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REVIEW

Is photodynamic therapy a good alternative to surgery and radiotherapy in the treatment of head and neck cancer?

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Summary The mainstay treatments for head and neck carcinomas are surgery, radiotherapy and chemotherapy. These treatment options may be associated with considerable complications. Radical radiotherapy and chemotherapy can generally be employed only once, which presents difficulties in cases of recurrent disease or second primaries within the irradiated field. Salvage surgery at the same site is often difficult, due to progressive tissue loss. In this respect photodynamic therapy (PDT) seems to be a good alternative treatment option for small, localized tumors; with a good outcome and with excellent functional and cosmetic results. Selected patients with advanced cancer of the head and neck, who have exhausted other treatment options, can also achieve improvement in quality of life with PDT. The advantages of PDT compared with surgery or radiotherapy are reduced long-term morbidity and the fact that PDT does not compromise future treatment options for recurrent, residual or second primary disease.

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Introduction

The worldwide incidence of squamous cell carcinomas of the head and neck is about 640.000 cases [1]. The mainstay treatments for early stage head and neck carcinomas are surgery, radiotherapy, including radiosurgery and IMRT, or a combination of surgery and radiotherapy. For locally advanced stage head and neck carcinomas chemoradiation has now become standard in most instances. In early stages, surgery and radiotherapy give good cure rates, but this is often associated with both functional and cosmetic impairments.

Surgery of squamous cell carcinoma requires wide excision margins and, due to the limited anatomical proportions in the head and neck, damage to adjacent or underlying structures can cause functional deficits in various degrees, e.g. ill fitting dentures, speech problem, impaired tongue mobility, difficulties with swallowing and deglutition [2—6]. In more advanced tumors requiring larger excisions, the resulting defect has to be reconstructed with pedicled or free revascularized flaps, which can cause even more morbidity and unsatisfactory scar formation. Patients with head and neck carcinomas primarily treated with surgery often have increased eating times, complaints about pocketing and not finishing their meal, and are reluctant to eat in restaurants [5,6].

Radiotherapy may also be associated with considerable short and long-term complications, such as xerostomia, mucositis, change in taste or impaired taste and increased tooth decay. Long-term toxicity is related to radiation-induced fibrosis and may consist of difficulties with swallowing and speech, aspiration, pocketing difficulties, and not finishing the meal. In more extreme cases, soft tissue and osteonecrosis, muscle and subcutaneous fibrosis, ulceration, dysphagia and osteoradionecrosis of the mandible may occur [3,4,7—12]. Another disadvantage of radiotherapy is the long overall treatment period of 6—7 weeks. Such a prolonged treatment schedule, requiring daily visits to the radiotherapy clinic, is burdensome for elderly patients and is often not feasible in developing countries. Effects of postoperative radiotherapy are even worse due to an increased fibrotic reaction. These patients report a significantly greater impact upon daily functioning and pain interfering with daily activities [8]. The acute and late effects of chemoradiation are similar in nature, but worse, than after radiotherapy alone. Radical radiotherapy and chemotherapy can generally be employed only once, which presents difficulties in cases of recurrent disease or second primaries within the irradiated field.

Head and neck squamous cell carcinomas are often accompanied by synchronous or metachronous second primary carcinoma of the upper aerodigestive tract. Field cancerization has been proposed to explain the development of multiple primary tumors in the head and neck region. This represents one or more areas around a primary head and neck squamous cell carcinoma consisting of epithelial cells that have genetic alternations that may develop into invasive carcinoma [13]. Four percent per year of patients with carcinoma of the oral cavity, oropharynx, hypopharynx, and larynx develop a second neoplasm, most frequently a carcinoma of the aerodigestive tract [14]. This leads to a lifetime risk of developing second cancers of 20—30% after radical treatment of a first primary head and neck cancer. Treatment of these lesions may be compromised by the effects of previous radical therapy [15]. Salvage surgery at the same site is difficult or even impossible in certain cases, due to progressive tissue loss [16]. Re-irradiation carries an increased risk of serious side effects because surrounding tissues have already received the maximum tolerable dose of ionizing radiation [17]. This creates a serious need for new treatment alternatives. In this respect PDT seems to be a good candidate.

