Photodynamic therapy with 3-(1′-hexyloxyethyl) pyropheophorbide-a for early-stage cancer of the larynx: Phase Ib study

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ABSTRACT: *Background.* The purpose of this study was for us to report results regarding the safety of 3-(1′-hexyloxyethyl) pyropheophorbide-a (HPPH) mediated photodynamic therapy (PDT) in early laryngeal disease, and offer preliminary information on treatment responses.

Methods. A single-institution, phase Ib, open label, noncomparative study of HPPH-PDT in patients with high-risk dysplasia, carcinoma in situ, and T1 squamous cell carcinoma (SCC) of the larynx. The primary outcomes were safety and maximum tolerated dose (MTD), and the secondary outcome was response.

Results. Twenty-nine patients and 30 lesions were treated. The most common adverse event (AE) was transient hoarseness of voice. Severe edema, requiring tracheostomy, was the most serious AE, which occurred in 2 patients within several hours of therapy. The MTD was 100 J/cm². Patients with T1 SCC seemed to have good complete response rate (82%) to HPPH-PDT at MTD.

Conclusion. HPPH-PDT can be safely used to treat early-stage laryngeal cancer, with potential efficacy. © 2015 The Authors Head & Neck Published by Wiley Periodicals, Inc. *Head Neck* **38**: E377–E383, 2016

KEY WORDS: photodynamic therapy, larynx, squamous cell carcinoma, dysplasia, carcinoma in situ

INTRODUCTION

Photodynamic therapy (PDT) is a minimally invasive treatment that involves the activation by light of a drug (photosensitizer) that generates cytotoxic reactive oxygen species, resulting in tumor destruction. Several studies suggest that PDT can be used for the treatment of early stage laryngeal cancer.[1–3] For early-stage glottic cancer, endoscopic laser resection and radiotherapy (RT) are considered standard treatments and several recent meta-analyses have shown them to produce excellent and comparable outcomes in local control and functional preservation of the larynx.[4–6] Both therapies have certain limitations: RT may cause dryness of the mucosa and fibrosis, affecting voice quality and swallowing.[7] Additionally, there are constraints in repeating RT in case of tumor recurrence or second primary tumors.[8,9] Patients who are cured with standard therapies also have a significant life-long risk of developing second primary tumors of the head and neck, which has been associated with poor prognosis.[10–12] Endoscopic laser resection may cause scarring, depending on the extent of the excision and the surgeon's expertise, which likewise can affect larynx function.[6] In 2013, an estimated 12,260 men and women were to be diagnosed with laryngeal cancer and 3630 were predicted to die of the disease. The majority of these patients have early-stage disease. Thus, there is still a need to offer these patients an additional curative therapy that is safe, repeatable, and has no long-term toxicities.

Numerous clinical studies, using the photosensitizers porfimer sodium (Photofrin, Pinnacle Biologics, Inc., Chicago, IL), U.S. Food and Drug Administration approved for esophageal and endobronchial cancer, and meta-tetra(hydroxyphenyl)chlorin (Foscan, Biolitec pharma Ltd, Dublin, Ireland), approved in Europe for the palliative use in head and neck squamous cell carcinoma (SCC) have revealed the effectiveness of PDT in the treatment of early SCC of the head and neck region.[1,13,14] Complete response rates with porfimer sodium PDT of 91%,[1] 84%,[3] and 83%[15] have been reported in studies, including dysplasia, carcinoma in situ, and T1 carcinoma of the larynx. A 90% complete response rate to primary meta-tetra(hydroxyphenyl)chlorin-PDT has been reported for a small series of patients with laryngeal

cancer.[16] Preservation of larynx function, when reported, was excellent in these studies. Importantly, several studies demonstrated that PDT can be safely and effectively preceded or followed with surgery and/or RT.[1,17,18]

Both of these photosensitizers have the drawback of persistent skin photosensitization that necessitates protection of patients from sunlight and other sources of bright light for long periods of time (30–90 days). Although this is considered a minor inconvenience by some,[3] it represents a hardship for many younger, active patients with early disease.

