

Results of photodynamic therapy in Barrett's esophagus: A review

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BF Overholt. Results of photodynamic therapy in Barrett's esophagus: A review. Can J Gastroenterol 1999;13(5):393-396. Barrett's esophagus is associated with an increased occurrence of mucosal dysplasia and adenocarcinoma in the specialized glandular mucosa, with a 30- to 52-fold increase in the occurrence of esophageal cancer compared with the normal population. An alternative to esophagectomy as a treatment modality is needed because of the high morbidity and mortality associated with it. Photodynamic therapy offers an alternative nonsurgical therapy that eliminates dysplasia and superficial cancer, and reduces Barrett's mucosa while reducing the risks and costs compared with those of esophagectomy. The use of photodynamic therapy in the ablation of Barrett's mucosa is reviewed.

Key Words: *Barrett's esophagus; Esophagectomy; Photodynamic therapy*

Synthèse des résultats du traitement photodynamique de l'œsophage de Barrett

RÉSUMÉ : L'œsophage de Barrett est associé à un accroissement de l'incidence de dysplasies et d'adénocarcinomes muqueux dans la muqueuse glandulaire spécialisée, avec une occurrence du cancer de l'œsophage qui se trouve multipliée par 30 à 52 par rapport à la population normale. Il faut trouver une solution de rechange à l'œsophagectomie comme modalité thérapeutique en raison de la morbidité et de la mortalité élevées qui y sont associées. Un traitement minimalement effractif qui puisse réduire la muqueuse de Barrett et éliminer la dysplasie et les cancers superficiels serait souhaitable. Le traitement photodynamique offre une solution thérapeutique non chirurgicale qui élimine la dysplasie, le cancer superficiel et réduit la muqueuse de Barrett tout en atténuant les risques et les coûts en comparaison avec ceux de l'œsophagectomie. Le recours au traitement photodynamique dans l'ablation de la muqueuse de Barrett est passé en revue.

Barrett's esophagus is associated with an increased occurrence of mucosal dysplasia and adenocarcinoma in the specialized glandular mucosa, with a 30- to 52-fold increase in the occurrence of esophageal cancer compared with the normal population (1-12). A minimally invasive treatment resulting in the reduction of Barrett's mucosa, and the ablation of dysplasia and superficial cancers is highly desirable. Certainly, an alternative to esophagectomy as a treatment modality is needed due to the high morbidity and mortality associated with this surgery (13-19).

Investigators have used medical (20-26) or surgical therapy (27-29) in attempts to reduce the extent of Barrett's mucosa. The results have been controversial (30), and have not consistently reduced either the dysplasia or the extent of

Barrett's mucosa. Others have used argon or neodymium:yttrium-aluminum-garnet (Nd:YAG) laser thermal ablation of Barrett's mucosa, followed by omeprazole therapy for acid suppression. This has been met with generally favourable, although limited, results (31-34). Brandt and Kauvar (31) treated one patient with Barrett's mucosa with Nd:YAG laser thermal ablation and achieved transient regression of the Barrett's mucosa. However, after 14 weeks, the specialized columnar mucosa recurred. In a subsequent communication, suppression of acid after additional Nd:YAG therapy eliminated Barrett's mucosa (32). Sampliner et al (33) reported in one patient a favourable result of treatment with Nd:YAG laser thermal ablation of Barrett's mucosa. Biopsies 11 months later demonstrated only squamous epithelium.

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Berenson et al (34) used argon laser thermal photoablation of Barrett's mucosa in 10 patients who were maintained on omeprazole 40 mg/day for acid inhibition. Patients underwent three to 12 endoscopies, and had one to eight locations ablated. Most ablated areas were re-treated one to six times. The authors felt that squamous epitheliation following laser ablation occurred both by spread from contiguous squamous epithelium and de novo from progenitor cells within the glandular mucosa. They emphasized the importance of abolishing the glandular mucosa and indicated that acid suppression is essential to allow restoration of squamous epithelium after mucosal ablation.

Sampliner et al (35) studied the effect of multipolar electrocoagulation as a means of thermal ablation in 10 patients with nondysplastic Barrett's mucosa averaging 4.4 cm in length. The treated esophageal segment demonstrated elimination of Barrett's mucosa by endoscopic and histological criteria. In nine patients who agreed to have the entire Barrett's segment treated, five had no endoscopic or biopsy evidence of Barrett's esophagus or intestinal metaplasia at the time of the report. More recently, Barham et al (36) described their results with thermal ablation in 16 patients with nondysplastic Barrett's esophagus treated with the potassium titanyl phosphate laser. However, during follow-up surveillance, subsquamous Barrett's mucosa was found in 11 of the 16 patients.