Principle of PDT

PDT is a local rather than a systemic treatment; therefore it is only suitable for localized disease. PDT involves the administration of a photosensitizer, which is preferentially concentrated in neoplastic cells, followed by local illumination of the tumor with light of an appropriate wavelength to activate the specific drug. When photosenstizers are activated, they interact with molecular oxygen to produce singlet oxygen. The singlet oxygen produced by a photochemical reaction is highly toxic and can directly kill tumor cells by apoptosis or necrosis. It also damages the tumor vasculature, resulting in indirect tumor cell kill via hypoxia and starvation. Singlet oxygen is highly reactive and can only diffuse 0.02 μm. Tissue damage is therefore restricted to the penetration depth of the light used to activate the photosensitizer. In addition to direct cell killing, the membrane damage caused by PDT is associated with the release of inflammatory and immune mediators, which initiate cascades of event responsible for further tumour cell death. After PDT with superficial illumination, deeper connective tissues are barely damaged, with maintenance of their architecture and elasticity [18,19]. Furthermore, PDT can be repeated without cumulative tissue toxicity and the patients still retain the possibility of (re)treatment with radiotherapy or surgery [19,20].

Photosensitizers

First generation photosensitizers are hematoporphyrin, its derivate, hematoporphyrin derivate (HpD), and the purified, commercially available Photofrin® (Wyeth-Ayerst Lederle,

Inc., for Axcan Pharma, Ireland). This was the first photosensitizer tested in the clinic. The absorption spectra of both HpD and photophrin have five peaks, with the strongest at about 400 nm and the weakest at 630 nm. Light at 400 nm will penetrate <1 mm in tissue and is not useful as an activator for PDT. The peak at 630 nm is generally used for clinical studies because the depth of necrosis that can be achieved is 5—10 mm in tissue [21]. Although this is sufficient for small superficial tumors, adequate illumination of deeply infiltrated lesions will never be reached with 630 nm light [22]. Because of the relatively weak absorption at this wavelength, light doses of 100—200 J/cm^2 are required for tumor control. A disadvantage of the first generation photosensitizers is the prolonged skin photosensitivity for 4—12 weeks [18]. The long illumination time of 30 min required to achieve curative PDT with HpD or photophrin is also a drawback for clinical application.

We will consider below second generation photosensitizers which have already entered clinical trials. The second generation photosensitizer 5-aminolevulinic acid (ALA, Levulan®, Dusa Pharmaceuticals, Inc., Wilmington, MA, Metvix®, Galderma, F) can be applied intravenously, orally or topically so a greater tumor selectivity can be achieved. The disadvantage of ALA is that it is strongly hydrophilic and therefore not able to enter cells easily [23]. It is only suitable for treating extremely superficial tumors of 1—2 mm depth and has not been widely used for head and neck cancers [23,24].

The most recently approved photosensitizer for cancer is meta-tetrahydroxyphenylchlorin (mTHPC; Foscan®, Biolitec Pharma, Edinburgh, Scotland) [25]. mTHPC has a much stronger absorption peak at 652 nm than the absorption peak for Photophrin at 630 nm. Longer wavelengths of light penetrate deeper in tissue, leading to more effective tumor treatment. mTHPC is therefore much more potent than the first generation photosensitizers or ALA, requiring light doses of only 10—20 J/cm^2 for tumor control [23,24]. In addition, photosensitivity of the skin is less prolonged than the first generation sensitizers, so patients can tolerate subdued indoor light 4 or 5 days after injection, and the period of photosensitivity persists for only 3 weeks after mTHPC compared with 6—12 weeks after photophrin [26].

Benzoporphyrin derivate (BPD) is a chlorin synthesized from protoporphyrin and has a strong molar absorption coefficient at 690 nm (13,000 M^{-1} cm^{-1}). There is minimal absorption by blood at this wavelength and light penetration is tissue is almost optimal. This drug is showing promise in phase I/II trials for PDT of psoriasis and cutaneous malignancies [27]. Mono-aspartyl chlorin e6 (Npe6) is another second generation photosensitizer with a very strong absorption peak (38,000 M^{-1} at 664 nm). Initial clinical reports with this sensitizer are promising [28]. Tin etiopurpurin (SnET2) has a strong absorption peak at 660 nm. SnET2 has reduced skin photosensitivity compared with photophrin—PDT and is used for cutaneous carcinomas [29]. Lutetium texaphyrin (Lu-Tex) is a water soluble sensitizer with a has a broad absorption peak at 732 nm and represents an interesting next class of photosensitizer. It accumulates preferentially in malignant tissue via an increased lipoprotein receptor mechanism and induces only mild transient skin photosensitivity [30]. Another novel second generation photosensitizer is Pd-bacteriopheophorbide (TOOKAD). This photosensitizer is endowed with strong light absorbance in the near infrared region (λ = 763 nm), allowing deep tissue penetration. It is mostly used for prostatic cell carcinoma.

