Role of Photodynamic Therapy in Unresectable Esophageal and Lung Cancer

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The incidence of esophageal cancer has increased dramatically in the Western population in the last two decades. Many of these patients tend to present late in the disease course with symptoms of dysphagia and malnutrition. Thus a majority of patients at presentation may require palliation of their symptoms. Lung cancer is the most common cause of cancer related mortality in the United States. Similar to esophageal cancer, many patients present in advanced stages where surgical resection for cure may not be an option. Endobronchial obstruction from both primary and metastatic neoplasm causes significant morbidity. The modalities, which are currently available for palliation of symptoms include surgery, photodynamic therapy, dilation, external beam radiation, stents, Nd:YAG laser therapy, and brachytherapy. Each of these modalities has their specific advantages and drawbacks. In this article, we discuss the role of photodynamic therapy in the palliation of esophageal and lung cancer. Lasers Surg. Med. 38:396–402, 2006. © 2006 Wiley-Liss, Inc.

Key words: photodynamic therapy; PDT; esophageal cancer; Barrett's esophagus; lung cancer; palliation; endobronchial disease; dysphagia; bleeding

PHOTODYNAMIC THERAPY

History

The history photodynamic therapy (PDT) began in 1900 with Raab and his observation that light and acridine together were toxic to living organisms, namely paramecium. This work was done under Professor von Tappeiner, who coined the term photodynamic action in 1907 [1–3]. In 1978 Dougherty and colleagues [4] demonstrated the photodynamic effect in several cancers sensitized to a photosensitizer and subsequently exposed to light at a specific wavelength. Table 1 summarizes how PDT has progressed since Raab's initial discovery [5].

Since the discovery of porfimer sodium, many FDA approved uses have surfaced which are listed on the National Cancer Institute website, including treatment and palliation for early- and late-stage lung and esophageal cancers. Specifically, there was recent FDA approval for use of porfimer sodium with PDT in the treatment of high-grade dysplasia in Barrett's esophagus. Currently, there are studies on potential therapeutic and palliative uses of PDT in other malignancies like mesothelioma and metastatic lung disease. This article will focus on the role of photodynamic therapy in the palliative treatment of advanced esophageal and lung cancer.

Mechanism of Action

Photodynamic therapy requires a photosensitizer that can accumulate in tumor tissue marked for destruction. The most widely used and studied photosensitizer is porfimer sodium (Photofrin, Axcan Pharma, Quebec, Canada)—the chemically altered hematoporphyrin derivative. Porfimer sodium is an aromatic ring complex, which achieves an excited state after exposure to 630 nm wavelength light, the absorption maxima of porfimer sodium. The excited molecule then reacts with oxygen to generate singlet oxygen and other reactive oxygen species [5]. Because of its hydrophobic nature, porfimer sodium tends to accumulate in membranes of cells and organelles (especially mitochondria), causing reactive oxygen-induced damage to the membrane as well as membrane-embedded proteins. This disruption leads to multiple intracellular changes that eventually result in cellular apoptosis, necrosis, ischemia, inflammation, and immune responses [3]. PDT-porfimer sodium also causes local vascular destruction, which depletes the nutrient and oxygen source for tumor cells [1].

The 630 nm wavelength of light leads to a penetration depth of 5–6 mm [5]. In general, the longer the wavelength of light, the greater the depth of penetration. Eight hundred nanometers is a good target wavelength for photosensitizer absorption maxima as determined by the attenuation depth equation which shows that tissue penetration by light is a function of particle scatter and local tissue light absorption [5]. Shorter wavelengths collide with molecules and thus have greater scatter and worse tissue penetration; wavelengths of light greater than 800 nm are absorbed by water molecules, converting light

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TABLE 1. History of the Development of PDT

Time	Author	Findings
1900	Raab	Light in combination with acridine was toxic to the paramecium
1920s	Policard	Tumor tissue fluoresced more than healthy tissue
1940s	Figge	Affinity of tumor tissue for porphyrins
1950s	Ronchese	Activation of fluorescent molecules with the Woods light to better delineate the cancerous tissue
1950s	Rasmussen	Hematoporphyrin intravenous injection led to fluorescence of cancer tissue
1960s	Winkelman	Synthetic porphyrins for tumor tissue localization
1960s	Lipson	Hematoporphyrin derivative could detect and photosensitize tumor tissue
1970s	Dougherty	Activated dyes such as flurescein were antitumor agents
1970s	Weishaupt	Molecular mediator of tumor death from photosensitizing agents was singlet oxygen
1990s	Schwartz	Hematoporphyrin derivative yielded high singlet oxygen species
1990s	Dougherty	Developed porfimer sodium (Photofrin®), a purified version of hematoporphyrin derivative

energy to heat energy [5]. PDT at 630 nm is called a non-hyperthermic treatment modality.

