REVIEW ARTICLE

Photodynamic Therapy for Laryngeal Cancers

[1]Nestor Rigual, [2]Merill Biel, [3]Kiskumar Thankappan, [4]Barbara Henderson

[1]Department of Head and Neck/Plastic Surgery, Roswell Park Cancer Institute, Buffalo, NY, USA

[2]Department of Otolaryngology, University of Minnesota, Minneapolis, MN, USA

[3]Amrita Institute of Medical Sciences, Elamakkara, Kochi, Kerala, India

[4]Department of Biophysics/Cell Stress Biology, Roswell Park Cancer Institute, Buffalo, NY, USA

Correspondence: Nestor Rigual, Department of Head and Neck/Plastic Surgery, Roswell Park Cancer Institute, Buffalo, NY USA, e-mail: nestor.rigual@roswellpark.org

Abstract

Laryngeal squamous cell carcinoma is a common cancer among men globally. Currently effective treatment modalities for early stage laryngeal cancer can associated with significant long-term morbidities. Photodynamic (PDT), a minimally invasive treatment that uses light of a specific wavelength to activate a photosensitizing agent in the tumor and its microenvironment, offers a viable alternative treatment for this patient population without permanent treatment related sequelae.

Our focus in this review is to discuss the existing evidence for the utilization PDT in treating laryngeal cancers and to summarize the advantages and limitations of this novel therapy.

Keywords: Larynx, Cancer, Photodynamic therapy, Treatment, Photosensitivity, Photosensitizer, Laser.

INTRODUCTION

Laryngeal squamous cell carcinoma is the 11th most common form of cancer among men worldwide and is the second most common malignancy of the head and neck. It is the dominant pathological type of malignancy affecting the larynx. A clear association has been established between smoking, excess alcohol ingestion, and the development of squamous cell carcinoma (SCC) of the upper aerodigestive tract.[1] Currently accepted treatments for early stage laryngeal cancer include endolaryngeal laser or cold instrument excision, open partial laryngectomy and radiotherapy.[2,3] These treatment options, although effective, may be associated with considerable morbidity. Voice quality for patients undergoing laser resection for limited glottic lesions has been comparable to that of patients receiving radiotherapy, whereas open partial laryngectomies consistently yield poor voice quality.[4,5] Radiotherapy requires extended treatment periods and is associated with short and long-term morbidities, such as mucositis, xerostomia, and tissue fibrosis.[6-10] There are also constraints in repeating radiotherapy in the event of a recurrence or a second primary tumor. Head and neck SCCs are associated with an annual rate of second primary upper aerodigestive tract cancers ranging from 3 to 10%.[11] The treatment of these lesions may be compromised by previous radical therapies. Reirradiation carries the risk of increased morbidity and is often restricted to tertiary care centers.[12] Surgical salvage is challenging due to loss of normal tissue.[13]

An optimal treatment modality for early stage laryngeal carcinoma would be safe, effective, repeatable, minimally invasive and devoid of any permanent sequelae. Photodynamic therapy (PDT), a minimally invasive treatment that uses light of a specific wavelength to activate a photosensitizing agent in the tumor and its microenvironment, offers some of these advantages. The purpose of this review is to discuss the existing evidence for the utilization of this modality in laryngeal cancers and to summarize the advantages and limitations.

Principles of Photodynamic Therapy

PDT is a minimally invasive local treatment that utilizes a light source to activate light sensitive drugs (photosensitizers) to produce tissue destruction. In addition to the photosensitizer and light, molecular tissue oxygen is a critical component of PDT. The generally accepted mechanism of action of PDT is that energy transfer occurs from the light activated, excited triplet state of the photosensitizer to oxygen to produce singlet oxygen, which in turn causes irreversible oxidation of essential cellular components. Cell death can occur by apoptosis and

necrosis.[14] Singlet oxygen is highly reactive and can diffuse only 0.02 micrometer.[15] Tissue damage is therefore restricted to the penetration depth of the light used. In addition to direct cell killing, the membrane damage caused by PDT is associated with release of inflammatory and immune mediators that stimulate responses in the tumor environment and systemically to further augment and tumor response. The tumor microvasculature is also an important target of PDT leading to vascular disruption and ischemia. The combined effect of these actions results in the remarkable necrosis of tumor tissue within two to five days following the treatment.[16,17]

Photosensitizers Under Evaluation for Head and Neck Cancer

An ideal photosensitizer is one that is highly selectively retained by the tumor cells, is activated at a long light wavelength, provides better tissue light penetration and has minimal side effects. No agent has yet been identified that fulfills all of these requirements but many groups are presently pursuing photosensitizer development.