Light source

Lasers are the preferred sources of light for PDT. They emit monochromatic coherent light; the power is greater than can be achieved with broadband lamps and can be channeled down a single fiber. The laser used in the early HpD-mediated PDT studies was an argon ion pumped dye laser. The Argon Ion dye laser produces up to about 20 W blue-green light, which generates up to 5 W red light useful for PDT. This combination laser is very inefficient, i.e. an output of 5 W red light requires roughly 50 kW electrical power. These lasers were also very large and relatively difficult to use. Nowadays semiconductor lasers, diode lasers, with outputs of >6 W at 652 nm and 2 W at 664 nm are available for Foscan PDT [23]. These lasers are very efficient with a high power output, portable and easy to use.

The development of PDT in the treatment of head and neck cancer

It is important to evaluate whether PDT will provide a significant clinical benefit and an improvement in quality of life for patients with head and neck cancer and whether PDT may serve as a suitable alternative treatment. To answer these questions and to understand the difficulties of the development of PDT in the treatment of head and neck cancer it is necessary to look back at the different PDT methods that have been used over the years. In this review we included only the larger studies where >20 patients were treated. We also excluded the studies where the first generation photosensitizer aminolevulinic acid (ALA) was used. ALA is only efficient for very superficial lesions and for treatment of small surface areas [23]. To date, there are no randomized phase III trials comparing PDT with other treatment modalities. All of the studies reviewed here rely on historical controls for comparison with other treatments, which is a major concern for rigorously evaluating any new treatment modality.

International clinical experience in PDT for palliative treatment of advanced head and neck cancer

One of the first studies of PDT for head and neck cancer, published in 1984 [22], was for the treatment of persistent or recurrent cancer of the head and neck, using the first generation photosensitizer HpD (Table 1). Patients entered in this trial had failed all forms of conventional therapy. Twenty-one patients with local recurrence were injected with HpD (3 mg/kg i.v.) and 3 days later the lesion was illuminated with red light of 625—635 nm, using an argon-ion pumped dye laser. The light intensity at the surface was in the range of 25—500 mW/cm^2 and total light doses of 17—91 J/cm^2 were given. There were 6 complete responses, some lasting for over 1 year, and 12 partial responses. Ten patients with cutaneous metastases from head and neck primary tumors

Table 1 Chronological table of PDT for advanced stage of squamous cell carcinoma in head and neck.

Year	Reference	Patients (*n*)	Lesion site	Pathology	Drug	Response (*n*/%)		
						CR	PR	NR
1984	Wile et al. [22]	21	Oral cavity Nasopharynx Oropharynx Maxilla Larynx Basal cell nevus syndrome	SCC[a] ACC[b] BCC[c]	HpD	6/29	12/57	3/14
		10	Regional recurrence head and neck			2/20	3/30	5/50
1985	Schuller et al. [31]	24	Neck Mandibula Skin head and neck Preauricular area Oral cavity Oropharynx Surgical Wound Max. Sinus Nose	Not described	HpD	2/11	17/89[d]	
1990	Zhao et al. [32]	20	Nasopharynx	SCC UCC[e]	HpD	8/40	10/50	2/10
2004	D'Cruz et al. [33]	145 (102 evaluable)	Oral cavity Nasopharynx Oropharynx Larynx Other	SCC	mTHPC	44/43[g]	59/58[f]	43/42
2004	Lou et al. [35]	45	Oral cavity Oropharynx Neck Maxillary sinus Nasal cavity Nasopharynx Parotid Thyroid	SCC	mTHPC	9/20	24/53	12/27

[a] Squamous cell carcinoma.
[b] Adenoid cystic carcinoma.
[c] Basal cell carcinoma.
[d] No difference reported between PR and NR.
[e] Undifferentiated cell carcinoma.
[f] 15 of these 44 lesions remained completely cleared 1 year after treatment.
[g] Complete response together with partial response.

were also treated, with only 2 complete responses and 5 no responses [22].

