Pilot Study on Light Dosimetry Variables for Photodynamic Therapy of Barrett's Esophagus with High-Grade Dysplasia

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Abstract

Purpose: Photodynamic therapy (PDT) is used to treat Barrett's esophagus with high-grade dysplasia and mucosal carcinoma. Outcomes are variable with some patients having persistent disease, whereas others develop strictures. The aims of this study were (*a*) to compare porfimer sodium tissue uptake, light dose, and esophageal thickness with clinical outcomes and (*b*) to determine the selectivity of porfimer sodium uptake in diseased and normal epithelium.

Experimental Design: Forty-eight hours after porfimer sodium infusion, patients underwent mucosal biopsy for quantification of the porfimer sodium. Laser light was delivered at 48 hours and again 24 or 48 hours later. Porfimer sodium was extracted from the biopsy samples and quantified using fluorescence spectroscopy. The enhanced photodynamic dose was determined as [porfimer sodium content * light dose/esophageal thickness]. PDT efficacy was determined 6 to 8 weeks later based on persistence or complete ablation of dysplasia or carcinoma.

Results: Mean porfimer sodium content of 6.2 mg/kg (range, 2.6-11.2 mg/kg) and mean total light dose of 278 J/cm (range, 225-360 J/cm) resulted in a complete treatment. Mean porfimer sodium tissue content of 3.9 mg/kg (range, 2.1-8.1 mg/kg) and mean total light dose of 268 J/cm (range, 250-350 J/cm) resulted in an incomplete treatment. The total esophageal thickness (range, 1.7-6.0 mm) and enhanced photodynamic dose were correlated with treatment outcome.

Conclusions: Esophageal thickness is the strongest predictor of treatment outcome. The porfimer sodium content of Barrett's and normal tissue is not significantly different. "Photodynamic dose" for esophageal PDT should incorporate the esophageal thickness.

Despite improved drug treatment for acid reflux disease, the incidence of esophageal adenocarcinoma has steadily increased over the last 4 decades (1, 2). Barrett's disease, the replacement of squamous epithelium by a premalignant specialized intestinal columnar mucosa, is the most important risk factor for the development of esophageal adenocarcinoma. Esophagectomy is the traditional treatment of Barrett's dysplasia and early carcinoma; however, it is associated with serious morbidity and risk of mortality (3). Therefore, minimally invasive endoscopic ablation therapies have been developed, including the use of porfimer sodium–sensitized photodynamic therapy (PDT). Porfimer sodium-PDT was approved by the Food and Drug Administration for the treatment of Barrett's high-grade dysplasia (HGD) in 2003 and is also used

in patients with mucosal adenocarcinoma. The mechanism of PDT ablation involves light activation of the photosensitizer, which then reacts with molecular oxygen to generate reactive oxygen species and trigger apoptosis, activation of the host immune system, and vascular damage resulting in tissue necrosis (4). PDT using porfimer sodium activated by 630-nm red light allows deep tissue penetration of light energy to drive the photodynamic reaction with little risk of perforation because there is no damage to the collagen gut wall infrastructure (5).

The use of porfimer sodium-PDT for Barrett's dysplasia and mucosal carcinoma is supported by the 5-year follow-up results from a prospective, randomized, multicenter trial that found significant reduction in the development of invasive adenocarcinoma in patients treated with porfimer sodium-PDT using the Food and Drug Administration–prescribed dose of 2 mg/kg i.v. porfimer sodium and 200 J/cm red 630-nm laser light (6, 7). By comparison, the approved porfimer sodium-PDT dose for obstructing esophageal carcinoma is 2 mg/kg i.v. and 300 J/cm red 630-mm laser light. To achieve this result, however, many patients underwent two or three courses of porfimer sodium-PDT, resulting in prolonged episodes of cutaneous photosensitivity (4-6 weeks) and a high rate of esophageal stricture formation. The clinical outcomes after porfimer sodium-PDT have been quite variable and unpredictable, as for some patients, the recommended dose of drug and light produces too little target tissue damage, resulting in residual disease, whereas other patients may experience a

