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Porfimer Sodium Photodynamic Therapy for Management of Barrett's Esophagus With High-Grade Dysplasia

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Porfimer sodium photodynamic therapy (ps-PDT) for Barrett's esophagus is a powerful endoscopic treatment that can eliminate high-grade dysplasia (HGD) and Barrett's mucosa and reduce the risk of development of cancer in these patients. Ps-PDT typically results in destruction of Barrett's esophagus in the majority of the treated area. However, residual small island of Barrett's mucosa may persist after PDT. Therefore, adjuvant thermal ablation should be available during follow-up endoscopies for ablation of residual islands of Barrett's mucosa. PDT should be applied concurrent with effective proton pump inhibitor therapy. This article provides a practical guide for application of porfimer sodium balloon PDT for management of Barrett's esophagus with HGD. Recommendations are provided for patient selection and screening, delivery of PDT to include light dosimetry, methodology for follow-up endoscopies, as well as discussing the potential side effects and complications. Lasers Surg. Med. 38:390–395, 2006. © 2006 Wiley-Liss, Inc.

Key words: adenocarcinoma of esophagus; KTP/dye laser; diode laser; argon/dye laser; PDT; porfimer sodium; thermal ablation

INTRODUCTION

Barrett's esophagus is a precancerous condition associated with gastroesophageal reflux disease (GERD) where the normal squamous lining of the esophagus is replaced by specialized columnar mucosa. Barrett's esophagus is associated with an increased risk of mucosal dysplasia and adenocarcinoma with a 30- to 125-fold increase in the occurrence of esophageal cancer compared to the normal population [1–3].

Until recently, esophagectomy was the standard treatment for patients with high-grade dysplasia (HGD) or early cancer in Barrett's esophagus. However, this surgical procedure is associated with 40–50% risk of major complications and mortality rate of 3–5% at high-volume centers and up to 20% at low-volume hospitals [4–10]. Photodynamic therapy (PDT) offers an alternative non-surgical outpatient procedure that eliminates dysplasia and superficial cancer and reduces length of Barrett's mucosa while reducing risks compared to esophagectomy [11–16].

PDT is an ablation technique that utilizes the photochemical reaction between a photosensitizing drug, light, and tissue oxygen. Interaction of the three components results is production of singlet oxygen and free radicals that are highly cytotoxic, resulting in the destruction of illuminated tissue. Porfimer sodium is a photosensitizer that has been used effectively for PDT of HGD and early cancer in Barrett's esophagus when delivered concurrently with effective acid suppression therapy [15,16].

Ps-PDT using the Xcell esophageal centering balloon was recently approved by the FDA for the treatment of patients with HGD in Barrett's esophagus [15].

In this article we will provide practical guidelines for application of ps-PDT for management of Barrett's esophagus with HGD. Since ps-PDT for Barrett's esophagus has evolved over the last several years, the published data are from different periods during protocol development. Special emphasis will be made here in providing information on the technique (and the associated side effects) that has been approved by the FDA and is currently available for others to implement. Throughout the article, we will provide comparison between the FDA approved technique and the relevant data published during previous phases of the development to clarify any confusions. This article is not intended to be a comprehensive review of literature on PDT for Barrett's esophagus. An update on advances in PDT for Barrett's esophagus is provided elsewhere [17].

Patient Selection

It is imperative that all patients have an endoscopy with four quadrant large particle biopsies at every 2 cm (or 1 cm). Biopsies should be examined by an expert GI pathologist trained in Barrett's diagnosis. Patients with nodular disease should have endoscopic ultrasound (EUS) to assist in proper cancer staging. EUS is performed for evaluation of esophageal wall layers (being intact or thickened) as well as examination of adjacent lymph nodes. Patients with abnormal appearing nodes or nodes larger than 1 cm in size should be referred for fine needle aspiration. Patients with T1 mucosal lesions should have an endoscopic mucosal resection (EMR) [18] followed in 4–8 weeks with balloon PDT to treat the remaining Barrett's mucosa.