Schuller et al. subsequently assessed the potential of PDT in advanced head and neck cancer by analyzing the feasibility, toxicity and tumor responses of various treatment techniques [31] (Table 1). A group of 24 patients were included with recurrent and or metastatic cancers. They were treated using doses of 3.0—5.0 mg/kg HpD and laser light delivered by an argon-dye laser with a wave length of 630 nm and a power output of 3 W. Six of the 24 patients developed complications after completing the therapy. Four of these developed chronic ulceration, necrosis or fistula within the illuminated area. One patient developed a second degree hand burn because of generalized photosensitivity that persisted following completion of the treatment. One patient died from massive bleeding after illumination of a tumor that involved the carotid artery. Of 5 patients where pain was a major problem before treatment, 3 had a reduction of pain after PDT. Only a short duration of tumor response was seen in this study and disease progression occurred within 6 weeks in 15 patients. Although the authors concluded that HpD-mediated PDT for advanced head and neck cancer was feasible and well tolerated these conclusions seem somewhat controversial, based on their published results [31].

Zhao et al. determined the efficacy and side effects of HpD-mediated PDT in a group of 20 patients with nasopharyngeal carcinoma [32] (Table 1). The patients were treated with an average of 3.3 courses each. Nine patients presented with previously untreated tumors and 11 had recurrent

tumors after previous radiotherapy. There was a complete response in 8 patients, and a partial response in 10 patients. Three patients developed mild generalized skin photosensitive reactions. It was concluded that PDT was highly effective in destroying tumor cells of nasopharyngeal carcinomas with few major side effects [32].

More recently, D'Cruz et al. published results from a large multicenter study of PDT using the second generation photosensitizer with meta-Tetrahydroxyphenylchlorin (mTHPC, Foscan®) [33] (Table 1). One hundred twenty-eight patients with advanced, incurable head and neck carcinomas were given 0.15 mg/kg mTHPC 4 days before illumination with red light of 652 nm. Light doses of 20 J/cm^2 were delivered from a diode laser, using a micro lens fiber, at an intensity of 100 mW/cm^2. One hundred forty-five lesions were treated and 102 lesions were evaluable for analysis. The aim of the study was to assess tumor response, quality-of-life benefit, survival, and toxicity after PDT treatment. Overall, 43% of the lesions achieved 100% tumor mass reduction on at least one occasion after treatment, the median duration of response was 117 days, with 35% of the lesions remaining completely cleared 1 year after treatment. Fifty-three percent of the patients experienced significant benefit in quality-of-life. The authors concluded that patients with advanced cancer of the head and neck who have exhausted other treatment options can achieve significant clinical benefit and improvement in quality of life with mTHPC-mediated PDT [33].

PDT is usually undertaken with external illumination of the target tissue. Larger lesions can be treated with interstitial therapy, in which case multiple laser fibers are inserted directly into the depth of the tumor through needles positioned under image guidance [34]. Lou et al. used interstitial mTHPC PDT to treat 45 patients with recurrent or persistent head and neck cancer unsuitable for further treatment with surgery, radiotherapy or chemotherapy [35] (Table 1). Patients were injected with mTHPC (0.15 mg/kg) 4 days prior to illumination. Nine patients achieved complete response, 5 were alive and free of disease 10—60 months later. In 24 patients symptomatic relief of pain was achieved. PDT seems to be a promising new form of salvage treatment for locally advanced head and neck tumors. Response rates after PDT are comparable with other conventional therapies and it provides good cosmetic outcomes and less functional morbidity than repeat surgery or radiation therapy [34,35].

Discussion of literature for PDT for advanced head and neck cancer

The studies described above included patients with recurrent tumors refractory to conventional therapy and most were treated using a first generation photosensitizer [22,31]. These studies generally achieved only moderate responses, but this is not surprising because it is a very difficult group of tumors to treat with any modality.

The patients with cancer recurrent in soft tissues in the head and neck region had aggressive tumors or were in advanced stage of disease. It is unreasonable to expect a local mode of therapy to alter the natural history of a disease that has already become regional or systemic [22].

Perhaps more surprisingly, treatment of cutaneous metastases with HpD-mediated PDT was also not very effective. These tumors lie beneath the keratinized layer of the epidermis and lack of response may be related to inadequate penetration of the light.

