



**TITLE:** Photodynamic Therapy for High Grade Esophageal Dysplasia

**AUTHOR:** Jeffrey A. Tice, M.D.  
Assistant Adjunct Professor of Medicine  
Division of General Internal Medicine  
Department of Medicine  
University of California San Francisco

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## PHOTODYNAMIC THERAPY FOR HIGH GRADE ESOPHAGEAL DYSPLASIA

### INTRODUCTION

The California Technology Assessment Forum has been asked to review the scientific literature on the safety and efficacy of photodynamic therapy (PDT) for the treatment of high-grade dysplasia in Barrett's esophagus.

This review will focus on the use of porfimer sodium, as it is the only photosensitizer currently approved by the Food and Drug Administration.

### BACKGROUND

#### Barrett's Esophagus and Dysplasia

Barrett's esophagus describes the condition in which the normal squamous epithelium lining the esophagus is replaced by columnar epithelium that is similar to the lining of the intestines. It is thought to reflect the response of the body to recurrent exposure to acidic fluid moving from the stomach into the esophagus (gastroesophageal reflux disease (GERD)). In some people, there are further cellular changes (dysplasia) progressing eventually to adenocarcinoma. Esophageal adenocarcinoma is increasing in incidence faster than any other cancer in the U.S. (Blot *et al.*, 1991). Prospective studies suggest that the annual risk of cancer for patients with Barrett's esophagus lies between 0.5 and 1% (Drewitz *et al.*, 1997; Shaheen *et al.*, 2000). The length of the abnormal mucosa and the degree of dysplasia are the primary risk factors for development of cancer (Pacifico *et al.*, 2002). High-grade dysplasia (HGD) is the stage immediately preceding cancer. A larger proportion of patients with HGD progress on to cancer, although some lesions regress over time. Estimates of the annual incidence of cancer for patients with HGD range from as low as 2%(Schnell *et al.*, 2001) to as high as 62% (Hameeteman *et al.*, 1989). All of the studies are relatively small (n<100) and have short follow-up. Most estimates from the larger studies cluster near the low end of the range (4-10% per year). It is not possible to predict which cases of HGD will progress to cancer and which cases will not. However, it is clear that a large proportion of patients with HGD will have occult cancer. Pathologists find cancer in up to 57% of specimens from patients with HGD who undergo esophageal resection (Collard, 2002; Dar *et al.*, 2003).

#### Esophageal Resection as Primary Therapy

A recent study evaluated the mortality associated with esophagectomy in the U.S. (Dimick *et al.*, 2005). The study evaluated 8,657 esophageal resections from 1988 to 2000 captured by the Nationwide Inpatient Sample, a 20% random sample of all hospital discharges in the U.S. The overall in-hospital mortality rate was 11.3%. This tended to go down over time (13.6% to 10.5%) and was lowest at high volume hospitals (11.0% decreasing to 7.5%).

Esophageal resection is also associated with considerable morbidity (Lerut *et al.*, 2004). In several large studies, 30 to 50% of patients experienced at least one serious post-operative complication (pneumonia, myocardial infarction, heart failure or wound infection) and the average hospital stay was at least two weeks. Late complications are also common. Stenosis at the site of anastomosis is relatively common, occurring in 10% to 56% of cases in the literature (Orringer *et al.*, 2000), and it usually requires approximately four follow-up endoscopies with dilation for treatment. Severe reflux has been reported in 21% (De Leyn *et al.*, 1992) to 58% (Shibuya *et al.*, 2003) of patients often leading to recurrent Barrett's in the esophageal remnant. The surgical procedure usually requires transection of the vagus nerve and a reduction in the size of the stomach in order to connect the gastrointestinal tract with the esophageal remnant. This can lead to a variety of motility disorders including delayed gastric emptying or dumping syndrome. Finally, the recurrent nerve is damaged in up to 22% of cases (Hulscher *et al.*, 1999) causing vocal cord paralysis which increases the risk of aspiration pneumonia.

Given the high morbidity and mortality associated with esophageal resection, there is tremendous motivation to develop a less invasive treatment for HGD. Alternative therapies include laser ablation, endoscopic mucosal resection and PDT.

