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EDITORIAL

Photofrin-mediated photodynamic therapy for treatment of early stage laryngeal malignancies

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Abstract To evaluate the efficacy of PHOTOFRIN-mediated photodynamic therapy (PDT) for the treatment of Tis-T1N0M0 squamous cell carcinoma (SqCCa) of the larynx in patients not amenable to or who failed conventional head and neck treatment. This is a retrospective study of 26 patients with early stage Tis-T1 SqCCa of the larynx treated with PHOTOFRIN-mediated PDT. Intravenous PHOTOFRIN (porfimer-sodium) (dose 2.0 mg/kg) was administered outpatient, followed by intraoperative photoactivation at 630 nm via fiberoptic microlens surface delivery (surgical light dose 50–100 J/cm^2) 48–60 h later. As much as 16 out of 26 patients (62%) have demonstrated complete remission (average follow-up 40 months). There were 10 patients who were noted to have partial remission with recurrence observed 2–33 months subsequently retreated with either repeated PDT therapy or conventional therapy. PHOTOFRIN-mediated photodynamic therapy can be used as a primary modality to treat Tis-T1N0M0 tumors of the larynx or for treatment for those who have failed prior surgery and/or radiation therapy. PDT allows for preservation of function and structure to maintain or improve voice with absence of systemic toxicity. Patients may have multiple drug administrations and laser light retreatment for local disease control.

Keywords Photodynamic therapy · Larynx · Photofrin · Head and neck cancer

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Introduction

It is estimated that in the United States there will be diagnosed 12,290 new cases of laryngeal cancer in 2009 [1]. Potential etiologies include tobacco, marijuana, and alcohol abuse, as well as tumorigenesis via genetic predisposition or epigenetic pathways involving DNA and histomodifications resulting in the heritable silencing of genes without a change in their coding sequence and/or aberrant DNA methylation whereby methyl groups are bound to the promoter sequence of tumor suppressor genes causing inactivation of the gene [2].

Numerous clinical investigations have demonstrated the effectiveness of photodynamic therapy (PDT) with dihematoporphyrin ether (PHOTOFRIN), 5-aminolevulinic acid (ALA), and meta-tetrahydroxyphenylchlorin (mTHPC) (FOSCAN) in the treatment of minimally invasive early squamous cell carcinoma (SqCCa) of the head and neck due to the ability of the activating 630–664 nm laser light to penetrate 0.5–1 cm into tissues resulting in destruction of microscopic tumor with preservation of protected normal tissues [3–8].

The most extensively studied first generation photosensitizer is PHOTOFRIN which is photoactivated at 630 nm, penetrating tissues to a depth of 0.5–1.0 cm, but limits curative treatment of deeper invasive solid tumors. Therefore, PHOTOFRIN-mediated PDT with a surface tissue effect of 1.0 cm is very effective for treatment of superficial, microinvasive squamous cell, basal cell, and adenocarcinomas with surface illumination using microlens (ML) fiberoptic tips. Treatment of deep seated, intraluminal bulky, or intracavitary tumors requires endoscopic placement of cylindrical diffusers (CDs), intracavitary placement of spherical diffusers or CDs, or interstitial placement of CDs for bulky solid tumors.

Currently, photodynamic therapy has been approved for clinical oncologic 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 PHOTOFRIN-mediated photodynamic therapy in obstructing esophageal and endobronchial tumors as well as minimally invasive endobronchial non-small cell carcinoma, and Barrett's esophagitis with high grade dysplasia and carcinoma in situ [9]. PHOTOFRIN-mediated photodynamic therapy is used off label in treatment of unresectable malignant brain tumors, prostate cancer, cholangiocarcinoma, and head and neck cancer. The senior author (VS) has also used PHOTOFRIN-mediated photodynamic therapy for treatment of adult and juvenile laryngeal papillomatosis, Tis-T2N0M0 laryngeal carcinoma, AIDS-related mucocutaneous Kaposi's sarcoma, aggressive squamous cell carcinoma and basal cell skin malignancies, and palliative treatment of end stage head and neck cancer [4].