The complications described after HpD and photophrin-mediated PDT, e.g. chronic ulceration, necrosis, or fistulas, together with the limitations imposed on the patient's lifestyle due to photosensitivity, limited the enthusiasm for PDT for palliative treatment of advanced head and neck cancers using first generation photosensitizers. Second generation photosensitizers like mTHPC have, however, been shown to give significant clinical benefit and improvement in quality of life for advanced head and neck cancer [33].

Patients with locally advanced cancer of the head and neck, who have exhausted other treatment options, can also achieve significant clinical benefit and improvement in quality of life, when treated by mTHPC-mediated PDT. However, the tumors must be carefully selected as they must be easily accessible to laser light. Patients should be in good general health and have a good nutritional state, with a Karnofsky performance of more than 70%, otherwise the immediate post-treatment period will be too burdensome.

Most patients experience moderate postoperative pain during the first few days, which can be controlled by a combination of opiate, opioid and NSAID analgesia.

International clinical experience in PDT in the treatment for early stage head and neck cancer

One of the first treatments for early stage head and neck cancer by PDT was performed by Zhao et al. in 1989 [36] (Table 2). Fifty patients with stage I to stage III carcinoma of the lip were treated using HpD. The distribution of tumor staging was not clearly described in this publication. After PDT there were 4 local recurrences and 4 patients developed submandibular node metastases, ''the results of others were satisfactory''. It remains unclear how many patients achieved complete response. However, the authors made an important remark that PDT is a useful treatment in cases where the lesion is superficial and involves a rather big area [36].

Feyh et al. treated 42 T1 carcinomas of the face and oropharynx, primarily with HpD-mediated PDT [37] (Table 2). They reported 40 complete responses, 1 recurrent and 1 residual nodule at a depth of 0.5 cm, where the underlying histology proved benign tissue [37].

Wenig et al. treated 26 patients with early stage squamous cell carcinoma of the head and neck by photophrin II-mediated PDT [38] (Table 2). All patients had either failed traditional treatment modalities or refused conventional therapies. Histological complete responses were achieved in 20 patients. Of these, 16 remained free of tumor for periods up to 51 months and 4 had local recurrent disease. Some complications were noted such as pain, odynophagia, skin coloration changes, and some minor bleeding and osteonecrosis of the mandibula. The authors concluded that PDT was an effective treatment modality for early stage head and neck squamous cell carcinoma [38].

Table 2 Chronological table of PDT for early stage of squamous cell carcinoma in head and neck.

Year	Reference	Patients (*n*)	Lesion site	Pathology	Drug	Response (*n*/%)		
						CR	PR	NR
1989	Zhao et al. [36]	50	Lip	SCC[a]	HpD	[b]		
1990	Feyh et al. [37]	42	Face Oropharynx	SCC BCC[c]	HpD	40/95	2/5	
1990	Wenig et al. [38]	26	Oral Cavity Oropharynx Maxillary Sinus Larynx Parotid Gland Nasopharynx Neck	SCC	Photophrin II	20/77	5/19	1/4
1990	Freche and De [39]	32	Glottis	EC[d]	HpD	25/78		7/22
1991	Gluckman [40]	33	Oral cavity Oropharynx Larynx Hypopharynx Nasopharynx Maxillary sinus Esophagus Trachea	SCC CM[e]	HpD DHE	21/64	7/21	5/15
1994	Biel [41]	36	Larynx Oral cavity Nasal cavity Nasopharynx	AC[f] SCC Leukoplakia	Photophrin	35/97	1/3	
2001	Kubler et al. [44]	25	Lip	SCC	mTHPC	24/96	1/4[g]	
2003	Copper et al. [42]	29	Oral cavity Oropharynx Cheek	SCC	mTHPC	25/86	4/14	
2004	Hopper et al. [43]	114[h]	Oral cavity Oropharynx Lip	SCC	mTHPC	97/85	13/11	

[a] Squamous cell carcinoma.
[b] No description about the responses; ''the results were satisfactory''.
[c] Basal cell carcinoma.
[d] Epidermoid carcinoma.
[e] Condemned mucosa.
[f] Adenocarcinoma.
[g] After second photodynamic therapy treatment complete response.
[h] Three patients were not assessed and 1 refused further treatment and died of extensive disease 1 year later.

In the same year, Freche and De published the results of 32 patients with primary and recurrent T1 carcinomas of the glottis without anterior commissure involvement with HpD-mediated PDT [39] (Table 2). These results show 25 complete responders and 7 failures. The authors suggested that these failures were due to dosimetric problems of insufficient light power or dose and incomplete illumination of tumors when the optical fiber was positioned too close to the tumor during operation [39].