Targeting of tumor tissue by porfimer sodium can be postulated by both the tumor cells' higher concentration of LDL receptors and porfimer sodium's affinity for lipoproteins. However, experiments by Korbelik and Hamblin show no increased uptake of porfimer sodium by the LDL receptor mediated pathway [5]. Instead, the main routes by which cells accumulate porfimer "may be passive diffusion thru the outer membrane or some other receptor-mediated transport process that is highly dependent on the aggregation state of the molecules" [5]. Tumor tissue selectivity can also be accounted for by the hypervascular cancerous tissue and poor lymphatic drainage, resulting in accumulation of photosensitizer in the target area. Attempts at increasing specificity of porfimer sodium accumulation in tumor cells by various methods have yielded disappointing results. One attempt was made at attaching antibodies specific to tumor cell proteins onto porfimer sodium molecules. No difference in accumulation was appreciated [5].

Tissue selectivity is more easily achieved by directing light onto the tumor, whether by local placement or impaling the tumor. As described later in this article, a balloon-centering device to flatten the esophageal folds may be used to allow a more homogenous distribution of light to diseased esophageal mucosa.

Photosensitizer and PDT Administration in General

Porfimer sodium is injected 24–72 hours before treatment at a dose of 1.5–2 mg/kg. We wait for 48 hours from photosensitizer injection to administration of light therapy because tumor cells need time to selectively retain more photosensitizer than normal tissue due to differences in cancerous tissue vascular supply and lymphatic drainage [6]. After 48 hours, the patient is lightly sedated and upper endoscopy or flexible bronchoscopy is performed. A diffusing tip fiber is introduced through the biopsy channel of the endoscope–bronchoscope and 630 nm light therapy is administered alongside or within tumor tissue, depending on size. Follow-up endoscopy–bronchoscopy is often done to assess degree of tumor necrosis and to clean up the necrotic debris. Sometimes patients get an additional dose of light therapy.

Role of Photodynamic Therapy in Unresectable Esophageal Cancer

The incidence of esophageal cancer has increased dramatically in the Western population in the last two decades [7]. In 1975, about three-fourths of the esophageal neoplasms were squamous cell carcinomas and the remainder were adenocarcinomas. During the last two to three decades, this pattern has changed dramatically. The incidence of squamous cell carcinomas has declined while the incidence of adenocarcinomas has increased. At presentation more than 50% of patients have metastatic disease or are unresectable. Many of these patients tend to present late in the disease course with the common and life-disrupting symptoms of dysphagia and malnutrition. Thus a majority of patients may require palliation of their symptoms. The modalities which are currently available for palliation of symptoms include bypass surgery, photodynamic therapy, esophageal dilation, external beam radiation, stents, Nd:YAG laser therapy, and brachytherapy. Each of these modalities has their specific advantages and drawbacks. In this article, we discuss the role of photodynamic therapy in the palliation of esophageal cancer.

Clinical Studies With Photodynamic Therapy for Advanced Esophageal Cancer

PDT has been shown in many studies to be effective in palliation and has proven beneficial in improving the common esophageal cancer-related symptoms of dysphagia and bleeding. Luketich and colleagues [8] from the University of Pittsburgh reported their experience with PDT in patients presenting with inoperable obstructing or bleeding esophageal cancer. This study included 77 esophageal cancer patients who were treated with porfimer sodium, followed by endoscopic light activation in 48 hours. The mean dysphagia score at 4 weeks after PDT improved significantly in 91% of patients from a mean score of 3.2 to 1.9 ($P<0.05$; 1 for no dysphagia to 5 for complete obstruction). PDT controlled bleeding in all six patients who had bleeding. The mean dysphagia free interval in this study was 80 days, and the median survival was 5.9 months. Of note, 38% of patients required greater than one PDT course

and 7 of the 77 patients required a stent for recurrent dysphagia.