Photodynamic therapy (PDT) offers an alternative non-surgical therapy that eliminates dysplasia and superficial cancer, and reduces Barrett's mucosa while reducing the risks and costs compared with those of esophagectomy (37-43). PDT combined with acid suppression as a treatment was first described in 1993 (37). Expanding on their work, Overholt et al (43) have described their results with porfimer sodium (Photofrin, QLT Photo Therapeutics Inc, Vancouver, British Columbia) PDT in 100 patients with Barrett's esophagus and dysplasia or early cancer using either a diffuser, centering balloon or both to deliver light to the abnormal tissue. All patients were maintained on long term omeprazole therapy to achieve acid suppression in order to allow mucosal repair to proceed in an anacidic environment.

Extensive mucosal ablation was observed after PDT. Follow-up endoscopic findings and biopsies demonstrated a reduction in the extent of Barrett's mucosa in all patients, with replacement of an estimated 75% to 80% of the treated mucosa by squamous epithelium. The replacement with squamous epithelium was associated with relocation of the squamocolumar junction distally an average of 6.0 cm (range 0 to 19 cm), including in patients with short segments of Barrett's mucosa.

Multiple biopsies of areas with squamous epithelium regrowth following PDT were taken. Two patients demonstrated minute subsquamous fragments of nonmetaplastic glandular mucosa. Two additional patients developed small subsquamous nodules of metaplastic tissue with high grade dysplasia 18 and 22 months after PDT. Both patients were treated with thermal ablation without recurrence on follow-up. Another patient developed a small subsquamous

adenocarcinoma that was successfully retreated with PDT. Extensive follow-up biopsies on the remaining patients demonstrated squamous mucosa without subsquamous metaplastic or glandular mucosa. The authors emphasized that Lugol's staining must be used to identify squamous mucosa in biopsies to determine the presence or absence of subsquamous Barrett's mucosa. They also found that Lugol's chromoendoscopy was essential to determine the presence of small, sometimes visually indistinct, islands of residual Barrett's mucosa following PDT.

Forty-three patients in their series had complete endoscopic and biopsy disappearance of Barrett's mucosa following PDT. Eight patients, typically those with less than 5 cm of Barrett's mucosa initially, were treated with PDT alone. Nd:YAG laser ablation was used in 35 patients to destroy small residual islands of Barrett's mucosa. Squamous epithelial regrowth over these islands was noted in follow-up, and biopsies confirmed the absence of Barrett's mucosa.

Dysplasia was eliminated in 69 of the 87 (79%) noncancer patients. Of the 73 patients presenting with high grade dysplasia, seven persisted with high grade dysplasia, while eight converted to low grade dysplasia and two were diagnosed as developing cancer. Surgery on these two revealed high grade dysplasia without cancer. Thirteen of the 14 patients with low grade dysplasia were cleared, but one developed high grade dysplasia in areas both treated and untreated with PDT.

The effectiveness of PDT in cancer, as expected, is dependent on the depth of tumour invasion. Ten of the 13 patients with superficial cancers in the series by Overholt et al (43) were cleared of their cancer, but three persisted with cancer following PDT. One of the three patients died of unrelated sepsis, one had only one node (of multiple) positive for adenocarcinoma at surgery and one had metastatic nodes in the celiac axis found at surgery.

In addition, another patient developed a subsquamous, 2×4 mm adenocarcinoma in the centre of a 5 cm site treated six months earlier for high grade dysplasia. The patient was re-treated with PDT, and no tumour recurrence has been detected over a 24-month follow-up period. They assumed that the cancer existed at the time of the initial PDT and was not adequately destroyed during the therapy. This raises concerns that even with deep PDT-induced mucosal damage, tumour can persist. Hence, the need for follow-up of treated sites for at least two to three years.

