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# Laryngotracheal Stenosis as a Complication of Photodynamic Therapy

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**Abstract**

**Objective:** Photodynamic therapy (PDT) has been proposed as an effective treatment for mucosal carcinomas such as early-stage laryngeal squamous cell carcinoma. Its advantage over other conventional modalities (surgery and chemoradiation) lies in its ability to treat disease while preserving the function and structure of the larynx. While not FDA-approved in the United States, it is used in some countries as a treatment for laryngeal cancer and is an area of active investigation. This report documents a severe complication of tracheostomy-dependent laryngotracheal stenosis resulting from PDT.

**Methods:** Methods include a case report and review of the literature.

**Results:** A 65-year-old male presented with severe stenosis of the supraglottic, glottic, and subglottic larynx following successful treatment of his laryngeal carcinoma with PDT. His presentation, staged airway reconstruction, and outcome are detailed.

**Conclusion:** PDT is a minimally invasive technique which in early clinical trials has matched the effectiveness of conventional therapies for treating early head and neck squamous cell cancers. It uses a photosensitizing agent that is retained by tumor cells, allowing for the selective destruction of neoplastic cells. Permanent sequelae following treatment have rarely been reported; the most commonly described adverse effects include pain, hoarseness, and phototoxicity. However, our case report discusses the potential for significant laryngotracheal stenosis requiring airway reconstruction following PDT.

**Keywords**

photodynamic, cancer, photosensitizer, laryngotracheal, stenosis, laryngeal

## Introduction

There are approximately 12 600 new cases of laryngeal carcinoma diagnosed annually in the United States. While treatment for this disease has traditionally consisted of surgical excision, radiation therapy, chemotherapy, or a combination thereof, local recurrence rates after salvage surgery in patients with head and neck squamous cell carcinomas are major causes of treatment failure and development of distant metastases.[1] Local intraoperative adjuvant treatment strategies are therefore of interest to improve outcomes.[2] Early-stage malignancy, dysplasia, and areas of "condemned mucosa" containing broad areas of premalignant and malignant change that may not typically be treated with cancer therapies may also benefit from local treatment to halt disease progression.[3,4]

Photodynamic therapy (PDT) is a minimally invasive treatment modality currently used in some countries and investigational within the US for laryngeal cancer.[2] PDT involves 3 elements—a photosensitizer, light, and oxygen; an intravenous or topical photosensitizer is first administered and then followed 48 to 60 hours later by intraoperative laser light photoactivation. Upon activation of the drug, cytotoxic reactive oxygen species are generated, causing damage to tumor cells through cell necrosis and microvascular collapse while sparing adjacent normal tissues that have not concentrated the photosensitizer.[2]

PDT is generally considered to be safe, with most adverse events related to transient pain, edema, and cutaneous phototoxic effects. In addition, PDT may be advantageous compared to radiotherapy as its action is more closely confined to the target tissue, with little or no treatment effect beyond the light-treated area. It can be repeated multiple times and does not preclude the use of radiation therapy in future recurrences.[5] Despite its good safety profile, however, we discuss a case of severe posttreatment laryngotracheal stenosis.

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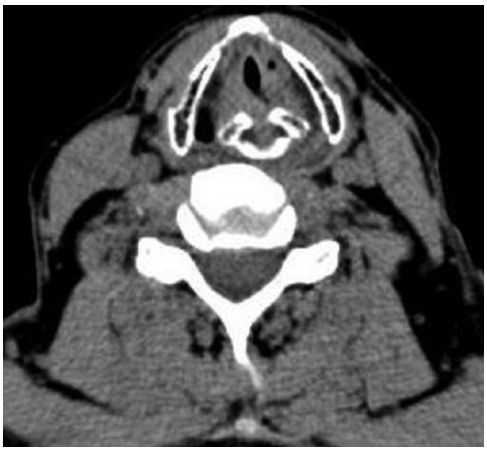

