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Endoscopic photodynamic therapy for obstructing esophageal cancer: 77 cases over a 2-year period

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Abstract

Background: Photodynamic therapy (PDT) is an alternative treatment option for the palliation of obstructive esophageal cancer. We report our experience with PDT for patients presenting with inoperable, obstructing, or bleeding esophageal cancer.

Methods: Seventy-seven patients with inoperable, obstructing esophageal cancer were treated with PDT from November 1996 to July 1998. Photofrin (1.5–2.0 mg/kg) was administered, followed by endoscopic light treatment (630 nm red dye laser) at 48 h. Dysphagia score (1 for no dysphagia to 5 for complete obstruction), dysphagia-free interval, and patient survival were assessed.

Results: Seventy-seven patients underwent 125 PDT courses. The mean dysphagia score at 4 weeks after PDT in 90.8% of the patients improved from 3.2 ± 0.7 to 1.9 ± 0.8 ($p < 0.05$). PDT adequately controlled bleeding in all six patients who had bleeding. The most common complications after the 125 PDT courses were esophageal stricture (4.8%), *Candida* esophagitis (3.2%), symptomatic pleural effusion (3.2%), and sunburn (10.0%). Twenty-nine patients (38%) required more than one PDT course, and seven patients required placement of an expandable metal stent for recurrent dysphagia. The mean dysphagia-free interval was 80.3 ± 58.2 days. The median survival was 5.9 months.

Conclusions: Photodynamic therapy is a safe and effective treatment for the palliation of obstructing and bleeding esophagus cancer.

Key words: Cancer — Endoscopy — Esophagus — Expandable metal stent — Palliation — Photodynamic therapy — Stent

The incidence of esophageal adenocarcinoma has been increasing during the past two decades [5]. Approximately 12,300 new cases of esophageal cancer were diagnosed in the United States in 1998, and the majority of these patients will die of their disease [13]. The primary treatment for patients with metastatic or unresectable disease is palliation of dysphagia and maintenance of adequate oral nutrition. The optimal treatment should be safe, effective, and cost-effective, with minimal morbidity.

Photodynamic therapy (PDT) is an alternative therapy to esophageal stent and Nd:YAG laser for the palliation of obstructing esophageal cancer. In a randomized trial, Nd:YAG laser was compared with PDT and found to have a higher perforation rate [14]. Expandable metal stents are also effective for the palliation of obstructive esophageal cancer. Potential disadvantages, include pain, severe gastroesophageal reflux, stent migration, and tumor ingrowth [1, 6]. PDT is a nonthermal process that uses selective endoscopic delivery of light with a specific wavelength to activate a photosensitizing agent that destroys tumor cells.

We report on a prospective study of patients with obstructing or bleeding esophageal cancer who underwent PDT treatment and subsequent follow-up at the University of Pittsburgh Medical Center during a 20-month period from November 1996 to July 1998.

Patients and methods

Patients with obstructing or bleeding esophageal cancer who presented to the University of Pittsburgh Medical Center from November 1996 to July 1998 were evaluated for PDT treatment. All patients had undergone previous endoscopy and had a biopsy confirming esophageal cancer. Patients with distant metastatic disease or advanced local-regional involvement were candidates for PDT for palliation of obstruction or bleeding. Advanced local-regional involvement was determined by the surgeon and included sites of grossly involved local-regional lymph nodes, matting of the gastrohepatic ligament lymph nodes, major gastric extension, and tumor extension into surrounding structures.

Bronchoscopy was performed on patients having a proximal or mid-esophageal tumor to determine whether there was involvement of the tracheobronchial tree. Patients with tracheal involvement were excluded from

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PDT treatment. Prior radiation or chemotherapy was not an exclusion criterion for PDT treatment.