In light of this finding, these workers raised concerns about PDT investigation involving existing and new PDT drugs that can be activated by different wavelengths of light. For example, sodium porfimer is activated by red light (630 nm) to capitalize on the deeper tissue penetration of red light. However, the drug can also be activated by green light (340 nm). Green light has very shallow penetration and is absorbed almost completely by hemoglobin and by the mucosa. Theoretically, green light could be used to destroy mucosa without producing significant submucosal damage, thereby reducing the incidence of stricture formation. Aminolevulinic acid (ALA) also holds promise for treating Bar-

rett's mucosa because it can be administered orally and is associated with only mucosal injury. However, it is known that high grade dysplasia is frequently associated with intra-mucosal and even submucosal carcinoma. If green light use with porfimer sodium or red light-induced ALA injury does not destroy the mucosa deep enough to totally ablate the abnormal mucosa, subsquamous Barrett's mucosa and carcinomas may persist. That three patients in the study by Overholt et al (43) developed subsquamous high grade dysplasia (two patients) and cancer (one patient) subsequent to apparent successful PDT therapy supports this concern. Similarly, Barr et al (41) found subsquamous Barrett's mucosa underneath regenerative squamous mucosa in two of five patients treated with ALA. Gossner et al (44) recently reported their experience with ALA-PDT in 10 patients with severe dysplasia and 22 patients with superficial cancer followed for a mean of nine months after therapy. Dysplasia was eliminated in all 10, and cancer in 17 of 22. Partial re-epitheliation with squamous mucosa was noted in all patients, and subsquamous Barrett's mucosa was noted in two. However, their biopsy protocol post-treatment was not well defined. More investigational work is needed in this area; the concept of less submucosal PDT injury is appealing because injury limited to the mucosa is likely associated with less toxicity and stricture formation.

Furthermore, considering their findings, Overholt et al (43) cautioned that new techniques of ablation of nondysplastic Barrett's mucosa, such as thermal ablation, may produce irregular and even less mucosal damage, thereby creating a potential for persistence of Barrett's mucosa or the occurrence of dysplasia or cancer in mucosa that was partially treated.

Follow-up studies in their patients demonstrated that dysplasia developed in untreated areas in 11 of 48 patients followed for between four months and three years after initial PDT therapy. These patients were subsequently treated successfully with PDT and/or Nd:YAG laser therapy. The authors indicated that follow-up and elimination of residual Barrett's mucosa with repeat PDT or thermal destruction are necessary to prevent the development of dysplasia in untreated areas. In patients with Barrett's esophagus, elimination of dysplasia is primary, but the ultimate goal is ablation of all Barrett's mucosa.

Others have used porfimer-PDT to treat Barrett's esophagus. Laukka and Wang (39) used low dose PDT for the treatment of Barrett's esophagus in five patients. They described a mean reduction of 2.4 cm (range 1 to 5 cm) in the length of the Barrett's segment in patients treated with low-dose PDT and maintained for six months on omeprazole 20 mg daily.

Complications following PDT included esophageal strictures in 34 patients. Typically, several dilations were needed to return swallowing to normal, but in 11 patients, strictures were severe, requiring multiple dilations. Three of the first 35 patients developed atrial fibrillation following PDT. Two required hospitalization and medical therapy for conversion to sinus rhythm. All three remain in regular cardiac rhythm. Pleural effusions were noted in most patients who underwent

chest x-rays 48 h post-PDT. All patients were asymptomatic relative to pulmonary symptoms, except for two who required thoracentesis for large pleural effusions. Photosensitivity was a minor problem for most patients, but four developed moderately severe sunburns following PDT.

The benefits of PDT for the treatment of Barrett's dysplasia include a minimally invasive technique for ablation of dysplastic mucosa and in some cases superficial cancers, fewer therapeutic endoscopic sessions than with endoscopic thermal ablative techniques, lower costs than surgery, and reduced morbidity and mortality compared with short term outcomes of surgical resection patients. Surgical costs are 1.5 to 4.5 times higher than the costs of PDT, and surgery requires a minimum of six weeks' recovery time compared with two to three weeks for PDT patients (42). There is also less morbidity following PDT. Although the incidence of strictures was high, all patients were dilated successfully. Furthermore, mild strictures are found in up to 64% of surgical patients (19). No mortality has been noted with PDT, whereas the mortality from esophagectomy ranges from 6% to 14% (13-19). Patient outcomes when defined as reduced recovery times, lower morbidity, lower mortality and lower costs improved when PDT was used as the treatment for Barrett's dysplasia and/or superficial carcinoma. It was concluded that PDT alone or in combination with thermal ablation could eliminate superficial cancers, dysplasia and Barrett's mucosa in many patients with Barrett's esophagus.

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