Translational Relevance

Porfimer sodium photodynamic therapy (PDT) is approved for the treatment of patients with esophageal carcinoma and Barrett's high-grade dysplasia (HGD), although its dosimetry is poorly understood, resulting in variable treatment results for patients who receive the same drug and light dose. Whereas previous PDT dosimetry studies have focused on PDT light dose, our project studied factors related to optimal treatment outcomes, including the porfimer sodium tissue content, photodynamic dose, and the distal esophageal wall thickness. A novel aspect of our study was the comparison of the esophageal wall thickness with PDT treatment outcomes for patients with Barrett's HGD and mucosal carcinoma. The present study shows that esophageal thickness is an important dosimetry factor and shows a correlation between esophageal wall thickness and "undertreatment" of Barrett's esophagus with HGD. The results indicate that an enhanced photodynamic dose, including esophageal thickness, may be predictive of treatment outcome.

severe reaction resulting in excessive scarring, impaired esophageal motility, and stricture.

Currently, there are no clinically available methods to determine the ideal dose of drug and light required in an individual patient for the improvement of esophageal porfimer sodium-PDT outcome while minimizing the risk of stricture. We hypothesized that the variation in clinical outcome might be related to the differences in the target tissue uptake of porfimer sodium, light dose, and esophageal thickness. The primary aim of this study was to determine porfimer sodium content with chemical extraction of the dye from biopsy samples and compare the porfimer sodium content, light dose, and esophageal thickness with clinical outcomes. The secondary aim was to investigate the selectivity of porfimer sodium uptake in Barrett's dysplastic tissue compared with normal esophageal tissue.

Materials and Methods

This pilot study includes 11 patients undergoing porfimer sodium-PDT for Barrett's esophagus with HGD (BE/HGD) or mucosal carcinoma. Approval was obtained by the Mayo Foundation Institutional Review Board and patients provided their informed consent for participation in this study of porfimer sodium-PDT dosimetry. Our standardized pretreatment evaluation of these patients has been described in detail elsewhere (8). All patients had an index upper endoscopy using a high-resolution endoscope with white light and narrow band imaging (Olympus GIF-H180). The Barrett's segment was characterized with an intensive biopsy protocol and expert secondary histology review to confirm the diagnosis of HGD and rule out the presence of erosive esophagitis or stricture (9).

Esophageal wall layer thickness was measured with endoscopic ultrasound (EUS) examination (Olympus GF-UE160-AL5, Olympus America, Inc.). Esophageal wall thickness was defined as the distance between the balloon-mucosal interface to the outermost hyperechoic layer. The esophageal wall thickness was measured in the distal esophagus at 1 cm above the level of the gastroesophageal junction (top of the gastric folds) and every 2 cm above in the Barrett's segment.

Among patients with short segment Barrett's (<2 cm), one measurement was obtained in the Barrett's segment. These esophageal wall thicknesses were correlated with histologic results of biopsies obtained from the same Barrett's segment levels. The thickness of each layer was measured in millimeters. The maximum focal wall thickness was considered for analysis. Forty-eight hours after infusion of 2 mg/kg of porfimer sodium, patients returned for endoscopy with PDT laser light application. Mucosal biopsies of the target Barrett's dysplasia as well as comparative biopsies of normal squamous mucosa (at least 10 cm proximal to the squamocolumnar junction) were obtained before light treatment and immediately frozen for subsequent fluorescence analysis of porfimer sodium content. All mucosal samples were obtained using Boston Scientific Radial Jaw 4 large-capacity biopsy forceps (Jaw outside diameter, 2.8 mm). PDT laser light treatment was done using 2.5- or 5-cm-length quartz optical fibers (without the use of a centering light balloon device). Follow-up endoscopy with additional laser light application was done 24 or 48 h after the initial light application. Patients returned 6 to 8 wk later for a follow-up evaluation.