Gluckman reported the results of HpD and dihematoporphyrin either DHE-mediated PDT treatment in 25 patients with T1—T2 carcinomas of the head and neck [40] (Table 2). These tumors were relatively superficial and frequently represented recurrence after failed previous therapy, either surgery or radiotherapy. The 13 oral cavity and oropharyngeal carcinomas were the easiest to treat and 11of these achieved complete response although 4 subsequently recurred. In the 6 laryngeal cancers the results were not as impressive. All of the laryngeal cancers represented radiotherapy failure and the extent of the lesions might have been underestimated, which could account for the poor success rate obtained. Two patients achieved a complete response. Of the 6 patients with early stage hypopharynx, esophagus, nasopharynx, trachea and sinus maxillary carcinoma, only 1 patient achieved complete response. Gluckman also reported on 8 patients with premalignant and overt

malignancy in the oral cavity, palate and buccal mucosa, and demonstrated excellent responses to PDT. Seven of the 8 patients achieved complete response [40]. It was then concluded that HpD-mediated PDT was an attractive technique for treating field cancerization of the mucosa, with the only major drawback being skin photosensitivity. Its potential role for treating early focal cancers was recognized, but at this time the technology was still in its infancy.

Biel subsequently treated 36 patients with early head and neck carcinomas with photophrin-mediated PDT [41] (Table 2). Twenty-seven patients with early carcinomas of the larynx, oral cavity, nasal cavity and nasopharynx obtained complete response. Six patients with CIS, severe atypia, and recurrent leukoplakia of the larynx achieved complete response. Two patients with a T2 larynxcarcinoma as a failure of radiotherapy were treated with PDT and 1 patient received a complete response. This study indicates that PDT is highly effective for the curative treatment of CIS and T1 carcinomas of the head and neck [41].

The most recent studies for the treatment of early stage head and neck carcinomas with PDT used the photosensitizer mTHPC [42—44] (Table 2). Kubler et al., evaluated the efficacy of mTHPC-mediated PDT in 25 patients with primary squamous cell carcinomas of the lip [44]. After 12 weeks, 24 of the 25 patients (96%) showed complete response. The 1 remaining patient showed a partial response and was successfully retreated by mTHPC-mediated PDT, with a complete response at 7 months after retreatment. The functional results were excellent in all patients, without any signs of restricted mouth opening or impaired lip closure [44].

Copper et al. performed a study to examine the long-term efficacy of mTHPC-mediated PDT in the treatment of 29 early stage squamous cell carcinomas of the oral cavity and oropharynx [42]. In 25 tumors (86%) a complete remission of the primary tumor was obtained. Four lesions developed local recurrent disease after 1—6 months. All these cases were salvaged by surgery and/or radiotherapy. None of the patients complained about impairment of mastication, swallowing, articulation or speech after PDT [42].

Hopper et al. conducted a multi-centre study to assess the efficacy and the safety of m-THPC-mediated PDT in 114 patients with early oral cavity carcinoma [43]. A complete response was maintained in 85% of responders at 1 year and in 77% at 2 years. Response rates were higher for smaller tumors. This study demonstrated that tumor clearance was accompanied by excellent cosmetic and functional results, without impact on the patient's performance status. Adverse events in the immediate post treatment phase were limited to pain (82%) and swelling (10%) at the treatment site due to the tumor necrosis caused by PDT. Sixteen patients showed photosensitivity reactions; in 13 patients this was only mild erythema with no long-term damage. The remaining 3 reactions were more severe and occurred in patients who failed to comply with the prescribed light regimen. The authors concluded that mTHPC-mediated PDT is a safe and effective method of dealing with early oral squamous cell carcinoma, with a number advantages over conventional treatments in term of improved organ function and cosmetic appearance [43].

Discussion of literature for PDT for early stage head and neck cancer

Some of the early studies described above included patients with recurrent or residual tumors that had failed traditional treatment [38—41]. These studies showed that in some cases, e.g. lip carcinoma and oral cancer, HpD and photophrin PDT achieved good responses, despite the limited penetration of light of 630 nm and the low-power output of the argon-ion pumped-dye lasers. The anatomy of the oral cavity and oropharynx usually allows adequate visualization of the cancer, and therefore a good exposure of the tumor to the laser light. Hence a wide surgical margin around the tumor can easily be reached in the oral cavity and oropharynx.

