



REVIEW ARTICLE

# Current state and future of photodynamic therapy for the treatment of head and neck squamous cell carcinoma



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## KEYWORDS

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**Abstract** Photodynamic therapy has shown promise in the treatment of early head and neck squamous cell carcinoma (SCC). In photodynamic therapy (PDT), a light sensitive drug (photosensitizer) and visible light cause cancer cell death by the creation of singlet oxygen and free radicals, inciting an immune response, and vascular collapse. In this paper, we review several studies that demonstrate the effectiveness of PDT in the treatment of early stage SCC of the head and neck, with some showing a similar response rate to surgery. Two cases are presented to illustrate the effectiveness of PDT. Then, new advances are discussed including the discovery of STAT3 crosslinking as a potential biomarker for PDT response and interstitial PDT for locally advanced cancers.

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## Introduction

In photodynamic therapy (PDT), a light sensitive drug (photosensitizer, PS), oxygen and visible light are required to achieve a therapeutic response. To activate the PS, a laser light is used to illuminate the treatment area. The specific laser wavelength depends on the PS. Most clinically approved PSs are activated with red light. PDT has 3 primary mechanisms of action: creation of singlet oxygen and free radicals, inciting an immune response, and vascular collapse.

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Modern PDT came to the forefront with the work of Dougherty et al in the 1970s at the Roswell Park Cancer Institute.<sup>1</sup> Their work led to the development of porfyrin sodium (Photofrin), a hematoporphyrin derivative, and its subsequent FDA approval. Porfyrin sodium is injected intravenously, and requires 24–48 h to preferentially retain in cancerous tissues. The other FDA approved photosensitizer, 5-aminolevulinic acid (5-ALA, Levulan) is used topically and mainly for dermatologic conditions. The ALA is absorbed through the skin or mucosa and is then converted to the active drug within tissues. Temoporfin (mTHPC, Foscan) is approved for use in Europe.

Multiple studies have demonstrated the effectiveness of PDT in the treatment of early stage squamous cell carcinoma (SCC) of the head and neck. In particular, it has been shown to result in acceptable response when used to treat T1/T2 SCCs of the oral cavity and glottic larynx.<sup>2–6</sup> The main advantages of PDT are that it can be safely repeated, the PS itself has few minor side effects, does not preclude further radiation or surgery, and heals with minimal scarring. The main disadvantages are photosensitivity (up to 6 weeks), pain, and cost of the FDA approved drug.

### PDT for early stage SCC

PDT is ideally suited to superficial SCCs which can be easily accessed by the treating surgeon. This has been investigated most extensively in the oral cavity and larynx, where PDT has been used to treat lesions ranging from dysplasia to locally advanced squamous cell carcinoma. Rigual et al demonstrated the efficacy of porfimer sodium for the treatment of oral cavity squamous cell carcinoma in 2006, and of HPPH in 2013.<sup>6,7</sup> Complete response rates in the 23 patient cohort of T1 SCCA treated with HPPH reached 82%. Durbec et al in 2013 examined the efficacy and safety of PDT in recurrent carcinoma of the oral cavity and oropharynx using Foscan, and observed a 93% complete response rate.<sup>8</sup> Jerjes observed a 5 year survival of 84.2% and a recurrence rate of 15.8% in T1–2 SCCA of the oral cavity treated with up to three rounds of mTHPC.<sup>9</sup> Biel, in a series of 113 oral cavity PDT patients, with 93.8% of patients with Cis-T2 tumors and 89.6% of patients with superficial T2–3 tumors remaining free of disease after a mean follow up of 90 months.<sup>3</sup> A recent meta-analysis by Cerrati et al found 24 studies comparing T1–2N0M0 squamous cell carcinoma of the oral cavity to surgery.<sup>10</sup> They found no statistically significant difference between rates of complete response to PDT, locoregional control with surgery, or recurrence rate between the two modalities. The similar response rates between surgery and PDT were supported by the work of de Visscher et al, who compared response rates, disease free survival and need for re-treatment in superficial (<5 mm) T1–2 squamous cell carcinoma of the oral cavity.<sup>11</sup> In tumors treated by PDT, an 86% complete response rate was observed in T1 lesions, and a 63% complete response rate was observed for T2 lesions. This was not significantly different than the control rates observed in surgically treated T1 and T2 tumors, which were 76% and 79%, respectively. Overall survival was similar between the two treatment modalities when controlled for stage.

PDT treatment of laryngeal squamous cell carcinoma is attractive because of the potential to preserve both voice and swallowing integrity. Biel reported on 115 patients with recurrent or primary laryngeal lesions, ranging from Cis to T2N0 SCC, and observed a 5 year cure rate of 91%.<sup>2</sup> All recurrences were successfully salvaged by either PDT or conventional means. A Phase Ib study carried out at Roswell Park Cancer Institute examined response of laryngeal T1 squamous cell carcinoma of the larynx to HPPH treatment as a secondary outcome, and observed an 82% complete response rate.<sup>12</sup>

### Case examples

#### Case 1 – oral SCC

A 65 year old woman presented with a T2 SCC of the mucosa of the lower lip and vestibule. She had no significant past medical history except for a 40 pack/yr smoking history. The lesion was superficial, but extended onto the vestibule and lower gingiva (Fig. 1). She was given the option of surgery, radiation, or PDT and chose PDT. Two days before the procedure she was injected with 2 mg/kg of porfimer sodium. The procedure was done in the operating room under general anesthesia. A laser was used to illuminate the treatment area with a wavelength of 639 nm and a light dose of 50 J/cm<sup>2</sup> and 150 mW/cm.<sup>2</sup> 6 months later, she remained disease free and had minimal scarring (Fig. 2).

#### Case 2 – T2 glottic SCC

A 63 year old man presented with a several month history of hoarseness and dysphagia. Office examination revealed an ulcerative left tonsil mass. Flexible laryngoscopy revealed a lesion on the left false and true vocal cords (Fig. 3). Direct laryngoscopy and biopsy showed a T2 SCC involving the left false cord and extending to the true cord and anterior commissure. He also had a concurrent T4N0 SCC of the left tonsil. He chose to have a standard treatment for the tonsil SCC (surgery and adjuvant treatment) and PDT for the



Fig. 1 Pre-PDT picture of a woman with a superficial T2N0 oral SCC.

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