Porfimer sodium (Photofrin), a derivative of hematoporphyrin, is the first photosensitizer with wide clinical use and regulatory approval in many countries, including the United States.[18] The absorption spectrum of Porfimer sodium has five peaks, the strongest at about 400 nm and weakest at about 630 nm. Light at 400 nm will penetrate less than 1 mm in tissue and hence cannot be used for clinical treatment. The absorption peak at 630 nm allows light penetration of 0.5-1 cm into tissues,[19] hence is useful for treatment of superficial lesions. Although Porfimer sodium has proven effective in the treatment of a wide range of solid malignancies, it induces prolonged cutaneous photosensitivity in patients, which is a major limitation.[20]

This limitation and the need for agents that are activated at longer wavelengths of light has stimulated the wide ranging search for improved, "second generation" photosensitizers. The prodrug 5-aminolevulinic acid (ALA, Levulan) and its methyl ester derivative MAL (Metvixia), which lead to high intracellular levels of the photodynamically active protoporphyrin IX, is attractive because of its rapid clearance and therefore absence of prolonged general photosensitivity. These agents, when light activated at wavelength 630 nm, are highly effective in the treatment of superficial skin lesions, where it is delivered topically. ALA given orally at effective doses is associated with nausea and vomiting, and has caused one death due to vascular instability when used for the treatment of Barret`s esophagus.[21] The use of orally administered ALA (60 mg/kg) in the treatment of premalignant and early malignant oral lesions was of limited effectiveness.[22]

Metatetrahydrophenylchlorin (mTHPC; Foscan) is an extremely potent photosensitizer that is activated at 652 nm allowing more depth of tissue penetration.[23] D'Cruz et al[24] has published results from a multicenter study using mTHPC in 128 advanced incurable head and neck carcinomas. Overall 43% of the lesions achieved 100% tumor mass reduction, while 35% achieved a 50% or greater tumor mass reduction. Of the lesions with complete mass reduction, 35% remained cleared one year after treatment. Adverse events included local pain and facial swelling. Mild to moderate photosensitivity reactions were observed in 19% of patients.

Mono-L- aspartyl chlorin e6 (talaporfin sodium, Npe6) with an activation wavelength of 664 nm has been used in >100 cases of early stage head and neck cancer.[25] In cases of cancer of the larynx the initial complete response rate was reported as 100%, with a 9% recurrence rate. No severe adverse events, including photosensitivity, have been reported. [2-(1-Hexyloxyethyl)-2-devinyl pyropheophorbide-a (HPPH, Photochlor)] has demonstrated a short duration minimal photosensitization in preclinical and clinical studies. This is attributed to the relatively short plasma half-lives of HPPH in patients (a and b half-lives 7.77 h and 596 h, respectively.[26] A study of 48 patients having received graded doses of HPPH evaluated cutaneous photosensitivity up to 3 days after HPPH administration. That study revealed that patients injected with 3 mg/m^2 or 4 mg/m^2 had no skin reaction following exposure of the volar part of their forearms to artificial solar-spectrum light; one of 2 patients injected with 5 mg/m^2 HPPH and 2 of 3 patients receiving 6 mg/m^2 HPPH had skin reactions limited to very minimal erythema.[20] HPPH strongly absorbs light at 665 nm and thus penetration into tumor tissue is increased beyond what is possible at 630 nm with Porfimer sodium. Six patients have so far been treated under an ongoing study of early laryngeal disease (moderate to severe dysplasia, CIS, T1) without any serious adverse events being observed. Temporary hoarseness was reported by 5 patients. All patients responded to treatment, but outcomes data are not yet available.

