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DQTC-SOS Advice Report 2 Version 2 EDUCATION AND INFORMATION 2012

The Role of Porfimer Sodium (Photofrin™) in the Ablation of High-Grade Dysplasia Associated with Barrett's Esophagus

R.A. Malthaner and R.B. Rumble,
on behalf of Cancer Care Ontario's Program in Evidence-Based Care

Report Date: June 14, 2006

This DQTC-SOS Advice Report was put in the Education and Information section in 2012. The PEBC has a formal and standardized process to ensure the currency of each document (PEBC Assessment & Review Protocol).
The report, which consists of a Summary and a Full Report, is available on the CCO web site (http://www.cancercare.on.ca).

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R.A. Malthaner and R.B. Rumble, on behalf of Cancer Care Ontario's Program in Evidence-Based Care.

The 2006 guideline recommendations were put in the

Education and Information section

This means that the recommendations will no longer be maintained but may still be useful for academic or other information purposes.

Report Date: June 14, 2006

SUMMARY

Question
What is the role of porfimer sodium in the ablation of high-grade dysplasia associated with Barrett's esophagus? Outcomes of interest include amelioration of dysplasia with biopsy evidence of eradication, prevention of esophageal cancer, adverse effects, strictures, and survival.

Target Population
These recommendations apply to adult patients with high-grade dysplasia associated with Barrett's esophagus that have either refused surgical treatment or who have contraindications to surgical treatment and for whom therapy with porfimer sodium is being considered.

Recommendations
- For patients with high-grade dysplasia associated with Barrett's esophagus and who are willing and able to tolerate surgery, surgery alone should be the first treatment of choice.
- For patients with high-grade dysplasia associated with Barrett's esophagus with contraindications to surgery, or who choose not to receive surgery, there are randomized controlled trial data confirming that photodynamic therapy (PDT) with porfimer sodium followed by laser light shows superiority over omeprazole alone in the ablation of high-grade dysplasia. Therefore, PDT with porfimer sodium could be considered a treatment option for these patients.

See Appendix 1 for recommended regimens and dosages, and Appendix 2 for the regimens and dosages used in the included trials.

Evidence

- One randomized controlled trial involving 208 patients comparing photodynamic therapy with porfimer sodium plus omeprazole versus omeprazole alone showed benefits for photodynamic therapy with porfimer sodium in both the complete ablation of high-grade dysplasia ($p<0.0001$) and the later development of adenocarcinoma ($p<0.006$).
- Two case-series of 100 patients (including 73 patients with high-grade dysplasia associated with Barrett's esophagus) and 102 patients (including 69 patients with high-grade dysplasia associated with Barrett's esophagus) using photodynamic therapy with porfimer sodium were able to remove 59% and 52% of high-grade dysplasia associated with Barrett's esophagus.
- Adverse effects associated with photodynamic therapy using porfimer sodium include esophageal strictures, perforation, photosensitivity, and mucosal overgrowth over remaining Barrett's epithelium.

Future Research

Future studies investigating PDT in the ablation of high-grade dysplasia associated with Barrett's esophagus should focus on answering the following three clinically important questions:

1. *Is red laser light the optimum in the treatment of high-grade dysplasia associated with Barrett's esophagus?*
   Porfimer sodium is typically activated by red light (630 nm) to facilitate deeper tissue penetration, but green laser light (532 nm) may be more efficacious in destroying Barrett's tissue as green laser light has much shallower penetration (6), which could potentially destroy the Barrett's tissue leaving deeper, unaffected tissues intact.
2. *Is porfimer sodium the best choice for the photosensitizing agent in PDT treatment of high-grade dysplasia associated with Barrett's esophagus?*
   For example, aminolevulinic acid (ALA), a newer, less studied photosensitizing agent, is an oral drug that may show benefits over porfimer sodium, as ALA only causes mucosal damage when activated (6). Similar to the possible benefit of green laser light described above, ALA could potentially destroy the Barrett's tissue leaving deeper, unaffected tissues intact. However, high-grade dysplasia can involve intramucosal and submucosal tissue, and porfimer sodium activated by red laser light may provide additional benefits over ALA. This comparison should be studied in a randomized and controlled study.
3. *Finally, if stricture development (mild or severe only) is related to the light dose administered as suggested by the Panjehpour et al trial (9), then what is the optimum light dose that should be used to minimize the development of strictures?*

Related PEBC Documents

- Practice Guideline Report #2-11: *Neoadjuvant or Adjuvant Therapy for Resectable Esophageal Cancer*.
- Practice Guideline Report #2-12: *Combined Modality Radiotherapy and Chemotherapy in the Non-Surgical Management of Localized Carcinoma of the Esophagus*.