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T1 submucosal lesions should be referred for surgical intervention. If patients are denied esophagectomy, they may be treated with PDT (or mucosal resection). Patients with involvement of the muscularis propria should be referred for surgical intervention.

Before availability of EMR, T1 mucosal lesions received an extra light dose using a small cylindrical diffuser before the entire area was treated using the balloon. If EMR is not performed, an extra light dose targeted to the nodular area is recommended [12,15]. This will be discussed in more detail later.

Histological evaluation of lesions removed using EMR techniques is a valuable tool for planning a treatment strategy. Patients with lesions extending into the submucosa or deeper layers should be referred for surgical intervention.

Several techniques are available for performing EMR. We currently use Duette® Multi-Band Mucosectomy device which allows maximum of six resections during one procedure.

Prior to PDT, a thorough history and physical to include laboratory work, chest X-ray and EKG should be performed. Patients with known porphyria or known hypersensitivity to porphyrins should not be treated.

Photodynamic Therapy

Patients may be treated as outpatient. All patients receive an intravenous (2 mg/kg) injection of porfimer sodium (Photofrin®, Axcan Pharma, Mont-Saint-Hilaire, QC). Two to three days after the drug injection, 630 nm light from a KTP/Dye laser (Laserscope, San Jose, CA), a diode laser (Diomed, Andover, MA) or an argon-pumped dye-laser (Lumenis, (previously Coherent), Santa Clara, CA) may be delivered using an Xcell PDT balloon (Wilson-Cook Medical, Winston Salem, NC). This is a 25 mm diameter esophageal PDT balloon that is provided with window lengths of 3, 5, and 7 cm. These balloons are provided with the matching cylindrical diffuser to be inserted into the balloon. The length of cylindrical diffuser is always 2 cm longer than the window length. Therefore, a 5, 7, or 9 cm cylindrical diffuser is packaged with 3, 5, and 7 cm windowed balloons, respectively. The balloon is placed into the esophagus using a guidewire. The position of the balloon window should be checked using an endoscope passed along side of the shaft of the balloon. A yellow marker on the balloon shaft (located 3 cm proximal to the edge of the window) allows for proper positioning of the window where the treatment is to be delivered.

It should be noted that the Xcell PDT balloon has a reflective inner surface which was used in the multicenter study and subsequently approved by Food and Drug Administration for treatment of HGD in Barrett's esophagus [15]. Other published data on balloon PDT from our group [11,12,16] used a 25 mm balloon with a non-reflective inner surface. When using the non-reflective balloon, the length of cylindrical diffuser was identical to the length of window on the balloon. The reflective balloon was developed to improve the uniformity of the light along the length of the window. The light dosimetry using the two balloon designs is different. This will be discussed in more detail later. For comprehensive discussion of different light delivery devices, see Ref. [19].

When selecting a balloon window length, at least 0.5–1 cm of normal tissue should be included in the treatment field to assure proper targeting of the Barrett's mucosa. This is important due to inadvertent movement of the balloon in the esophagus during the treatment. Due to the length of typical Barrett's segment and constant movement, a 3 cm windowed balloon is rarely recommended. A maximum of 7 cm of Barrett's mucosa may be treated in one session. However, in our recent work, we have been treating longer segments by delivering additional laser light to the remaining Barrett's mucosa during the 48 hours follow-up endoscopy, particularly in healthier patients.

The balloon pressure should be maintained at 20 mm Hg during the procedure (regardless of the treatment location), starting with balloon pressure of 80–100 mm Hg to fully inflate and flatten the esophageal folds, followed by reduction to 20 mm Hg immediately before initiation of the laser treatment. While high balloon pressure is desired to keep the balloon fully inflated, it has the potential to press against the esophageal wall, affecting the blood flow to the treatment area. The reduction in blood flow lowers the oxygen concentration in tissue, which in turn reduces the PDT injury. In our earlier studies, we used higher balloon pressures which resulted in frequently occurring large areas of very mild injury (called skipped areas). Gradual reduction of inflation pressure in subsequent patients proved effective in eliminating the majority of the skip areas [11].