The chlorin-based compound, 3-(1′-hexyloxyethyl) pyropheophorbide-a (HPPH), which has more favorable photophysical and pharmacokinetic properties,[19] has been shown to exhibit effective antitumor activity in a number of experimental tumor models.[20] Clinical studies conducted in patients with lung, esophageal, and head and neck cancer have also revealed good responses.[21–23] We have shown that HPPH at clinically effective antitumor doses is associated with significantly reduced cutaneous photosensitivity that rapidly declines over several days.[24]

In this study, we report results regarding the safety of HPPH-PDT in early laryngeal disease, and offer preliminary information on treatment responses.

MATERIALS AND METHODS

Study design

This was a single-institution, phase Ib, dose finding, open label, noncomparative study (NCI-2010-02361) of HPPH-PDT in patients with high-risk dysplasia, carcinoma in situ, and SCC of the larynx. The trial was carried out at Roswell Park Cancer Institute (RPCI) from June 2008 to July 2013. Candidates were identified in the head and neck oncology clinic. HPPH was used at a fixed, previously determined dose of 4 mg/m^2, administered systemically 22 to 26 hours before light delivery.[21] The study followed a conventional 3 + 3 dose-escalation scheme with an expanded cohort at the maximum tolerated dose (MTD) of light. This design is a special case of the A + B design described by Lin and Shih.[25] Rationale behind the design is nested in the assumption that both the probabilities of toxicity and efficacious response are continuous monotonic nondecreasing functions of the dose. The MTD was defined to be the highest PDT dose level, which results in <2 instances of dose-limiting toxicities (DLTs) among 6 treated patients. The DLT were defined as grade 3 or higher systemic toxicity or grade 3 or higher normal tissue toxicity that is probably or definitely related to PDT.

The primary purpose of this study was to establish the safety profile, and to determine the MTD. Secondary purposes were assessments of HPPH levels in the blood, and treatment response, as determined clinically 3 months posttreatment and clinical follow-up. In cases of uncertainty of outcome, biopsies were obtained for pathological response assessment.

Written informed consents were obtained from all patients, and all protocol-related procedures were approved by the RPCI Institutional Review Board and overseen by the RPCI Data and Safety Monitoring Board.

Patient selection

Patient eligibility criteria included: biopsy confirmed moderate to severe dysplasia, carcinoma in situ or T1 SCC of the larynx, primary or recurrent, any type of prior therapy allowed, age at least 18 years, men or nonpregnant women using medically acceptable birth control, Eastern Cooperative Oncology Group score 0 to 2, and signed informed consent.

Patients were excluded because of: T2 or greater SCC of the larynx, porphyria or hypersensitivity to porphyrins or porphyrin-like agents, impaired hepatic alkaline phosphatase or serum glutamic oxaloacetic transaminase >3 times the upper normal limits, minimal impairment of renal function (total serum bilirubin >2 mg/dL, serum creatinine >2 mg/dL), and concurrent chemotherapy, RT, or <4 weeks after the last dose of such therapies.

Patients underwent a pretreatment evaluation that included medical history and physical examination, baseline biopsy that was submitted to pathological examination, performance status, and laboratory studies. If clinically indicated, patients received an electrocardiography, chest X-ray, and/or CT scan of the neck to exclude the presence of nodal disease.

The patient population included individuals with multicentric isolated lesions or large confluent lesions. Multicentric disease is defined as: (1) >1 separate lesion per subsite in the larynx or (2) >1 subsite of the larynx involved. In cases in which remaining disease was observed because of a partial response, no response, or a geographic miss during the first treatment, a second or third treatment session could be carried out with a time interval of at least 8 weeks after the first HPPH infusion. Blood work, medical history, and physical examinations were repeated.