Photodynamic therapy (PDT) treatment

Porfimer sodium (Photofrin II; Quadra Logic Technologies Phototherapeutics Inc., Vancouver, BC, Canada) was administered intravenously in the outpatient clinic at a dosage of 1.5–2 mg/kg injected for 3–5 min. After administration of the photosensitizing agent, patients were instructed to avoid direct sunlight for the next 4 weeks. At 48 h after administration of Photofrin, endoscopy was performed under intravenous sedation. Patients with a large obstructing esophageal tumor were dilated endoscopically with a hydrostatic balloon to allow passage of the endoscope. An optical quartz fiber (Optiguide; QLT Phototherapeutics) with a 2.5-cm tip was positioned at the distal aspect of the esophageal tumor for the initial light treatment. The tunable dye laser was calibrated to deliver light at a specific wavelength of 630 nm, with a light dosage ranging from 300 to 400 J/cm^2. The endoscope was sequentially withdrawn to deliver light over the entire tumor surface. For bulky endoluminal disease, the cylindrical quartz fiber was embedded into the tumor to minimize exposure of the surrounding normal esophageal mucosa. In all cases, the endoscopist positioned the light fiber so that delivery to normal esophageal mucosa was minimized.

Repeat endoscopy was performed 48 h after the initial treatment to assess tumor response, debride necrotic tumor, and, if needed, deliver a second light treatment. Mechanical debridement of necrotic tumor was performed using snares, balloon dilation, and liberal saline irrigation to enhance luminal patency. Liberal use of balloon dilation (18-mm Microvasive Balloon; Boston Scientific Corp., Natick, MA, USA) was performed in an effort to minimize subsequent stricture formation.

We also treated patients with PDT who presented with tumor ingrowth or overgrowth as a complication of esophageal stent. Tumor ingrowth and overgrowth were seen endoscopically in patients who had an uncovered esophageal stent; tumor overgrowth was seen in patients who had a covered esophageal stent. The same light dosage used to treat tumor ingrowth and overgrowth was used in patients with a primary esophageal tumor.

Clear liquid was started on day 1 following the initial PDT treatment. Patients remained on a liquid diet until completion of the PDT treatment. If they could tolerate it, all patients were advanced to a soft diet 2–3 days after PDT treatment.

Analysis of results

Data were collected prospectively and entered into a computerized database (Microsoft Excel). They included demographic data, reason for treatment (bleeding or obstruction), history of prior esophageal stent, history of prior chemotherapy or radiation therapy treatment, tumor characteristics (histology, tumor length, tumor location), total amount of light delivered, dysphagia score, dysphagia-free interval, posttreatment complications, and survival.

The primary end point was the impact of treatment on dysphagia. Dysphagia was graded prospectively during follow-up visits by a registered dietitian using the following scale [14]: grade 1 = asymptomatic, grade 2 = difficulty swallowing some solid foods but ability to swallow semisolid foods, grade 3 = difficulty swallowing solids but ability to swallow liquids, grade 4 = difficulty swallowing liquids, grade 5 = inability to swallow anything, including saliva.

Improvement in dysphagia was considered successful if the baseline dysphagia score decreased by at least one point after treatment and the patient achieved a dysphagia score of 3 or better. The dysphagia-free interval was calculated from the date of documented dysphagia improvement until the date of documented worsening of dysphagia or death.

Persistent dysphagia was defined as continued dysphagia after treatment without an improvement in swallowing. *Recurrent dysphagia* was defined as redevelopment of dysphagia after initial improvement 30 days post-PDT. *Complications* were reported as the number of adverse events after the 125 PDT courses. *Esophageal perforation* was reported as the number of perforations occurring in 77 patients. *Survival* was calculated using the Kaplan-Meier method from the time of first PDT treatment until death. All values were reported as mean ± standard deviation. Differences in dysphagia scores were analyzed using a paired Student's *t*-test; *p* values of <0.05 were considered statistically significant.

Follow-up

A registered dietitian clinically evaluated all patients for dysphagia at 4 weeks post-PDT, then every 6 weeks upon presentation of clinical deterioration until death. Patients identified with recurrent obstructive tumor were given the option of further PDT treatment or the placement of an expandable metal stent (Ultraflex; Boston Scientific Corp.) if they had severe extrinsic tumor compression. An uncovered esophageal stent was routinely used, unless there was radiologic evidence of esophageal perforation, in which case a covered flexible esophageal stent was placed.

