# Photodynamic Therapy for Esophageal Cancer

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## Photodynamic Therapy

Photodynamic therapy (PDT) involves the administration of a chemical sensitizer that selectively accumulates in areas of tumor with greater concentration than in normal tissue. The chemical is then activated by the application of light to the area of the tumor, usually with a low power laser, resulting in tumor necrosis by a photochemical rather than a thermal effect[1-3]. Porphyrin compounds, most notably porfimer sodium (Photofrin), have been most frequently used clinically[4].

## PDT for Esophageal Cancer

A variety of methods have been used to carry out PDT. In the largest trial of treatment of esophageal cancer with PDT, the following method was employed[5] : Porfimer sodium (Photofrin, QLT Phototherapeutics Inc., Vancouver, B. C., Canada) was given at a dose of 2.0 mg/kg body weight by single intravenous injection over 3 to 5 minutes. After 40 to 50 hours following injection, the area of the esophageal cancer was treated with red light at a wave length of 630 nanometers from a continuous wave argon-pumped dye laser. The laser energy was delivered via an optical quartz fiber with a cylindrical diffusing tip with a power density of 400 milliwatts/cm$^2$ of diffusing tip for a total light dose of 300 Joules/cm$^2$ of tumor. The longest diffusing tip used was 2.5 cm, and for longer tumors, sequential applications were carried out to treat the entire tumor surface. After 2 to 3 days, patients were re-endoscoped to debride necrotic tumor, and residual tumor at that time (96 to 120 hours after injection of porfimer sodium) could be treated with a second application of laser light at the same light dose.

## PDT vs. Nd : YAG Laser

We carried out a multicenter study, in which patients with esophageal cancer were randomized to receive PDT with porfimer sodium and argon-pumped dye laser or Nd : YAG laser therapy[5].

A total of 236 patients were randomized and 218 treated (PDT 110, Nd : YAG 108) at 24 centers. Improvement in dysphagia was equal between the two treatment groups. Objective tumor response was also equal at week 1, but at one month, complete response (no visible tumor) and partial response (> 50 percent increase in lumenal diameter) was recognized in 32% who received PDT, and 20% who received Nd : YAG ($P < 0.05$). There were 9 complete tumor responses after PDT and 2 after Nd : YAG.

There were more mild to moderate complications from PDT. Porfimer sodium causes skin photosensitivity for 4～6 weeks, and sunburn occurred in 19% of patients. Severe treatment-associated complications were equal, except for perforations which occurred after PDT in 1 percent, Nd : YAG 7 percent ($p < 0.05$). Termination of laser sessions due to adverse events occurred in 3 percent of PDT-treated patients and 19 percent of Nd : YAG-treated patients ($p < 0.05$).

Pervious studies have clearly established areas where Nd : YAG laser therapy is less efficacious in palliating esophageal cancer : long tumors, tumors in areas that are narrow or angulated, and flat infiltrating tumors. (7～10) In our subgroup analyses, PDT showed trends for better tumor response than Nd : YAG therapy in tumors longer than 10 cm, in tumors located in the narrow upper third, and in the angulated lower third of the esophagus, and in patients who failed or recurred after primary therapies, such as radiation and chemotherapy, where the cancer tends to be flat.

### Complete Esophageal Obstruction

PDT has been used successfully to open the esophageal lumen in patients with complete obstruction of the esophagus, defined as being unable to pass a guide wire beyond the malignant stenosis[6]. Completely obstructed patients were not included in the randomized study[5], because Nd : YAG therapy was considered to be of too high a risk in this situation.

### Early Esophageal Cancer

PDT has been advocated as a potentially curative treatment for early and superficial esophageal cancer[7-9]. With its wide treatment area, PDT would seem to be particularly useful in diffuse and multifocal cancer, and it has recently been used successfully to treat early stage cancer and high grade dysplasia in Barrett's esophagus[10].

### Option for Palliation of Esophageal Cancer

Most patients with cancer of the esophagus and gastric cardia present with dysphagia, which usually presages advanced disease. The majority of patients are unresectable or incurable by surgery, or have disease which is locally recurrent or unresponsive to radiation, chemotherapy, or multimodality therapy[11,12]. These patients almost all have difficulty swallowing food and secretions, and require palliative therapy.

Several different methods of endoscopically guided palliation in patients with advanced esophageal cancer have been developed. Mechanical methods include dilation with polyvinyl wire-guided bougies or with balloons (13), and the implantation of plastic or, more recently, expandable metal stents[14]. Tumor necrosis has been carried out on a limited scale by the injection of sclerosants such as ethyl alcohol[15], and thermal tumor ablation has been accomplished with bipolar electrocautery[16], and most frequently with high power Nd : YAG laser[17~19].