Photodynamic therapy

All patients received PDT in the operating room while under monitored anesthesia control or general anesthesia to allow adequate light delivery and positioning of the treatment fiber. Each lesion was illuminated with light of 665 $\pm$ 3 nm wavelength, delivered by a tunable dye laser via optical fibers with microlens. The overall power output was measured with an integrating sphere, immediately before the illumination. The light dose rate (W/cm^2), irradiance, was calculated by knowing the divergence angle of the microlens and measuring the distance from the microlens to the lesion (with a ruler). The irradiance was constant (100 mW/cm^2) and the light dose (J/cm^2) was escalated in increments of 25 J/cm^2 from 50 to 125 J/cm^2 by increasing the illumination time from 500 to 1250 seconds. The treatment field included the visible lesion and about a 5-mm margin around the lesion. A single spot of 0.5 to 2 cm in diameter was used to illuminate the target region. Each lesion (premalignant or malignant) was treated at the light dose level in which it was recruited.

After treatment, patients were monitored in the Ambulatory Center by a physician until ready for release, or hospitalized overnight for observation if deemed advisable. All patients were given prednisone for 9 days, starting 1 day after treatment, to control swelling. Pain was treated with oral narcotics if needed. All patients were instructed to avoid exposure to sunlight or bright indoor light for at least 7 days by wearing protective clothing and specific sunglasses provided by the RPCI PDT Center. They were also advised to expose small areas of skin

to sunlight on day 8 for 10 minutes to detect any remaining photosensitivity.

Patient follow-up

Patients were seen at approximately 1 week, 1 month, and 3 months after treatment to assess treatment-related toxicities and clinical response. Some patients had a biopsy of the tissue from the treated field if the clinical examination revealed abnormal areas. Thereafter, individuals were examined at 3-month to 6-month intervals at the discretion of the treating physician.

Assessments

Safety. Patients were monitored for systemic toxicity at the time of HPPH administration, laser treatment, and at each follow-up visit. Safety was determined by recording the occurrence of adverse events (AEs) during the first 30 days posttreatment using the revised National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0. Perilesional and skin normal tissue toxicity was scored (in parenthesis) according to the following criteria: (0) = no change; (1) = mild edema; (2) = moderate edema; (3) = severe edema, ulceration ≫4 mm in depth (as determined by the physician); and (4) = respiratory distress because of edema, ulceration ≫4 mm in depth (as determined by the physician).

At each clinic visit, patients were examined for local normal tissue toxicity, performance status, pain level, and skin phototoxicity. All AEs and serious adverse events (SAEs) were documented as to onset and resolution date, classification of intensity, relationship to treatment, action taken, and outcome. AEs and SAEs were recorded as per Medical Dictionary for Regulatory Activities coding.

Response. Responses reported here are based on clinical examination and, if indicated, biopsy and pathological analysis. All tissue biopsies were reviewed and interpreted by the study head and neck pathologist. Tumor and lesion response to therapy was graded as follows: complete response (CR) = complete absence of visible lesion and/or negative biopsy; partial response (PR) = reduction of the lesion area by 50% or more; stable disease = all responses <PR; and progressive disease (PD) = any increase in lesion size or increase in grade of the treated lesion.

3-(1′-hexyloxyethyl) pyropheophorbide-a fluorescence assay.

HPPH serum levels were determined based on fluorescence.[19] Coagulated blood was collected within 2 hours before light treatment in anticoagulant-free tubes and centrifuged (Centrific 228; Fisher Scientific, Pittsburgh, PA). Serum was analyzed by recording the amplitude of the fluorescence emission maximum (λ_{ex} = 412 nm, λ_{em} = 670 nm) followed by baseline correction.

Statistical analysis

Statistical analyses were primarily descriptive. Calculated p values were based on the unpaired t test, analysis of variance, or Fisher's exact test, as appropriate. For all tests, a p value of < .05 was considered significant. Statistical

TABLE 1. Patient and lesion characteristics.

