REVIEW

Clinical photodynamic therapy of head and neck cancers—A review of applications and outcomes

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Summary   As local control is tantamount to cure in head and neck cancer, an aggressive regimen of surgery and radiation remains the standard of care for most patients. Despite significant technical advances, these treatments are highly morbid. Further, patients who fail treatment have limited salvage options.

Photodynamic therapy (PDT) and photodiagnosis (PD) of head and neck cancer offer significant potential for improved outcomes in a myriad of clinical indications ranging from in situ to recurrent disease. However, despite promising results, these modalities remain at the fringe of head and neck treatment options.

Photofrin®, Photosan and Foscan® are photosensitizers used clinically in head and neck PD/PDT. In addition, aminolevulinic acid (ALA), which gives origin to Proto-porphyrin IX, an endogeneous photosensitizer, is also used for PD/PDT. We review the clinical literature on these photosensitizers to assist in the integration of these important modalities into the mainstream of head and neck oncological therapy.
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Introduction

The foundation of head and neck management is based on the premise that for most patients, achievement of local tumor control is tantamount to cure [1]. This has translated into a classical treatment approach which emphasizes local control through radical surgery and radiation therapy [2]. While potentially successful, this treatment paradigm often leads to severe and chronic functional loss and disability [3]. Historically, loss of voice and swallowing often accompanied surgery for invasive cancer [4]. Similarly, xerostomia, loss of taste and soft tissue fibrosis leading to ''woody skin,'' generally accompanied radiation treatments [5]. Furthermore, when radical surgery was combined with radiation to improve local control and survival, it was often at the cost of increased permanent morbidity [6].

With advances in treatment techniques and technology, improved or equivalent outcomes have recently been obtained through less radical treatments [7]. Surgery has progressed to allow function sparing surgeries while improvement in reconstruction unheard of even a decade ago, such as microvascular free flaps, enable advanced reconstruction of the tumor site. These have created cosmetically acceptable end points [8]. Similarly, radiation has been altered by intensity modulation, allowing critical normal tissues such as the salivary glands to be conformally avoided [9]. This has created the potential for radiation treatment that is significantly less morbid.

Perhaps the greatest shift in the management of head and neck cancer has been the widespread acceptance that organ and functional sparing therapy can be curative. This began with the landmark 1980s Department of Veteran Affairs (VA) studies [10] showing that even for very advanced larynx cancer, the combination of radiation and chemotherapy allow for retention of a viable voice and swallowing without significant compromise in long term survival. Recent work involving function preservation by more advanced surgical and radiation techniques have not contradicted this landmark finding [11].

Of particular relevance is the fact that 10—20% of head and neck cancer patients will develop a second malignancy [12]. Once a patient has undergone a major oncological head and neck surgery or full dose of radiation, the ability to offer further meaningful therapy by these modalities is very limited. Similarly, patients who locally recur after combined surgery and radiation have few salvage options to regain local disease control. Consider too patients with very early in situ disease which in many cases is multi-focal due to condemned mucosa or field cancerization [13]. Standard surgery and/or radiation are very morbid and may not be curative. Additional local intervention for disease progression or a second primary may be an extremely difficult position for these patients.

Photodynamic therapy (PDT) then could be an ideal option in the management of head and neck tumors. PDT has shown success on a wide variety of lesions including both primary and recurrent tumors [14]. Notably, PDT has had good response

and healing even in surgical and high dose radiation beds [15]. A great advantage of PDT is its ability to spare function in addition to the technique's minimal normal tissue toxicity. As the treatment can often be done in an outpatient setting without the need for extraordinarily expensive devices, PDT may also have a particularly useful role promoting organ sparing treatment in developing countries [16]. It should be emphasized that organ sparing surgery and radiation require state of the art operating rooms, surgical devices, linear accelerators and support staff. These items may be readily available in large cities, but overall are relatively sparse in the world. When one considers that over 300,000 patients [17] are diagnosed with head and neck cancer annually with only a minimal percent able to undergo organ sparing therapy, the extent of the problem becomes evident. PDT, even delivered in relatively primitive conditions, may be one solution to improve patient lives.

This paper will outline the clinical results of PDT for head and neck patients as published in the peer-reviewed literature. We will highlight the potential benefits and consequences of this therapy and its evolving role for this particular family of cancers.

PDT

PDT is the culmination of literally thousands of years of observations on the interaction of light with matter. Only in the last 100 years though have these observations been rigorously tested and modified to create a reproducible treatment technique [18].

While the basic science of PDT is still in its infancy, it is clear that as currently practiced, the generation of singlet oxygen which is cytotoxic and vasculotoxic is the key to therapeutic success [19]. Fundamentally, a photosensitizing agent interacts with light to create the oxygen mediated photodynamic reaction. This reaction may initiate apoptosis, cell death and vascular shutdown leading to clinical tumor control [20]. In addition, regional and systemic immune interactions may occur, improving outcomes but also potentially increasing morbidity. Controlling or modifying the photodynamic reaction is the basis of the art and science of clinical PDT.

While thousands of compounds are inherent photosensitizing agents [21], only a handful have been found to be clinically successful and nontoxic. A particularly potent family includes dyes such as those used in ink. In fact, an eosin dye was highly successful in the early 1900s for the treatment of extensive cutaneous head and neck tumors [22]. Subsequently, porphyrins were found to be clini-cally useful particularly by intravenous introduction which allowed for the treatment of deep seated lesions [23]. Most recently, chlorophyll based sensitizers have shown outstanding potential [24].

All sensitizers used in the clinic share some common characteristics. They should be relatively nontoxic, easy to formulate, reliably create a photodynamic reaction, accumulate preferentially in malignancy or neo-vascularity and most importantly, be available for use. Many outstanding photosensitizers are not available commercially. Also, it is critically important for clinicians to understand that each photosensitizer has its own clinical characteristics and cannot be readily interchanged, and each has its own clinical learning curve.

As PDT's name implies, the photosensitizer must be activated by light. Each sensitizer has a particular wavelength of optimal activation [25]. In general red light (wavelength 630 nm) activation is an important characteristic of sensitizers as red light travels through tissue to about 1 cm. This allows for a clinically useful depth of treatment. Other sensitizers will activate at blue light (~400 nm) which allows for 1−2 mm of tissue penetration which may be useful for surface treatment. Newer sensitizers activate at longer wavelengths to allow deeper penetration, a clinical benefit in some situations. But too great a depth of light penetration may in fact increase morbidity by injuring deep seated tissues and inducing vasculature damage at depth. The clinically useful range of photosensitization is actually very limited because of the absorption of light by water and blood, so longer wavelengths may not allow for successful PDT.