Assessment of the tissue porfimer sodium concentration determined by fluorescence methods. Frozen biopsy samples ranging in mass from 1.0 to 8.1 mg were thawed, weighed, and then placed in 1 mL Solvable (Fisher Scientific) for 48 h in the dark at 50°C to break down the tissue and extract the porfimer sodium. Two milliliters of 1% detergent (Triton X-100, Fisher Scientific) were added to each sample to solubilize the extracted porfimer sodium. Porfimer sodium fluorescence was then measured with a spectrofluorimeter with 405-nm excitation and 627-nm emission. Finally, porfimer sodium content was determined by comparison with the fluorescence emission of several standardized porfimer sodium solutions. Porfimer sodium was reported as mg of porfimer sodium per mg of biopsy sample.

Assessment of treatment effectiveness. The follow-up assessment was done by endoscopic examination 6 to 12 wk after the initial porfimer sodium-PDT treatment. The clinical outcomes after porfimer sodium-PDT were divided into three groups: (*a*) undertreatment group, (*b*) ideal response group, and (*c*) overtreatment group. The ideal response was defined as 100% replacement of Barrett's mucosa with squamous mucosa or 100% eradication of carcinoma, whereas undertreatment was defined as the presence of any residual Barrett's mucosa or carcinoma. Overtreatment was defined as the presence of post-PDT complications, such as stricture or perforation. Postablation stricture was diagnosed by the presence of concentric esophageal narrowing and dysphagia. The mean porfimer sodium tissue content, light dose, and esophageal thickness were compared between the ideal and undertreatment groups to determine the relationship between these variables and clinical outcome. An unpaired *t* test was used to give a two-tailed *P* value.

Photodynamic dose. Two different forms of photodynamic dose were calculated. The first form was a product of the administered light dose in units of J/cm and the porfimer sodium tissue content in mg/kg.

$$\text{PDT Dose} = [\text{porfimer sodium}] * \text{light dose} \tag{A}$$

A second form of photodynamic dose incorporated the variable of esophageal thickness.

$$\text{Enhanced PDT Dose} = [\text{porfimer sodium}] * \text{light dose} *$$
$$(1/\text{total esophageal thickness}) \tag{B}$$

Results

Table 1 presents the age, diagnosis, and PDT treatment variables for 11 patients. Six patients were found to have complete ablation of Barrett's mucosa or carcinoma; five of

Table 1. Patient characteristics and treatment outcomes

Patient	Age (y)	Barrett's length (cm)	Esophageal thickness (mm)*	PDT light dose (J/cm)[†]	Histologic diagnosis	Barrett's porfimer sodium (mg/kg)	Selectivity ratio for BE or ACA vs normal squamous	Outcome
1	68	3	3.1	175 + 100	ACA	8.3	0.81	Ideal
2	66	11	3.0	175 + 50	HGD	11.2	1.01	Ideal
3	72	15	4.4	155 + 100	HGD	3.7	1.42	Under
4	70	10	3.0	175 + 50	HGD	5.2	1.63	Ideal
5	83	5	3.9	300 + 250	ACA	3.3	1.27	Under
6	75	3		200 + 100	ACA	2.1	1.31	Under
7	71	3	6.0	175 + 175	ACA	8.1	1.80	Under
8	79	6	2.4	200 + 80	HGD	4.9	1.40	Ideal
9	79	3	3.4	200 + 160	HGD	2.6	1.37	Ideal
10	53	1	4.0	250 + 50	HGD	2.5	0.78	Under
11	79	1	1.7	200 + 100	HGD	5	0.65	Over

Abbreviation: ACA, adenocarcinoma.
*Total esophageal wall thickness.
[†] Initial light dose + follow-up light dose.

these had no evidence of squamous or subsquamous abnormalities on follow-up endoscopy and one was found to have an esophageal stricture. Five other patients were found to be "undertreated" with residual Barrett's dysplasia or carcinoma.