	Patients/lesions (N = 29/30)
Median age, y/range	63 (40–86)
Male/female	23/6
Race	
White	28
American Indian	1
Smoking history	
Nonsmoker	3
Former smoker	22
Smoker	4*
Prior treatment	
Excision	7
RT	2
Chemotherapy	1
Chemoradiation	1
PDT (Photofrin)	2
Lesion type	
Moderate dysplasia	4
Severe dysplasia	2
Carcinoma in situ	5
T1 SCC, primary	15
T1 SCC, recurrent	3
T2 SCC	1[†]
Lesion location	
Glottis	24
Subglottis	2
Supraglottis	2
Vocal cord/glottis	2

Abbreviations: RT, radiotherapy; PDT, photodynamic therapy; SCC, squamous cell carcinoma.
* One marijuana smoker.
[†] Lesion initially understaged.

calculations and analyses were done using GraphPad InStat ver. 3.10 (GraphPad Software, La Jolla, CA).

RESULTS

Patients and lesions baseline characteristics

Details of patient and lesion characteristics are presented in Table 1. A total of 29 patients were enrolled. Thirty lesions, comprised of 6 moderate/severe dysplasia, 5 carcinoma in situ, 15 primary T1 SCC, 3 recurrent T1 SCC, and 1 T2 SCC (initially understaged) were treated with HPPH-PDT. All patients received a single dose of HPPH at 4 mg/m² via intravenous infusion, 24 ± 2 hours before light illumination. Initially, cohorts of 3 patients were treated with 50, 75, and 100 J/cm². After 2 additional patients treated at 125 J/cm² experienced DLT, the light dose was deescalated to 100 J/cm² and that light dose was declared as MTD. A total of 22 lesions were treated at the MTD in the extended cohort.

Adverse events

AEs by light dose are shown in Table 2. The most common AE after HPPH-PDT was transient hoarseness of voice, which usually resolved within days. Although pain is a common AE in PDT, it was rarely reported in this study. Edema at the treatment site was the most worrisome AE and was present in 17% of all patients and 22% of patients in the 100 J/cm² cohort. Two consecutive patients treated at a light dose of 125 J/cm² developed

TABLE 2. Distribution of morbidities by light dose.

Morbidity	50 J/cm^2 (n = 3)	75 J/cm^2 (n = 3)	100 J/cm^2 (n = 22)	125 J/cm^2 (n = 2)
Pain, no.				
Mild	1	0	2	1
Moderate	0	0	2	0
Severe	0	0	0	0
Edema, no.				
Mild	0	1	1	0
Moderate	0	0	3	0
Severe	0	0	2*	2[†] (DLT)
Obstruction, debris	0	0	1[‡]	0
Dysphagia, no.				
Mild	0	0	0	0
Moderate	0	0	1	0
Severe	0	0	1[§]	0
Respiratory distress, no.	0	0	0	1
Weight loss, mild, no.	0	0	2	0
Transient hoarseness of voice, no.	2	3	15	1
Sunburn				
Mild	1	0	1	0
Moderate	1	0	1	0
Severe	0	0	0	0

Abbreviation: DLT, dose-limiting toxicity.
* Two patients in the extended cohort, after the maximum tolerated dose (MTD) was established, experienced grade 3 laryngeal edema; 1 patient required a tracheostomy.
[†] Two patients in the original cohort experienced grade 3 edema (DLT); 1 patient required a tracheostomy.
[‡] Removal of tissue debris resolved the event without need of further intervention.
[§] Patient suffering from severe anxiety reported to the emergency department for complaint of dysphagia a few hours after PDT; he had no dysphagia in the emergency department or the following day at the PDT clinic.