Patients should be treated using an energy density dose of 130 J/cm. If possible, the power density should be set at 270 mW/cm of cylindrical diffuser length. This would mean that a total power of 2,430 mW is required when using a 9 cm cylindrical diffuser in a 7 cm balloon (270 mW/cm$\times$9 cm). The illumination time is calculated by dividing the energy density (in J/cm) by the power density (in W/cm). For example, using the power density of 270 mW/cm, it requires 480 seconds to deliver a light dose of 130 J/cm [(130 J/cm)/(0.27 W/cm)]. Some lasers (such as Diomed laser) do not provide sufficient output power to deliver 2,430 mW from a 9 cm cylindrical diffuser. In such cases, the power density of 200 mW/cm may be used. Therefore, the total power from a 9 cm diffuser is reduced to 1,800 mW (200 mW/cm$\times$9 cm). Using a power density of 200 mW/cm, it requires 650 seconds of illumination to deliver 130 J/cm. Power densities lower than 200 mW/cm require illumination times that become impractical. For example, using a power density of 150 mW/cm (or 0.15 W/cm), it requires 866 seconds to deliver 130 J/cm [(130 J/cm)/(0.15 W/cm)].

It should be noted that light dosimetry associated with the non-reflective balloon [11,12,16] was different than that used with the Xcell reflective PDT balloon and should not be confused. The optimum energy density delivered using the non-reflective balloon was 200 J/cm. The power density was 400 mW/cm which required 500 seconds to deliver a treatment. The equivalency studies to compare non-reflective and reflective balloons were performed in canine esophagus by measuring the actual light dose delivered to

the mucosa using isotropic probes attached to the outside of the balloon window (unpublished pharmaceutical sponsored studies used to introduce reflective balloon for the multicenter randomized study).

If a patient has a nodular area within the Barrett's esophagus not removed by mucosal resection (such as T1 mucosal) an extra 50 J/cm should be targeted to the nodule using a short cylindrical diffuser before delivery of 130 J/cm using the Xcell PDT balloon. The power density from short cylindrical diffuser should be set at 400 mW/cm. For example, using a 2.5 cm diffuser, the total power will be 1,000 mW (2.5 cm×400 mW/cm) from the diffuser. Delivery of 50 J/cm at the power density of 400 mW/cm, requires 125 seconds of illumination time [(50 J/cm)/(0.4 W/cm)]. The dose of 50 J/cm was selected and tested during the protocol development and proved to be a safe dose as a boost to the balloon treatment [12,15].

Proper light dosimetry requires accurate measurement of laser power. When using the Diomed laser, an internal power meter is provided which must be used for calibration of the fiber and setting the power. An external integrating sphere power meter (with a large diameter sphere) should be used when using Laserscope or Lumenis lasers. Currently, UDT Instruments (Model 371, Baltimore, MD) manufactures a power meter that is specifically designed for PDT. One should be aware that the power meter provided with the Laserscope PDT system is not recommend for use with cylindrical diffuser longer than 3 cm.

Two days after the laser treatment, the mucosal injury should be evaluated endoscopically. A supplemental dose of 50 J/cm (or more at the discretion of physician) [12,15] may be delivered to areas with mild response using a short cylindrical diffuser inserted through the biopsy channel of the scope. At the discretion of the physician, if a patient with Barrett's segment longer than 6–7 cm is doing well and is clinically stable at the 48 hours follow-up, additional treatment may be delivered to the untreated segment using the standard light dose. The additional treatment will likely produce more post-procedure discomfort. Treatment overlap should be avoided to reduce the risk of excessive treatment of the previously treated area, which may increase the risk of stricture development.

Most patients experience some chest pain, nausea, and low-grade fever. Following PDT, oral narcotics may be given for control of chest discomfort in addition to antiemetics for nausea. Acetaminophen may be taken for low-grade fever as needed.

Prophylactic IV hydration over the first 12–24 hours should be considered to prevent dehydration. Typically, patients remain on soft foods for several days after the laser treatment. Patients may return to normal diet as tolerated. Most patients return to normal diet within 2–3 weeks.