In the European Union, PDT has been approved for treatment of both early stage head and neck cancers and palliative treatment of head and neck cancer using the photosensitizer meta-tetrahydroxyphenylchlorin (FOSCAN) and for treatment of non-melanoma skin cancers using the photosensitizer Metvix [5, 10, 11]. Data are now available for over 1,500 patients treated with PDT using PHOTOFRIN, 5-aminolevulinic acid (ALA), and meta-tetrahydroxyphenylchlorin (FOSCAN) for the treatment of head and neck cancers. Multi-Institutional Phase II–III clinical trials in Europe evaluating FOSCAN-PDT treatment for head and neck cancers have demonstrated efficacy for this minimally invasive therapy for treatment of primary and recurring cancers as well as palliative treatment of refractory head and neck cancers using FOSCAN photodynamic therapy [7]. The USA FDA rejected FOSCAN for treatment of oral cavity carcinoma because of extensive normal mucosal damage (Dougherty T, PhD, Roswell Park Institute, Buffalo, NY, personal communication).

The purpose of this report is to summarize encouraging clinical data in 26 early stage laryngeal cancer patients treated at Henry Ford Health System by the senior author from 1986 to 2009. Summarized are details of the light dosimetry, treatment technique, procedure precautions, and possibilities for future applications of PDT in malignant head and neck early stage disease corroborating studies by multiple other authors.

Materials and methods

Clinical use of porfimer-sodium (PHOTOFRIN) for head and neck cancer in the United States is still investigational and follows specific FDA approved guidelines. It was previously administered by Quadra Logic Technologics, Inc., Vancouver, British Columbia, Canada and currently is distributed by Axcan Pharma Inc., Birmingham, Alabama. The study was performed following human rights approval through the Henry Ford Health System IRB.

Patients were selected if they had (1) moderate to severe dysplasia or squamous Tis of the larynx demonstrated on biopsy; (2) stage I (T1N0M0) squamous cell carcinoma of the larynx demonstrated on biopsy; (3) either already received or did not desire alternate therapy, such as cold knife surgery, radiation therapy, or CO_2 laser therapy; or (4) recurrent lesions still staged as Tis or T1.

Patients were excluded if they (1) were pregnant; (2) had hypersensitivity to porphyrins; (3) had impaired hepatic or renal function; or (4) had stage II or more advanced stage disease.

PHOTOFRIN was supplied in 2.5 mg/ml and 30 ml vials, stored lyophilized at 0°C in the dark until used, when reconstituted with D50 at room temperature immediately before administration. It was administered intravenously over 10 min at a dose of 2 mg/kg in the outpatient setting. As much as 48–60 h following administration, patients were treated in outpatient surgery and were placed under general anesthesia via Hunsaker-Mon Jet ventilation with an FiO_2 of 100%. Photoactivation was administered from an Argon-pumped Rhodamine B-dye Coherent (630 nm) laser, a Laserscope Series 600 PDT dye module (630 nm), or a Diomed portable laser (630 nm). Light was delivered to the tumor bed through a 400 μm fused silica fiber using a flat ML tip with dosimetry guidelines 50–100 J/cm^2 (Fig. 1). There are no previous large institutional studies regarding optimal light dose and dosages were based on the principal investigator's prior experience and other investigators [4, 7]. If a patient required repeated administration of PDT, light dosimetry of 80–100 J/cm^2 was utilized.