Generating the wavelength necessary to activate a sensitizer can be as simple as the use of a strong light bulb with proper filtering, but for head and neck treatment highly precise wavelengths, in combination with optical fibers which aim the light at the anatomical site requiring PDT, are commonly used [26]. The light source is usually a laser to generate the appropriate wavelength and intensity. Recently, light emitting diodes (LED) devices have been developed [25]. The latter have a distinct advantage in lower costs and maintenance needs as well as being compact and mobile. This has direct implications world wide as the light source is often the most expensive component of PDT. These small reliable devices will allow PDT to be spread to many communities. Ultimately, the light activates the sensitizer to create the photodynamic reaction [27].

Clinically, the photosensitizer is generally intravenously injected and allowed to accumulate preferentially in the malignant region and to a lesser extent in the normal tissue [28]. Alternately, the

Table 1 Commonly used photosensitizers in head and neck PDT.

Drug	Dose (mg/kg)	Light (J/cm^2)	DLI (h)	Wavelength (nm)	Photosensitivity (days)
Photofrin®	2.0	80	48	630	28
Foscan®	0.15	20	96	652	14
ALA	30—60[a]	80	6	630	1

These parameters are open to optimization (see text for details).

[a] Also used as a topical cream with 10—20% ALA, with only local photosensitivity.

sensitizer may be topically applied. With currently available sensitizers intravenous injection allows for reliable accumulation into even deep seated lesions while topical applications penetrates to only 1—2 mm. Each sensitizer has its own appropriate time frame needed for accumulation/clearing to occur prior to activation by illumination.

The commercially available photosensitizers currently in use for head and neck treatments are Photofrin®, aminolevulinic acid (ALA) and Foscan®. These photosensitizers main characteristics are summarized in Table 1. Photofrin® [29], the first generation sensitizer is a mixture of porphyrins. This sensitizer has been employed in several thousand patients since becoming commercially available in the 1980s. Several similar sounding sensitizers, i.e. Photosan, which are similar but not necessarily identical in structure and activity to Photofrin® are available. These drugs have multiple wavelengths of activation from 400 to 630 nm. Photofrin® also accumulates and is retained in normal tissue, such as the skin for at least four weeks post infusion. In general, 2 mg/kg is infused and illumination occurs around 48 h to allow the drug to clear from normal tissue.

ALA [30] is also a member of the porphyrin family. This is actually a pro drug that is metabolized to protoporphyrin IX, which is a potent photosensitizer. ALA has similar activation bands to Photofrin® from 400 to 630 nm. When formulated as a topical cream of 10—20%, it is highly selective in terms of photoactivation to only the applied area. ALA can also be formulated for oral or intravenous use at 30—60 mg/kg. This creates generalized photosensitivity to the entire body, particularly the skin, for about 48—72 h. When introduced systemically, liver enzyme elevation is common. In most cases, illumination occurs at 6 h post application as this is its peak of accumulation in malignant tissue.

Foscan® [31] is a synthetic second generation sensitizer with numerous characteristics that have brought it to the forefront of clinical PDT. The drug is very highly active. The activation is done at 652 nm and the treatment time is measured in seconds. It also activates at blue and green light wavelengths so more superficial treatment is read-

ily available. The drug itself is infused at very low doses. Currently, 0.15 mg/kg is the standard with illumination at about 96 h. Interestingly, this sensitizer is so potent that it needs little light to become active. For the first 24—48 h post infusion, patients must remain in very dim lighting (60 W bulb) as they can experience a photosensitivity reaction. Photosensitivity precautions must remain in place for at least two weeks, though not as severely as for the first 48 h.

Intensity of light is also a very critical consideration as this in many ways clinically controls the intensity of PDT. The choice of light intensity, is a key component of successful PDT versus morbid PDT and requires the practitioner to have a good handle on this parameter [32].

Complicating matters are the important interactions of drug dose, light dose and drug infusion to illumination interval (DLI). With too little photosensitizer, no PDT will occur. With too much photosensitizer, all tissues will react as so much drug is in all tissues that selectivity is lost. Too little light will create an ineffective treatment, while too much light will damage normal tissue. Too short a DLI will not allow for accumulation/clearance differences in tumor versus normal tissue and give a non-selective reaction. Too long a DLI will allow enough sensitizer to clear from tumor to prevent successful PDT. While drug dose, light dose and DLI guidelines are available for head and neck treatment with the currently available sensitizers, the clinical reports reviewed in later sections, clearly show very disparate outcomes. It is clear that these three parameters have in no way been perfected to create a standard for treatment. Until this occurs, PDT will remain more art than science.

PD

An alternate pathway for photosensitizer activation is fluorescence [33]. Here, in excited singlet states, the electron in the excited orbital is paired to the second electron in the ground state orbital. When the electron returns rapidly to the ground state it emits a photon. This is referred to fluorescence

[34]. Clinically, fluorescence occurs to a greater extent where the photosensitizer accumulates. The tumor bed will literally light up to assist in location and demarcation. Fluorescence may also occur with inherent chromophores as well as by introduction of a photosensitizer [35]. Theoretically, the change in fluorescence pre and post PDT may allow for predicting treatment success or the need for further intervention and could form the basis of PDT dosimetry [36]. Another important application would be to use fluorescence as a means of optical biopsy [37,38] as the characteristics of fluorescence appear to be different in benign versus malignant tissue. Broadly, this is termed photodiagnosis (PD) [39]. In some cases this could save patients the need for histological evaluation.

Anatomical considerations

Cancers of the head and neck can arise from more than 25 distinct anatomical sites [3]. Based on embryology, each subsite has its own characteristic oncological behavior and specific draining lymphatic system. The propensity for lymphatic metastasis is highly variable but predictable. This has direct implications for cancer treatment in general and PDT in particular. For example, even fairly large invasive lesions of the true vocal cord rarely have lymphatic metastasis, whereas early cancers of the nasopharynx and base of tongue often spread to the lymphatics system in the course of their development. This means that a local treatment to the vocal cord alone, such as PDT, can be curative while a local treatment to the nasopharynx alone will allow failure in the neck nodes. Similarly, very early and in situ cancers which in general have low risk of nodal spread may be ablated just by treatment to the primary site, while the same treatment to advanced lesions will ultimately lead to failure from lymphatic metastasis. Since PDT is only able to treat what is illuminated, and so far PDT has had limited success in the treatment of the neck, the selection of patients for curative PDT is critical. It does the patient little benefit to control the primary tumor only to have disease spread and grow regionally in the neck. However, for patients with low risk of nodal disease, PDT may be a great benefit as a single modality treatment of choice.