Selectivity of porfimer sodium uptake in Barrett's dysplasia. In 11 patients, porfimer sodium ranged from 2.1 to 11.2 mg/kg (mean, 5.2 ± 2.9) in Barrett's dysplasia and 1.6 to 11.1 mg/kg in normal mucosa (mean, 4.7 ± 3.4; Fig. 1). There was no significant difference in the mean porfimer sodium uptake between the Barrett's dysplasia and normal mucosa ($P = 0.05$). The average porfimer sodium uptake in cancer tissue was similar to that found in Barrett's HGD tissue (5.5 ± 3.2 and 5.0 ± 2.9, respectively). Selectivity of porfimer sodium uptake in Barrett's dysplasia or cancer ranged from 0.65 to 1.80 (Table 1). Selectivity was not significantly correlated to treatment outcome ($P = 0.34$).

Effect of esophageal thickness on treatment outcome. The total esophageal thickness for patients who received an ideal treatment was significantly less than those who received an undertreatment ($P = 0.007$; Fig. 2A). The analysis was repeated for the subset of patients with HGD. The total esophageal thickness for patients with BE/HGD also correlated significantly with the treatment outcome ($P = 0.0221$).

Mucosal thickness was not found to be predictive of treatment outcome (Fig. 2B) for either Barrett's dysplasia or cancer patients, although measurements of the combined mucosa and submucosa (measured in six patients) showed a trend toward statistical significance. The combined measurement was 1.2 to 2.0 mm for patients with an ideal outcome and 2.2 to 2.5 mm for patients who were undertreated ($P = 0.1175$).

Tissue porfimer sodium content and treatment outcome. Five of 11 patients had residual disease (undertreated), 5 had an ideal response, and 1 had overtreatment complications (Table 1). The mean porfimer sodium concentration in the "undertreatment" group was 3.9 mg/kg (median, 3.3; range, 2.1-8.1 mg/kg). The "ideal treatment" group had a mean porfimer sodium concentration of 6.2 mg/kg (median, 5.1 mg/kg; range, 2.6-11.2 mg/kg; Fig. 3). The ideal and undertreated groups were not statistically different ($P = 0.2077$) for this limited sample size.

Initial and total PDT light dose. The Food and Drug Administration–prescribed light dose for the treatment of BE/HGD is 200 J/cm and 300 J/cm for esophageal cancer. The mean initial light dose given for BE/HGD in this study was 190 J/cm (range, 155-250 J/cm; median, 200 J/cm) with a mean second application 24 or 48 hours later of 85 J/cm (range, 50-163 J/cm; median, 80 J/cm). The mean initial light dose for patients with esophageal cancer was 213 J/cm (range, 175-300 J/cm; median, 188 J/cm) and the mean second light application was 156 J/cm (range, 100-250 J/cm; median, 138 J/cm).

Neither the first light dose ($P = 0.2852$) nor the total light dose ($P = 0.1969$) was significantly different for the undertreated or ideal groups. The mean of the undertreated total light dose was actually larger than the ideal treatment due to the cancer patients who were included in the study. Excluding the cancer patients, the total mean light dose was the same with 279 J/cm for the ideal group and 278 J/cm for the undertreated group.

Photodynamic dose. The photodynamic dose (from Eq. A) was not predictive of the treatment outcome for the first light
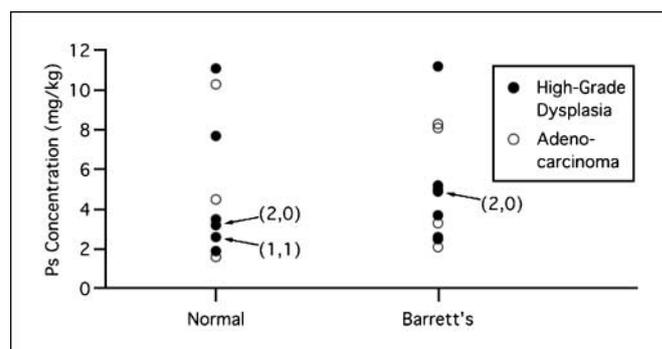

Fig. 1. Porfimer sodium content (mg/kg) in normal squamous tissue compared with Barrett's dysplasia or esophageal carcinoma. The numbers in parentheses indicate overlapping data points for patients with a diagnosis of Barrett's HGD and adenocarcinoma, respectively. There was no significant difference in the mean porfimer sodium uptake between the Barrett's dysplasia and normal mucosa.