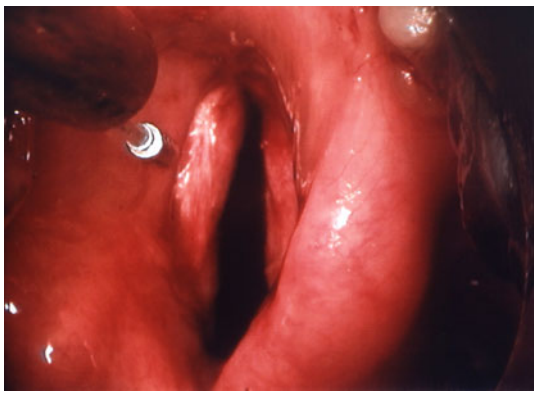

Fig. 1 Intraoperative positioning of microlens fiber using Hunsaker-Mon Jet ventilation. Patient with Tis-T1 laryngeal cancer with history of prior CO_2 laser treatment

Hospital based, drug-related photosensitivity reactions were minimal due to education of hospital support staff including residents, housekeeping, ambulatory surgery operating room, and inpatient nursing staff. Patients signed and detailed informed consents outlining drug-related information and reviewed pharmaceutical brochures and videotapes regarding photosensitivity precautions, including clothing and travel-related measures to minimize post-operative photosensitivity within the first 4 weeks following drug injection. During daylight hours, patients are instructed to wear long sleeves shirts, slacks, gloves, socks, shoes, and a wide brimmed hat when outdoors. Tightly woven light colored fabrics are preferred. Patients are instructed to wear dark sunglasses (less than 4% white light transmittance). They are instructed to wear protective clothing and sunglasses even on cloudy days and particularly while driving a car. Indoor lighting is encouraged in order to facilitate photobleaching of the drug from the skin. Patients are to avoid skylights, direct sunlight, undraped windows, but other activities, such as computer work, watching television, movie theaters, etc. are encouraged. Intraoperatively all finger jewelry is removed, finger pulse oximeters (wave length 600 nm) are rotated every 15 min, and no direct overhead surgical lights unless covered with yellow acrylic filters passing 600 nm wavelength are used. All skin and mucosal surfaces not in the treatment field are completely covered. Eye and dental protection secured, and headlights worn for intraoperative procedures.

Perioperative care consisted of intraoperative steroids (10 mg intravenous decadron after treatment), occasional medrol dose pack postoperatively, and analgesics for 1–2 weeks (which may include morphine elixir, Tylenol with codeine elixir).

Patients were examined for pain, bleeding, glottic swelling, inflammation, and tumor slough postoperatively and were monitored for recurrence (Figs. 2, 3). Treatment response for laryngeal disease in this series following physical evaluation is defined as: (1) complete response (CR)—no visual or biopsy proven disease up to 2 years or length of follow-up, (2) partial response (PR)—reduction of 50% or more in maximum diameter of affected area or 50% reduction in number of visible tumors or negative visual exam with positive random biopsy of treatment site, or (3) no response (NR)—reduction of diameter of initially affected area by less than 50%, increase in the size of the tumor and/or new tumor growth (progression of disease). Biopsies are performed within 6–8 weeks of PDT treatment for any persistent lesions and periodically to verify response as per the decision by the senior author to document recurrence or until patient was lost to follow up.

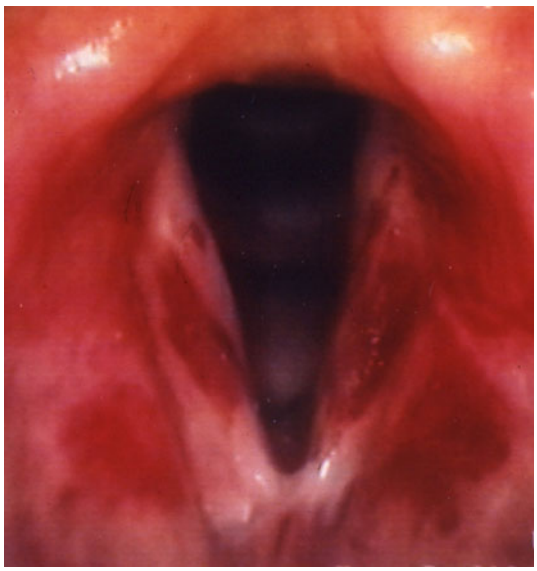

Fig. 2 Post-operative day 18 following PDT therapy. Evaluation of the glottis using videostroboscopy demonstrates typical petechial changes