FULL REPORT

I. QUESTION

What is the role of porfimer sodium in the ablation of high-grade dysplasia associated with Barrett's esophagus? Outcomes of interest include amelioration of dysplasia with biopsy evidence of eradication, prevention of esophageal cancer, adverse effects, strictures, and survival.

II. CHOICE OF TOPIC AND RATIONALE

Barrett's esophagus, identified by its characteristic columnar-cell lined esophagus, may be the cause of cancer that arises from glandular tissue (adenocarcinoma) in over half of all presenting patients (1). While the relationship between Barrett's esophagus and adenocarcinoma is not completely clear, 59% to 86% of all adenocarcinomas may originate with Barrett's, leading clinicians to suspect that both Barrett's and adenocarcinoma may have a common etiology (1). As Barrett's cells are frequently found at the edges of esophageal adenocarcinomas, clinicians have suspected that adenocarcinomas may arise from Barrett's mucosa, but this does not hold true for all patients, and this association may be spurious, caused by either the growth of adenocarcinoma into areas that were previously occupied by Barrett's and/or the adenocarcinoma originating in an area that was not previous Barrett's (1). Generally, Barrett's esophagus is considered to be a pre-malignant condition that requires attention.

The natural history of Barrett's is such that if it occurs, it is unlikely to resolve on its own, and therapeutic intervention seems to have little impact on the later development of malignancy (1). Current practice is that all patients with Barrett's esophagus should receive annual or biannual screening, and if severe dysplasia is found, it should be resected (1). Surgical resection remains the standard treatment for patients with Barrett's esophagus that have high-grade dysplasia (1). Once Barrett's esophagus has been diagnosed, any surveillance program chosen must be followed for life (1). However, the utility of annual or biannual surveillance must be questioned, as there is observational evidence from a cohort study that shows no survival difference between patients that underwent surveillance compared with those that did not (1).

In Canada, the projected 2005 incidence rates for esophageal cancer are 1,450 new cases (1,050 in males and 400 in females) (2). The projected mortality rates for esophageal cancer are 1,600 deaths (1,200 in males and 420 in females), equal to a deaths/case ratio of 1.13 for the total population (1.16 for males and 1.05 for females) (2). While the exact risk is not known, current best estimates are that people with Barrett's esophagus are 50 times more likely than people without this condition to develop esophageal cancer, therefore, any effective treatment for Barrett's esophagus may lower the incidence and later mortality rates for esophageal cancer in any population (3). For this reason, clinicians would be interested in any intervention in addition to surgical resection that would help to reduce the burden of this disease in the population. Photodynamic therapy with porfimer sodium may be a suitable candidate for this.

Photodynamic therapy (PDT) is possible because of the differential accumulation of photosensitizing agents in dysplastic or malignant tissue (4). After administration, the photosensitizer drug predominantly accumulates in tumour tissue and remains available until light activation (4). Three elements are required for a PDT reaction to occur: the photosensitizing agent, light, and oxygen (4). When light is applied directly to the sensitized tissue, the photodynamic reaction induces photochemical destruction of the tumour cells by several mechanisms including: singlet oxygen release, direct mucosal damage leading to cell necrosis, apoptosis, or ischemia combined with vascular shutdown and also inflammatory immune responses (4). Any PDT effect will vary according to the type of photosensitizer used, the wavelength and intensity of the light source used, and the type of light distribution system (4).

Most studies of PDT in gastroenterology performed to date have focused on hematoporphyrin derivative or its derivative porfimer sodium (marketed as Photofrin™ by Axcan Pharma Inc.) (4). Other PDT agents available include meta-tetrahydroxyphenal chlorine, 5-aminolevulinic acid, and 2-(1-hexyloxyethyl)-2-devinyl pyropheophorbide-a, but evidence on these agents is lacking (4).

Considering the interest by some Ontario clinicians to have access to this new treatment, the Drug Quality Therapeutic Committee's Standing Oncology Subcommittee (DQTC-SOS) approached Cancer Care Ontario's Program in Evidence-Based Care (PEBC) to provide advice, informed by the clinical evidence, as to the role of porfimer sodium in the ablation of high-grade dysplasia associated with Barrett's esophagus. This advice report, developed by the PEBC with feedback from the Gastrointestinal Disease Site Group (DSG), provides a systematic review of the available evidence, data synthesis, clinical interpretation, and recommendations that will be used by the DQTC–SOS to make funding and policy recommendations.