An effective acid suppression protocol is extremely important after endoscopic ablation of Barrett's mucosa, either thermal or photochemical [15,20]. Patients should start high-dose PPI therapy twice daily for at least 3 months after the treatment. On the day of laser treatment, gastric pH should be checked. If the pH is four or less, the dose of PPI should be doubled and the pH checked during the 48 hours follow-up endoscopy to assess the effectiveness of PPI therapy. We recommend patients remain on high-dose PPI therapy for at least 1 year after they have been fully cleared of Barrett's mucosa. Thereafter, patients may reduce their dose to once daily. If their symptoms are controlled, they may continue with daily PPI medication. We recommend long-term PPI treatment for all patients. If a patient is an operative candidate, surgical (laparoscopic) repair of the hiatal hernia may be recommended.

Evaluation of Treatment Efficacy

Patients should be followed with endoscopy 3 months after PDT to allow for complete healing of the treated area following treatment. The 3-month follow-up consists of two endoscopy procedures. The first endoscopy should include visual examination of the treated area, Lugol's chromoendoscopy for detection of small islands of Barrett's mucosa, and four quadrant large particle biopsies every 2 cm of the treated area and untreated area, if any. Large particle biopsies are preferable to detect any subsquamous Barrett's cells. A second endoscopy with thermal ablation may be performed in patients who have residual Barrett's mucosa. We recommend endoscopy with biopsies (and possible ablation) be repeated at 6-month intervals for at least 2 years. This would allow for five consecutive biopsies to confirm clearance of Barrett's mucosa. When possible, we follow patients for 5 years [16].

Supplemental Ablation During Follow-Up Endoscopies

During follow-up endoscopies, residual small islands of Barrett's mucosa may be found within the treated area. These islands should be biopsied carefully. Thermal ablation techniques such as Nd:YAG laser [11] and APC [14] may be used to ablate the residual Barrett's mucosa. In our institution, we use contact Nd:YAG laser which allows for accurate targeted treatment of small islands of residual Barrett's mucosa within the treated field or untreated Barrett's mucosa (outside the treated field). If the residual segment does not contain HGD, then thermal ablation may be used to treat that area during subsequent visits. If HGD is present, additional PDT, mucosal resection or, in some cases, aggressive thermal ablation should be considered. We repeat PDT a maximum of three times.

When a second PDT is delivered, overlapping of the first and second fields should be avoided, if possible. This strategy would reduce the risk of stricture development seen with overlapping of the PDT fields [11].

Management of Esophageal Strictures After PDT

One of the complications after PDT for Barrett's esophagus is formation of strictures. Patients should be contacted by phone weekly. Dysphagia may be diagnosed by persistent difficulty in swallowing solid foods over several days. Those with documented dysphagia should be assessed by endoscopy for the presence of a stricture. In some patients, dysphagia may be due to transient esophageal spasms. While others have reported [21] abnormal esophageal motility following PDT, we consider persistent

solid food dysphagia a symptom highly suggestive of stricture formation. The length of strictures are typically short, ranging from 1 to 2 cm. Esophageal strictures typically occur 3–4 weeks after PDT. If a stricture is present, dilations should be performed twice a week, starting with Savary #33 or 36 until Savary #48–#51 is reached, then weekly for several weeks with Savary #51 or 54, then monthly for several months. Methylprednisolone acetate (Depo-medrol, Pharmacia & Upjohn Company, Kalamazoo, MI) may be injected (20 mg in four sites) into the inflamed stricture weekly during the first 3 weeks.