### **Photodynamic Therapy**

PDT combines a photosensitizer that tends to accumulate in dysplastic or malignant cells with a device that delivers light of a specific wavelength to the target tissue in order to produce cell death (Prosst *et al.*, 2003). The photosensitizing drug is activated by light of a specific wavelength matched to its absorption spectrum. In the presence of oxygen, the activated drug produces oxygen species that are cytotoxic. Thus, cellular damage and tumor necrosis occur via a nonthermal photochemical reaction. Recently, it has been suggested that the immune response and inflammation generated are partly responsible for the therapeutic effect (Oleinick *et al.*, 1998). Mucosal healing and repair occurs over two to three months following treatment. PDT is also called phototherapy, photoradiation therapy, photosensitizing therapy and photochemotherapy.

A variety of PDT techniques are reported in the literature including the use of different photosensitizing agents (porfimer sodium, hematoporphyrin derivative, 5-aminolevulinic acid, temoporfin, etc.), different light sources and either fractionated or continuous light applications. Laser irradiation is usually performed 48 to 72 hours after injection of porfimer sodium, although this varies depending on the pharmacokinetics of the drug used (Prosst *et al.*, 2003). The depth of light penetration varies with the wavelength of the light source, but is usually 5-10 mm. Most commonly, a 630-nm visible red laser beam is directed at the target area through a flexible quartz fiber. Generally, PDT delivers therapy with light intensity between 100 and 400 J/cm<sup>2</sup> and a light intensity of 100 mW/cm<sup>2</sup> (Prosst *et al.*, 2003).

Treatment is usually performed as an outpatient. Due to the risks of stricture, the maximum extent of disease that is treated in one session is 7 cm. If a larger area needs to be treated, the patient is brought back for a second session.

Administration of photosensitizing drugs is contraindicated in patients with porphyria. Patients administered the photosensitizing drugs are instructed to avoid direct exposure to sunlight or bright indoor lights for 30 days or longer depending on the drug used.

### Technology Assessment (TA)

**TA Criterion 1: The technology must have final approval from the appropriate regulatory bodies.**

Photofrin PDT® (porfimer sodium, Axcan Scandipharm Inc.) was approved by the FDA under section 505(b) on August 4, 2003 for the treatment of precancerous lesions of Barrett's esophagus.

On August 1, 2003 the Wizard X-Cell™ Photodynamic Therapy Balloon with Fiber Optic Diffuser (Axcan scandipharm, Inc.) received FDA PMA approval. This device is to be used with the photosensitive drug Photofrin for the ablation of high-grade dysplasia in Barrett's esophagus patients who do not undergo esophagectomy.

TA Criterion 1 is met.

**TA Criterion 2: The scientific evidence must permit conclusions concerning the effectiveness of the technology regarding health outcomes.**

The Medline database, Cochrane clinical trials database, Cochrane reviews database, and the Database of Abstracts of Reviews of Effects (DARE) were searched using the key words photodynamic therapy, porfimer, photochemotherapy or photosensitizing agents. These were cross-referenced with the keywords dysplasia and human. The search was performed for the period from 1966 through April 2005. The bibliographies of systematic reviews and key articles were manually searched for additional references. Further references were also solicited from the manufacturer, local experts and gastroenterology societies. The abstracts of citations were reviewed for relevance and all potentially relevant articles were reviewed in full.

The search identified three uncontrolled case-series (Panjehpour *et al.*, 2000; Overholt *et al.*, 2003b; Wolfsen *et al.*, 2004) describing the outcomes for a total of 265 patients. Each of these studies reported on a mixed population of patients being treated for low-grade dysplasia (n=24), HGD (n=192) and early adenocarcinoma (n=49). There were at least 12 publications identified describing different aspects of these three series (Overholt *et al.*, 1993; Overholt *et al.*, 1995b; Overholt *et al.*, 1995a; Overholt *et al.*, 1997; Overholt *et al.*, 1999; Panjehpour *et al.*, 2000; Wolfsen *et al.*, 2002a; Wolfsen *et al.*, 2002b; Overholt *et al.*, 2003b; Prosst *et al.*, 2003; Wolfsen *et al.*, 2004). It appears that the 60 patients in the clinical trial of prednisone for the prevention of PDT-associated strictures (Panjehpour *et al.*, 2000) were not included in the larger case-series from the same center (Overholt *et al.*, 2003b), so both will be described. One moderate sized randomized trial has been reported in abstract form (Overholt *et al.* 2003a), but the complete

results have not been published in a peer-reviewed journal. The published studies were uncontrolled, single center reports without standardized entry criteria and without standardized, independent outcome assessment.