Technical considerations

When undertaking PDT for patients with head and neck cancer a definite treatment goal should be designed. As only the illuminated region will be treated the clinician should be reasonably sure that the tumor has not spread beyond the illumination field. Often complete head and neck exams including endoscopy, CT, PET and MRI scans can help define the treatment field. It needs to be emphasized again, that PDT has not yet been shown to treat subclinical disease in the neck. In many cases, head and neck cancers have a propensity for neck metastasis. In individuals at risk, the neck should be addressed preferentially by neck dissection or radiation. Observation may be considered in select individuals. If surgery or radiation is required possibly this patient is not an ideal candidate for PDT and the primary tumor should be treated by the same modality as the neck. However, in some instances PDT may be less morbid a treatment approach to the primary tumors over surgery and/or radiation. In these cases surgery/radiation could address the neck. This determination should be made on a case by case basis.

PDT may also be employed to improve disease control at the margins of resection or as palliation for advanced lesions that have failed prior treatment. A potentially important role for PDT is in in situ disease where surgery or radiation is often morbid with resulting functional loss. PDT in this situation has great potential as it does not prevent future surgery or radiation but rather may be the least morbid initial treatment to this group of patients.

For all patients considered for PDT, the initial important question to be answered is: will the patient follow sunlight precautions. As photosensitizers will accumulate in all tissues, including skin, unintended and potentially high morbidity can occur with sunlight exposure. If the patient will not follow sunlight precautions, even the best treatment will be ruined by the morbidity associated with light exposure. No patient should be infused with photosensitizer who will not follow this critically important precaution.

For potential candidates, the next important question is: will the PDT treatment compromise the airway. PDT is generally associated with some post treatment swelling. This can be critically important if it compromises the airway. If the tongue is treated, airway compromise is guaranteed. Crucially, reflected light may also cause tongue swelling requiring a temporary tracheotomy. In this case, PDT would be a poor choice over other types of therapy.

A critical component to PDT is illuminating the region at risk and avoiding areas not needing therapy. Light reflects off many surfaces, particularly mucosa and saliva. In the oral cavity and pharynx reflected light can be of significant consequence

and morbidity. Every effort needs to be made to physically block light where it is not needed. This can be done mechanically by gauze with aluminum foil or other opaque material. These blocking agents should not block the light from entering the treatment field, creating a technical failure.

Illuminating the tumor bed homogeneously is also a critical aspect for successful treatment. Over illumination can be morbid and under illumination leads to treatment failure. As an illumination field can take more than 20 min with some sensitizers, patient motion or motion of the light source can be a significant source of treatment error and must be monitored closely. Angulation of the light will result in inhomogeneous treatment. Irregular surfaces will cause shadowing, also leading to therapy compromise. Clearly, a great deal of preparation and thought must be given prior to treatment. In some cases, these technical difficulties will even prevent an ideal tumor from receiving proper treatment. The importance of clinical judgment cannot be overemphasized.

Post PDT medical management is also important. Treatment reactions generally arise and depart quickly. Most patients will benefit from a short course of post PDT pain control, steroids and antibiotics. In general, narcotic type analgesics will be needed for 1—2 weeks and we recommend a week of steroids and antibiotics. Some patients with extensive disease or swelling post treatment may require temporary enteral feeds and hydration. Maintaining a patent airway in these individuals cannot be stressed enough. An ounce of prevention is preferable to a pound of cure.

The patients who are exposed to sunlight should have treatment as if it were any other burn. Pain control, steroids, antibiotics and hydration are the mainstay of treatment, and as little manipulation of the burned tissue as possible will result in the fastest healing.

Dosimetry

Dosimetry is critical for PDT in general and head and neck treatment in particular. Ideally, dosimetry would allow the practitioner to illuminate the region at risk and destroy the tumor without injury to surrounding normal tissue. Unfortunately, PDT dosimetry remains limited [40]. Currently dosimetric variables are generally limited to drug dose, light dose and DLI. This is crude and explains the difficulty in obtaining reliable and reproducible results. Realistically, dosimetry needs to include the feedback of these interactions with tissue in a real time fashion. This would ensure appropri-ate treatment to the tumor and warn of impending morbidity to normal tissue. Until accurate dosimetry is available head and neck PDT will be held back. As an example, Tan et al. [41] reviewed in situ light dosimetry for oral cavity tumors. These investigators showed that these interactions were extremely complex and that light behaves differently in many individuals. This has real and important consequences for clinical treatment. However, until dosimetry is improved, clinicians can exploit photobleaching kinetics. Here one uses the fact that more photosensitizer is in the malignant region than in the benign anatomy. Theoretically, by using the absolutely minimal amount of drug, clinically significant PDT should still occur in the tumor but not in normal tissue that has less sensitizer. This will exploit the sensitizer's ability to seek out the abnormal tissue. The key is to find the minimal amount of drug, the appropriate fluence and DLI. This requires clinical trials. In the skin, Photofrin® has been examined with a wide variety of parameters. Interestingly, 0.8 mg/kg offers very select response and spares normal tissues [15,42]. Foscan® has been examined less rigorously, but 0.1 mg/kg appears to improve selectively as well [43]. This needs to be explored further.

Historical review

Despite all these technical concerns, PD and PDT have been highly successful for head and neck cancers. In the early 1900s very advanced lesions of the face and oral cavity were controlled by dye based PDT activated by very primitive but powerful light sources. Little came of these initial efforts. PD/PDT re-emerged in the 1960s with the introduction of the hematoporphyrin derivative (HpD) [44]. HpD was initially used extensively for photo detection of lesions [45] and ultimately for PDT [46]. Even though results were promising, it was not until Dougherty's [47] development of Photofrin® in the late 1970s that PD and PDT re-emerged as a powerful tool for cancer detection and treatment. By the mid 1980s several studies revealed the potential for Photofrin® based head and neck PDT, but results were hampered by technical difficulties in illumination and difficulties in assessing optimal drug and light doses.

Photofrin® (and derivatives)

As this family of sensitizers has been available for clinical use over the longest time frame, it serves several masters: first, as the learning curve in which

technique and patient selection are practiced; second, as the role model for future studies that aim to enhance response; third, sadly, as the punching bag to show supposed superiority of current second generation sensitizers.

Among the first uses of hematoporphyrins was to aid in detection of malignancy. This is a proven benefit of these sensitizers. In the head and neck, porphyrins can fluoresce and aid in malignancy detection. Unfortunately, many other tissues as well as saliva can fluoresce making PD an unfulfilled promise. The same difficulties encountered in early reports in the 1980s [48] were still seen a decade later [49]. With improved tools one can only hope that PD will become a clinical reality rather than an experimental tool.