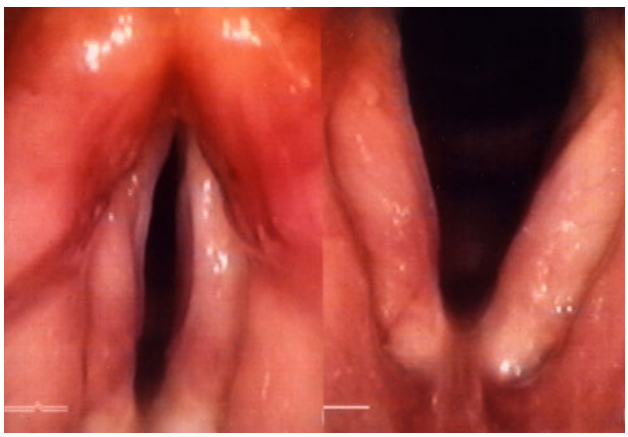

Fig. 3 Post-operative evaluation of the glottis 2 years following therapy. Patient does not have evidence of disease 14 years post treatment

Results

There were a total of 26 patients who were treated and monitored from 1985 through June 2008. Of the 26 patients, 5 were female and 21 were male. The ages ranged between 29 and 85 years at first treatment. Three patients had undergone radiation therapy prior to PDT and 2 patients had undergone CO_2 laser excision prior to PDT therapy. The remaining 21 had primary disease. As much as 8 patients had evidence of T1 disease and 18 patients had carcinoma in situ. The patients were followed up for an average of 40 months (range 2 weeks to 156 months).

A total of 16 out of 26 manifested complete local remission (62%). One patient (patient 8) died 2 weeks

Table 1 Photofrin-mediated PDT for treatment of early stage laryngeal malignancies

Patient	Age/sex	Stage	Prior treatment	Date of PDT treatment	Best Response	Time to recurrence (months)	Survival time post PDT or time of follow up (months)	PDT treatment	Comments/ complications
1	68/WM	T1N0M0, SqCCa, R TVC		1985	CR		95	50 J/cm^2 ML, 100 mW/cm^2 ML	
2	46/WF	T1N0M0, SqCCa, Larynx	CO_2	15/7/96, 13/01/97	PR	2	156	50 J/cm^2 ML, 200 mW/cm^2 ML	Underwent repeat PDT, continues to be disease free
3	64/WM	TisN0M0, SqCCa, Larynx	CO_2	16/12/1996	CR		12	80 J/cm^2 ML, 200 mW/cm^2 ML	
4	75/WM	T1N0M0, SqCCa, Larynx	RT	24/3/1998	CR		136	50 J/cm^2 ML, 200 mW/cm^2 ML	
5	51/WM	T1N0M0, SqCCa, Larynx		10/8/1998	CR		131	50 J/cm^2 ML, 200 mW/cm^{2}ML	
6	45/WM	TisN0M0, SqCCa, Larynx		29/3/1999	CR		4	80 J/cm^2 ML, 200 mW/cm^2 ML	
7	85/AAM	TisN0M0, SqCCa, L TVC		28/6/1999	CR		0.5	80 J/cm^2 ML, 200 mW/cm^2 ML	Died of MI 2 weeks following PDT
8	72/WM	TisN0M0, SqCCa, Larynx		22/1/2001, 30/4/2001	PR	3	71	100 J/cm^2 ML, 400 mW/cm^2 ML	Underwent repeat PDT was disease free until 2007, then underwent RT
9	52/AAM	TisN0M0, SqCCa, Larynx	RT	01/07/2002, 28/3/2005	PR	33	84	80 J/cm^2 ML, 200 mW/cm^2 ML	Underwent repeat PDT, continues to be disease free
10	29/WM	T1N0M0, SqCCa, Larynx (superficial)		16/12/2002	CR		34	80 J/cm^2 ML, 200 mW/cm^2 ML	
11	73/AAM	TisN0M0, SqCCa, Larynx		24/2/2003, 17/11/2003	PR	7	76	100 J/cm^2] ML, 200 mW/cm^2 ML	Underwent repeat PDT, continues to be disease free
12	65/WM	TisN0M0, SqCCa, Larynx		19/5/2003	PR	10	20	80 J/cm^2 ML, 200 mW/cm^2 ML	Underwent RT
13	75/WM	TisN0M0, SqCCa, Larynx		15/12/2003	CR		18	100 J/cm^2 ML, 200 mW/cm^2 ML	
14	29/WM	TisN0M0, SqCCa, Larynx (superficial)		22/3/2004	CR		21	100 J/cm^2 ML, 400 mW/cm^2 ML	
15	36/WF	TisN0M0, SqCCa, Larynx (superficial)		23/8/2004, 13/12/2004	PR	2	58	100 J/cm^2 ML, 200 mW/cm^2 ML	Underwent repeat PDT, continues to be disease free