**Figure 1.** Computed tomography (pretreatment). A computed tomography scan shows significant supraglottic stenosis.

## Case Report

We present the case of a 66-year-old male, otherwise healthy, nonsmoker who developed supraglottic, glottic, and subglottic stenosis following PDT for early (T1aN0M0) vocal fold squamous cell carcinoma. The patient sought PDT treatment in China in 2010. His records from that hospitalization indicate that he received an intravenous infusion of 325 mg of hematoporphyrin-derivative (HPD) photosensitizer, followed by endoscopic laser treatment 2 days later. He was subsequently hospitalized for 12 days in a darkened room and was also treated with inhaled steroids and bronchodilators for post-PDT shortness of breath and cough. His dyspnea progressed rapidly after his return to the United States, and he ultimately required a tracheostomy due to airway stenosis.

The patient was treated extensively at another institution for his stenosis. Multiple biopsies confirmed no cancer recurrence. He underwent numerous endoscopic procedures including $CO_2$ laser laryngoplasty and balloon dilations, which only transiently improved his voice and breathing. He also underwent an open laryngofissure procedure with scar excision but had persistent stenosis with failure to decannulate his tracheostomy. Therefore, he presented to our clinic for a second opinion. A computed tomography scan and physical examination revealed near complete supraglottic stenosis (Figures 1, 2). The patient was aphonic, but his swallowing function was largely unimpaired.

The patient was taken to the operating room for staged laryngotracheoplasty. During the first stage, open laryngofissure revealed dense scar tissue in the posterior commissure obliterating the false and true vocal folds. Subglottic scar tissue extended to the cricoid. Scar tissue was sharply excised, the denuded tissue was covered with a buccal mucosa graft, and a soft molded stent was placed. One week later, he underwent a second procedure with stent removal, closure of the laryngeal trough, and Montgomery T-tube stent placement. His airway remained widely patent with the T-tube stenting the subglottis and posterior glottis (Figure 3). After 4 months, he tolerated T-tube exchange for a temporary trachesotomy tube (Figure 4) that was subsequently removed. One year later he remains free of a tracheostomy and has good vocal performance, despite a rough voice quality.

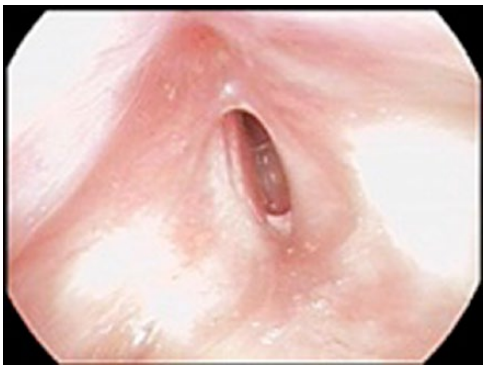

**Figure 2.** Laryngoscopy (pretreatment). Fiberoptic larynogoscopy shows significant supraglottic, glottic, and subglottic stenosis.

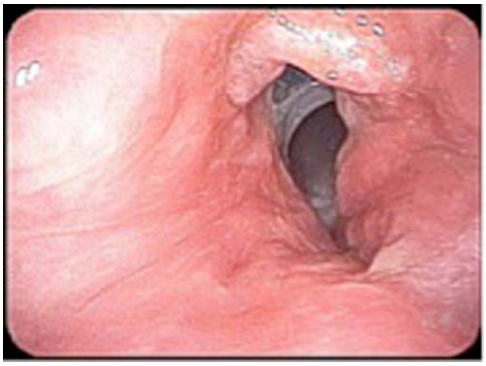

**Figure 3.** One month following stage I laryngotracheoplasty. Fiberoptic laryngoscopy shows a patent supraglottis, with the T-tube visible in the subglottis.

