment and four outside the field of surgical and PDT therapy. Importantly, the first 10 patients admitted to the trial were randomized to surgery only or surgery and intra-operative adjuvant PDT. Of the first 10 patients, 5 in the surgery only control group were all dead at 10 months post-surgery and 3 of 5 surgery and PDT patients remain alive and free of disease greater than 5 years post-treatment.

Although this represents a small single institution trial, based on these results there is some indication that adjuvant intra-operative PDT may improve cure rates of recurrent head and neck malignancies by providing for larger tumor-free margins of resection while preserving normal structures. It may also be of benefit as an adjuvant intra-operative treatment at the time of primary resection of tongue base and hypopharyngeal carcinomas and skull base tumors, as well as the neck at the time of neck dissection for lymph node involvement with extracapsular spread.

In the entire series, of 297 patients only 2 patients sustained a significant sun-induced photosensitivity reaction with significant facial edema. This resolved with oral steroids in 5 days without sloughing of skin. In all patients, the treated area demonstrated maximal necrosis by 7 days after light treatment, and there was complete healing by 4 weeks after treatment. The degree of treatment-related pain was quite variable with some patients having mild pain and others, usually those with extensive oral tumors, having severe pain. In all cases however, the pain was adequately controlled with oral analgesics. The pain was uniformly resolved within 2–3 weeks of treatment.

DISCUSSION

Data are available for over 1,300 patients treated with PDT using Photofrin, HPD, ALA, or Foscan for the treatment of head and neck cancers. These patients include a mixture of presentations including primary, recurrent, and metastatic lesions. The predominant histology is squamous cell carcinoma, but other histologies treated include mucosal melanoma, Kaposi's sarcoma, adenocarcinoma, metastatic breast carcinoma, and adenoid cystic carcinoma. Fortu-

nately, in the last 2 years, the first multi-institutional Phase II–III clinical trials evaluating PDT treatment of head and neck cancers have been completed. These trials have demonstrated the efficacy of this minimally invasive therapy in the treatment of early oropharyngeal primary and recurrent cancers as well as the palliative treatment of refractory head and neck cancers. Although this author has presented the results of Photofrin-based PDT for the treatment of head and neck cancers, it is important to recognize that other photosensitizers have been used and continue to be investigated for the treatment of head and neck cancers with very similar results.

Early Stage Head and Neck Cancer: Photofrin-HPD-Based PDT

Patients with early stage cancers or early recurrences in the oral cavity and larynx (Cis, T1,T2) tend to have an excellent response to PDT. Of 505 patients treated with Cis, T1, or T2 cancers of the oral cavity, larynx, pharynx, and nasopharynx, 450 (89.1%) obtained a complete clinical response after one PDT treatment (Table 2). Laryngeal cancers, comprising 166 patients in this group, obtained a durable complete response rate of 88% with up to a 15-year follow-up.

Keller reported three patients with T1 and T2 oral carcinomas treated with HPD, all of which obtained a complete response without recurrence [2].

Feyh treated 27 patients with Tis–T2 carcinomas of the oral cavity and larynx. Of 15 patients with oral cancers, 13 obtained a complete response. One patient with recurrent disease occurred submucosally in the tongue. Of 12 patients with laryngeal cancers, 11 obtained a complete response (91%) [3,4].

Wenig reported on 26 patients treated with early recurrent squamous cell carcinomas. Light delivery was at 75–125 J/cm^2. A complete response was achieved in 20 of 26 (77%) patients treated, with 6–51 months follow-up [5]. Grossweiner treated nine patients with early recurrent carcinomas of the oral cavity with light administration 24 hours after intravenous Photofrin injection. Eight of nine (88%) patients had a complete response after one PDT treatment [6].

Freche treated 32 patients with T1 carcinomas of the true vocal cords treated with HPD or Photofrin. A complete response was achieved in 25 of 32 patients (78%), with 12–48 months follow-up [7]. Schweitzer reported 20 patients with Tis–T2 carcinomas, 10 of the oral cavity and 10 of the larynx, treated with Photofrin and 50–150 J/cm^2 laser light. Eight of 10 (80%) patients with oral carcinoma and 8 of 10 (80%) patients with laryngeal carcinoma obtained a complete response [8,9].

Gluckman reported on 23 patients with early head and neck carcinomas (Cis, T1, T2) treated with Photofrin. Twenty of 23 (87%) patients obtained a complete response with an 8–53 months follow-up. Carcinomas of the oral cavity were particularly sensitive to PDT treatment [10].

Grant reported 12 patients with T1 carcinoma (field cancerization) of the oral cavity treated with Photofrin at 2 mg/kg and light administered 48 hours after injection at 50–100 J/cm^2 at 150 mw/cm^2. Ninety-two percent (11 of 12) obtained a complete response with up to 19 months follow-up [11].