Fig. 2. *A,* total esophageal thickness versus treatment outcome for patients diagnosed with HGD or esophageal carcinoma. The numbers in parentheses indicate overlapping data points for patients with a diagnosis of Barrett's HGD and adenocarcinoma, respectively. Total esophageal thickness is inversely related to treatment outcome ($P = 0.007$). *B,* mucosal thickness versus treatment outcome for patients with HGD or esophageal carcinoma. Mucosal thickness alone was not significantly related to treatment outcome.
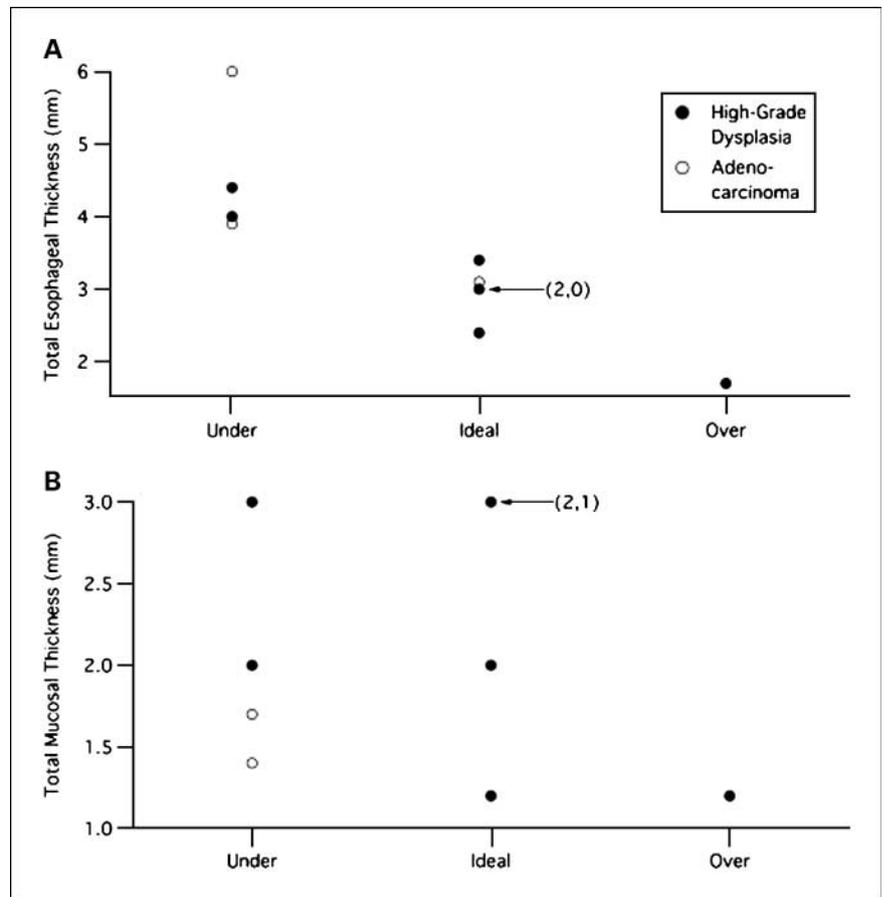
dose ($P = 0.2625$) or total light dose ($P = 0.6265$; Fig. 4A). An enhanced photodynamic dose calculation (from Eq. B) that also includes the effect of thickness was significantly higher for the ideal group compared with the undertreated group and strongly related to outcome (Fig. 4B). The enhanced photodynamic dose was more strongly related to the outcome when calculated with the initial light dose ($P = 0.0414$) than the total light dose ($P = 0.0955$).