The primary outcomes reported are the percentage of patients with Barrett's esophagus and HGD completely eliminated, the incidence of strictures and the incidence of cancer during follow-up.

Level of evidence: 5.

TA Criterion 2 is not met.

**TA Criterion 3: The technology must improve net health outcomes.**

The primary advantage of PDT would be the prevention of the development of esophageal cancer in patients at high risk due to HGD while avoiding the high morbidity and mortality associated with the standard treatment, esophageal resection.

**Case Series**

The largest study with the longest follow-up (Overholt *et al.*, 2003b) summarized the results of the treatment of 103 patients, 80 of which were treated for HGD. The remainder of this discussion will focus on the 80 patients with HGD, when possible. Two pathologists confirmed the diagnosis of HGD. All patients received porfimer sodium followed by light therapy delivered by laser using a balloon device to flatten the esophageal mucosa and center the light source. The device attempts to deliver uniform light dosing to minimize the risk for stricture formation. In the entire case-series, 69 patients were treated with one session of PDT, 29 patients with two sessions and 5 patients with three sessions. All patients were maintained on high dose proton pump inhibitor therapy (omeprazole 20 mg, twice daily). Endoscopy was performed at 3, 6, 9, and 12 months and then annually. If residual Barrett's mucosa was visible on endoscopy more than three months after treatment, it was treated with Nd:YAG laser photoablation. A total of 84 patients required Nd:YAG laser photoablation of residual Barrett's tissue. Average follow-up in the study was 51 months (range 2-122 months). The mean age of the patients with HGD was 64 years and 80% were male. All patients with EGD required follow-up photoablation with the Nd:YAG laser. Barrett's esophagus was completely eliminated in 54% (43/80) of patients and HGD was eliminated in 78% (62/80). Strictures developed in 30% of patients overall, but were more common in patients undergoing two sessions (50% with strictures) than in those undergoing only one session (18% with strictures). A total of 7.5% (6/80) of patients with HGD were diagnosed with esophageal carcinoma during follow-up. Four of these patients were diagnosed within six months of initial treatment; the remaining two were diagnosed at 46 and 52 months after PDT. Given the widely varying estimates for progression of HGD to cancer, it is not clear whether this represents a decrease from the expected four-year rate of cancer occurrence.

The second case series (Wolfsen *et al.*, 2004) describes 102 patients (69 with HGD, 33 with cancer) treated with one session of PDT using porfimer sodium. The median age of patients was 72 years and 20% were female. Two pathologists confirmed the diagnosis of HGD. Argon beam laser was used to ablate any residual Barrett's mucosa seen on endoscopies performed at least three months after PDT. Endoscopy was performed every three months for two years following PDT and subsequently every six months. The median follow-up was 19 months (range 6 to 78 months). Barrett's esophagus was completely eliminated in 52% (36/69) of patients with HGD. From an earlier report of the same series with fewer patients, HGD was eliminated in 98% (47/48) (Wolfsen *et al.*, 2002b). One patient (1%) developed metastatic adenocarcinoma. Strictures developed in 22% of patients treated for HGD and required a median of five dilations per patient for treatment. Severe photosensitivity reactions requiring medical treatment (usually oral corticosteroids) developed in 18%. Additional complications included esophageal perforation (1%), atrial fibrillation (1%) and congestive heart failure (1%). Both stricture formation and incomplete ablation of Barrett's mucosa were associated with the length of the diseased segment of the esophagus.