In an updated series from the University of Pittsburgh Litle and colleagues [9], reported their experience in 215 patients with bleeding, obstructing, or bleeding, and obstructing esophageal cancer who were treated with PDT (Figs. 1,2). They evaluated the dysphagia scores, duration of palliation, reinterventions, complications, and survival. They noted an improvement in dysphagia in 85% of the patients with a mean dysphagia free interval of 66 days. Bleeding was controlled in 93% (29/31) of patients with one PDT course. Further, a subgroup of patients (30%) were able to discontinue their supplemental nutrition as they were able to nourish themselves by mouth. Esophageal stents were placed in 35 patients, with a mean interval to reintervention of 58.5 days. The complications noted in this study were perforation (2% of courses), stricture (2%), candida esophagitis (2%), symptomatic pleural effusions (4%), and sunburn (6%). Given these findings, the investigators concluded that PDT offers an effective palliation in patients with obstructing esophageal cancer in 85% of treatment courses. They also concluded that the ideal candidate for PDT is a patient who has an obstructing endoluminal cancer. However, in some patients, reintervention and a multimodality approach is required to maintain palliation. Further, a treatment algorithm for palliation of locally advanced esophageal carcinoma was proposed (Fig. 3). Table 2 summarizes the work of several investigators in the use of PDT for inoperable esophageal cancer [8–12].

In another interesting study, Lightdale and coworkers conducted a prospective randomized multicenter trial to compare the efficacy and safety of PDT with porfimer
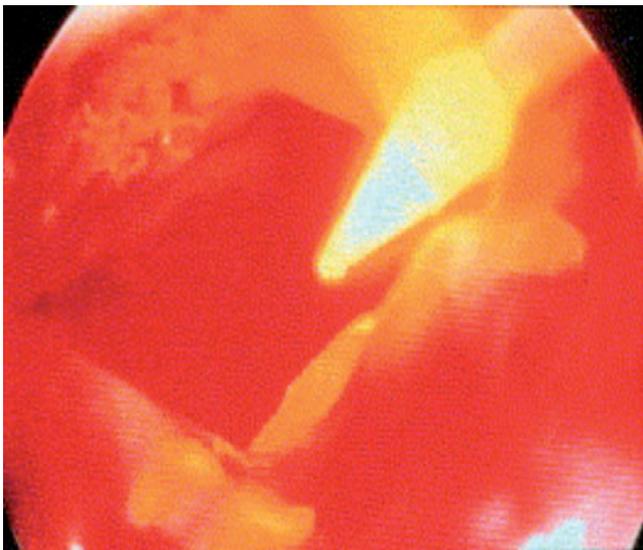

Fig. 1. Endoscopic view of light application for photodynamic therapy. Reprinted from Surgical Clinics of North America, 85, Christine N, Patel A, Landrenean R. Photodynamic therapy/stents/brachytherapy, 569–582; 2005, with permission from Elsevier.
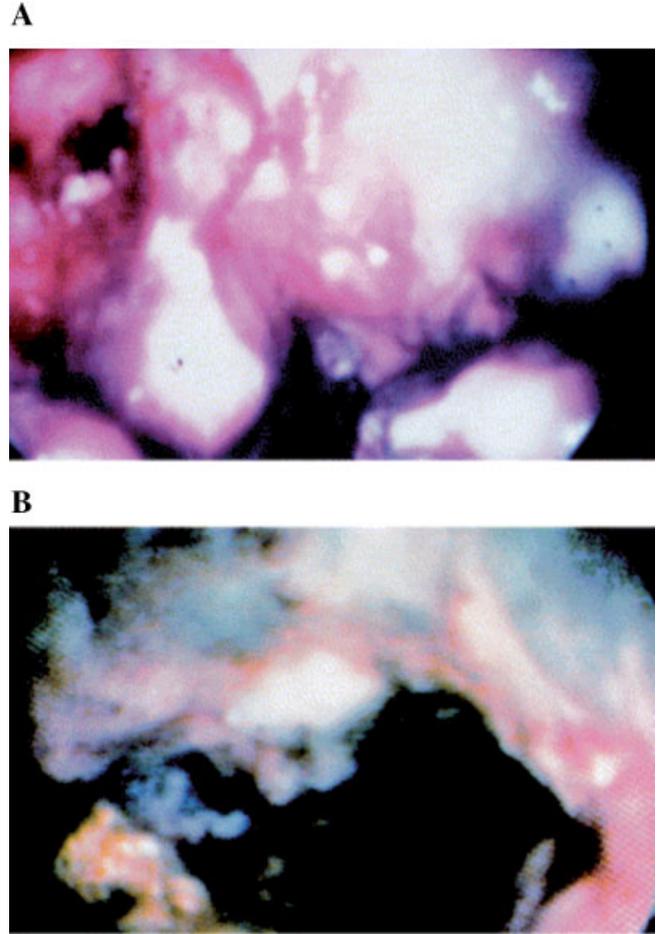