Table 1 continued

Patient	Age/sex	Stage	Prior treatment	Date of PDT treatment	Best Response	Time to recurrence (months)	Survival time post PDT or time of follow up (months)	PDT treatment	Comments/ complications
16	79/OM	TisN0M0, SqCCa, Larynx (superficial)		18/10/2004	CR		10	80 J/cm^2 ML, 200 mW/cm^2 ML	
17	29/WF	TisN0M0, SqCCa, Larynx		18/4/2005, 12/9/2005, 20/3/2006, 10/7/2006, 19/2/2007	PR	5	37	100 J/cm^2 ML, 400 mW/cm^2 ML	Underwent RT
18	64/WM	TisN0M0, SqCCa, Larynx		17/8/2005	CR		10	100 J/cm^2 ML, 200 mW/cm^2 ML	
19	41/WF	T1N0M0, SqCCa, Larynx	RT	10/10/2005	CR		13	50 J/cm^2 ML, 200 mW/cm^2 ML	
20	79/AAM	T1N0M0, SqCCa, R TVC		19/6/2006	CR		36	80 J/cm^2 ML, 200 mW/cm^2 ML	
21	63/WM	TisN0M0, SqCCa, Larynx		5/2/2007	CR		28	50 J/cm^2 ML, 100 mW/cm^2 ML	
22	61/WM	TisN0M0, SqCCa, Larynx		2/4/2007, 12/11/2007, 8/6/2009	PR	6	26	100 J/cm^2 ML, 200 mW/cm^2 ML	Underwent repeat PDT
23	35/WF	T1N0M0, SqCCa, Larynx		6/8/2007	CR		22	100 J/cm^2 ML, 200 mW/cm^2 ML	
24	73/WM	TisN0M0, SqCCa, Larynx		19/11/2007	PR	4	11	100 J/cm^2 ML, 200 mW/cm^2 ML	Underwent surgical excision
25	63/WM	TisN0M0, SqCCa, Larynx		6/10/2008	CR		8	50 J/cm^2 ML, 400 mW/cm^2 ML	
26	71/AAM	TisN0M0, SqCCa, Larynx		6/10/2008	PR	7	8	100 J/cm^2 ML, 200 mW/cm^2 ML	Underwent RT

S surgical excision, *SqCCa* squamous cell carcinoma, *CR* complete response, *ML* microlens, CO_2 carbon dioxide, *PR* partial response, *ML* microlens, *RT* radiation therapy

following therapy from a myocardial infarction not related to the PDT treatment. Details of this patient series, treatment responses, and time of follow up are listed in Table 1. The average length of follow up for this group was 36 months (range 2 weeks to 136 months).