A particularly interesting finding from Braichotte et al. [49] is that Photofrin®'s maximum selectivity for head and neck patients may well be 1—2 h post infusion for both PD and PDT. At 48—72 h post infusion selectively between normal tissue and tumor is significantly diminished. This underappreciated finding should be evaluated and tested in clinical trials. With few exceptions, all the following studies, as summarized in Table 2, employed Photofrin® at 2 mg/kg and illumination at 48 h. Light dose, generally by surface microlens was the major variable in treatment and not always specified. Morbidity appeared minimal and generally consisted of moderate site pain for several days which was controlled by oral analgesics. Very few cases of photosensitivity exposure were reported. As this morbidity is sometimes subjective, caution is advised in interpreting this aspect of the results. No permanent fistula or carotid blowout was reported.

What was noted in early studies was the potential for unexpected clinical success in certain bulky lesions and the usual good outcome in small superficial cancers [48,50]. Edge and Carruth [51] were also able to show both PD and PDT success on select individuals. All these authors noted technical limitations and had thoughtful suggestions for improvements. During the same time frame of the late 1980s, Wenig et al. [52] showed excellent response in 26 patients undergoing PDT mainly for other treatment therapy failures. In this report, patients with local failure who had lesions amenable for illumination were treated with light doses of 75—125 J/cm^2. Histological complete response was possible for 77% of patients with follow up to 4 years. Morbidity and photosensitivity reactions were minimal.

Grossweiner et al. [53] treated nine patients with local recurrence in the oral cavity who failed surgery or radiation. In this study, illumination occurred 24 h post Photofrin® infusion. Eight of nine patients achieved complete response with minimal morbidity reported. In a study of 32 patients with T$_1$ true vocal cord cancers, Freche and De Corbiere [54] were able to achieve a complete response in 25 patients. Most patients were treated with Photofrin® though several were illuminated post HpD infusion. In an interesting report, Zhao et al. [46] treated 100 patients with true squamous cell cancer of the lip. Most patients had HpD infusion in the early part of this study. Overall, all lesions were controlled with excellent function and cosmesis retained. Schweitzer [55,56] summarizing her own results, reported 16 of 20 patients achieving complete response, though several PDT sessions were sometimes required. Patients included had treatment failures from surgery and radiation as well as patients with ''condemned mucosa'' or field cancerization. Notably, patients with larynx cancer lesions also responded extremely well with voice preservation. Illumination for larynx cancer was with 80 J/cm^2 while other lesions were usually treated between 50 and 150 J/cm^2.

Summarizing these early studies, Gluckman [57] lamented on the relative lack of multi-institutional reports and the heavy reliance on case reports and individual researcher's experience. Now, nearly 25 years later, this same charge can still be made. Additionally, Gluckman [57] reported tantalizingly excellent results on select patients in his relatively large series of 45 individuals. Early larynx, oral cavity and pharynx lesions generally were controlled. Locally advanced disease generally failed.

Grant et al. [58] published on field cancerization of the oral cavity. Eleven patients were infused at 2 mg/kg of Photofrin® and illuminated at 48 h with 50—100 J/cm^2. A total of 10 patients received complete response with prolonged followup.

In a series reported by Feyh [59,60], 20 patients with either early stage oral cavity or true larynx cancer underwent PDT. Photosan was delivered intravenous at 2 mg/kg. After 48 h, illumination occurred with 100 J/cm^2. A microlens was used in the oral cavity and a diffuser in the larynx. Overall, PDT eliminated disease in 90% of patients. With surgical salvage, this improved to 100%. In addition, 24 patients, adult and children, with laryngeal papillomatosis underwent PDT with the same parameters. A total of 60% of patients achieved prolonged complete response. Voice preservation was reported as excellent. Ofner et al. [61], also employing Photosan at 2.5 mg/kg, found palliation for select patients with advanced disease.

Kulapaditharom and Boonkitticharoen [62—64] treated 41 patients with in situ or early stage oral cancer and pharynx cancers. Included were a select group of early nasopharynx lesions in which local

Table 2 Summary of Photofrin® and derivatives PDT for head and neck squamous cell cancer.

Study	Location	Stage	Patient number	Complete response	Morbidity	Photosentizer
Keller et al. [48]	Oral cavity	T_1/T_2	3	100		HpD/Photofrin®
	Neck	Bulky	5	0		
Schuller et al. [50]	Oral cavity/pharynx	Localized recurrence	2	100		HpD/Photofrin®
		Bulky recurrence	22	0		
Edge and Carruth [51]	Oral cavity/pharynx	Recurrent	5	40		HpD/Photofrin®
Wenig et al. [52]	Oral cavity/pharynx	Local recurrence	26	77		Photofrin®
Grossweiner et al. [53]	Oral cavity	Local recurrence	9	89		Photofrin®
Zhao et al. [46]	Lip	T_1/T_2	50	100		HpD/Photofrin®
Freche and De Corbiere [54]	Larynx	T_1	32	78		HpD/Photofrin®
Gluckman [57]	Oral cavity larynx	T_1	15	87	PS	HpD/Photofrin®
	Condemned mucosa	T_{IS}	8	88		
	Various	Bulky	18	20		
Schweitzer [55,56,70]	Oral cavity	T_1	10	80		Photofrin®
	Larynx	T_2	10	80		
Grant [58]	Oral cavity	T_{IS}/T_1	11	92		Photofrin®
Feyh [59,60]	Oral cavity	T_1/T_2	8	85		Photosan
	Larynx	T_{IS}/T_1	12	92		
Ofner et al. [61]	Various	Recurrent	4	50		Photosan
Kulapaditharom and Boonkit-ticharoen [62—64]	Oral cavity/pharynx	$T_{IS}/T_1/T_2$	41	73		HpD/Photofrin®
Biel [14,68,69]	Larynx	T_1	103	89	PS (2 cases)	Photofrin®
	Oral cavity/pharynx	T_1/T_2	178	92		
	Various	Advanced	24	50		
	Various	Intraoperative	17	65		
Allison et al. [71]	Oral cavity/larynx	T_{IS}	12	100	PS	Photofrin®

PS: Photosensitivity reaction requiring treatment.

control was achieved in T_1 cancers. A complete response post PDT for patients with localized disease was 92%. However, overall a 25% failure rate was reported.

The largest series of head and neck patients treated with Photofrin® based PDT has been reported by Biel [14,65−69]. In several well-written and elegant reports on a cumulative series of 330 patients, patient selection and treatment parameters have been rigorously explored. Uniformly, treatment related pain and photosensitivity were relatively rare (two cases). A major finding is the highly successful treatment of early true larynx cancer with Photofrin® PDT. A nearly 90% complete response rate can be obtained, even for patients who failed initial treatment (usually radiation). This series includes in situ, T_1 and recurrent disease. In general, 2 mg/kg Photofrin® was infused with microlens illumination with 80 J/cm^2 at DLI of 48 h. Followup was beyond 2 years and no photosensitivity morbidity was reported. Critically important was the excellent level of voice preservation. This outstanding treatment and results need to be brought to a multicenter trial to allow this voice preservation option to be available to a larger community of patients.