grade 3 edema at the treatment site, establishing the DLT. One patient, who suffered from several comorbidities, including obesity and sleep apnea, experienced respiratory distress and required a cricothyrotomy (and then converted to a tracheostomy). He was given ventilator support for 1 day, after which time he recovered. The second patient treated that same day at that light dose did not report any problems, but was contacted at home and asked to report to the clinic. An examination of the vocal cords revealed grade 3 edema. The patient was hospitalized, given steroids, and recovered without further AEs. These events led to the light dose deescalation to 100 J/cm^2. None of the first 6 patients treated at this light dose experienced DLTs, and this light dose was declared the MTD. There were, however, several SAEs reported in the extended cohort of 100 J/cm^2. One patient had 1 episode of dysphagia at home, which was not evident when he checked into the emergency department a few hours later and when he was seen in the clinic the next day. This patient had anxiety, so it was assumed that this single episode was probably related to anxiety. Two patients experienced severe laryngeal edema in the immediate post-PDT period. One patient developed stridor and dyspnea after PDT while in the ambulatory area. A tracheostomy was performed urgently because of incipient laryngeal edema. Another patient's edema was successfully treated with intravenous administration of steroids. One patient required removal of obstructive debris. Four patients (13%) experienced mild to moderate skin photosensitivity because of noncompliance

with instructions. All tracheostomized patients were successfully decannulated.

3-(1′-hexyloxyethyl) pyropheophorbide-a levels

HPPH serum levels, assessed by fluorescence assay of 29 evaluable patient samples, revealed a normal distribution[19] and there was no significant difference among HPPH levels from patients with dysplasia, carcinoma in situ, and SCC (data not shown).

Response

Details of outcomes by light dose at 3 months posttreatment (except for no responses that were determined at 1 month), are shown in Table 3. Thirty lesions treated, including dysplasias, carcinoma in situ, and SCCs, were evaluable for response. Given the small numbers and heterogeneity of lesions in each light dose cohort, no light dose or lesion type dependence was discernible.

There was 1 no response each in the 50, 75, and 125 J/cm^2 cohorts, in a recurrent SCC, a T2 SCC, and a T1b lesion, respectively. There was 1 PD in a carcinoma in situ at the 100 J/cm^2 cohort. Two SCC lesions that were recurrent after radiation and chemoradiation treatment, had a PR after the initial PDT treatment, but required more treatments later at 100 J/cm^2 (1 patient required 2 and the other required 3). One carcinoma in situ with PR had 2 treatments. In none of these cases was CR achieved. Only the expanded 100 J/cm^2 cohort (n = 22) was large enough to give some insight into the response rates. Taking into account all lesions treated at that light dose, the CR rate was 68%. The CR rate in dysplasia/carcinoma in situ was 63%. The best outcomes were observed in primary T1 SCC with 82% CRs (n = 9) after just one HPPH-PDT treatment. Among these there were 2 recurrences at 1 and 2 years, respectively. One patient was lost to follow-up and 6 patients are still disease-free (disease-free intervals, 12–45 months).

All patients who did not have a CR to PDT were successfully treated with subsequent standard of care therapies.

Two representative examples of lesions that were treated in this study are shown in Figures 1 and 2. These patients were treated with 100 J/cm^2. One patient had a high-grade dysplasia in the right vocal cord (Figure 1A). The response to PDT 1 week after treatment is seen in Figure 1B. No clinical evidence of the disease was seen about 1.5 years after PDT (Figure 1C), and videostroboscopy showed that the mucosal wave was preserved. The

TABLE 3. Lesion responses by treatment light dose (3 months posttreatment).

Light dose J/cm^2	No. of lesions (responses)
50	3 (1 NR,* 2 CR)
75	3 (1 NR,* 2 CR)
100	22 (6 PR, 15 CR, 1 PD*)
125	2 (1 NR,* 1 CR)