Biel treated 262 patients with early head and neck squamous cell carcinomas. Of these, 110 were early laryngeal tumors (Tis,T1,T2), 33 of which were radiation failures, treated with Photofrin 2 mg/kg using a microlens fiber at 80 J/cm^2, 48 hours after Photofrin injection. All but 10 patients (90.9%) obtained a durable complete response with follow-up to 189 months (mean 90 months) [12–15]. In addition, 112 patients with early carcinomas (Tis, T1, and T2) of the oral cavity, nasal cavity, and nasopharynx and 40 patients with superficial T2–T3 carcinomas of the oral

TABLE 2. Summary of Published Results with Photofrin PDT of Early Head and Neck Squamous Cell Cancer

Study	Patients	Lesion and site	Drug, dose, mg/kg	Response, n		
				Complete	Partial	None
Keller et al. [2]	3	T1 and T2, oral cavity	Photofrin, 1.5-2	3	0	0
Feyh et al. [3,4]	15	T1 and T2, oral cavity	Photosan III	13	2	0
	12	T1 and T2, larynx	Photosan III	11	1	0
Wenig et al. [5]	26	T1 recurrent, various sites	Photofrin, 2	20	6	0
Grossweiner et al. [6]	9	Early oral cavity and pharynx	Photofrin, 2	8	1	0
Freche et al. [7]	32	T1, larynx	HPD, 3 Photofrin, 2	25	7	0
Schweitzer [8,9]	10	T1, oral cavity	Photofrin, 2	8	2	0
	10	T1, larynx		8	2	0
Gluckman [10]	13	T1, oral cavity	Photofrin, 2	11	2	0
	2	T1, larynx		2	0	2
	8	Cis, condemned mucosa		7	1	0
Grant et al. [11]	12	T1, oral cavity	Photofrin, 2	11	1	0
Biel [12–15]	110	T1 and T2 larynx	Photofrin, 2	100	10	0
	112	T1 and T2 oral cavity		106	6	0
	40	T2, T3 superficial		37	3	0
Zhao et al. [16]	50	Lip cancer	HPD, 3	50	0	0
Kulapeditheron [18,19]	41	Oral and nasopharynx	Photofrin, 2	30	11	0

cavity were treated. All obtained a complete response after a single PDT treatment. With follow-up to 6–190 months (mean 80 months), 106 of 112 (94.6%) patients with Tis–T2 carcinomas remain free of disease and 37 of 40 patients (92.5%) with superficial T2–T3 oral carcinomas remain free of disease with 6–116 months follow-up. Two of these patients however, recurred at the margins of the PDT treatment but were treated with limited laser resections of the recurrence and remain free of disease. Only one patient developed regional metastases 2 months post-PDT [12–15].

Zhao treated 50 patients with lip cancer using HPD with a 100% cure rate (50 of 50) [16]. In addition, they treated 31 patients with combined cobalt radiation therapy and HPD-PDT for various head and neck cancers. They demonstrated a 100% response rate and suggested that HPD-PDT may enhance the effects of radiotherapy when carried out 48 hours after intravenous HPD injection [17].

Kulapaditharom treated 41 patients with pre-cancerous and T1–T2 nasopharyngeal and oral carcinomas. He achieved a 91.67% complete response rate for T1 primary and recurrent tumors with a recurrence rate of 27.27% (mean follow-up 28.3 months). All T1 and T2 nasopharyngeal tumors responded completely [18,19].

Early Stage Head and Neck Cancer: Foscan (mTHPC)-Mediated PDT

Second generation photosensitizers have the potential to improve the effectiveness of PDT by providing for greater tumor selectivity and deeper light penetration into tissue with the use of longer wavelengths of activating light. In addition, side effects such as the length of skin photosensitivity are reduced.

Foscan (mTHPC, Biolitec, Germany) is a potent second generation photosensitizer that is activated at 652-nm light. To date, this is the only photosensitizer that has been evaluated in multi-institutional trials for the treatment of head and neck cancers. The use of Foscan-mediated PDT by single investigators demonstrated the efficacy of this treatment for early oral and pharyngeal cancers (Table 3). Dilkes reported on 19 patients with T1 and T2 lesions of the oral cavity and pharynx using Foscan and 20 J/cm^2 laser light. Some patients received multiple PDT treatments. Of the 19 patients treated, 90% obtained a documented complete response and 10 of 19 patients remained free of disease with follow-up of 6–100 months [20–22]. Monnier treated four patients with Tis and T1 lesions of the oral cavity with a complete response [23]. Fan treated 19 patients with Tis–T4 carcinomas of the oral cavity. A single treatment with Foscan PDT was able to eradicate Tis–T2 lesions [24]. Kubler treated 25 patients with Tis–T2 lip cancers and reported a 96% cure rate at 3 months with two recurrences, one at 4 months and one at 18 months post-PDT [25]. Dilkes treated five patients with T1-2 laryngeal tumors with Foscan PDT. Only one of the five patients had no recurrence of disease [22].