EFFICACY RESULTS OF MULTICENTER RANDOMIZED PDT STUDY

PDT for Barrett's esophagus with HGD received regulatory approval in the U.S. based on the results of a multicenter, randomized trial [15] using the techniques described in this article. This was a report on a minimum 2-year follow-up of a 2:1 randomized controlled trial of ps-PDT plus omeprazole (treatment arm) versus omeprazole only (control arm) in the treatment of Barrett's HGD. The study enrolled 208 patients with 138 in the PDT treatment arm and 70 in the control arm. At the end of a minimum 24-month follow-up, ps-PDT plus omeprazole showed statistically significant improvement in elimination of HGD and in the reduction of the incidence of adenocarcinoma compared to the control arm. Ablation of all HGD was noted in 77% of patients in the PDT arm versus 39% in the control arm. Complete ablation of all Barrett's epithelium and dysplasia was achieved in 52% of patients in the PDT group versus 7% in the control arm. A reduction in the progression to cancer from 28% in the control arm to 13% in the PDT arm was found. It is noted that during the follow-up biopsies, any pathologic interpretation that raised any suggestion of cancer, for example, "cannot rule out adenocarcinoma," was classified as progression to cancer in these patients. It should also be noted that no adjuvant therapy such as Nd:YAG laser or APC was used to treat residual Barrett's mucosa upon follow-up endoscopy.

OTHER RELEVANT PUBLISHED DATA

While results of the multicenter randomized study best represents the expected outcome from the technique described in this article, one should be familiar with the relevant publications on ps-PDT for Barrett's esophagus. Overholt et al. [11] reported on treatment of 100 patients with Barrett's dysplasia including 13 with superficial cancers using ps-PDT. They used either a non-reflective balloon or cylindrical diffusers alone to deliver a light dose of 100–250 J/cm. All patients were on long-term PPI therapy. Nd:YAG laser was used to ablate small residual areas of Barrett's mucosa. Patients were followed for 4–84 months (mean of 19 months). Conversion of approximately 75–80% of treated Barrett's mucosa to normal squamous epithelium was found in all patients with complete elimination in 43 patients. Dysplasia was eliminated in 78 patients. Ten of the thirteen malignancies were ablated. Of clinical importance, in their initial work, PDT was directed only to the dysplastic segment of Barrett's mucosa. Dysplasia developed during follow-up in 11 of 48 patients in *untreated* Barrett's mucosa requiring additional therapy.

Panjehpour et al. [12] used a 5 or 7 cm non-reflective PDT balloon and Nd:YAG thermal ablation in 60 patients with Barrett's esophagus with low-grade dysplasia, HGD, and early cancer. Patients were followed for 3–18 months (mean of 9.8 months). While the protocol was designed to deliver 175 J/cm for low-grade dysplasia and 200 J/cm for HGD, the majority of patients received 200 J/cm due to history of high grade or presence of nodular disease. Nodular areas received an extra light dose of 50–75 J/cm using a short diffuser prior to balloon treatment. Balloon pressure was maintained between 20 and 30 mm Hg during laser delivery. They reported ablation of cancer in all patients, and elimination of HGD in 96% of patients. Cancer and dysplasia was eliminated in 77% of patients. Barrett's mucosa was totally eliminated in 42% of patients. The overall length of Barrett's segment was reduced by 5.22 cm. Wang [13] used hematoporphyrin derivative as the photosensitizer and short cylindrical diffusers passed through the biopsy channel of the endoscope. Using a light dose of 200 J/cm, they treated 26 patients and achieved elimination of HGD in 88%. Elimination of Barrett's mucosa was seen in 35% of patients. Wolfsen et al. [14] reported results of ps-PDT in 102 patients with HGD and mucosal adenocarcinoma. The median follow-up was 1.6 years. They used 2.5–5.0 cm cylindrical diffusers passed through the endoscope and delivered a light dose of 150–225 J/cm. Using a single dose of PDT, complete ablation of Barrett's epithelium was obtained in 56% of patients. They used argon plasma coagulator to ablate the residual Barrett's mucosa in the remaining patients. Four patients (4%) had incomplete ablation of Barrett's mucosa. In three patients, subsquamous HGD and carcinoma was detected. Esophagectomy was used to successfully resect the intramucosal cancer without any evidence of submucosal or lymph involvements. The fourth patient had previously undergone EMR documenting intramucosal carcinoma with extensive thermal effect limiting evaluation of deeper tissue layers. CT and EUS demonstrated abnormal lymphadenopathy. Despite radiation and chemotherapy, the patient developed metastatic adenocarcinoma.

