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Review Article

Photodynamic therapy in esophageal cancer

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ABSTRACT

Historically, photodynamic therapy was an additional mechanism, along with external beam irradiation or brachytherapy, Nd:YAG laser tumor ablation or esophageal stent placement and to a lesser extent, chemotherapy, used to reestablish esophageal continuity in patients with esophageal malignancy who could not undergo resective surgery by virtue of infirmity or tumor stage. However, it has been virtually abandoned for this indication by most practitioners for over a decade. More recently, it has been used in the West to eradicate high-grade dysplasia and superficial malignancies arising in Barrett's esophagus, although its expense, limited availability, and side effect profile make widespread use unlikely, particularly given the widespread availability of other effective techniques. The latter include endoscopic submucosal resection, endoscopic submucosal dissection, radio-frequency ablation, and cryotherapy. This review highlights the historical use of photodynamic therapy in the treatment of esophageal malignancy and potential roles for its application in the future.

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Keywords: Barrett esophagus; Dysphagia; Dysplasia; Esophageal cancer; Photodynamic therapy

Introduction and Photosensitizing Agents

Photodynamic therapy (PDT) was first described by Dougherty et al¹ in 1978. These authors used a hematoporphyrin derivative (HpD) followed by exposure to red light and demonstrated cell death and clinical response in a wide variety of malignant tumors. However, it was not until 1995 that the U.S. Food and Drug Administration approved porfimer sodium PDT (Photofrin; Pinnacle Biologics, Bannockburn, IL, USA) for the palliation of malignant dysphagia in esophageal malignancy and 2003 as an alternative to esophagectomy in patients with high-grade dysplasia (HGD) in patients with Barrett's esophagus.²

Since that time, a variety of photosensitizers have been released in the U.S. as synopsed in Table 1,^{3,4} but perhaps the most commonly used and heavily studied has been aminolaevulinic acid (ALA), a compound associated with more superficial cell death in tissue and the absence of cutaneous photosensitivity.^{5,6}

Mechanism of Action and Treatment Techniques

PDT presupposes intravenous injection or occasionally, topical application of photosensitizer to malignant or dysplastic tissue. These substances, most of which are porphyrin derivatives, prefer-

entially accumulate in malignant tissue, and when exposed to red light applied through an endoscopically placed probe or centering balloon, result in oxygen transformation into singlet oxygen. The latter leads to cell membrane destruction and subsequent apoptosis.^{6–11}

Using porfimer sodium as an example, 1.5 to 2 mg/kg is injected intravenously 24 to 72 hours prior to endoscopic activation using a balloon or diffusing fiber transmitting light at a wavelength of 630 nm.² Tissue reaction is dramatic, and contingent on blood flow, light intensity and local diffusion dosimetry, light penetration of up to 5 to 6 mm in depth is possible. The latter results in variably severe edema, mucosal ulceration, and sloughing, and elicitation of a submucosal necrosis and attempt at repair within 24 to 48 hours of application (Fig. 1, 2). When used to allow neo-lumen formation when treating high-risk or surgically unresectable patients with dysphagia, retreatment is often undertaken with an additional light application 48 hours after the initial procedure. Because this chemical also concentrates in skin tissue, there is a significant risk of sunburn for up to 2 months later, and avoidance of direct sunlight plus use of sunscreen is advisable post treatment.

ALA, in turn, has been used in Europe for almost 2 decades because of its shorter period of photosensitivity, approximating

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Table 1 Types of Photosensitizers for Esophageal Photodynamic Therapy