All of these remain reasonable options for palliation. Dilation usually provides too short a period of palliation to be effective on its own, but remains the initial step for most other palliative measures. Injection of sclerosants using a free-hand technique may be the cheapest method to achieve tumor necrosis, but the lack of control of the sclerosant diffusion has been associated with significant side effects. Bipolar cautery probes have had similar problems in contolling depth of injury in an irregularly shaped tumor mass.

Expandable metal stent placement has replaced conventional rigid plastic stent insertion for most gastroenterologists, and for many, expandable stent insertion has become the first choice in palliation of malignant dysphagia. There are numerous expandable stents available, with four types currently approved for marketing in the United States. All the stents are relatively easy to insert, and have markedly decreased the insertion complication rate compared to rigid stents. On the other hand, later subacute complications have been described in one-third to more than half of the patients treated with stents. (17)

In a series using a barbed stent to decrease migration, there was a 10% incidence of relatively mild ealy complications, but a 37% incidence of late complications. The later complications were life threatening in 15% of patients, and these occurred significantly more often in patients who had prior radiation or chemotherapy. (18)

All would agree that stents are the best treatment for patients with esophago-bronchial fistulas, but stents are not ideal for every patient. Placement in the cervical esophagus is possible, but tracheal compression can be a serious problem. Stenting the esophago-gastric junction can result in varying degrees of reflux, and stents are more likely to migrate. Soft or flat tumors may not hold a stent. Stents with more tensile strength may cause ulceration and bleeding. Patients with poor dentition or inability

to follow dietary proscriptions can develop food impactions.

In any case, the ease of insertion and ability to carry out expandable stent placement in most endoscopy suites will no doubt lead to an increasing use of these devices for palliation of esophageal cancer. Photodynamic therapy can be performed with even greater technical ease, but requires less available and currently expensive lasers.

For high esophageal cancers, for patients with prior radiation and chemotherapy, for some esophago-gastric junction cancers, and for patients with complete esophageal obstruction, PDT should be considered as another alternative to open the esophageal lumen. PDT can also be used as salvage therapy in patients whose stents have failed due to migration or tumor ingrowth or overgrowth[20]. Since PDT causes tumor necrosis with a photochemical rather than a thermal reaction, there is no risk of damaging the indwelling stent during the application of laser energy.

Expandable metal stents are likely to improve with fewer late complications. Photodynamic therapy is also certain to improve with new sensitizers that do not induce skin photosensitivity, and new diode lasers providing a relatively inexpensive and portable light source. Eventually, it may be found that photodynamic therapy will be the first-line palliative approach with stent implantation reserved for sealing airway fistulas.

**Barrett's Esophagus and Adenocarcinoma**

Barrett's esophagus has been increasingly recognised as an important premalignant condition[20]. The past two decades have witnessed a striking increase in the incidence of adenocarcinoma of the distal esophagus and grastric cardia[21,22] It has been estimated that the incidence of these highly lethal cancers is accelerating at a faster rate than any other malignancy in the United States[21]. This almost certainly is not just an ascertainment or classification phenomenon. Esophageal adenocarcinoma and adenocarcinoma of the gastric cardia are rising in parallel, in the face of a falling incidence of squamous cell cancer of the esophagus[21,22]. In most U.S. centers, more than half of the new cases of esophageal cancer are adenocarcinomas.

The cause of these dramatic epidemiologic changes in the incidence of upper gastrointestinal cancer is unclear, but there is no doubt as to the assocation of Barrett's esophagus and adenocarcinoma. Barrett's esophagus is most notably characterized by metaplastic specialized columnar epithelium, and short segments of such tissue at the esophago-gastric junction probably underlie most cases of cardia cancer as well. The development of cancer is thought to progress throuth a series of molecular events in the unstable metaplastic epithelium leading to mutant clones of cells that progress morphologically to low-grade and then to high-grade dysplasia, to early invasive carcinoma, and finally to advanced carcinoma.

The incidence of adenocarcinoma of the esophagus in Barrett's has been estimated at 1 per 125 patient years, or 800 cases per 100,000 population per year, or an annual incidence of 0.8%[20]. The risk of cancer is considered high enough to recommend surveillance in patients with Barrett's esophagus with endoscopy and systematic biopsy to identify patients with dysplasia. Once high-grade dysplasia is identified and confirmed, the standard recommendation is that patients have an esophagectomy. This is a highly curative but draconian approach, involving considerable morbidity and some mortality[23].

Levine et al. at the University of Washington, Seattle, have suggested that by following patients with high-grade dysplasia using frequent endoscopy and extensive, laborious biopsy techniques, it is possible to defer esophagectomy pending biopsy evidence of invasive carcinoma[24]. Others argue that because of biopsy sampling error, a confirmed biopsy showing high-grade dysplasia is associated with a 30% likelihood of invasive carcinoma, and therefore esophagectomy remains the treatment of choice for severe

dysplasia[20].