Fig. 2. **A**: Shows an endoscopic view of an obstructing esophageal cancer; **B**: Shows tumor necrosis noted on endoscopy 48 hours after PDT. Reprinted from Annals of Thoracic Surgery, 76, Litle V, Luketich J, Christine N, Buenaventura P, Alvelo-Rivera M, McCaughan J, Nguyen N, Fernando H, Photodynamic therapy as palliation for esophageal cancer: experience in 215 patients, 1687–1693, 2003 with permission from the Society of Thoracic Surgeons.

sodium versus Nd:YAG laser in the treatment of patients with obstructing esophageal cancer [13]. A total of 236 patients were randomized from 24 institutions, of which 218 patients were treated (110 with PDT and 108 with Nd:YAG laser). Objective tumor response was equivalent at 1 week, but was significantly better at 1 month in the PDT
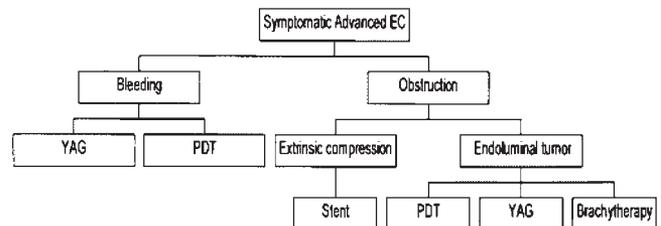

Fig. 3. Treatment algorithm for endoscopic palliation of advanced esophageal neoplasm.

TABLE 2. Summary of Selected Reports in the use of PDT for Inoperable Esophageal Cancer

	Number of patients	Mean dysphagia-free interval	Mean survival (months)
McCaughan et al.	77	Not specified	6.3
Moghissi et al.	65	Not specified	7.7
Marcon et al.	83	6 weeks	4.0
Luketich et al.	77	11 weeks	5.9
Litle et al.	215	9 weeks	4.8

group. Improvement in dysphagia was equivalent in the two groups and there was trend towards improved response with PDT in tumors located in the upper and lower third of the esophagus, long tumors and in patients who had received prior therapy. Of note, sunburn occurred in 19% of patients in the PDT group and termination of the laser session due to adverse reaction occurred more frequently in the Nd:YAG group (19% vs. 3%; $P<0.05$). Similarly perforations from the treatment or associated dilation occurred significantly more often in the Nd:YAG group (7%) compared to 1% in the PDT group ($P<0.05$). These authors concluded that PDT and Nd:YAG laser ablation resulted in equal relief of dysphagia, however the objective tumor response was equal or better in the PDT group. Further, PDT was associated with fewer acute perforations when compared to the Nd:YAG group.

Heier and colleagues [14] performed a light dosimetry analysis in 10 patients with esophageal cancer in a preliminary trial. They subsequently conducted a randomized trial in a total of 42 patients comparing PDT with Nd:YAG laser in the treatment of esophageal neoplasm. There were a total of 22 patients in the PDT group and 20 patients in the Nd:YAG laser group. Both group of patients had improvement in dysphagia, but the patients in the PDT group had a significantly longer duration of response (84 days vs. 57 days; $P<0.008$). In addition, PDT also resulted in a significantly improved Karnofsky performance status at 1 month when compared to Nd:YAG laser treatment ($+7$ vs. -7; $P<0.001$).

Adjunct therapy such as Nd:YAG laser and stenting can be used along with PDT in the palliative treatment of symptomatic esophageal cancer. Scheider and colleagues [15] evaluated PDT for the treatment of tumor ingrowth in patients with esophageal stents. In this study, four patients with tumor ingrowth into self-expanding uncovered stents developed progressive dysphagia. PDT was used to treat these patients with the dysphagia score improving in all these patients. The mean dysphagia free interval after PDT was 92 days. These authors concluded that the use of PDT for tumor ingrowth through self-expanding metal stents is safe and effective.