Class	Photosensitizer	Treatment wavelength (λ , nm)	Diagnostic fluorescence wavelength (λ , nm)	Comments
Porphyrins	Porfimer sodium; also HpD; DHE	630	665–690	Porfimer sodium excellent red light tissue penetration with risk of stricture and prolonged skin sensitivity (Photofrin; also Photosan)
	5-ALA, a precursor of endogenous porphyrins	630–635	525, 665–690	Limited tissue penetration (≤ 2 mm); less photosensitivity (Levulan; Metvix)
Chlorins	mTHPC; temoporfin	650–660 (red), 514 (green)	525	Highly selective, potent 514 (green) compound suitable for less powerful light sources. Approved in European Union, Norway and Iceland (Foscan; Biolitec Pharma)
Purpurins (porphyrin macromolecules)	Mono-L-aspartyl chlorine e6 (NP6; talaporfin or LS11); tin-etio-purpurin (SnEt2)	660–665	675	Phase III study using LS11 for hepatoma activated with light emitting diode (LED) (Light Sciences Oncology, Bellevue, WA, USA ³)
Phthalocyanine	Silicon phthalocyanine (Pc4); aluminum disulfonated phthalocyanine (AISPc); chloroaluminum phthalocyanine tetrasulfonate (AIPcS ₄)	675	610	Limited phototoxicity and limited clinical information hydrophobic compounds that are difficult to purify. Selective tumor retention, minimal dark and cutaneous photosensitivity and excellent photodynamic activity are expected (Photosens)
Benzoporphyrins	Benzoporphyrin derivative (BPD); benzoporphyrin derivative monoacid (BPDMA); diethylene glycol benzoporphyrin derivative (Lemuteporfin)	690	690	Rapid tumor accumulation; transient limited skin photosensitivity and prominent vascular effects produced approval for use in macular degeneration (Visudyne); new diethylene glycol functionalized chlorine-type photosensitizer ⁴
Porphyrin-like compounds	Motexafin lutetium; lutetium texaphyrin	730–740	730–740	Rapid tissue uptake and clearance and tissue penetration; used for photochemical angioplasty (Antrin, Lutrin, Lu-TeX)
Pheophorbides: (tetrapyrrole) chlorophyll derivatives	2-[1-Hexyloxyethyl]-2-devinyl-pyropheophorbide-a (HPPH)	680	680	Undergoing evaluations for use in esophageal, skin, and recurrent breast cancer (Photochlor)

Reused from the article of Gross and Wolfsen (*Gastrointest Endosc Clin N Am.* 2010;20:35–53)² with original copyright holder's permission. HpD, hematoporphyrin derivative; DHE, dihematoporphyrin ether; 5-ALA, 5-Aminolevulinic acid; mTHPC, m-tetrahydroxyphenylchlorin.

Fig. 1. (A) Distal esophageal adenocarcinoma in the background of Barrett's esophagus. (B) Note the light delivery probe used to deliver red light to activate Photofrin (Pinnacle Biologics). Note effects of photodynamic therapy at 48 hours (C) and 96 hours (D) later. (E) Note subsequent complete healing with tubular stenosis of the esophagus and resolution of the Barrett's epithelium.

1 to 2 days, and the preferential concentration in the superficial mucosal layer which has been associated with less post-PDT esophageal stricturing.^{5,12} It has also been administered topically using a spray catheter at time of endoscopy, although suboptimal Barrett's eradication and upstaging of patients from low- to HGD

has led to abandoning this method of ALA delivery.⁶

Indications and Results

As noted previously, PDT has been used to palliate patients

Fig. 2. (A) Nodular esophagogastric malignancy in patient who underwent treatment with photodynamic therapy (B–D). Endoscopic exam and retreatment at 72 hours (E, F) resulted in endoscopic cure as evidence of negative imaging and biopsies at 2 years post-photodynamic therapy (G, H).

with unresectable esophageal malignancy and to ablate Barrett's esophagus when associated with HGD or early esophageal malignancy.

Most of the use of PDT has been historical,^{13–17} as has previously been mentioned, other modalities have supplanted its application,^{18–27} in part because of its side effect profile (pain, esophageal stricturing, perforation, and cutaneous photosensitivity) and cost of the drug which can approximate \$100,000 in the U.S., contingent upon patient weight. Nevertheless, there are a number of recent publications deserving of mention. Yano et al²⁸ reported results of salvage PDT following local failure of disease control following chemoradiation. Although a complete response of local tumor control and improvement in dysphagia was noted in 22 of 37 consecutive patients (59.5%), an esophageal fistula resulted in 4 patients (10.8%), stenosis in 20 patients (54.1%), and phototoxicity in 2 of patients (5.4%), respectively. The 5-year progression-free survival and overall survival of the patients who responded to PDT were 17.6% and 34.6%, respectively.