Biel [14] also found outstanding results with similar treatment parameters for early oral cavity lesions. These were T_1 and T_2 lesions. Illumination was usually with 50−75 J/cm^2. A 2 year complete response of 92% was reported. More advanced lesions can respond but overall, failure was high. In this setting, despite surface and interstitial implantation and good initial response, 50% of patients ultimately failed local-regionally. Interstitial illumination was at 100 J/cm.

A particularly important report was on patients who had PDT as an adjunct to surgery [14]. Here individuals with recurrent disease who had failed surgery, radiation and chemotherapy underwent maximal resection of the recurrent tumor with intraoperative PDT. Two days prior to surgery, 2 mg/kg of Photofrin® was infused and at surgery, after resection, microlens illumination to the entire surgical bed was accomplished with 50 J/cm^2. At this drug, light and DLI, no wound healing difficulties occurred and high local control rates were reported for 17 patients with only six regional failures.

Schweitzer [70] also employed Photofrin® PDT for intraoperative treatment of aggressive recurrent head and neck tumors. Infusing 1 mg/kg with surface illumination during surgery at 48 h produced excellent local control rates. Despite light doses of 200 J/cm^2 no wound healing difficulties were seen.

All patients remained locally NED throughout follow up.

Our group has explored low dose Photofrin® for head and neck treatment [71]. Our preliminary series of 12 patients reveals that 1.2 mg/kg of Photofrin® can achieve excellent response. Many of the patients reported here had diffuse lesions in which illumination overlap was likely. With 1.2 mg/kg illumination overlap did not cause increased morbidity and this drug dose offered highly selective treatment response. This was particularly impressive as all patients had failed prior surgery or radiation. This again shows the need to further explore optimal treatment parameters.

In a feasibility study, Tanaka et al. [72] reported on the treatment of tongue cancer with interstitial illumination. Photofrin® at 2 mg/kg was infused and 48 h later intraoperative illumination occurred. Tumor necrosis of 2.4 cm beyond the illumination fiber was seen. This reveals the ability to clinically treat beyond the predicted depth of light penetration.

Photofrin® while approved for esophageal and pulmonary indications in the US is not yet FDA approved for head and neck treatment in the US or anywhere in the world.

ALA

The pro drug ALA may be formulated for topical application, oral or intravenous administration. The topical form has selectivity for photosensitivity to the applied area. In its other formulations, systemic photosensitivity is an issue. ALA has played a great role in PD for many organ systems [73]. In head and neck, some difficulties have arisen from mucosal reflectance and inflammation.

Therapeutic reports are sparse but revealing. Grant et al. [74], using oral ALA, found that this sensitizer may have a role for superficial lesions. In this series, 30−60 mg/kg of ALA was orally ingested. Patients were kept in a semi-darkened room for 4−6 h. The lesions were then illuminated with 50−100 J/cm^2. All three patients had surface necrosis within the light fields. Selectivity was minimal, and all patients reported pain during treatment. Fan et al. [75] continuing the study, reported on 18 patients. Here 60 mg/kg of ALA was administered orally. Illumination with 100 or 200 J/cm^2 followed. Patients were photosensitive for about 48 h. Maximum necrosis was only 1.3 mm, but usually less. All 12 patients with dysplasia responded, but complete response was rare. Patients with more extensive squamous cell disease did less well. The authors found ALA not satisfactory for invasive dis-

ease, but had a role for dysplasia. Sieron et al. [76] also reported on ALA PDT. Five patients with dysplasia had 10% ALA cream applied locally. Illumination with 200 J/cm^2 occurred 4—5 h post ALA application. Up to five weekly sessions were undertaken. All patients experienced burning and pain in the illumination field. Narcotic analgesia was required to complete therapy. Four of five patients had clinical complete response. The patient who failed was salvaged by additional PDT. ALA was also given orally, 3 g in three equal fractions prior to PDT in five patients with invasive cancer. All required narcotic analgesia to complete PDT. Post treatment edema occurred in all patients showing the potential need to guard the airway. Only one patient had prolonged response.

ALA is FDA approved for actinic keratosis but not for head and neck cancers.

Foscan®

Treatment outcomes for head and neck patients with Foscan® appeared in the peer-reviewed literature beginning in the mid 1990s. Many of these authors had experience with Photofrin® based head and neck treatment and applied this knowledge to try to improve outcomes and minimize toxicity with this second generation sensitizer. Unfortunately, as summarized in Table 3 most reports do not appear to support these conclusions. Poate et al. [77] reported on Foscan® mediated PDT treatment for a solitary soft palate lesion for which the patient refused surgery. With 20 J/cm^2 of illumination, significant pain and edema resulted requiring a 3-day hospital stay. Substantial analgesics were required and healing took 2 months. However, the patient was rendered disease free. Similarly, Dilkes et al. [78—80] reported on 22 additional patients with a wide variety of head and neck lesions. Seven had failed radiation and surgery and six had primary T_1/T_2 lesions. Seven had PDT as an adjunct to surgery and two underwent multiple PDT. Drug dose was 0.15 mg/kg (0.3 mg/kg in two cases) and 20 J/cm^2 illumination with DLI of 96 h. All patients had treatment related pain that required analgesia for about 2 weeks. Three patients had sunlight photosensitivity morbidity. Four of six primary

Table 3 Summary of Foscan® PDT for head and neck squamous cell cancer.

Study	Location	Stage	Patient number	Complete response	Morbidity
Grosjean et al. [82]	Oral cavity	T_{IS}	5	100	PS
Fan et al. [84]	Oral cavity	$T_{IS}/T_1/T_2$	5	80	PS, S, P
		T_3/T_4	7	57	
		Diffuse	14	64	
Kubler et al. [43,85]	Lip	$T_{IS}/T_1/T_2$	25	92	PS, P
Cooper et al. [5,86]	Oral cavity/oropharynx	T_1	22	95	PS, P
		T_2	7	57	
Hopper et al. [87,92]	Oral cavity/pharynx/lip	T_{IS}/T_1	95	93	PS, P, S
		T_2	19	58	
Tan et al. [41,88]	Oral cavity	Second primary/local recurrence	96	58	PS
		Local recurrence < 2 cm	41	89	
		Local recurrence > 2 cm		29	
D'Cruz et al. [89]	Oral cavity/pharynx	All recurrence	99	16	PS, P
		Limited recurrence	37	30	
Lou et al. [90]	Various	Recurrent	39	20	PS, CB
	Neck	Recurrent	6	0	
Suhr et al. [91]	Various	Recurrent	12	50	PS, CB
Dilkes et al. [80,81]	Larynx	T_1/T_2	4	25	PS, P, CB, F
	Oral cavity/pharynx	T_1/T_2	15	93	
	Oral cavity/pharynx	T_3	5	40	
		Palliative	7	29	
	Oral cavity/pharynx/neck	Adjuvant therapy	7	43	

PS: Photosensitivity requiring treatment, P: pain beyond 2—4 weeks, S: scar, CB: carotid blowout, F: fistula.