The final series (Panjehpour *et al.*, 2000) of 60 patients (48 with HGD) was performed at the same center by the same investigators as the first series using a similar protocol. The study randomized 30 patients to PDT alone (6 patients had two sessions) and 30 patients to PDT plus oral prednisone (4 patients had two sessions, 2 patients had three sessions). Median follow-up was 9.8 months (range 3-18 months). For this review, it can be considered as a third uncontrolled series of patients with HGD treated with PDT. Endoscopies were performed every three to six months to evaluate the response. Residual or recurrent Barrett's was treated using Nd:YAG laser. Barrett's esophagus was completely eliminated in 42% (25/60) of patients and HGD was eliminated in 96% (41/43). Strictures developed in 16% of patients randomized to PDT alone and 29% of patients randomized to PDT plus prednisone.

It is clear from the uncontrolled case-series above that PDT combined with follow-up laser thermoablation is effective at eliminating visible HGD in most patients (78-98%) and Barrett's esophagus in about half of patients (42-56%). However, all three studies were uncontrolled and only the first had sufficient follow-up to estimate the efficacy of PDT for preventing the development of esophageal cancer. Controlled studies with longer follow-up are needed.

### **Randomized Clinical Trials**

One multi-center, randomized clinical trial has been presented in abstract form. Patients with HGD were randomized in a 2:1 ratio to either PDT with porfimer sodium plus omeprazole for acid suppression (n=138) or omeprazole therapy alone (n=70). Patients were followed for a minimum of two years. The abstract suggests that there was a significant difference in the incidence of esophageal adenocarcinoma (10% vs. 30%), but details about the study are limited.

## Risks / Harms

Intravenous injection of porfimer sodium is generally well tolerated. Photosensitivity reactions have been reported for up to eight weeks after injection in between 13% (Sibille *et al.*, 1995) and 24% (Cortese *et al.*, 1997) of patients treated for palliation of cancer. Similarly, about one-third of patients treated for HGD reported skin reactions with between 3% (Overholt *et al.*, 2003b) and 18% (Wolfsen *et al.*, 2004) reporting severe photosensitivity reactions requiring medical treatment.

Esophageal strictures can occur in up to one-third of patients, although the incidence is closer to 15% for patients who can be treated with a single session of PDT (Sibille *et al.*, 1995; Panjehpour *et al.*, 2000; Wolfsen *et al.*, 2002b; Overholt *et al.*, 2003b). These are usually manageable with dilation (McCaughan *et al.*, 1996). Stenoses appear to be related to the use of circumferential radiation (360°) of the esophageal wall and can be limited by using a 180° or 240° light distributor (Savary *et al.*, 1998). One randomized trial found no benefit to the use of oral prednisone for the prevention of stenosis (Panjehpour *et al.*, 2000) even though steroids are typically used as an adjunct to dilation when treating stenosis occurring after PDT.

Esophageal perforation, candidal esophagitis, pleural effusions and atrial fibrillation were also reported in 3-4% of treated patients.

The major long-term concern is that regions of dysplasia greater than 5 to 10 mm in depth remain untreated by PDT. In addition, unsuspected carcinoma that is present in up to 50% of patients with HGD may be inadequately treated. Ideally, randomized clinical trial data would be available comparing PDT to esophageal resection with at least five years of follow-up to assess cancer free survival. Short of that, case series with several years follow-up comparing the outcomes of patients treated with PDT with controls matched on age, sex and extent of disease would allow for a more balanced assessment of the relative risks and benefits of PDT compared with esophagectomy.

## Cost-effectiveness Analysis

At least three cost effectiveness analyses (Hur *et al.*, 2003; Shaheen *et al.*, 2004; Vij *et al.*, 2004) of the use of PDT to treat HGD have been published. All used estimates of efficacy based on results from studies using porfimer sodium as well as studies using alternative agents as the photosensitizing drug. All three analyses concluded that PDT is cost-effective compared with esophagectomy or surveillance. Estimates of the increase in quality-adjusted life years gained compared with esophagectomy ranged from 0.5 to 2.2 and cost-effectiveness ranged from \$12,000 to \$47,000 per quality-adjusted life year. Based on their analysis, at least one of the authors called for randomized clinical trials to confirm these projected benefits.

TA Criterion 3 is not met.