A recent Korean study, in turn, demonstrated a significant reduction in dysphagia score in 90% of 20 patients treated de novo with the Photofrin PDT. The rate of major complications (esophageal stricture) was 10% and median survival approximated 7.0 ± 0.6 months.^{29,30}

A third, recent study reviewed 640 patients with esophageal cancer treated at the Medical University in Graz, Austria, between 1999 and 2009.³¹ Two hundred and fifty patients (39.1%) were treated with palliative intent using a variety of techniques to include dilation, esophageal stenting, endoluminal brachytherapy, chemotherapy, external beam irradiation, and PDT. Palliation with PDT was ultimately undertaken in 171 patients, 118 patients as initial therapy. Median survival in the latter group was 50.9 months compared with 17.3 months if other therapies were initially used ($P = 0.012$), and overall survival of the palliative group was 34 months. The authors suggested that prolonged survival in the patients initially treated with PDT was more likely related to

a secondary immune response by T cells activated by the inflammatory necrosis as opposed to the acute local effect of PDT.

Finally, Rupinski et al³² randomized 93 patients with malignant dysphagia to 3 palliative regimens to include brachytherapy, PDT, and argon plasma coagulation (APC) alone. APC therapy was included in an attempt to facilitate neolumen formation in both the brachytherapy and PDT groups. The time to first dysphagia recurrence was significantly different between the PDT and brachytherapy groups and those patients treated with APC alone ($P = 0.006$) but not between the combination groups. Complications were limited to fever in 3 of the PDT patients, and there was a median survival of 6.2 months with no significant difference between the groups.

From the perspective of PDT use in Barrett's esophagus and early esophageal cancer, one of the earliest and largest studies was published by Overholt et al.¹³ These authors used a cylindrical inflatable balloon to deliver light in 101 patients treated with Photofrin. At a mean follow-up of 4 years, 54% of patients demonstrated complete resolution of Barrett's metaplasia whereas 78% resolved HGD and 48% of early cancers were deemed cured. Treatment-related stenosis occurred in 30% of patients.

A subsequent multicenter trial by Fleischer et al²¹ demonstrated complete eradication of HGD in 77% of 28 patients followed over 5 years. Additional studies at Mayo Clinic (Jacksonville, FL, USA) demonstrated complete Barrett's ablation in 50% and elimination of HGD in 100% at a mean follow-up of 19 months.¹⁴ Twenty percent of these patients developed esophageal strictures that required dilation.

To date, there are a paucity of studies comparing PDT to techniques that have mostly supplanted its application. These include endoscopic submucosal resection, endoscopic submucosal dissection, radiofrequency ablation and cryotherapy.² However, there are uncontrolled studies using ALA and a randomized controlled trial comparing ALA to Photofrin for Barrett's patients with HGD by Dunn et al.³³ Sixty-four patients with HGD were randomized

to ALA (34 patients) or Photofrin (30 patients). In 47% of the patients treated with ALA and 40% of those treated with Photofrin, complete regression of HGD was noted. Strictures and photosensitivity were more common in Photofrin patients (33% vs 9%) and buried submucosal glands significant more common after than before PDT (48% vs 20%). Because 14% of these patients went on to develop cancer, the authors concluded that neither drug was efficacious enough for routine use.

Discussion

So where are we in 2014 when it comes to PDT application in esophageal cancer and its precursors, particularly Barrett's esophagus? On the one hand, the combination of procedural expense, suboptimal efficacy, and side effect profile to include chest pain, iatrogenic strictures, and esophageal fistulas has limited our initial enthusiasm for this procedure. On the other hand, the procedure has proven useful in high-risk patients with de novo malignancy or those who develop recurrent dysphagia following previous chemo-irradiation or surgery.^{34–37} As such, it is likely to continue to play a minor role in patients with invasive malignancy.

In contrast, the use of alternative endoscopic techniques has virtually supplanted PDT for the treatment of Barrett's with HGD or T1a early malignancies. While beyond the scope of this manuscript, the latter includes endoscopic submucosal resection or endoscopic submucosal dissection to define the depth of early malignancies or assurance that all HGD has been resected, as well as radiofrequency ablation or cryotherapy to treat residual metaplastic epithelium.^{18–25}

Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

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