There were 10 patients who were noted to have partial remission with recurrences observed between 2 and 33 months subsequently retreated with either repeated PDT therapy or conventional therapy. One of the partial remission patients was noted to originally have a T1 lesion and had previously undergone CO_2 laser surgery prior to the PDT therapy. The other 9 patients were noted to be Tis at original presentation.

As much as 7 out of the 10 patients underwent repeated PDT therapy. Two patients required more than 2 treatments with PDT. Of the 2 patients who required more than 2 treatments, one subsequently had radiation therapy for cure following 5 PDT treatments, and one continues to be disease free after a third PDT treatment. One patient developed a new primary 6 years after the second PDT treatment and then underwent radiation therapy for cure. The total complete response rate for the patients who received one or more PDT treatments with 2 years of subsequent disease free follow-up is 84%. A total of 3 out of the 10 patients who developed recurrence and did not elect to undergo repeated PDT underwent radiation therapy for cure and one patient underwent surgical excision for cure.

Furthermore, for all patients voice quality via perceptual analysis was stable or improved post treatment.

Discussion

Many patients with early stage Tis-T1 laryngeal squamous cell carcinoma will undergo surgical excision (partial cordectomy, cordectomy), CO_2 laser therapy, radiation therapy, or a combination for persistent disease. Each of the conventional treatment modalities poses unwanted side effects with surgical excision causing structural defects leading to dysphonia and dysphagia, and ionizing radiation therapy producing side effects, such as dysphonia, hyperpigmentation, vocal cord scarring, and xerostomia.

There has been an increase in the use of photodynamic therapy (PDT) over the past few decades as an alternative for treating minimally invasive cancers of the head and neck. Rather than radiation which has a limited cGy dose, photodynamic therapy can be used multiple times without systemic toxicity. Once photochemically activated, Photofrin works by (1) irreversibly oxidizing cellular tissue, leading to free radicals, mitochondrial damage, and cell apoptosis and (2) through vascular endothelial damage [12]. It does not damage the collagen or elastin structures, so normal tissue can be regenerated following the procedure [3]. PDT does not predispose patients to the risk of osteoradionecrosis unlike those who undergo radiation therapy.

PDT resulted in complete remission in 62% of cases of Tis-T1N0M0 laryngeal squamous cell carcinomas, 84% complete response rate when looking at patients with one or more PDT treatments. This is comparable to studies published by Biel [7], demonstrating an 89% complete response rate while looking at 171 laryngeal squamous cell carcinoma patients with a 16-year follow up. A more recent prospective trial demonstrated 5 out of 6 patients (83%) demonstrating a complete response in Tis and T1 laryngeal squamous cell carcinoma patients [8].

A minor inconvenience of PDT is that patients are photosensitive for a minimum of 4 weeks following the procedure. This can be a disadvantage to the active individual who spends a majority of their time outdoors at work or on vacation. Patients must receive extensive education regarding sun protection to prevent severe sunburns, which has never been a major problem in our series. Patients also experience hoarseness temporarily, but have been shown to subjectively have improvement in their voices overall [7].

Promising advancements that can be made in the field of PDT include newer photosensitizing agents that cause less skin photosensitivity. Newer agents can be explored that have the ability to penetrate tissues at depths greater than 1 cm so that more advanced tumors can also be treated with photodynamic therapy. Future studies at our institution will compare voice as observed by videostroboscopy and tumor responses following PDT therapy.

Conclusion

Photodynamic therapy is an effective first alternative to radiation therapy, CO_2 laser therapy, and surgical resection for treatment of early laryngeal squamous cell carcinomas. It does not damage the underlying tissue which allows for multiple treatments, allows it to be given prior to or following other therapies. Photosensitivity is a short-term side effect. Future studies by the senior author will be focused on PDT with PHOTOFRIN as the sensitizing agent and its treatment effects on voice quality.

Conflict of interest None.

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