T_1/T_2 tumors had complete response. None of the surgery/radiation failures had prolonged salvage by PDT. Of the seven patients with PDT used as an adjunct to surgery all had initial response but none appeared to have prolonged disease control and one suffered a carotid blowout.

In an update on 25 cases of squamous cell carcinoma treated by Foscan®, Dilkes et al. [81] again showed promising results. Infusing 0.15 mg/kg and activating at 96 h with 20 J/cm^2, this study reported post treatment pain generally peaking at 48 h but potentially extending to two weeks. In addition, most patients were treated under general anesthesia. Normal tissue shielding was always undertaken. One patient experienced severe sunlight photosensitivity and two others had less severe reactions. Of four patients with true larynx cancers, three failed PDT. Ten patients with oral cavity lesions underwent PDT with seven achieving complete response, though two additional patients failed in the neck. Six patients with oropharynx cancer achieved complete response, but one subsequently failed in the neck. Overall, except for true larynx cancers, 93% of T_1/T_2 lesions achieved complete response. T_3 lesions generally failed and also more often than not, developed severe morbidity. Of note, two of these patients developed fistulas post PDT.

Grosjean et al. [82] and Savary et al. [83] treated patients with in situ or micro invasive squamous cell carcinomas including the head and neck with Foscan®. Intravenous injection of 0.15 mg/kg with 8—12 J/cm^2 illumination occurred at 96 h. All five oral lesions had complete response. Nearly half the patients in this study had a photosensitivity reaction. The one patient in this report with invasive tongue cancer failed despite interstitial illumination. With additional evaluation, the authors felt that an ideal drug dose was 0.15 mg/kg with illumination at 96 h; however, they also found sunlight photosensitivity 6 weeks post infusion.

Fan et al. [84] reported on 20 patients with squamous cell carcinoma or dysplasia of the oral cavity. A total of 0.15 mg/kg of Foscan® was infused generally 96 h prior to illumination via micro lens. Light dose varied from 5 to 20 J/cm^2 and illumination overlap was allowed. Twenty-eight lesions were treated in 26 sessions. Four patients had multiple PDT sessions usually due to partial response. Significant treatment pain occurred in three patients and all patients had ulceration of their illumination beds. All patients required opioid analgesia for at least 1—2 weeks post therapy. Notably, five patients had scarring in the treatment field. Scattered and reflected light were causes of normal tissue damage outside the treatment field requiring extremely careful shielding. One quarter of patients also had sunlight photosensitivity morbidity. The 12 patients with isolated disease responded well. A dose of 5 J/cm^2 eliminated dysplasia, T_1 and T_2 lesions in four of five lesions, while 20 J/cm^2 appeared to locally control T_3/T_4 cancers in four of seven lesions. The eight patients with field cancerization did less well. Five J/cm^2 offered poor control to dysplasia, T_1 and T_2 lesions as did 10 J/cm^2. It appeared that 20 J/cm^2 was necessary for these lesions. Notably, two of three diffuse T_2 lesions cleared with 5 J/cm^2. Also, many patients in this series required re-treatment at higher light doses due to local failure. Likely, the larger lesions also had multiple illumination fields offering a cumulative higher light dose or a better chance of accurate targeting. What is particularly noteworthy is that at even low light dose, no selectively was seen in the illuminated region between normal tissue and tumor. Further, a number of patients failed in the neck and distantly showing again the need for caution when selecting patients for PDT.

Kubler et al. [85] reported on therapy to lip cancers for in situ, T_1 and select T_2 lesions. Foscan® at 0.15 mg/kg was infused and illumination at 96 h was initiated with 20 J/cm^2. Biopsy proven complete response was initially seen in 24 of 25 patients. Most patients had significant swelling and pain at the treatment site. Despite biopsy proven complete response, two patients experienced local failure and one additional patient failed in the neck. One quarter of patients had clinically significant photosensitivity reaction. The authors felt that cosmesis ultimately was better than for an equivalent surgical excision.

Similarly, Copper et al. [86] published on Foscan® mediated PDT for oral cavity and oropharynx squamous cell lesions. In this study, 25 patients with T_1 or T_2, node negative tumors, were infused at 0.15 mg/kg and illuminated at 96 h with 20 J/cm^2. Treatment took place under general anesthesia and appropriate shielding. Patients remained hospitalized from the time of infusion to 3 days post therapy (7 days total) under subdued lighting conditions. Despite this, a patient experienced significant sunlight morbidity. Pain was also significant for several days post therapy. One patient required temporary nasogastric tube due to swallowing difficulties. Of all T_1 lesions 95% achieved a complete response, while only 57% of T_2 lesions achieved complete response. Five patients developed nodal metastasis requiring neck dissection. Ultimately, all patients were successfully salvaged by surgery and/or radiation. Functional outcome post PDT was described as excellent.

In a large multicenter study of Foscan® for early oral squamous cell cancer, Hopper et al. [87]

reported excellent results. To be eligible, patients had to have a solitary biopsy proven lesion less than 2.5 cm in diameter and less than 0.5 cm in depth. No nodal or systemic metastasis was allowed. Foscan® was delivered at 0.15 mg/kg and 96 h later 20 J/cm² was used to illuminate the lesion by microlens. Most illuminations were done under local anesthesia, but all patients were hospitalized overnight following treatment. One hundred and twenty one patients were enrolled, but only 114 were included in the study due to protocol violations. Over 80% of patients had significant post treatment pain for up to 2 weeks. Thirteen percent experienced a sunlight photosensitivity reaction. One patient required skin grafting due to light induced burn. One patient had mouth necrosis following PDT requiring extensive surgery. Notably, no selectivity was seen in the illumination field. Overall, a 93% complete response was found for T_1 lesions and a 58% complete response was found for T_2 lesions. In general, this was done by clinical assessment and not biopsy proven. It should also be noted that most patients had floor of mouth, lip and anterior tongue lesions. Relatively few others sites were included. It is also noteworthy that no patient required airway management or enteral feeding and all patients maintained an excellent functional status post PDT. It would appear that for T_1 lesions of certain oral cavity locations, local treatment with PDT and observation of the neck is an acceptable treatment option.

A sister trial enrolled patients with second primary tumors or localized recurrences that had failed initial treatment. Reporting on 96 patients, Tan [88] published a 58% complete response rate. In a subset of 41 patients, those with lesions less than 2 cm had a complete response rate of 89%. Those with lesions greater than 2 cm had a 29% complete response rate. Photosensitivity was the major morbidity reported.