Long-term results of PDT for Barrett's esophagus have also been reported. Overholt et al. [16] reported on 103 patients in a Phase I/II study evaluating ps-PDT in the treatment of Barrett's dysplasia or early cancer using a cylindrical diffusers or non-reflective balloon. Eighty-two patients completed a mean follow-up of 58.5 months (range 41–132). Following PDT, the length of Barrett's mucosa decreased by a mean 6.92 cm (range 1–22 cm). Fifty-six of eighty-two patients (68%) had elimination of Barrett's mucosa. Of the 65 patients with HGD followed for the entire 5-year follow-up, 60 (94%) had elimination of HGD.

Three patients (4.6%) developed subsquamous adenocarcinoma. The first case was diagnosed 6 months after PDT. We believe the cancer was pre-existing and that the initial PDT did not clear the lesion. The patient was non-operative and was therefore treated with PDT a second

time. The lesion was cleared and the patient remained free of disease when last seen 3 years from the second PDT session. In two patients, subsquamous cancer was found 5 years post-PDT. Both patients had initially been cleared of all Barrett's as determined by biopsies on their previous two annual exams. Interestingly, both cancers were 1–3 mm in size, were endoscopically visualized as small submucosal nodules and both occurred within 1–2 cm of the neo-squamocolumnar junction. Both patients had reduced their PPI medications over the proceeding 1–2 years. One was retreated with PDT and was clear 2 years after retreatment. The third patient was treated with brachytherapy but died 6 months later. Based on the medical and surgical literature, an expected incidence of cancer in these 65 patients would have been between 16 and 32, indicating a marked reduction in the incidence of cancer in patients with HGD treated with ps-PDT, thermal ablation and PPI therapy. Subsquamous, non-dysplastic metaplastic epithelium was found in four patients (4.9%). It should be noted that these patients were treated at different stages of a Phase I–II PDT protocol which included optimization of different treatment parameter such as light dose and balloon pressure, two very important parameters.

POTENTIAL SIDE EFFECTS AND COMPLICATIONS

The side effects and complications reported in the multicenter study best represent the expected such incidences using the PDT techniques described in this article. During the multicenter randomized study, patients reported chest pain (20%), nausea (11%), vomiting (32%), constipation (13%), dysphagia (19%), dehydration (12%), and hiccups (10%) [15]. While not reported in the multicenter study, we typically see patients running a low-grade fever following PDT. Chest pain, nausea and vomiting and, dysphagia were transient and were controlled with medications. Overall, 36% of patients developed strictures which were managed successfully with dilations. Twelve percent of patients developed strictures after one PDT as opposed to 32% from two treatments and 9% after a third treatment [15].

Others have reported different rates for incidence of esophageal strictures. Overholt et al. [11] reported an overall esophageal strictures in 34% of patients. They indicated that use of longer centering balloons reduced the incidence of strictures possibly due to elimination of treatment overlaps when using sequential PDTs using short balloons. In another publication, Overholt et al. [16] reported strictures in 18% of patients who received one PDT and 50% of those who received two PDT treatments, 30% overall. Using a light dose of 200 J/cm, Panjehpour et al. [12] reported an overall 31% esophageal strictures using a 7 cm and 7% strictures using the 5 cm non-reflective balloons. Additionally, they reported no improvement in rate of stricture formation when oral steroids were administered after PDT. Wang [13] reported strictures in 27% of patients treated with hematoporphyrin derivative and cylindrical diffusers. Wolfsen et al. [14] reported strictures requiring dilations in 20% of patients. A median of five dilation procedures were needed to restore stable lumen patency. One should note that above data represents information collected during different treatment protocols where critical treatment parameters, such as light dose, and delivery technique (balloon vs. diffuser treatment), number of treatment, etc. were different in each report. Therefore, a direct comparison of reported stricture rates is difficult and should be done cautiously.

Photosensitivity reaction is a drawback of ps-PDT. In the multicenter study [15], sunburn-like reactions affected mostly the skin of the face, hands, and neck. The majority of reactions were mild and resolved without any medical intervention. Seven percent of cases had severe reactions. Wolfsen et al. [14] reported skin phototoxicity in 18% of patients due to inadvertent exposure to sunlight. Severe reactions may require treatment to include steroids to reduce the symptoms. Patients receiving porfimer sodium must protect their skin and eyes from sun and bright lights for at least 30 and up to 90 days. The importance of proper patient education about photosensitivity cannot be overemphasized.