Results

Seventy-seven patients underwent 125 PDT courses for obstructing or bleeding esophageal cancer. Our study group was comprised of 14 women and 63 men; their mean age was 69 years (range, 51–86). PDT was administered as the primary palliative treatment for esophageal obstruction ($n = 87$), bleeding ($n = 6$), or tumor ingrowth/overgrowth through a previously placed esophageal stent ($n = 32$).

Histology showed adenocarcinoma in 64 patients and squamous cell carcinoma in 13 patients. The mean tumor length was 6.2 ± 2.8 cm (range, 3–15). Tumor location was in the upper esophagus in 10 patients, mid-esophagus in 13 patients, and distal esophagus in 54 patients. Thirty-three patients (43%) had previously undergone radiation or chemotherapy treatment. Our mean total light dose delivered for a single course of PDT was 1,225 J.

Endoscopic views at 48 hs after PDT treatment routinely showed edema, tumor discoloration, and necrosis and minimally affected normal tissue (Fig. 1). Patients with residual viable tumor had additional light delivered without reinjection of Photofrin. At 4 weeks after PDT, significant improvement was seen in dysphagia scores in 90.8% of the patients from 3.2 ± 0.7 to 1.9 ± 0.8 ($p < 0.05$, Student's paired *t*-test). PDT adequately controlled bleeding in all six patients without the need for Nd:YAG laser therapy.

Twenty-nine patients (38%) required retreatment with PDT for recurrent dysphagia. Sixteen patients received two PDT courses, eight patients received three courses, four patients received four courses, and one patient received five courses. The overall mean dysphagia-free interval was 80.3 ± 58.2 days (range, 5–345). Overall median survival was 5.9 months following initial PDT treatment.

Nineteen patients had had an existing esophageal stent placed prior to PDT ($n = 12$), and we placed a stent in seven patients following PDT ($n = 7$). The indication for PDT treatment in the 12 patients with a previously placed stent was tumor ingrowth or tumor overgrowth above and below the stent. A total of 23 PDT courses were delivered to these 12 patients whose subsequent dysphagia scores improved from 3.3 ± 0.6 preoperatively to 2.0 ± 0.7 at 4 weeks post-PDT ($p < 0.05$, Student's paired *t*-test). Complications after PDT included stent migration that required subsequent endoscopic retrieval in three of 12 patients.

In seven patients, an expandable metal stent was placed after the initial PDT treatment; indications for adding an expandable metal stent after PDT were persistent dysphagia ($n = 2$) and recurrent dysphagia ($n = 5$). Upon endoscopy 48 hours post-PDT, the two patients with persistent dysphagia showed minimal tumor necrosis and were therefore classified as early PDT failures. When dysphagia persisted be-