Another larger multicenter trial was reported by D'Cruz et al. [89]. Foscan® was infused at 0.15 mg/kg and after 96 h, illumination with 20 J/cm² was undertaken. In this 126 patient study, inclusion criteria were incurable or recurrent disease. Most lesions were tongue, buccal mucosa, gum and floor of mouth. Fifteen patients had multiple lesions. About 16% of patients achieved a complete response. Better response was seen with lesions having 10 mm invasion and those lesions amenable for full illumination where a 30% complete response was reported. However, about two of three patients demonstrated significant improvement in quality of life. Also, 20% of patients had significant phototoxicity requiring some form of intervention and 20% had significant treatment related pain. The authors felt this group of individuals who

had exhausted surgery and radiation could benefit from salvage PDT to assist in relieving local signs and symptoms of disease.

The bulk of the prior studies relied on surface illumination which allows only limited light penetration. It is no coincidence that in D'Cruz et al.'s study 10 mm of tumor invasion was a significant factor as this likely is the limit of Foscan® penetration when 20 J/cm² or less are employed. An alternative treatment paradigm would include interstitial illumination of the lesion from the inside out. This would be accomplished in a manner similar to brachytherapy. In a study by Lou et al. [90], interstitial implantation of optical fiber were undertaken in 45 patients who failed or were unsuitable for surgery, radiotherapy and/or chemotherapy. As a ''last hope'' salvage, patients were infused at 0.15 mg/kg and illuminated at 96 h with 20 J/cm. The optical fibers were implanted via image guidance using ultrasound, CT or MRI. A total of 67 treatments took place. Thirty patients had one PDT session and the remaining had up to 5. A complete response was seen in 20% of cases. Seven patients were felt to be of curative potential due to small recurrence and four of these patients were rendered disease free. Thirty-eight patients had extensive local recurrence and only four of these patients were rendered disease free. Despite neck PDT no patient with bulk neck nodes had permanent complete response in the neck. Subjective benefit was seen in 18 cases, but no patient regained the ability to swallow. One patient had significant sunlight photosensitivity and a 33-year old female died due to carotid blowout. Of particular note, several patients with sarcomas of the head and neck responded to treatment.

Similarly, Suhr et al. [91] reported interstitial Foscan® based PDT employing 0.15 mg/kg with illumination at 96 h with 20 J/cm on 12 patients. These patients had advanced disease and were symptomatic due to tumor invasion of critical structures. The authors reported good palliation in 11 patients; however, a carotid blowout was also seen. An important consideration is that implantation of light sources changes PDT from a potentially minimally invasive outpatient treatment to one requiring far more technology including image guidance, additional anesthesia and possibly, rapid surgical intervention for an interstitially based complication.

A particularly interesting analysis and one that is relatively unique was reported by Hopper et al. [92] concerning the cost effectiveness of Foscan® PDT compared to palliative surgery and chemotherapy for patients with advanced head and neck cancer in the United Kingdom. In this analysis, PDT was shown

to be highly cost effective and compared extremely favorably in most variables examined. This was for microlens therapy and interstitial treatment may have altered the costs. Palliative radiation was not examined.

Despite these encouraging results, Foscan® was unable to achieve FDA approval for head and neck treatment in the US. However, it is available for this indication in Europe and other countries.

Summary of clinical indications

Both PD and PDT are versatile complimentary modalities that can play many roles in head and neck cancer management.

PD

PD can assist in screening and diagnosis of malignancy, but clinical results remain scarce. Fluorescence can have a role in directing therapy by improving localization of the lesion, but in the head and neck this is underutilized. Potentially, fluorescence could play an active role in dosimetry, but currently this is unfulfilled as is its role in followup.

PDT

PDT has been utilized in several distinct indications summarized below.

In situ disease
PDT has shown excellent potential ability to control this disease. ALA [75], Photofrin® [14,71] and Foscan® [82] based therapies can offer nearly 100% control of localized in situ disease. More diffuse in situ changes as occurs in condemned mucosa appear to be more difficult to eradicate due to difficulties in illuminating broad areas by current tools, but also likely due to the inherent nature of this disease. Any under illumination will allow disease to progress. With all the surface irregularities in the oral cavity the current use of spot illumination or poorly controlled diffusers will not improve outcome [93]. With low dose Photofrin® illumination overlap appears possible without additional morbidity. The same cannot necessarily be said at higher doses of this drug or ''standard doses'' of Foscan®. In contrast to isolated in situ disease, diffuse in situ complete response rates appear to be 50—100% [57,71,75].

Early stage disease
The majority of early stage disease so far reported on is anatomically in the oral cavity or pharynx. Most of these lesions are selected to allow for relatively easy and homogenous illumination. One cannot extrapolate reported results to other areas of the head and neck. Despite these limitations, several distinct lesions appear readily amenable to PDT. This includes solitary T_1/T_2 squamous cell cancers of the lip, buccal mucosa, gingiva, floor of the mouth, soft palate and exophytic oral tongue. While ALA based therapy does not offer complete response [75,94], both Photofrin® [14] and Foscan® [87] treatments appear readily able to control this disease. Several reports show greater than 90% complete response rates with a single treatment. Many patients can subsequently be salvaged if they do not achieve complete response. PDT may very well be the treatment of choice for these select individuals. As some of these patients subsequently fail in the neck, close followup is required. Morbidity profile and cosmetic outcome may be superior to conventional treatment, but no randomized trial exists to prove this fact.

Larynx
Early stage larynx cancer may be the ideal candidate for PDT as chance for regional and nodal disease is low. Salvage of PDT failure is possible. Most reported series includes radiation failures but despite this, nearly a 90% complete response based on one PDT session is expected for T_{IS}, T_1 and T_2 lesions. Photofrin® at 2 mg and 80 J/cm^2 illumination by microlens at 48 h DLI appears safe and effective based on more than 100 patients [54,56,65]. The ultimate test of this hypothesis will require multicenter clinical trials, perhaps with a randomization to radiation and vocal cord sparing surgery. Voice preservation is outstanding, but this too must be assessed in a blinded fashion. Foscan® has a limited database for larynx cancer.

Advanced disease
T_3/T_4 lesions are generally bulky and infiltrative which make homogenous illumination difficult. This likely explains the overall limited success of PDT, as currently practiced for this subset of patients [69,89]. Still significant response can occur. A difficulty with deep seated lesions is the possibility of unexpected encroachment of these tumors on critical structures such as the carotid artery. Carotid blowout appears to be a real risk. Image guidance to assess tumor and critical structures is a key ingredient to successful PDT for advanced disease.