**TA Criterion 4: The technology must be as beneficial as any established alternatives.**

The primary alternative treatment for HGD is esophagectomy. As noted in the background section, this therapy is associated with high mortality (7-15%) and morbidity (up to 50%). Some centers offer aggressive surveillance with high dose proton pump inhibitor therapy as an alternative with good outcomes (Schnell *et al.*, 2001), but this has been associated with poor outcomes in other studies (Weston *et al.*, 2000; Romagnoli *et al.*, 2003). The complete lack of controlled clinical trials makes it difficult to relate the risks and benefits of PDT compared to either esophageal resection or acid suppressive therapy with regular endoscopy for surveillance. The three case series discussed above appear to have lower rates of cancer diagnosis than would be predicted from what is known about the natural history of HGD, but comparative studies are needed to ensure that this does not simply reflect differences in the natural history of the populations studied. It is likely that patients treated with esophagectomy are different than those treated conservatively, so direct comparisons of the results of these treatments are likely to be biased.

TA Criterion 4 is not met.

**TA Criterion 5: The improvement must be attainable outside of the investigational setting.**

PDT has been performed successfully at multiple centers in the U.S. and Europe and has been found to meet TA Criteria 1 through 5 when used for palliation of esophageal cancer in an earlier review.

However, given that no improvement has clearly been demonstrated in the investigational setting for PDT when treating HGD, no conclusions can be drawn regarding device effectiveness in the community setting.

TA Criterion 5 is not met.

**CONCLUSION**

In Barrett's esophagus with HGD, uncontrolled trials suggest some efficacy for PDT using porfimer. Unfortunately, the published literature is limited to small, uncontrolled single center case series. In the absence of a single randomized controlled trial, there cannot be a conclusive assessment of the efficacy of PDT. One randomized trial comparing PDT to surveillance plus PPI therapy has been completed, but not yet published. Furthermore, excitement about porfimer sodium is tempered by its long half-life, which leaves patients vulnerable to cutaneous photosensitivity reactions for up to two months, and the relatively high risk of strictures in some case series. Thus, alternative photosensitizing agents are under active investigation. Given the high morbidity and mortality of esophageal resection, PDT would be a welcome alternative if it were demonstrated to be more efficacious than surveillance. No clinical trials have been reported directly comparing PDT to the current standard, esophagectomy.

**DRAFT RECOMMENDATION**

It is recommended that the use of PDT with porfimer sodium as the photosensitizing agent does not meet Technology Assessment Criteria 2, 3, 4 or 5 for safety, effectiveness and improvement in health outcomes for patients with high-grade esophageal dysplasia.

June 15, 2005

*The California Technology Assessment Forum panel voted unanimously to accept the recommendation as written.*

## RECOMMENDATION OF OTHERS

### **Blue Cross Blue Shield Association (BCBSA)**

The BCBSA Technology Evaluation Center Medical Advisory Panel has not evaluated the use of this technology for esophageal high-grade dysplasia.

### **Centers for Medicare and Medicaid Services (CMS)**

The CMS does not have a national coverage determination for Photofrin for use in the treatment of Barrett's esophagus. A few Medicare contractors have developed local coverage determinations for Photofrin use in cancer of the lung and esophagus. Some of these contractors cover Photofrin for its Barrett's labeled indication.

### **American Gastroenterological Association (AGA)**

#### **American Society of Gastrointestinal Endoscopy (ASGE)**

A representative of the AGA and ASGE attended the meeting and provided comment supporting the use of this technology.

### **American Cancer Society (ACS)**

The ACS does not have an opinion on this condition and its treatment.

### **Association of Northern California Oncologists (ANCO)**

The ANCO does not have an opinion regarding this topic.

### **Medical Oncology Association of Southern California (MOASC)**

A MOASC representative attended the meeting and provided testimony.

### **American College of Surgeons, California Chapter (ACSCA)**

The ACS CA chapter has will have a representative at the meeting.

### **California Thoracic Society**

The CTS has been invited to provide a position statement and representation at the meeting.

## ABBREVIATIONS USED IN THIS REVIEW

GERD: Gastroesophageal Reflux Disease

PDT: Photodynamic Therapy

HGD: High-grade Dysplasia

PPI: Proton Pump Inhibitor

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