Other complications have been reported in publications prior to the multicenter trail. There is a small risk of atrial fibrillation after PDT. No atrial fibrillations were reported in the 138 patients treated during the multicenter study [15]. In a series of 100 patients treated during initial phase of the protocol development, 3 patients developed atrial fibrillation [11]. All cases responded to medical intervention. In a series of 102 patients, Wolfsen et al. [14] reported atrial fibrillation in one patient who received a PDT treatment to a 15 cm length of Barrett's esophagus. Cardiac evaluation did not reveal any significant underlying coronary artery disease. Patient responded to oral anticoagulant therapy and converted spontaneously to normal sinus rhythm. Another patient with significant coronary artery disease and history of heart failure, developed recurrent congestive heart failure after a 12 cm segment of Barrett's was treated. This patient required hospitalization and responded to medical intervention. In a series of 12 patients treated by Overholt et al. [22] evaluation of cardiac enzymes and EKG demonstrated no myocardial abnormalities. It should be noted that treatment parameters in the multicenter study [15] were optimized compared to those patients treated in the initial phases of the study using different light delivery devices, higher light doses, and long treatment segments [11,14]. We believe atrial fibrillation is related to the depth and extent of esophageal injury and the associated inflammation resulting in some underlying cardiac conduction disturbance. Atrial fibrillation occurs only in cases treated at the level of the left atrium.

Another potential complication may be perforation of the esophagus. No perforation was reported in the multicenter randomized study using the balloon light delivery technique [15]. Using diffuser light delivery device, Wolfsen et al. [14], reported perforation in one patient who was treated for a 7 cm segment of Barrett's esophagus. The patient

developed severe chest pain within 2 days of PDT. Patient showed no changes in physical examination, hemodynamic instability or cardiopulmonary symptoms. While contrast esophageal radiography showed no sign of the perforation, CT demonstrated free air in the chest and abdomen indicating a transient perforation of gastroesophageal junction possibly due to vomiting. Patient was admitted for observation, bowel rest, and antibiotic. His symptoms were completely resolved within a week without the need for surgery.

In addition, patients may develop small pleural effusions that are asymptomatic. In a group of 14 patients who underwent chest X-ray 48 hours after PDT, 6 had bilateral plural effusions, 4 had left pleural effusion, 1 had small right plural effusion, and 3 patients had normal chest x-rays [11]. Overall, pleural effusion was symptomatic in 2% of patients requiring thoracentesis [11]. Patients should be monitored closely for signs and symptoms of dyspnea indicating the possibility of pleural effusion, typically detected 2–4 days after PDT. Pleural effusions typically clear spontaneously over several weeks. Oxygen saturation in the high 80s is typical when patients return for their 48 hours follow-up endoscopy.

CONCLUDING REMARKS

In summary, porfimer sodium balloon PDT for Barrett's esophagus is a powerful endoscopic treatment that can effectively eliminate Barrett's HGD and reduce the development of cancer. Patient selection should be done carefully to include EUS evaluation of nodular area. EMR is recommended for treatment of nodular areas prior to PDT. High-dose proton pump inhibitor (PPI) therapy should be an integral part of PDT management of Barrett's esophagus. Long-term follow-up endoscopies should be performed at regular intervals. Lugol's chromoendoscopy and adjuvant thermal ablation should be available on follow-up endoscopies for detection and ablation of residual small islands of Barrett's mucosa. Proper patient education is extremely important to provide detailed instructions for management of side effects and reduce the risks of photosensitivity reaction [23]. Lastly, application of PDT for management of Barrett's esophagus requires a team effort to include dedicated PDT nurses, technicians, and supporting staff in addition to the physician.

ABBREVIATIONS

ps: porfimer sodium
PDT: Photodynamic therapy
EUS: endoscopic ultrasound
EMR: endoscopic mucosal resection
HGD: High-grade dysplasia
PPI: Proton pump inhibitor

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