The FDA has approved the use of PDT as a minimally invasive prophylactic therapy for Barrett's esophagus (BE) with high-grade dysplasia (HGD) in patients not suited for esophagectomy. Recently, we have reviewed several endoscopic therapeutic modalities for Barrett's esopha-gus—specifically laser ablation modalities, in the treatment of BE in patients unfit for surgery [3]. The focus of this article however is primarily in the role of PDT in the palliative treatment of advanced esophageal and lung cancer.

Complications

Complications of PDT in the treatment of esophageal cancer include cutaneous photosensitivity, requiring patients to avoid sunlight for 4–6 weeks to prevent sunburn. Strictures typically develop 10–14 days after PDT. Most of these strictures respond to esophageal dilation. Attempts at reducing stricture formation have been made with prednisone administration along with PDT, decreasing the light energy, and using a balloon-centering device with PDT. Panjehpour and coworkers studied the effect of oral steroids in the prevention of strictures in 60 patients with Barrett's esophagus and HGD [16]. Strictures developed in 29% of patients who underwent PDT and received prednisone versus 16% who had PDT alone but the difference did not reach statistical significance [16]. The use of the centering balloon has been discussed as a way to more uniformly deliver light and perhaps minimize the incidence of stricture, but randomized trials are needed to evaluate its efficacy [3]. Other perioperative complications of PDT include Candida esophagitis 1.6%, pleural effusion 3.5%, aspiration pneumonia 1.3%, and perforation 1.6% [9].

At the University of Pittsburgh Medical Center, PDT's role in esophageal cancer is primarily palliative for symptomatic late stage disease. Patients living more than 2 months may need reintervention and adjunct therapy such as esophageal stents. In our institution, minimally invasive esophagectomy is offered to patients with high-grade dysplasia (HGD) and resectable cancer. The role of PDT in our institution as a definitive treatment in patients with HGD and early cancer is limited to high-risk patients who are not candidates for a minimally invasive esophagectomy [3,17].

Photodynamic Therapy for Endobronchial Tumors

Lung cancer is the most common cause of cancer related mortality in the United States. Similar to esophageal cancer, many patients present in advanced stages where surgical resection for cure may not be an option. Endobronchial obstruction from both primary and metastatic neoplasm causes significant morbidity, especially when present in the larger airways. Patients often complain of shortness of breath, coughing, recurrent and unresolving pneumonias, and hemoptysis. Tumors in the larger airways lend themselves more easily to endoscopic interventions. The advantage of this is obvious: patients who are not surgical candidates–which may be the case given a high prevalence of smoking, chronic obstructive pulmonary disease (COPD) and the aging population—could receive palliative or rarely even curative treatment with minimally invasive bronchoscopic interventions. Furthermore, with the limited lung function in those with severe COPD and prior lung resection, bronchoscopic therapy may serve as a tissue

sparing modality as well as the only suitable treatment alternative [18].

Clinical Studies With Photodynamic Therapy for Advanced Lung Cancer

PDT was first used for lung cancer in 1982 by Hayata and colleagues [19] when they found that PDT was able to achieve tumor necrosis with resultant reopening of the airway. In another study by LoCicero and coworkers, PDT was useful in palliation of late stage non-small cell lung cancer [20]. This study included a total of 10 patients followed over 4 years. All patients had an improvement of symptoms, especially coughing, after PDT. The average luminal obstruction was 86% which improved to 57% after treatment. At 6 months, half the patients had greater than a 50% reduction in endoluminal obstruction [15]. McCaughan and Williams reported their experience with PDT in a large series of 175 non-surgical lung cancer patients [21]. Most of these patients had advanced lung cancer. Multivariate analysis of survival showed clinical stage to be the most statistically significant factor. They concluded that length of palliation for advanced disease was equal or better than other reported treatment regimens. Another study of 100 patients by Moghissi and coworkers [22] exploring the palliative role of PDT in advanced unresectable lung cancer supports these results. In this study a total of 90 patients with advanced non-small cell lung neoplasm and 10 patients with small cell cancer were treated with PDT. PDT consisted of administration of porfimer sodium and light activation after 24–72 hours. Endoscopic debridement was performed in 5–7 days and PDT was repeated if required. PDT was associated with improvement in endobronchial obstruction, ventilation, and performance status of patients 6–8 weeks after treatment. Mean endoluminal obstruction decreased from 86% to 18%, the mean forced vital capacity (FVC) increased by 0.43 L and the mean forced expiratory volume in 1 second (FEV1) increased by 0.28 L. A total of 87 patients had a good performance status in the post-treatment evaluation compared to 43 patients in the pre-treatment period. Multivariate analysis showed that patients with a good performance status gained a survival benefit from PDT.