## Discussion

Photodynamic therapy involves the use of a photosensitizing agent that is either injected or topically applied. The agent becomes selectively concentrated in malignant tissue and is then activated by penetrating light of a wavelength

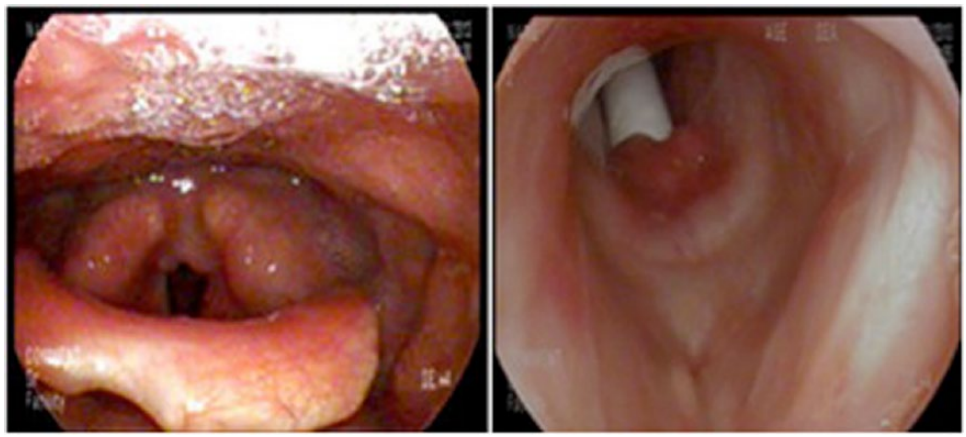

**Figure 4.** Four months following stage I laryngotracheoplasty. (Left) Fiberoptic laryngoscopy shows maintained airway patency. (Right) A close-up view of subglottis shows airway patency with the tracheostomy tube visible.

matching the absorption characteristics of the drug. The activated drug then generates cytotoxic reactive oxygen species that cause direct damage to tumor cells through mitochondrial damage, intracellular oxidation, vascular endothelial damage, and cell apoptosis.[2,5]

The earliest photosensitizers were biological extracts based on hemoglobin that exhibited variable purity and activity. The term "hematoporphyrin derivative" (HPD) was applied to all these agents. Photofrin (porfimer sodium) was the first commercially standardized photosensitizer, although also a biological HPD. It has been approved by the Food and Drug Administration for several clinical indications such as non-small-cell lung cancer, obstructing esophageal cancer, and high-grade dysplasia in Barrett's esophagus. Photofrin-PDT for laryngeal cancer and dysplasia is an off-label use that is currently undergoing clinical trials.[2,6] While HPD is composed of a mixture of several porphyrins which absorb light at several wavelengths, newer agents are completely synthetic and allow for more control of the light-activation chemistry.

Data from existing studies generally depict rare and mild posttreatment side effects and complications with porfimer sodium use. A commonly seen adverse side effect of PDT is photosensitivity;[5] the agent may persist in the skin, requiring patients to practice diligent measures to protect themselves from sunlight and other sources of bright light for weeks after the procedure.[2] Airway swelling is also a common complication following PDT for tongue base tumors. To ameliorate these effects, some studies suggest limiting patient exposures to lengthy surgical operations at the time of treatment to control the light exposure.[1]

Stenosis following laryngeal PDT has only rarely been documented. One case report[7] described significant airway complications in a pediatric patient who received PDT with podophyllum resin to treat recurrent respiratory papillomatosis. She developed bronchial stenosis, worsening of anterior glottic webbing, and posterior glottic stenosis—all of which ultimately required laryngotracheal reconstruction and delayed decannulation. The authors noted the difficulty in determining the appropriate podophyllum dose for their patient. Gluckman et al[3] also reported 1 case of severe laryngeal stenosis requiring a tracheostomy despite appropriate dosimetry and light delivery. It is possible that airway stenosis following PDT is underreported, since laryngeal PDT in the United States is generally performed only within formal clinical trials. Patients outside the United States may be more likely to develop complications due to protocol deviations, and their physicians may be less likely to publish the findings.