There are multiple reasons why photodynamic therapy may turn out to be successful treatment for Barrett's esophagus with high grade dysplasia. Barrett's esophagus can involve long segments of the esophagus, and dysplastic changes are often multifocal with an unpredictable distribution. Dysplasia can occur in flat Barrett's tissue that cannot be distinguished from surrounding non-dysplastic tissue. The selectivity of photodynamic therapy for neoplastic tissue should be an advantage here.

Unlike more focal treatments such as thermal ablation with Nd : YAG laser, argon laser, diode laser, electrocautery, or mucosectomy techniques, photodynamic therapy does not require precise aiming, but rather uses a light diffuser to treat large areas of tissue with a calculated light dose. Laukka and Wang reported eradication of a focus of high grade dyplasia in one patient[25] and in the report from Overholt and Panjehpour, 29 of 36 patients had high grade dysplasia eliminated, and all 14 patients with early cancer were treated successfully[10]. Careful staging of patients with endoscopic ultrasonogrphy seems essential before therapeutic decisions are mede, [26] but if occult invasive carcinoma is present in a patient with only high grade dysplasia on biopsy, it seems likely to be simultaneously treated.

Side effects from the ulcerated esophagus resulting from photodynamic therapy were nausea, anorexia, and chest pain, mostly mild to moderate and easily managed, although long lesions of Barrett's esophagus requires segmental treatement[20]. Strictures are a potential problem after induction of circumferential tissue necrosis, as found by Overholt and Panjehpour, but seemed manageable with dilation[10]. Patients treated with hematoporphyrin derivatives including porfimer sodium are temporarily photosensitive and must avoid daylight skin exposure for about a month after treatment. A fascinating observation from both Laukka and Wang and Overholt and Panjehpour was a reduction in the length of Barrett's epithelium after photodynamic therapy, and subsequent gastric acid inhibition with omeprazole. Laukka and Wang reported 4 cm and 5 cm reductions in 2 of 5 patients[20], and Overholt and Panjehpour found a 75% ~80% reduction in Barrett's area, and complete elimination of Barrett's epithelium in 10 of 36 patients[10]. This is consistent with reports indicating that Barrett's epithelium ablated with thermal laser techniques healed in some cases with normal-appearing squamous epithelium, if acid suppression was maintained[27-29].

The concept of eradicating Barrett's epithelium has tremendous appeal. It is an active response to the presence of Barrett's esophagus, in contrast to the essentially passive method of periodic surveillance waiting for a potential neoplastic change. The relatively localised area of tissue that needs to be treated makes this approach possible, unlike the comparable situation in the patient with ulcerative colitis. Again, the ability of photodynamic therapy to treat extensive areas of surface at once would seem to make this treatment preferable to thermal laser methods, where treating large areas in an even manner can be very time consuming and technically difficult. Effective acid suppression is essential, but neither proton pump inhibitor therapy nor antireflux operations have convincingly led to major regression of Barrett's epithelium or high grade dysplasia on their own[30].

Studies with photodynamic therapy for Barrett's esophagus are promising, but still in an early stage, and clearly much work needs to be done to follow the leads of the first investigations.

**Conclusions** :

Photodynamic therapy with Photofrin is an important new therapy for palliation of dysphagia in advanced esophageal cancer. PDT can be successfully used in cancers difficult to treat with thermal laser ablation because of the morphology or location of the tumor. PDT seems to be more compatible with radiation therapy and chemotherapy than expandable metallic stents, and can be applied in the upper esophagus and esophagogastric junction where stents may be problematic. PDT can be curative when

applied to the treatment of early esophageal cancer, and may be especially useful in patients with Barrett's esophagus.

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## Photodynamic Therapy for Gastric Cancer

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### ABSTRACT

We treated 63 patients (67 lesions) with early gastric cancer by photodynamic therapy (PDT), who were poor risks for surgery. From 1981 to 1990, we treated 38 cases (41 lesions) by PDT with HpD (Photofrin I) or DHE (Photofrin II) and an argon dye laser. The energy intensity of the argon dye laser was over 90 J/cm$^2$. At first we expected epoch-making efficacy, however, the rates of cure were only 59% (13/22) in mucosal cancer, 53% (10/19) in submucosal cancer, and 56% (23/41) in total. These data indicated that the argon dye laser beam could not penetrate and supply sufficient energy to activate HpD or DHE, not only in the submucosal layer but also in the mucosal layer of the stomach. In order to improve the therapeutic effectiveness of PDT with PHE (freeze-dried Photofrin II) in gastric cancer, we began to employ an excimer dye laser instead of an argon dye laser in 1990. The energy intensity of the excimer dye laser was over 60 J/cm$^2$. The rates of cure markedly improved to 93% (14/15) in mucosal