Discussion

Esophageal PDT is a complex interaction of a photosensitizer drug activated by light to induce apoptosis, mucosal inflammation, vascular thrombosis, and immune system activation in the setting of clinical factors, such as aggressive suppression of acid and bile gastroesophageal reflux, to promote the ablation of Barrett's dysplasia with remodeling to a squamous epithelium. Despite the numerous factors involved in PDT, most previous studies have focused on the light dose. PDT light delivery for the esophagus is unique because the esophagus is a hollow organ in which reflected light enhances the light fluence that is delivered directly from the fiber optic light source. Panjehpour et al. (10) and van Veen et al. (11) measured the actual light fluence at the mucosal surface and found that it was 1.5 to 3.9 times higher than expected. Mackenzie et al. (12) reported that esophageal 5-aminolaevulinic acid-PDT treatment success was correlated to the administered PDT light dose. However, Panjehpour et al. (13) investigated the effect of

light dose on PDT-induced stricture formation and found that each of the light doses (85-115 J/cm) led to a range of treatment outcomes from residual disease to stricture formation, giving evidence that the incident light dose is only one factor in treatment outcome. An intriguing observation of our study was the development of post-PDT stricture in the patient with the smallest esophageal wall thickness (1.7 mm). This patient had a successful result with complete ablation of all 4 cm length of Barrett's disease. Two dilation procedures of the structure were subsequently done to establish a patent, stable esophageal lumen and restoration of normal swallow function.
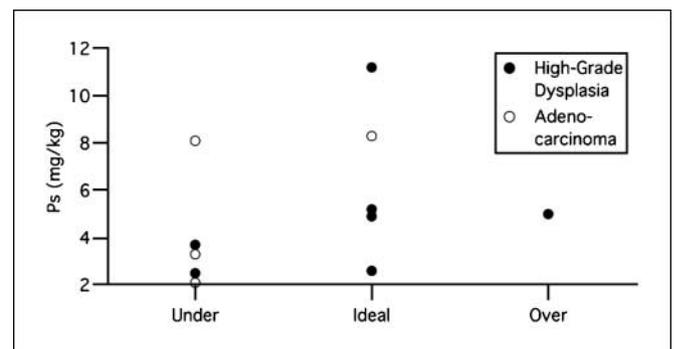
Fig. 3. Porfimer sodium tissue content versus treatment outcome for patients diagnosed with HGD or esophageal carcinoma. Porfimer sodium content was not statistically correlated with treatment outcome.

Along with other factors, the possible association of esophageal wall thickness and the development of postablation stricture require further study.

Recently, the development of advanced optical techniques has improved the real-time tissue characterization of Barrett's disease, including the detection of submucosal disease after ablation therapy (14). Holmer et al. (15) measured the optical properties of normal, Barrett's, and cancer tissue for modeling of light flux and absorption throughout the esophagus during PDT. Improved tissue characterization and more accurate determination of optical properties are critically important for mathematical modeling and Monte Carlo simulations of optimal PDT dosimetry for PDT light dosimetry planning (16, 17).

In addition to light fluence, the local photosensitizer tissue content strongly affects the distribution of absorbed energy that is necessary for tissue destruction. Several groups have used fluorescence methods to quantify photosensitizers *in vivo* in various tissues. Braichotte et al. (18) quantified esophageal tetra(meta-hydroxyphenyl)chlorin with fluorescence and showed that the tissue level was related to treatment response. Glanzmann et al. (19) also correlated mucosal content of tetra(meta-hydroxyphenyl)chlorin with PDT response. These studies confirm the findings of a clinical study where reducing the photosensitizer dose of hematoporphyrin was associated with poor ablation results (20). The present study, which used an extraction method to quantify the porfimer sodium in mucosal biopsy samples, reports a 10-fold variability in esophageal uptake of porfimer sodium. A similar wide

variability among patients in porfimer sodium concentration has been reported in previous studies of other tissues (17, 21). Perhaps related to the limited number of patients in this study, this variation in the porfimer sodium tissue content in itself was not shown to be predictive of treatment outcome. There are many other factors that affect PDT results. Potentially, one of the most important of these variables in the planning of PDT dosimetry is the mucosal oxygen content. Some groups have used noninvasive fiber optic diffuse reflectance measurements to determine local oxygenation of various tissues (22, 23).

