Photodynamic therapy in esophageal cancer

Richard A. Kozarek*

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, radiofrequency 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.

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

Introduction and Photosensitizing Agents

Photodynamic therapy (PDT) was first described by Dougherty et al. 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 photofrin 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.

Since that time, a variety of photosensitizers have been released in the U.S. as synopsed in Table 1, 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.

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, preferentially 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.

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 mm. 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...
1 to 2 days, and the preferential concentration in the superficial mucosal layer which has been associated with less post-PDT esophageal strictureing.\textsuperscript{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.\textsuperscript{6}

\textbf{Indications and Results}

As noted previously, PDT has been used to palliate patients...
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, as has previously been mentioned, other modalities have supplanted its application, in part because of its side effect profile (pain, esophageal stricture, 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 al 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.

A third, recent study reviewed 640 patients with esophageal cancer treated at the Medical University in Graz, Austria, between 1999 and 2009. 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 al 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. 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 al 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. 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. 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. 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, esophageal cancer and its precursors, particularly Barrett's esophagitis epithelium. As radiofrequency ablation or cryotherapy to treat residual metaplasia, the latter includes endoscopic submucosal resection for Barrett's high-grade dysplasia and early esophageal adenocarcinoma: an essential staging procedure with long-term therapeutic benefit. Am J Gastroenterol. 2010;105:1276-83.

In the contrast, 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.

Conflicts of Interest

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

Acknowledgments

All images are courtesy of Yazen Quimsiyeh and Herbert Wolfsen, MD, Mayo Clinic, Jacksonville.

References

1. Dougherty TJ, Kaufman JE, Goldfarb A, Weishaupt KR, Boyle D, Mittelman A. Photoradiation therapy for the treatment of malignant tumors. Cancer Res. 1978;38:3628-35.
2. Gross SA, Wolfsen HC. The role of photodynamic therapy in the esophagus. Gastrointest Endosc Clin N Am. 2010;20:35-53.
3. Stepinac T, Gospodan J, Woodall A, Monnier F, van den Bergh H, Wagnières G. Optimization of the diameter of a radial irradiation device for photodynamic therapy in the esophagus. Endoscopy. 2002;34:411-5.
4. Brachhotte DR, Savary JF, Monnier F, van den Bergh H. Optimizing light dosimetry in photodynamic therapy of early stage carcinomas of the esophagus using fluorescence spectroscopy. Lasers Surg Med. 1996;19:340-6.
5. Gossner L, Stolte M, Sroka R, Rick K, May A, Hahn EG, et al. Photodynamic ablation of high-grade dysplasia and early cancer in Barrett's esophagus by means of 5-aminolevulinic acid. Gastroenterology. 1998;114:448-55.
6. Gummey BA, David W, Wolfsen HC. Photodynamic therapy for Barrett's esophagus and esophageal carcinoma. Clin Endosc. 2013;46:32-7.
7. Moghissi K. Where does photodynamic therapy fit in the esophageal cancer treatment jigsaw puzzle? J Natl Compr Canc Netw. 2012;10(Suppl 2):S52-5.
8. Wang KK, Kim JY. Photodynamic therapy in Barrett's esophagus. Gastrointest Clin N Am. 2003;33:483-9.
9. Yang PW, Hung MC, Hsieh CY, Tung EC, Wang YH, Tsai JC, et al. The effects of Photofrin-mediated photodynamic therapy on the modulation of EGFR in esophageal squamous cell carcinoma cells. Lasers Med Sci. 2013;28:605-14.
10. Shishkova N, Kuznetsova O, Berezov T. Photodynamic therapy in gastroenterol. J Gastrointest Cancer. 2013;44:251-9.
11. Davila ML. Photodynamic therapy. Gastrointest Endosc Clin N Am. 2011;21:67-79.