Recurrent disease
As many patients still fail locally despite surgery, radiation and chemotherapy, regaining local control can impact survival and quality of life. Patients

with isolated recurrences, particularly those not deeply invasive, can benefit from PDT as shown by a multicenter clinical trial [89]. Massive, diffuse recurrences rarely can be benefited with superficial illumination. Interstitial illumination may play a role; however, caution must be exercised not to create a fistula or damage critical structures like major blood vessels [90]. The use of CT, MRI and ultrasound can assist in this decision process. While it is true that nothing ventured, nothing gained, this should not be the basis of clinical decision making as PDT in these patients may increase morbidity.

Operative bed treatment
As improved local control can translate into increased survival, this would seem to be an ideal treatment venue for PDT; however, this tantalizingly promising treatment approach has been reported upon in a very limited set of patients. Biel [14] clearly feels that in a select group of individuals undergoing intraoperative PDT with Photofrin® PDT contributed to improved local control. In a report by Dilkes et al. [80] using Foscan® less benefit was seen, but this may have been due to differences in patient populations. Clearly, an intraoperative approach would require photosensitizer infusion prior to surgery and alter the mindset of the surgeon and patient. If a randomized trial showed benefit, then intraoperative PDT might be of great use improving tumor control by eradicating disease, particularly at the margins of resection.

Interstitial treatment
This approach, similar to brachytherapy, could revolutionize head and neck PDT by allowing homogenous illumination. This of course changes PDT from a minimally invasive treatment approach. Still, if clinical trials showed benefit, then interstitial PDT might be an avenue to improve results, particularly for bulky disease. Preliminary studies show feasibility and success; however, morbidity, particularly to vasculature, is a potential downfall [72,90,91]. An interesting review was done by Vogl et al. [95] showing technical difficulties and means to improve success of interstitial PDT.

Neck disease
The majority of advanced patients have neck disease and even many patients with T_1/T_2 cancer are at high risk for nodal failure. This is readily apparent even in select individuals chosen for PDT due to low disease spread risks. So far, PDT has shown poor results for treatment of bulky neck nodes either by surface or interstitial treatment [48,80]. As many nodes are just under the skin surface, con-

ceivably, one could illuminate the neck to attempt treatment. Potentially, a sentinel node procedure [96,97] could be used to assess the need for isolated neck treatment or no neck treatment at all. The sentinel node procedure could also assist in the decision process as to whether this particular patient is a PDT candidate.

Non squamous cell cancer of the head and neck
An even more limited number of non squamous cell cancers have been treated. Buchanan et al. [98] were able to achieve local control of adenoid cystic cancer with Photofrin®. Schweitzer [99] obtained response for Kaposi sarcoma as did Biel [66]. Local control for small mucosal melanoma was also achieved but patients developed distant metastasis [14,48].

Papillomatosis may also respond but recurrence rates appear to be high [100]. In the report by Lou et al. [90], several patients with sarcoma responded as did those in Suhr et al. [91] series.

Discussion

It is clearly evident that PDT can offer great success to patients with head and neck cancer. In situ, early lesions, late tumors and recurrent cancers can successfully be treated. The key to impressive outcomes appears to be a combination of patient selection and technical expertise. It is readily seen that solitary in situ and T_1 cancer respond well to PDT with a variety of sensitizers. Select larger lesions with limited invasion which are amenable to complete illumination can also respond but at lesser rates. Diffuse disease, even when in situ, responds to a much lesser extent, likely due to an inability to homogeneously illuminate the anatomical site at risk. Therefore, with today's technology, patient selection is important. Further, locally controlling tumors by PDT may not impact overall disease control if the neck is a region at high risk for failure. This again shows the need for careful patient selection and also why solitary in situ and T_1 lesions have excellent overall outcomes.

The technical deficiencies for successful head and neck PDT should not be minimized. The ability to homogeneously illuminate lesions via a microlens is very limited. Interstitial placement of catheters as in brachytherapy is an underutilized treatment option, but alters PDT from a minimally invasive procedure. Even with interstitial placement light dosimetry remains in its infancy, so over-treatment to normal tissues leading for example to carotid blowout is a real risk. A great need exists for improved illumination tools, particularly if diffuse

or deep regions are to be homogeneously illuminated.

A particular distressing finding is the apparent relative lack of selectivity of Foscan® mediated PDT when 0.15 mg/kg and 20 J/cm² of light are employed. This leads to inferior overall results and severe pain, edema, and normal tissue injury. While the actual illumination is short, the recovery appears long. In cases where normal tissues are not completely shielded, these regions will also react severely. Further, while many authors tout Foscan®'s shorter photosensitivity, almost all series report this particular toxicity with several severe cases. Foscan®'s photosensitivity at 0.15 mg/kg generally lasts several weeks and optical injury can be evident to several months [83]. Additionally, for several days post infusion Foscan®, patients are dark light sensitive which obviously is not an advantage over other sensitizers. A particularly interesting report for squamous cell lesions of the skin by Kubler et al. [43] reported that Foscan® doses of 0.10 mg/kg with illumination at 96 h with 10 J/cm² offered improved selectively when compared to 0.15 mg and 20 J/cm² illumination. The drug dose, light and DLI needs to again be explored rigorously in a well defined clinical trial. The current standard of 0.15 mg/kg with 20 J/cm² illumination at 96 h does not seem to be optimal. It also seems apparent that the outpatient treatment status with Foscan® PDT is lost due to the level of pain during treatment requiring anesthesia and observation post treatment.

What is also apparent is the outstanding outcome achievable with Photofrin® based PDT for laryngeal cancer. With practice, high tumor control with minimal morbidity is possible. The high level of voice preservation should not be undersold. This treatment option should be rigorously explored in multicenter clinical trials.

In situ disease is extremely common and any treatment that can diminish the chance of progression to invasion should be explored as well. PDT seems to be ideal for localized lesions and with improved illumination devices could become an accepted option for more diffuse disease. It is interesting to note that low dose Photofrin® (1.2 mg/kg) is able to eradicate the disease and even with illumination overlap, at this drug dose, no excess normal tissue morbidity is seen.

Conclusion

Overall PDT remains on the fringes of therapy for head and neck cancer as it is viewed as a competitive option rather than a complimentary treatment choice. Further, the lack of accurate dosimetry, primitive illumination devices and poorly defined treatment parameters diminish this therapy's success. For PDT to become a major player all of these potential obstacles must be overcome. This can only occur through well designed randomized trials that seek to answer specific questions. It will not be achieved through continued reliance on case reports and small single institution studies. While head and neck PDT has come a long way since the early reports of the 1980s, it is distressing to see many of the same road blocks today as were lamented on by these prior authors. Clinicians, scientists, manufacturers and governments must come together to sponsor independently reviewed work in this arena so that more patients may ultimately benefit from this remarkable therapy.

Acknowledgment

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