The recommended porfimer sodium-PDT drug and light doses do not accommodate the variability in photosensitizer uptake, tissue optical properties, tissue oxygenation, and drug-light-tissue interactions (24). In addition to these PDT variables, there are other clinical and physiologic factors that contribute to the treatment outcome. Yachimski et al. (25) found that the length of BE was associated with PDT-related strictures, although the treatment length was not. This study, however, characterized Barrett's disease only by segment length and histology. A novel aspect of our study was the comparison of the esophageal wall thickness in patients with Barrett's HGD and mucosal carcinoma with tissue photosensitizer content and treatment outcomes. The present study shows that esophageal thickness is an important dosimetry factor and shows the importance of esophageal thickness measurement before PDT (and perhaps other forms of endoscopic ablation treatment, as well). Further, our results agree with the previous results of Gill et al. (26) who used EUS to measure esophageal thickness for 76 patients with BE and 53 normal controls. The mean
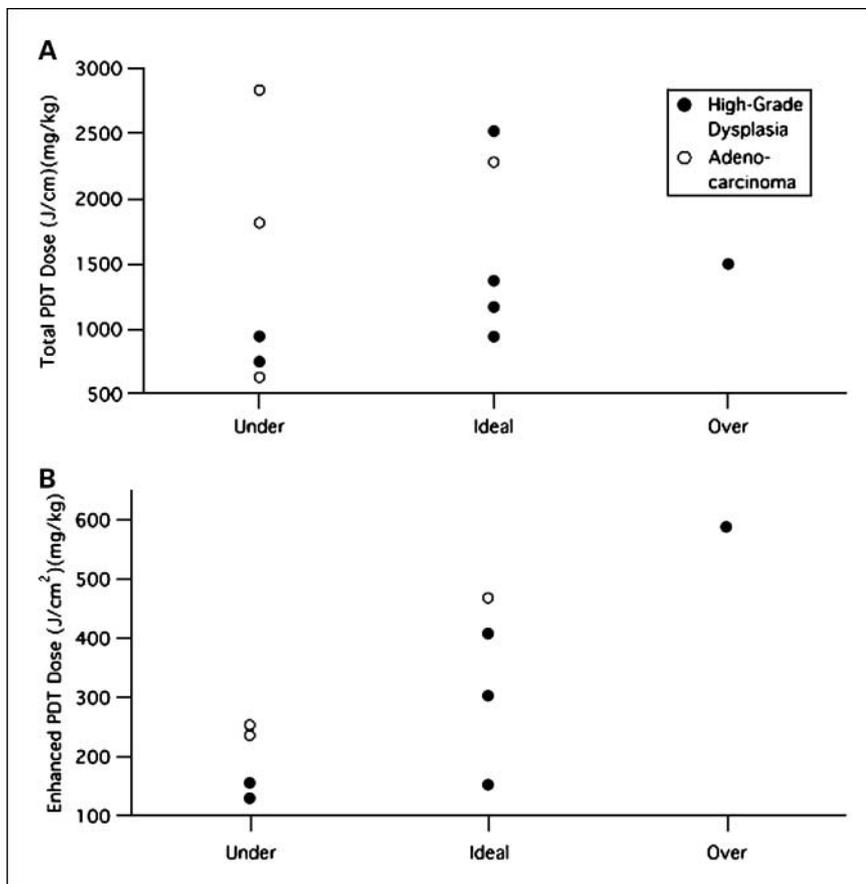

Fig. 4. *A,* PDT dose calculated as [total light dose * porfimer sodium content] versus treatment outcome for patients diagnosed with Barrett's dysplasia or esophageal carcinoma. *B,* enhanced PDT dose versus treatment outcome versus treatment outcome calculated as [initial light dose * porfimer sodium content/total esophageal thickness]. Enhanced PDT dose is predictive of treatment outcome ($P = 0.0414$).

distal esophageal wall thickness was 2.4 ± 0.6 mm for controls and 3.4 ± 1.1 mm for HGD. Faigel et al. (27) used EUS to measure esophageal thickness for Barrett's tissue both before and after multipolar electrocoagulation and found a small but significant decrease in thickness for successful treatments. EUS and OCT, both of which probe the submucosa, may be very useful in the future to monitor microvascular changes associated with optimal treatment and to supplement post-ablation mucosal biopsies for the detection of residual disease (4, 28, 29).