Two large multi-institutional Phase II trials have recently been completed evaluating the efficacy of Foscan PDT in the treatment of primary oropharyngeal cancers and recurrent and second primary oral carcinomas. The trial evaluating Foscan PDT for the treatment of primary oropharyngeal cancers involved 114 patients with Tis–T2 oropharyngeal cancers. These patients received Foscan 0.15 mg/kg intravenously and underwent light activation at 652-nm light at 20 J/cm^2 at 100 mw/cm^2. Up to three light treatments were allowed under the protocol. A complete response rate of 85% (97 of 114) was achieved at completion of therapy. With 2-year follow-up there was a 77% complete response rate at 2 years with disease-free survival of 89% and 75% at 1 and 2 years after PDT treatment, respectively. This trial demonstrated complete durable response rates that are equivalent to those obtained with conventional therapies [26,27]. The second trial evaluated Foscan PDT in 96 patients with recurrent or second primary carcinomas in the oral cavity. These patients demonstrated a 50% histologically confirmed complete response rate with a 79% survival rate at 1 year [28]. Further follow-up is ongoing. Adverse events in these two trials consisted of pain at the treatment site, easily treated with oral analgesics and narcotics, and residual skin photosensitivity which lasted up to 2 weeks post-Foscan injection. Both of these events were expected and manageable. These two clinical trials, the first multi-institutional PDT trials to be performed in the treatment of head and neck cancers, demonstrated that Foscan PDT results in cure rates that are equivalent to conventional

TABLE 3. Summary of Published Results with h ALA and Foscan PDT of Early Head and Neck Squamous Cell Cancer

				Response, n		
Study	Patients	Lesion and site	Drug	Complete	Partial	None
Grant et al. [29]	4	Oral cavity	ALA	3	1	0
Fan et al. [30]	18	Dysplasia, ca oral cavity	ALA	14	4	0
Sieron et al. [31]	5	Larynx and hypopharynx	ALA	0	5	0
Kubler et al. [32]	12	Oral leukoplakia	ALA	5	4	3
Dilkes et al. [22]	19	T1, T2 oral cavity and pharynx	Foscan	10	9	0
Savary et al. [23]	4	Tis, T1 oral cavity	Foscan	4	0	0
Fan et al. [24]	6	Tis, T1, T2 oral cavity	Foscan	6	0	0
Kubler et al. [25]	25	Tis-T2 lip cancer	Foscan	22	3	0
Hopper et al. [26]	114	Tis- T2, oral cavity	Foscan	97	17	0
Cooper et al. [27]	25	T1, T2 oral cavity and pharynx	Foscan	25	4	0

therapy with less treatment-associated morbidity, especially systemic toxicities [26–28].

Early Stage Head and Neck Cancer: ALA-Mediated PDT

Grant treated four patients with oral carcinoma following the oral administration of ALA [29]. Light (630 nm) of 50–100 J/cm^2 was delivered 6 hours after oral ingestion of the ALA. All patients sustained tumor necrosis but normal surrounding tissue also necrosed, indicating no tumor selectivity. Fan treated 18 patients with dysplasia and malignant lesions of the oral cavity with ALA. Only two of six patients with carcinomas obtained a complete response [30]. Sieron treated five patients with larynx and hypopharynx carcinomas using ALA PDT. All five patients only achieved a partial response [31]. Transient liver function abnormalities occurred in all patients. Due to the limited depth of accumulation of ALA and the limited penetration of 635-nm light, tumors of greater than 2-mm depth are not consistently cured [29–31].

Kubler treated 12 patients with oral leukoplakia with 20% ALA cream and 630-nm light. Five patients demonstrated a complete response, four patients a partial response and three patients no response. One patient with a partial response was retreated resulting in a complete response [32].

Intra-Operative Adjuvant Photodynamic Therapy for Massive Recurrent Head and Neck Cancers

Biel reported the first human clinical trial with long-term follow-up using PDT as an intra-operative adjuvant treatment for recurrent head and neck cancer [15,33]. Eighteen patients with recurrent infiltrating squamous cell carcinoma of the head and neck were treated. Each patient had undergone previous treatment of the primary lesion of the head and neck with surgical resection, radiotherapy, and chemotherapy. All patients were followed post-operatively (minimum 133 months, maximum 164 months) with only six patients developing recurrent or metastatic disease, two inside the field of PDT treatment and four outside the field of surgical and PDT therapy. In another treatment group, PDT was performed for curative intent following gross tumor debulking on 17 patients, 11 laryngeal and 6 oral cavity. Of the 11 laryngeal, 8 were supraglottic and 3 were glottic. The oral cavity lesions were tongue and floor of mouth. For the laryngeal tumors treated, with follow-up to 16–69 months, there have been no recurrences. For the six oral cavity tumors, with follow-up to 12–58 months there was one recurrence that went on to conventional surgical resection and remains free of disease.