Abbreviations: NR, no response; CR, complete response; PR, partial response; PD, progressive disease.
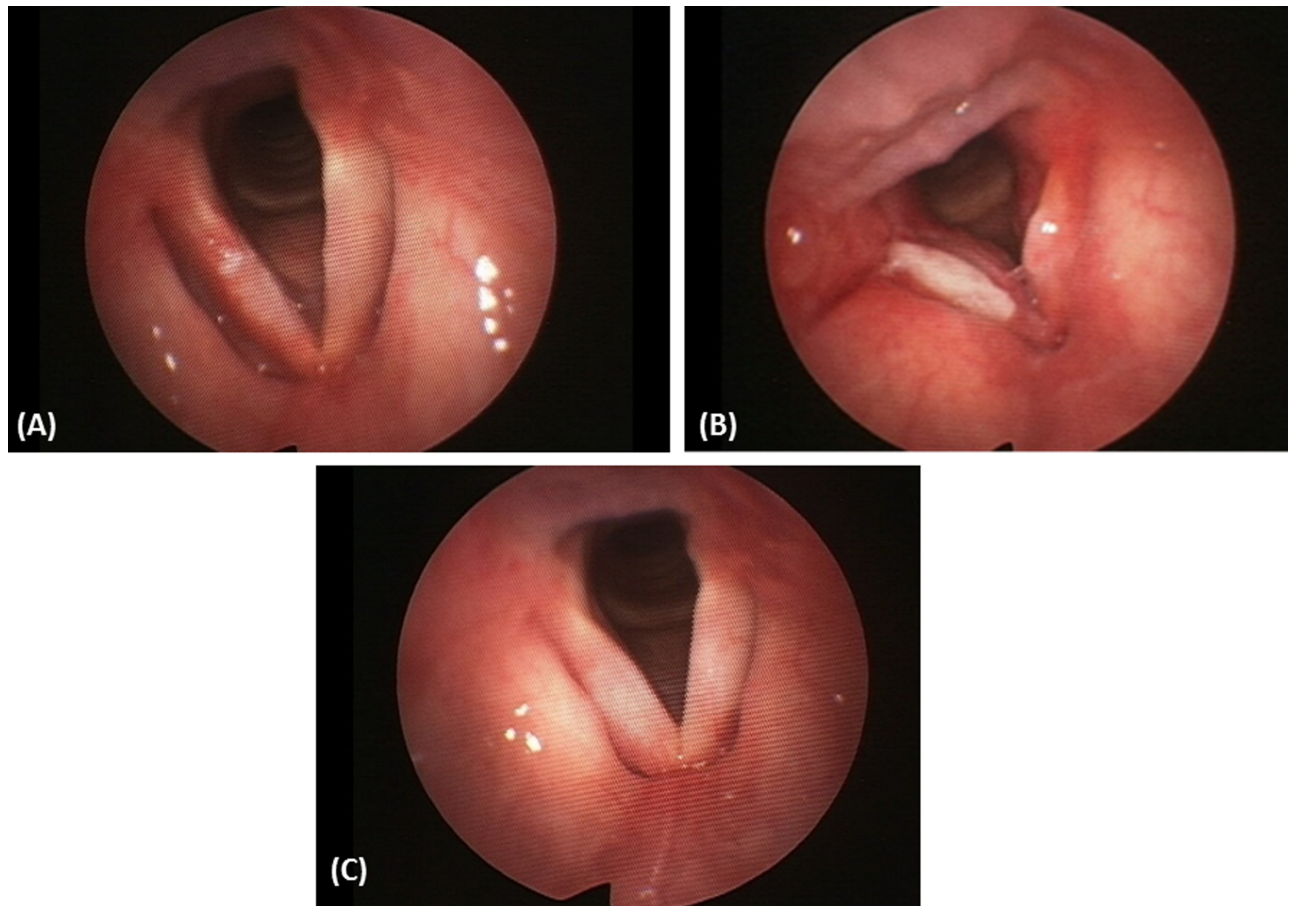* Determined at 1 month posttreatment.

FIGURE 1. (A) A high-grade dysplasia in the right vocal cord. (B) The response to photodynamic therapy (PDT) 1 week after treatment. (C) No clinical evidence of the disease seen, 1.5 years after PDT.

second patient had T1 SCC of the right vocal cord (Figure 2A). The response to PDT 1 week after treatment is seen in Figure 2B. No clinical evidence of the disease was seen at approximately 2 years after PDT (Figure 2C).