Tumor Illumination

The activation of the tumor localized photosensitizer requires light of the photosensitizer specific wavelength at

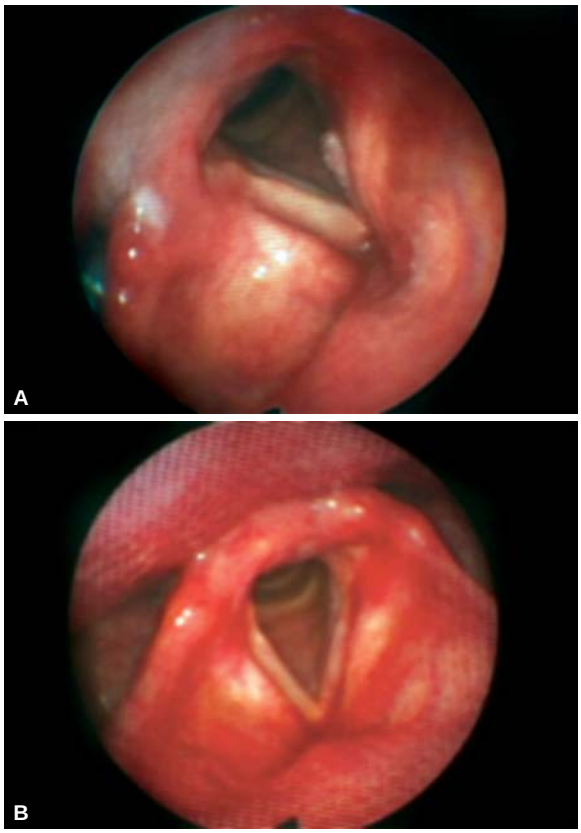
sufficient power to illuminate the entire tumor volume. This is commonly achieved through the use of lasers. The initially available large frame lasers, such as tunable argon ion-pumped dye lasers or gold vapor lasers, are gradually being replaced by more user-friendly, portable diode lasers. Light is transmitted to the tumor tissue through quartz fiber optical cables fitted with appropriate light distributing tips, i.e. microlenses for flat tumor surfaces or cylindrical diffuser fibers for luminal surfaces. In head and neck applications, microlens equipped fibers are usually employed to distribute light in uniform fields to superficial surfaces. Cylindrical diffuser tips distribute light 360 degrees along the axis of the fiber and are occasionally used in the treatment of head and neck tumors. The fiber-based optical delivery systems are compatible with clinical instrumentation, such as endoscopic devices.

Laryngeal PDT-Technique

The photosensitizer is injected intravenously as an outpatient procedure. Patients are advised to avoid exposure to sunlight after the injection. The tumor is exposed via direct laryngoscopy under anesthesia and the light activation treatment is performed using a pumped dye laser and a fiberoptic microlens fiber. It is important to keep the treatment field dry and free of blood during the application of light. The fiber usually is passed through the laryngoscope keeping the lens tip a short distance away from the treatment field thereby delivering uniform tumor surface illumination. Alternatively, the fiberoptic flexible fiber may be delivered via a flexible endoscope with a working channel. Of note is that the light output of the fiber should be measured immediately prior and after treatment. The light dose, duration of treatment and laser light source may vary depending on the photosensitizer used. After the completion of PDT the patient receives a dose of corticosteroid and discharged the same day on oral analgesics. Patients are reminded to follow sunlight avoidance precautions. Figures 1A and B shows the pre- and post-treatment video-endoscopic view of a T1 larynx carcinoma treated with PDT.

Published Experience with Laryngeal PDT

Porfimer sodium (Photofrin, HpD), being the first photosensitizer with wide clinical use, has been tested most extensively in the treatment of laryngeal cancer. Freche and DeCorbiere[27] reported treatment in 32 patients with T1



Figs 1A and B: Pre- and post-treatment video endoscopic view of a T1 larynx carcinoma treated with PDT

carcinomas of true vocal cords with Hpd or photofrin. A complete response was achieved in 25 of 32 patients (78%) with 12 to 48 months follow-up. Feyh[28] treated 12 patients with Cis-T2 laryngeal carcinomas. 11 of 12 patients obtained a complete response (91%). Schweitzer[29] used photofrin PDT to treat ten patients with Cis-T2 carcinomas of the larynx of which eight had complete response (80%). Gluckman[30] reported on 23 patients with early head and neck carcinomas, including cases with recurrences after failed previous therapy. 20 of 23 patients obtained a complete response with an 8 to 53 month follow-up. This series contained 2 patients with T1 laryngeal cancer and both obtained complete response.