In the larynx, hypopharynx, esophagus, nasopharynx, trachea and maxillary sinus carcinoma, the complex nature of the anatomy makes adequate illumination of the tumor extremely difficult. Inadequate tumor illumination together with limited penetration of light of 630 nm and the low-power output of the argon ion pumped-dye laser used in these studies probably explains the poor success rate of the PDT using first generation photosensitizers for these sites [40].

Carcinoma in situ, field cancerization with large areas of superficial premalignant and malignant changes, and multicentric malignancies appear to be amenable to PDT. Such tumors are difficult to treat with conventional therapies without morbidity. PDT allows relatively large affected areas to be treated with preservation of normal tissue and treatment can be repeated as often as necessary [40,41]. Even better results would be expected for treating early stage head and neck carcinomas by PDT using more powerful second generation photosensitizers and more penetrating laser light of 652 nm. The response rates in the 3 recent articles for mTHPC-mediated PDT for early stage head and neck carcinomas are very good and comparable with the outcomes of treatment with conventional therapies but without impairment of organ functions [42—44].

Is PDT a suitable alternative treatment for early stage head and neck cancer?

The choice for an optimum therapy for cancer of the head and neck is a multidisciplinary decision. Because of the unique anatomic and functional characteristics of this area, head and neck cancer and its treatment have a remarkable impact on the patient's daily life. When deciding on treatment options for these patients, treatment related morbidity and the quality-of-life as well as the risk of developing secondary primary tumors, should be considered in addition to the probability of achieving tumor control.

Surgery and radiotherapy give good cure rates in early stage head and neck cancer. The local tumor control for T1 and T2 oral cavity and oropharyngeal carcinomas is between 72 and 93% with conventional therapies [45,46]. However, both surgery and radiotherapy in the head and neck region can also result in significant morbidity, because of the complex anatomy and the extensive functions in this area. Re-irradiation or surgery in a previously reconstructed area

is difficult and brings a significantly increased risk of severe morbidity or disfiguration in cases of recurrences or second primaries in the head and neck.

The studies of Kubler, Copper and Hopper [42—44] show that PDT with second generation mTHPC gives tumor responses that are comparable with the outcomes of the conventional therapies, but with much less morbidity. All successfully treated patients had ablation of their disease without major reduction of function, e.g. mastication, articulation and swallowing. The mouth remained moist with normal healing and no functional salivary gland damage. Although PDT does have major acute toxicities (pain necrosis and generalized photosensitivity), these effects are not long lasting. The necrosis will resolve after about 6 weeks and the pain can be well controlled by a combination of opiate, opioid and NSAID analgesia. Because of generalized photosensitivity, patients have to stay indoors for 1 week after mTHPC injection and must avoid direct sunlight during the second week. Mild photosensitivity will remain for 3 months after injection of mTHPC.

If a complete tumor response is not achieved after PDT, the option of retreatment with PDT or conventional therapy remains. Previous treatment with mTHPC-mediated PDT does not compromise salvage treatment with PDT, radiotherapy or surgery [19,20,43]. Another advantage is that in certain circumstances PDT does not require general anesthesia and can be performed in the outpatient clinic. However, in many situations, general anesthesia might be necessary to achieve access and adequate shielding.

The most important consideration before choosing PDT treatment for early stage head and neck cancer is to stage the tumor carefully and make a clear treatment plan. The tumor should be a superficial carcinoma, with an infiltration depth of less than 1.0 cm. The tumor should also be easily accessible to laser light for a complete illumination and performing dosimetry. If mTHPC, a potent second generation photosensitizer, is combined with complete illumination with light of 652 nm, superficial tumors of the oral cavity will be effectively treated.

Conclusions

Selected patients with advanced cancer of the head and neck who have exhausted other treatment options, can achieve significant clinical benefit and improvement in quality of life with PDT using a second generation photosenitizer, like mTHPC, and new specific light delivery systems.

For early stage squamous cell carcinoma of the oral cavity and oropharynx mTHPC-mediated PDT with a diode laser is associated with a very good outcome and with excellent functional and cosmetic results. The advantages of PDT compared with surgery or radiotherapy are reduced long-term morbidity and the fact that PDT does not compromise future treatment options for recurrent, residual or second primary disease.

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