DISCUSSION

The primary purpose of this study was to determine the safety profile of HPPH-PDT for the treatment of dysplasia, carcinoma in situ, and early SCC of the larynx. The MTD was established to be a light dose of 100 J/cm^2 with an HPPH dose of 4 mg/m^2. The DLT at 125 J/cm^2 was laryngeal edema. The major SAE and DLT was immediate post-PDT severe edema in the larynx. The latter seems to be pronounced with HPPH, and may be caused by increased vascular leakiness induced by HPPH-PDT.[26] Because the PDT induced severe laryngeal edema, which can require tracheostomy, and occurred within several hours of therapy, it is recommended that patients be kept for overnight observation after HPPH-PDT. PDT-induced edema is directly proportional to the light dose for a fixed photosensitizer dose.[23] Therefore, it is possible to lower the chance of PDT-induced severe edema by reducing the light dose to 75 J/cm^2 (below the 100 J/cm^2 MTD). The relatively small sample size precluded us from examining the potential efficacy of 75 J/cm^2 in this phase Ib study. In the design of a follow-up phase II study, we will consider evaluating the efficacy at 75 J/cm^2 before escalating the light dose to the MTD.

We also encountered one incident of obstructive debris, which required removal. Removal of debris through cleanup bronchoscopy is routinely performed after endobronchial PDT.[22] It is therefore recommended to have a 24 to 48-hour follow-up visit to examine the airway after HPPH-PDT treatment of the larynx.

The most frequent AE was transient hoarseness, which occurred in 79% of patients. Pain was rarely reported and skin photosensitivity reactions (7% of patients) were minimal if present. These results compare favorably with those obtained with photofrin[3] where phototoxicity was observed in 58% of patients. The minimal pain in our study is an improvement when compared with Foscan-mediated PDT, where pain has been reported in 83% at the injection site and in 46% of the patients at the treatment area.[27] Although PDT-induced pain and phototoxicity can be controlled, minimizing these effects is clinically important because it has the potential to improve the patients' quality of life. Noteworthy, in several patients there was no damage to the mucosal wave of the vocal folds, suggesting that the voice quality can be preserved. This finding is in agreement with another study reporting that PDT can preserve the voice quality.[2] The
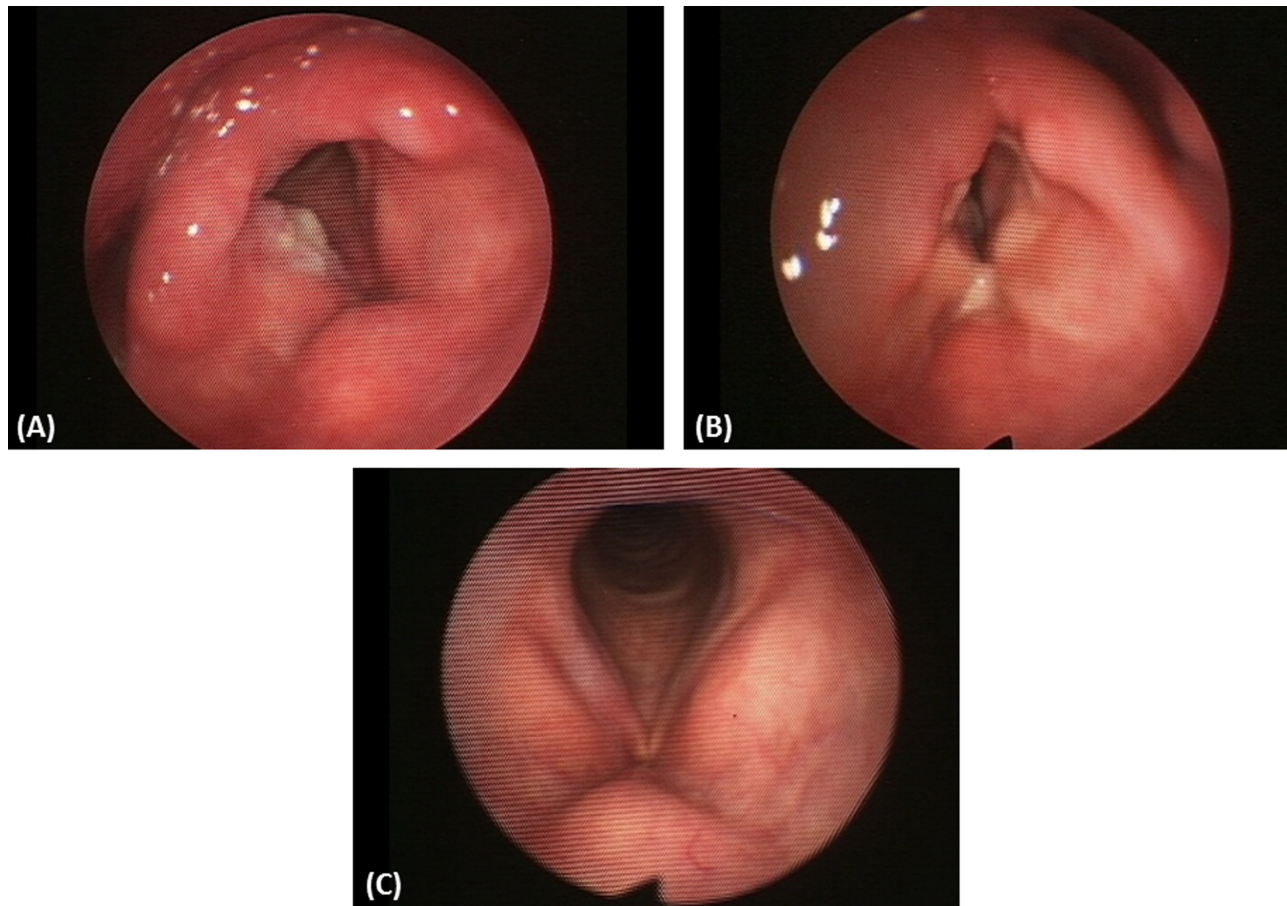
FIGURE 2. (A) A T1 squamous cell carcinoma in the right vocal cord. (B) The response to photodynamic therapy (PDT) 1 week after treatment. (C) No clinical evidence of the disease seen 2 years after PDT.