This investigator determined that adjuvant intra-operative PDT may improve cure rates of recurrent head and neck malignancies by providing for larger tumor-free margins of resection while preserving normal structures. It may also be of benefit as an adjuvant intra-operative treatment at the time of resection of tongue base and hypopharyngeal carcinomas and skull base tumors, as well as the neck at the time of neck dissection for lymph node involvement with extracapsular spread.

Dilkes treated 14 patients with intra-operative Foscan-mediated PDT. Two patients remain free of disease with up to 5-month follow-up. Two patients suffered carotid blow-outs [21].

Lou described the method of interstitial PDT using Foscan to treat 39 patients with recurrent unresectable head and neck cancers. The overall median survival was 14 months with 72% overall palliative benefit achieved. Importantly, the local control rate at 12 months was 41% [34].

The present studies indicate the effectiveness of PDT in the treatment of specific anatomic areas in the head and neck. In particular, Tis and T1 carcinomas of the larynx appear to be particularly effectively treated with PDT. A literature review of control rates of various treatments for Tis of the vocal cord were as follows: laser excision (104 patients) 20% initial failure rate requiring further therapy, 1% larynx lost; vocal cord stripping (235 patients) 34% failure rate, 12% larynx lost; radiotherapy (481 patients) 16% failure rate, 7% larynx lost [35]. The literature demonstrated that surgical techniques to treat Tis are best limited to those patients where the Tis does not involve the anterior commissure or the bilateral vocal cords. The present clinical series demonstrates the efficacy of Photofrin-mediated PDT as a curative treatment for Tis, T1 (85–91%), and T2 (72%) squamous cell carcinomas of the larynx. PDT for laryngeal carcinomas results in no glottic scarring as compared to conventional laser or surgical excision or vocal cord stripping. For recurrent carcinomas of the larynx that have failed conventional radiation therapy, PDT allows excellent voice preservation and may eliminate the need for partial or total laryngectomy. Also, PDT can be repeated without additional functional laryngeal compromise that can occur from repeated conventional laser surgery or cordectomy. Importantly, PDT treatment of primary T1 and T2 laryngeal carcinomas reserves radiation therapy for treatment of recurrences or of second head and neck primaries that may occur in these high-risk patients.

The side effects of PDT treatment of laryngeal carcinomas are quite minimal as compared to conventional radiotherapy or surgery. PDT treatment is performed as a single out-patient procedure as compared to 6–7 weeks of radiotherapy or the hospitalization associated with a partial or total laryngectomy. The photosensitivity of Photofrin is a temporary inconvenience not associated with systemic toxicity and is minimized by patient education and temporary changes in daily outdoor activities. The photosensitivity does however last for approximately 4 weeks.

PDT for treatment of T1 and T2 laryngeal carcinomas in the present series has cure rates that are comparable to if not better than that of conventional therapies with less morbidity of treatment. PDT should be considered as a reasonable option for the treatment of primary and recurrent Tis, T1, and T2 squamous cell carcinomas of the larynx.

PDT also is effective in the treatment of Tis and T1 primary and recurrent carcinomas of the oral cavity including the palate, floor of mouth, nasopharynx, and posterior pharyngeal walls. These results have been demonstrated in the multi-institutional Phase II Foscan PDT clinical trials and in single investigator Photofrin trials in which cure rates were comparable to those of conventional therapy with less morbidity.

The adjuvant intra-operative use of PDT to treat recurrent infiltrating carcinomas of the head and neck has been impressive to date. In this group of patients with a very high incidence of recurrence, adjuvant intra-operative PDT may improve cure rates by providing for larger tumor-free margins of resection while preserving normal structures. In addition, the use of interstitial PDT for the treatment of large recurrent head and neck cancers appears to provide good local control and palliation for this difficult patient population.

CONCLUSION

PDT is an excellent modality for the treatment of carcinomas of the head and neck. Great advances have been achieved in the past few years in defining the role of PDT in the treatment of head and neck cancers. The future for the use of PDT in the treatment of head and neck cancers lies in its ability to treat early carcinomas of the head and neck with minimal morbidity and its potential use as an adjuvant therapy intra-operatively to treat surgical margins following resection for T3 and T4 head and neck and skull base tumors via superficial or interstitial light applications. In order to further assess the effectiveness of this treatment on various areas within the head and neck, further standardized controlled studies are necessary. In addition, the development of new, more tumor-specific photosensitizing agents and light delivery systems will improve the effectiveness of this therapy. The present studies indicate that PDT is an effective primary or alternative treatment modality for carcinomas in specific areas of the head and neck.

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