Large deviations in medication dosing and light delivery among providers across the world may lead to variable outcomes. Currently accepted dosimetry guidelines include a Photofrin dose of 2 mg/kg, photoactivated at 630 nm. For cancers of the larynx, the total light dose should be 50-80 J/cm$^2$ via a microlens fiberoptic tip (for superficial and microinvasive tumors) and 80-100 J/cm$^2$ through a cylindrical diffuser for bulky, solid tumors.[8] Appropriately tailoring the use of these delivery mediums to the structure and extent of disease can individualize and focus the treatment strategy. Particularly true for the complex laryngeal anatomy, the need for precise light application highlights the importance that a skilled endoscopist with experience using PDT performs the treatment.

The stenosis reported here occurred after PDT treatment in China, where uncertainties in the quality of care exist. The findings were further complicated by his prior surgical attempts at correction, which may have altered the scar tissue location or severity. Potential contributors to this case include variable potency and excessive dosing of the HPD photosensitizer. This patient received 325 mg of HPD, over twice the recommended dose of 2 mg/kg. The light application method, dose, and site were not described in his medical records and represent other possible errors.

Geometrically complex T1 or T2 tumors of the upper aerodigestive tract exhibit complicated dosimetry; selection of the appropriate drug and light dose, light wavelength, and light delivery with adequate exposure of the treatment site can affect the extent of treatment depth during both topical and intravenous applications.[9,10] Suboptimal dosimetry can lead to treatment variability and, consequently, mucosal stenosis or fistula.[9] Risks for esophageal stenosis following PDT for Barrett's esophagus and esophageal carcinoma are better recognized than those for laryngeal pathology and may be considered when treating the larynx. Multiple variables including previous mucosal insults, patient comorbidities, depth of treatment, extent of intramucosal disease, acid reflux, and a previous history of tobacco and alcohol use all likely contribute to stenosis or stricture development.[11,12]

Despite the occasional complications in both laryngeal and esophageal applications, studies have generally shown minimal side effects and promising results with PDT in the treatment of patients with early stage cancers or early recurrences in the oral cavity and larynx. A number of studies looking at treatment of primary or recurrent laryngeal tumors (CIS, T1, T2) treated with PDT found a cure rate of up to 91% with a single treatment; in addition, there were no serious complications or episodes of airway compromise, and immediate postoperative pain and hoarseness usually improved within 2 weeks.[13]

The theoretical advantage of PDT over conventional treatment modalities is its minimally invasive nature; less photosensitizer uptake in adjacent normal tissues translates to more effective targeting of the neoplasm. In areas such as the larynx where tissue loss can result in grave functional and structural deficits, minimally invasive techniques such as PDT are highly advantageous.[13] Vocal fold vibration after photofrin-mediated treatment of Tis and T1 laryngeal cancer is generally preserved. Posttreatment vocal cord ecchymosis and tissue sloughing occur but significantly improve within 10 to 20 weeks.[5]

In addition, unlike radiation, PDT treatments can be performed repeatedly even after failure of conventional modalities.[5,12] It can be used prior to or after these traditional treatments without negatively impacting their effects.[1] Contrary to a 6- to 7-week duration of radiotherapy, PDT treatments occur during a single outpatient procedure which can have major social and economic benefits.

## Conclusion

Photodynamic therapy (PDT) has been proposed as an effective treatment for mucosal carcinomas such as early-stage laryngeal squamous cell carcinoma. Its advantage over conventional treatment modalities lies in its ability to target disease while preserving the function and structure of the larynx. We report an uncommon case of severe post-PDT laryngotracheal stenosis leading to tracheostomy dependence and multiple surgical procedures. The PDT treatment in this case did not meet current standards of care, but illustrates the potential severity of complications from this seemingly benign therapy.

### Declaration of Conflicting Interests

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