In an interesting study, Diaz-Jimenez and colleagues [23] reported the results of a prospective randomized controlled trial comparing PDT with Nd:YAG laser resection in 31 patients with endobronchial obstruction due to inoperable non-small cell lung neoplasm. In this trial, 14 patients were treated with PDT and 17 patients were treated with Nd:YAG laser. The PDT group had lesser patients with more advanced cancer. The two groups experienced similar symptomatic relief from treatment. Patients in the PDT group had a significantly longer duration until treatment failure ($P<0.05$), with the median time to treatment failure in the PDT group being 50 days versus 38 days in the Nd:YAG group. In addition, a significant increase in median survival ($P=0.007$) was noted in the PDT group when compared to the Nd:YAG group (265 days vs. 95 days). The increase in median

survival however may also be related to the lesser number of patients in the PDT group who had advanced cancer.

For patients with earlier stage lung cancers, some investigators have used PDT with a curative intent. This article however focuses on the role of PDT in advanced lung
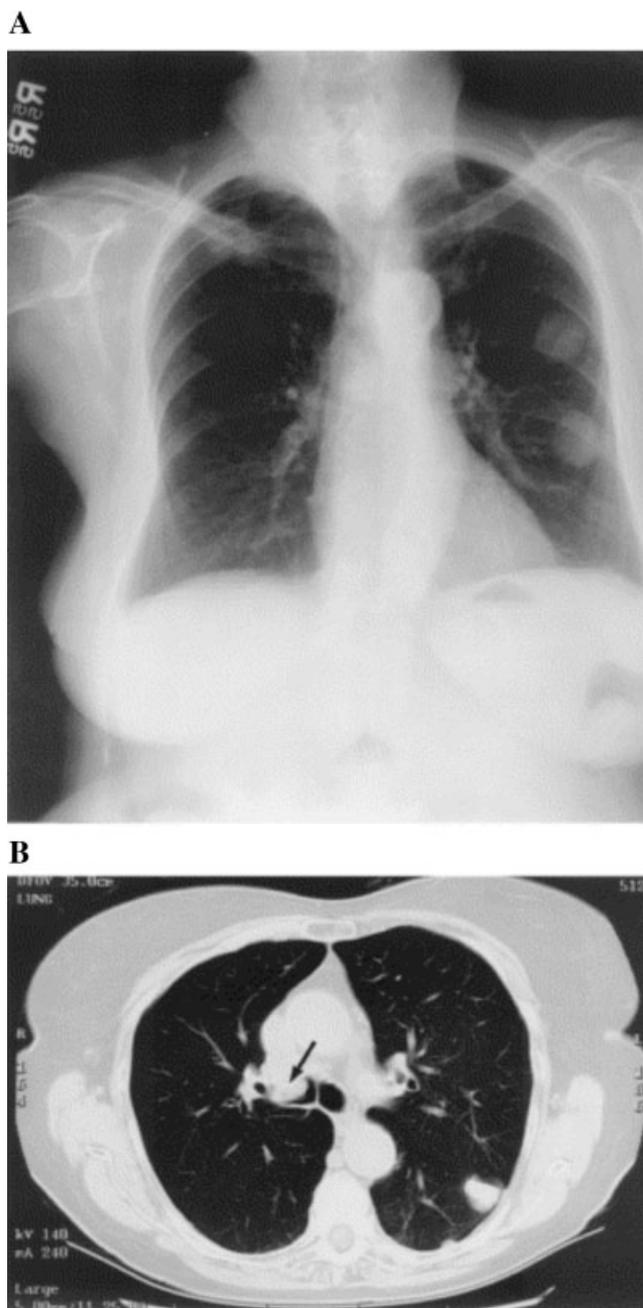