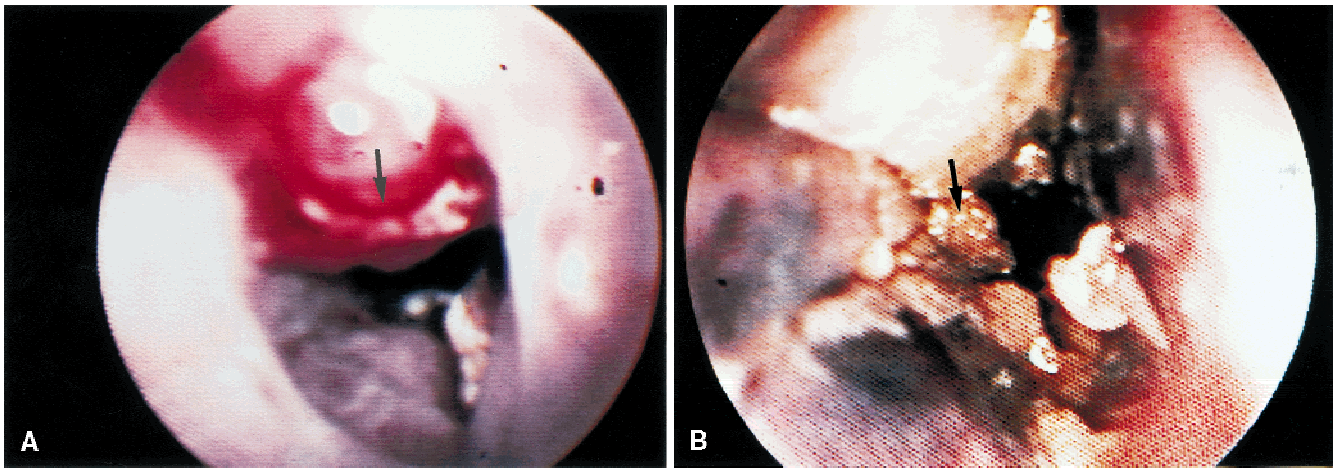

Fig. 1. **A** Endoscopic view of obstructing and bleeding esophageal carcinoma. **B** This endoscopic view at 48 h after photodynamic therapy (PDT) shows tumor necrosis (arrow).

yond 4 days postoperatively, stents were placed at 5 and 26 days.

Intravenous administration of Photofrin was not associated with any acute toxicity. A total of 120 of the 125 PDT courses were performed under awake sedation. During five treatments, general endotracheal anesthesia was required to protect the airway from impending aspiration or to achieve adequate patient comfort. Postoperative complications after the 125 PDT courses included esophageal stricture (4.8%), *Candida* esophagitis (3.2%), symptomatic pleural effusion (3.2%), aspiration pneumonia (1.6%), and sunburn (10.0%). Most sunburn was limited to erythema (first degree); blistering (second degree) occurred in one patient.

Three of 77 patients (3.9%) developed esophageal perforation identified on barium swallow after PDT. Taking into account the total number of PDT treatments ($n = 125$), the incidence of esophageal perforation was 2.4%. The three patients who developed perforation had undergone balloon dilation at the time of PDT for major luminal obstruction that prohibited the passage of the endoscope. In two patients, the perforations were treated successfully by nonsurgical means with placement of a covered esophageal stent; the third patient required an esophagectomy with diversion. This patient later died from sepsis.

Esophageal strictures after PDT were treated with endoscopic balloon dilation. Symptomatic pleural effusions were managed by thoracentesis. The 30-day mortality rate was 3.9% ($n = 3$). One patient died from aspiration pneumonia, one from disease progression, and another from esophageal perforation.

Discussion

There are many methods for the palliation of malignant esophageal obstruction [1–4, 6–12, 14–20]. Surgical bypass for palliation has been curtailed almost completely due to the availability of less invasive endoscopic methods. The two methods most frequently used for the palliation of malignant dysphagia are Nd:YAG laser treatment and expandable metal stents. Bourke reported effective palliation of malignant dysphagia in 96% of 70 consecutive patients treated with Nd:YAG laser [3]. In their series, 73% of patients remained free of dysphagia until death. Complications of laser therapy included perforation (1.4%), retrosternal chest pain (6%), and bleeding (3%) [3].

Expandable metal stents have also demonstrated effective palliation for malignant dysphagia [1, 6]. Reported complications include unrelenting pain, severe gastroesophageal reflux, stent migration, and tumor ingrowth. In a small prospective randomized trial, an expandable metal stent demonstrated superior palliation of malignant dysphagia over Nd:YAG laser therapy [2]. Controversy over the best modality for palliation of malignant dysphagia continues, and the availability of several modalities indicates that the ideal treatment has not been established. One treatment option is often chosen over another based on the availability of instrumentation and equipment, the physician's experience with the procedure, and the patient's preference.

PDT is the most recent FDA-approved modality for the palliative treatment of obstructing esophageal cancer. Prior to FDA approval, phase II and III trials were reported by several groups for palliation of dysphagia in patients with obstructing esophageal cancer. McCaughan reported the results of PDT treatment in 77 patients with esophageal carcinoma during a 12-year period [16]. All their patients had failed conventional treatment or were ineligible for surgical therapy. Median survival for their patients was 6.3 months. Their only major variable affecting survival after PDT treatment was the clinical stage. The low incidence of complications in their series included transient elevation of temperature, pleural effusions, infiltrates, pulmonary edema, aspiration pneumonia, respiratory-esophageal fistula, strictures, and sunburn. Lightdale reported the only prospective, randomized, multicenter study comparing PDT with Nd:YAG laser therapy for obstructing esophageal cancer [14]. In their study, 236 patients at 24 centers were randomized to undergo PDT or Nd:YAG laser therapy. Improvement of dysphagia was equivalent between the two groups, but PDT caused fewer acute perforations (1%) than Nd:YAG laser therapy (7%).