minimal long-term AE is also in agreement with the good healing that was observed at the treatment site (Figures 1C and 2C).

Current treatments for dysplasia, carcinoma in situ, and T1 SCCs of the vocal cords include radiation and surgery (transoral laser surgery or open partial laryngectomy), depending on the severity of the lesion. Surgery and radiation both can have negative effects on the voice. Radiation also requires multiple treatments over the course of several weeks. PDT has the advantage of potentially treating the lesion in one sitting and preserving voice quality. This, in turn, can preserve or improve the patient's quality of life.

In this phase Ib trial, clinical outcomes have limited significance. Notwithstanding, for patients treated at MTD in the expanded cohort ($n = 22$), the CR rate was 68% for all patients. When examining the outcomes by stage, a CR of 82% was calculated for T1 SCC. This rate was higher than the 63% CR observed in patients with dysplasia and carcinoma in situ. These results were very similar to those achieved in our recent study of HPPH-PDT of oral cavity lesions.[23] In both studies, primary T1 SCC showed the best responses, with 82% CR after 1 treatment. The majority of these were durable. There were only 2 recurrent lesions treated and both showed only PRs, despite multiple HPPH-PDT exposure. In oral cavity lesions, results could be related to lower HPPH localization in the precancerous lesions. These results suggest that patients who may benefit the most from a single session of HPPH-mediated PDT are those with frank squamous cell carcinoma, rather than dysplasia or carcinoma in situ. In patients who do not respond to PDT, other standard therapies should be considered. In this study, all patients who did not have a CR were successfully salvaged by standard methods of treatment.

CONCLUSIONS

HPPH-PDT can be safely used to treat early-stage laryngeal cancer, providing that the light dose does not exceed 100 J/cm^2 with 4 mg/m^2 of HHPH and patients are carefully monitored for laryngeal edema in the immediate post-PDT period. Early-stage T1 SCC lesions seem to respond better than dysplasia/carcinoma in situ to this therapy. The results warrant a phase II study to evaluate the efficacy of HPPH-PDT in the treatment of stage 1 T1 SCC of the larynx.

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