Fig. 4. **A**: Shows a Chest X-ray and (**B**) a computed tomography scan of a patient with endobronchial metastases in the right main stem bronchus. Reprinted from Annals of Thoracic Surgery, 76, Photodynamic therapy for endobronchial metatases from nonbronchogenic primaries, 370–375, 2005, with permission from Society of Thoracia Surgeons.
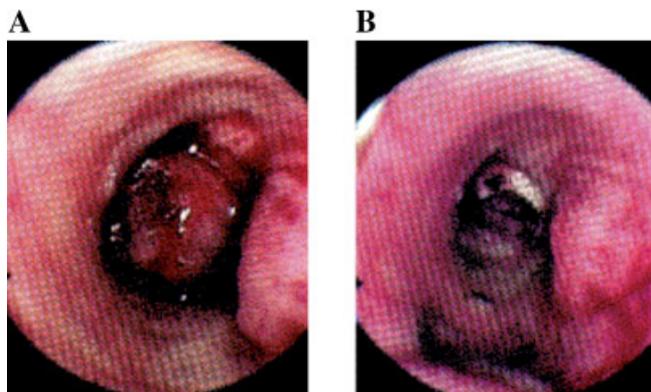
Fig. 5. **A**: Shows obstructing endobronchial lesion prior to treatment. **B**: Shows improved patency of the lumen after follow-up bronchoscopy and debridement. Reprinted from Annals of Thoracic Surgery, 76, Litle V, Christine N, Fernando H, Buenaventura P, Ferson P, Luketich J, Photodynamic therapy for endobronchial metastases from nonbronchogenic primaries, 370–375, 2003, with permission from Society of Thoracia Surgeons.

cancer and its use as definitive treatment in high-risk patients is beyond the scope of this article.

Other investigators have explored the use of PDT prior to surgical resection [24,25]. Often, these tumors were more advanced and greater than 1 cm in surface diameter brochoscopically. In a study by Kato and co workers [24], four of five patients who were originally inoperable became qualified for operation after preoperative PDT decreased the tumor burden. Seven of 10 patients who were originally thought to require pneumonectomy were able to undergo lobectomies after PDT treatment. This suggests an expanded therapeutic role for PDT from palliation to a role in pre-operative therapy prior to surgical resection.

For non-brochogenic or metastatic endobronchial lung lesions, Litle and colleagues [26] found that PDT was effective in palliation of dyspnea and hemoptysis. In this series of 27 patients, many of whom had renal cell cancer primaries, were treated with a median of two PDT sessions. All patients had a follow up bronchoscopy at 24–48 hours showing tumor necrosis (Figs. 4,5). More significant was that 85% of patients had acute relief of their primary symptoms which included hemoptysis and dyspnea. However 15% of patients developed post-operative respiratory distress. The initial respiratory insufficiency appears to be due to swelling of the endobronchial lesion and routine follow-up bronchoscopy with debridement of necrotic tumor may minimize airway compromise. Patients with extensive mediastinal adenopathy or pulmonary metastases are at higher risk of post-procedural respiratory insufficiency. Median survival time after PDT was 4 months.

At our institution, the role of photodynamic therapy in the treatment of endobronchial tumors consists primarily of palliative treatment of symptomatic airway tumors in patients precluded from surgical resection. Its use as a curative treatment is still under investigation.

CONCLUSION

In conclusion, photodynamic therapy is effective in palliation of advanced esophageal cancer and lung cancer. The ideal candidate for PDT primarily has endoluminal disease with minimal extrinsic compression. In patients with esophageal cancer, it is effective in relieving both dysphagia from obstruction and in controlling bleeding [8,9]. In particular it may be effective in treating ingrowth and obstruction of previously placed stents, and in the palliation of patients with cancer involving the high cervical esophagus [11,15]. Stents in this location are typically not used due to the proximity of the larynx and photodynamic therapy is effective in palliation for these tumors. PDT when compared to Nd:YAG laser ablation appears to provide a more durable response, duration of palliation and a lower risk of perforation. PDT can also be given concurrently with other therapies such as chemotherapy, radiation or stents. Similarly, PDT offers an effective palliation in patients with advanced lung cancer with endobronchial lesions and in patients with endobronchial metastases. Similar to esophageal cancer, it appears that PDT provides a longer duration of palliation when compared to Nd:YAG therapy in patients with non-small cell lung cancer. The main disadvantages of PDT are photosensitivity, expensive equipment and cost of the photosensitizing agent. Its advantages include relative simplicity of use, limited treatment time, and minimal associated pain. Photodynamic therapy plays an important role in the treatment of advanced esophageal and lung cancer and should be in the armamentarium of surgeons, gastroenterologists, pulmonologists, oncologists, and other specialists who play a role in the management of these patients.

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