One of the most basic dosimetry methods is the calculation of a "photodynamic dose," which is the product of the incident light dose and local photosensitizer content. Good results were obtained using this methodology for PDT of implanted tumors with varying photosensitizer content if the photodynamic dose (product of light dose and photosensitizer concentration) remained constant (30). However, the results of our study, done in a clinical setting in patients undergoing PDT for BE/HGD, showed that an "enhanced photodynamic dose" must include the esophageal thickness to be predictive of treatment outcome. Zhu and Hahn at the University of Pennsylvania have developed dosimetry systems to quantify and independently factor the light and tissue optical properties, photosensitizer drug concentration, and tissue oxygenation for PDT of the prostate. This "explicit dosimetry" requires the invasive placement of numerous isotropic light detectors into the target tissue to measure both incident and scattered light (i.e., total fluence) along with diffusion theory–based models of tissue optical properties and oxygenation (31, 32). A more common approach for the esophagus is to make noninvasive optical measurements to monitor PDT progress. Sheng et al. (33) and Pogue et al. (34) used fluorescence methods to monitor photobleaching during esophageal PDT. Oxygen consumption and singlet oxygen generation are assumed to be directly proportional to the rate of photobleaching. In addition to the consumption of oxygen by the PDT process, oxygenation is also affected by damage to the blood vessels. Light dose fractionation may enable the tissue to reoxygenate to continue treatment in hypoxic tissue. Pogue et al. showed that light fractionation improved PDT results in an animal model of BE.

In our study, the PDT light dose alone was not found to have a significant relationship with the treatment outcome. The enhanced photodynamic dose was most predictive of outcome when the initial light dose was used rather than the total light dose. One possible explanation is that the "incomplete response" noted after the initial treatment is because of low photosensitizer mucosal content and this can never be overcome by adding additional light energy. Another possibility is that the extensive mucosal edema and inflammation prevents any further meaningful photodynamic reaction regardless of the amount of light that is applied. Or the drug may have been inactivated or "bleached" preventing any further photodynamic ablation. Whatever the mechanism, it is very likely that the initial PDT light dose is the one that really counts. It is critical to develop a method to optimize the initial light dose.

The factor most strongly correlated with treatment outcome was the esophageal wall thickness and, more specifically, the combined thickness of the mucosal and submucosal layers. This finding is interesting for several reasons. First, in most clinical series, the diagnosis and treatment of patients with Barrett's HGD is based on the grade of histology and segment length. Further, the utility of endosonography has been questioned for the evaluation of patients with Barrett's dysplasia (35). However, our work suggests that the thickness of the esophageal wall layers is important, particularly in patients who are being considered for endoscopic therapy using comparatively thin-layer ablation techniques such as radiofrequency ablation. This is the first study, to our knowledge, to systematically determine the thickness of the esophageal wall and correlate these findings with a treatment outcome. In the subset of patients where detailed esophageal layer measurements were obtained, these differences in total wall thickness were related to the mucosal and submucosal layers that contain the Barrett's dysplasia and mural blood supply, respectively. The values of porfimer sodium tissue content in this study were derived from mucosal biopsy samples. Further studies are necessary to investigate the porfimer sodium distribution in the submucosa.

Our study has several limitations, including the sample size, the lack inclusion of other clinical variables that could influence these results, such as tissue oxygenation, control of gastroesophageal bile, and acid reflux, and physiologic factors affecting laser light application (esophageal peristalsis and respiratory motion). The study also used a limited number of mucosal biopsies of Barrett's disease to determine the porfimer sodium tissue content and variability (sampling error) is certainly possible. Finally, this pilot study showed a correlation between esophageal wall thickness and undertreatment of BE/HGD, indicating that an enhanced photodynamic dose that includes esophageal thickness may be predictive of treatment outcome. We noted the development of stricture in only one patient who had the thinnest esophageal wall. Further studies are needed to determine if there is a relationship between the higher photodynamic dose and porfimer sodium-PDT–related complications.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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