Biel et al[31] published the results of the largest cohort treated with Photofrin PDT. Of 115 patients with Cis, T1and T2 laryngeal cancers, there was durable complete response in 105 (91.3%) after a single treatment. Notably, all the recurrences were salvaged using PDT, surgery or radiotherapy to achieve a total five year cure rate of 100 %. Biel et al also reported on 113 patients of early carcinomas of oral cavity in the same paper. In the entire series of 276

Table 1. Summary of publications on PDT for laryngeal lesions

Study	No. of patients	T stage	Response complete	Partial	None
Feyh et al	12	T1T2	11	1	0
Freche et al	32	T1	25	7	0
Gluckman et al	2	T1	2	0	0
Yoshida et al*	12	T1, T2, T3	10	2	0
Schweitzer et al	10	T1	8	2	0
Biel et al	115	Cis,T1,T2	105	10	0
Rigual et al	6	Dysplasia, T1,T2	5	0	1

* These patients were treated with HpD

patients by Biel et al only two patients sustained sun induced photosensitivity with significant facial edema. The degree of treatment related pain varied with patients. However, in all patients the pain was adequately controlled with oral analgesics and uniformly resolved within two to three weeks of treatment. Rigual et al[32] reported the results of a prospective trial using Photofrin PDT for head and neck dysplasia and cancers. This included six patients with laryngeal pathology. All the three laryngeal dysplasias exhibited a sustained complete response. Two of the 3 laryngeal carcinomas had a complete response. One patient with a primary glottic cancer had no response and progressed locally during radiotherapy and was salvaged by means of a total laryngectomy. No airway compromise was reported and all the patients subjectively reported voice quality improvement compared with their pretreatment status.

Yoshida et al[33] have reported their experience with PDT with HpD in laryngeal cancer. The effect of PDT as a primary treatment for ten patients was classified as a complete response in eight (80%) and partial response in two cases. When evaluated only for T1 patients, the results were classified as CR in eight and PR in one. The results from these studies are summarized in Table 1. To date, there is no prospective Phase III curative intent clinical randomized trial comparing PDT *vs* conventional treatments in head and neck cancers, including laryngeal cancers.

Advantages of PDT include its effectiveness in properly selected cases, such as Tis and T1. Biel et al demonstrated the efficacy of Photofrin PDT with curative intent for Tis, T1(85-91%) and T2(72%) squamous cell carcinoma of the larynx. More importantly, if salvage treatment is included, the curative rates are up to 100%. PDT for treatment of T1 and T2 laryngeal cancers has cure rates that are comparable to, if not better than conventional therapies. PDT is minimally invasive and performed as a single outpatient procedure as compared to 6 to 7 weeks of radiotherapy. Of note is that the treatment may be repeated without permanent complications. PDT results in selective tumor destruction with preservation of mesenchymal tissues. This is of particular significance in larynx, where tissue loss can result in functional deficits. Post PDT healing results in normal mucosa and submucosa.[26] Histological evidence of the healing process has demonstrated the preservation of cellular collagen matrix with repopulation of the normal mucosal cells into the preserved collagen matrix scaffold. PDT for laryngeal carcinomas results in no glottic scarring even if used multiple times as compared to conventional laser or surgical resection. For limited recurrent carcinomas of the larynx that have failed radiotherapy, PDT, if successful, allows excellent voice preservation. Importantly, the use of PDT does not interfere with other therapies. In other words, standard therapies may be used effectively for salvage if necessary.

Limitations of PDT include the fact that it remains a treatment modality for local disease.

The photosensitizers can distribute in a tumor unevenly, allowing some regions to escape the effective treatment. The photosensitizers can remain in the skin for varying duration making the patient photosensitive. Newer photosensitizers like HPPH have a much shorter half-life and hence the period of photosensitivity is limited to a few days. Finally, therapeutic effectiveness of PDT is affected by the depth of tissue penetration of the laser light.

CONCLUSION

PDT as currently practiced appears to be highly effective for early stage laryngeal cancers. Nevertheless, commercial availability of photosensitizers with limited photosensitivity remains a challenge for wide dissemination of this treatment modality. Multi-institutional Phase II clinical trials are required to develop, and incorporate PDT into the treatment algorithm of laryngeal cancer. Finally, the future of PDT is promising with the development of newer photosensitizers that have reduced photosensitivity and longer light wavelength activation resulting in deeper tissue penetration and improved therapeutic effectiveness.

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