Our study is one of the first reports of the clinical application of PDT for palliation of malignant dysphagia since

FDA approval. In our series of 77 consecutive patients treated during a 20-month period, PDT was 90% effective in palliating malignant dysphagia at 4 weeks after PDT and in controlling bleeding in a subset of six patients. The mean dysphagia-free interval in our study was 80 days. This surpassed the time to palliation failure of 34 days that was as reported in Lightdale's multicenter trial [14]. One explanation for our longer dysphagia-free interval might be that our experience was limited to a large, single-institution, tertiary-care center, as opposed to the 24 different institutions included in the multicenter trial.

The depth of penetration and tumor necrosis after PDT is limited to approximately 5 mm. This limited depth provides a safety factor and is probably responsible for the low perforation rate of 0–1% [9, 13, 17, 18]. However, full-thickness perforation can occur if the light dose is too high [15]. The incidence of esophageal perforation in our series (3.9%) was higher than that of previous published series. In our three cases of esophageal perforation, balloon dilation was performed before PDT to allow passage of the endoscope through the obstructing tumor. It is unclear whether the mechanical dilation of the esophagus, the use of PDT, or a combination of these two factors contributed to the perforation. We do not believe that these perforations were related to our learning curve with the procedure or to any minor changes in our technique.

An important aspect of the PDT treatment is the repeat endoscopy performed at 48 hours after the initial PDT treatment. The purpose of the second endoscopy is to debride necrotic tumor, treat residual viable tumor, and gently dilate the treated area to minimize subsequent stricture formation. Residual tumors identified during endoscopy received a second light treatment but no subsequent debridement.

Patients who present with dysphagia from tumor ingrowth or overgrowth represent a difficult problem. The published incidence of tumor ingrowth has ranged from 1.6% to 36% [1, 6]. Endoscopic treatment options for tumor ingrowth include thermal ablation (such as Nd:YAG laser therapy), argon coagulation, or insertion of a second self-expandable metal stent [8, 12]. These thermal ablative measures can treat the tumor ingrowth adequately, but they may damage the esophageal stent.

Successful palliation of dysphagia in four cases of tumor ingrowth was reported after PDT by Scheider et al. [18]. In our study, we treated 12 patients who presented with recurrent dysphagia from tumor ingrowth. All patients achieved some improvement of their dysphagia score after PDT. Complications specific to PDT treatment for patients with a previously placed esophageal stent included stent migration in three of 12 patients. Gross examination of these stents after endoscopic removal revealed no evidence of PDT-induced damage.

Median survival in our study was 5.9 months (S.E.M. 1.4), which is comparable to the median 189 days reported by McCaughan [16]. Heier [9] reported a mean survival of 145 days, as compared with 258 days (S.E.M 27) for our study. Lightdale [14] reported a median survival of 123 days, but up to 40% of their study participants were lost to follow-up at 1 month. These similar survival data indicate that PDT is a primary palliative modality and does not increase survival time.

The advantages of PDT over Nd:YAG laser relate to the nonthermal photochemical process of tumor ablation. PDT is simple to perform and patients can tolerate the therapy under awake sedation. There is minimal pain associated with the light delivery in the perioperative period. Disadvantages of PDT include the requirement for expensive equipment (laser), the long waiting period between the time of drug injection and treatment, the high cost of the photosensitizing agents, and skin photosensitivity.

Photodynamic therapy is a safe and effective modality for the palliation of obstructive esophagus cancer. The procedure should be performed by surgeons or endoscopists with experience in all aspects of endoscopic treatment of obstructing esophageal cancer, especially balloon dilation and insertion of an expandable metal stent. Ideal candidates for PDThave aprimarily endo-luminal tumor with minimal stricturing or extrinsic compression. Close follow-up is important to identify any patients with early PDT failure or recurrent dysphagia. Several PDT treatments may be required in patients who have a prolonged survival period. Further studies are needed to determine the cost-effectiveness of PDT and relative patient quality of life, as compared with other modalities, that can be achieved with this mode of palliation.

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