III. METHODS

This advice report was commissioned by the Program in Evidence-Based Care. A member of the Gastrointestinal Cancer DSG (Dr. Malthaner) agreed to serve as the clinical lead on this topic as it was not formally part of the Gastrointestinal Cancer DSG's guideline portfolio. This advice report is a convenient and up-to-date source of the best available evidence on the role porfimer sodium in the ablation of high-grade dysplasia associated with Barrett's esophagus, developed through a systematic review of the available evidence. The authors disclosed any potential conflicts of interest. Feedback from the Gastrointestinal Cancer DSG's Chair (Dr. J. Maroun) was obtained on an early draft report that did not include the results from the single randomized controlled trial (RCT) obtained.

The PEBC has a formal standardized process to ensure the currency of each clinical guidance report. This process consists of the periodic review and evaluation of the scientific literature and, where appropriate, integration of this literature with the original clinical guidance report information.

Literature Search Strategy

The MEDLINE database was searched from 1966 to May (week 4) 2006. The following Medical subject headings (MeSH) "dihematoporphyrin ether", porfimer sodium", "photofrin", Barrett's esophagus", and "esophageal neoplasms" were combined, with results limited to English only. The Cochrane library database of systematic reviews was also searched through Issue 4, 2005 for completed reviews or posted protocols of in-progress reviews. Relevant articles were selected and read by two reviewers, and the reference lists from those sources were searched for additional trials.

Additionally, the National Cancer Institute's database of ongoing clinical trials (http://www.cancer.gov/Search/SearchClinicalTrialsAdvanced.aspx) was searched for open trials investigating the use of porfimer sodium in the ablation of high-grade dysplasia in patients with Barrett's esophagus (Appendix 3).

Inclusion Criteria

Articles were selected for inclusion in the systematic review of the evidence if they were fully published English-language reports of:

1. Randomized controlled trials (RCTs) comparing porfimer sodium with any other therapy in the ablation of high-grade dysphasia associated with Barrett's esophagus.
2. Phase II trials comparing porfimer sodium with any other therapy in the ablation of high-grade dysphasia associated with Barrett's esophagus.
3. Any other study design that provided data on porfimer sodium with any other therapy in the ablation of high-grade dysphasia associated with Barrett's esophagus.

Exclusion Criteria

1. Letters and editorials.
2. Non-English publications.
3. Non-human studies.
4. Studies reporting on fewer than 10 patients.

Synthesizing the Evidence

As only one of the trials obtained was an RCT (5), no pooling of outcome data was possible.

IV. RESULTS

Literature Search Results

A total of six studies met the inclusion criteria and were obtained (5-10). Of these trials, one was an RCT (5), three were prospective case-series (6,7,9), one was retrospective (8), and one was a post-treatment patient satisfaction survey (10). Three trials reported either partial or complete pharmaceutical sponsorship for the trial (5,9) (Axcan Pharma Inc. PQ) (6) (Quadralogics, Inc. BC) and three reported either hospital or university sponsorship (7,8,10). Two of the authors on two of the trials reported conflicts of interest (6,9) as they hold the patent for the centering balloon used in the two trials. The number of patients in the obtained trials ranged from a low of 33 (8) to a high of 208 (5). The patient satisfaction survey (10) reported on 16 patients.

Two studies (6,7) reported results for Barrett's esophagus patients with high-grade dysplasia separately from patients with early adenocarcinoma (Table 1), and two studies (8,9) did not report outcomes for Barrett's patients separately from patients with early adenocarcinoma. The patient satisfaction survey (10) only included Barrett's esophagus patients with high-grade dysplasia (HGD).

Outcomes

See Appendix 2 for the specific regimens used in the trials reviewed.

Efficacy Outcomes – Randomized Controlled Trial

The single RCT that was obtained (5) randomized patients with HGD to either PDT using porfimer sodium plus omeprazole or omeprazole alone using a method of randomization that distributed patients into treatment arms on a 2:1 basis (PDT+omeprazole:omeprazole). In this RCT report, only the pathologists were blinded as to treatment assignment, and all analyses were performed using the intent-to-treat principle.

Results showed superiority for PDT+omeprazole over omeprazole alone for both the complete ablation of HDG associated with Barrett's esophagus (77% versus 39%; $p<0.0001$) and progression to adenocarcinoma (13% versus 28%; $p=0.006$). Of all patients in the PDT treatment arm, 133 received the initial porfimer sodium injection (132 completed the first cycle), 90 of these 132 patients had either a previously treated segment that still displayed HGD or a new untreated segment and received two cycles, and 42 of 90 patients received three cycles.

The adverse effects reported with PDT were photosensitivity reactions (69%), esophageal strictures (36%), vomiting (32%), non-cardiac chest pain (20%), pyrexia (20%), dysphagia (19%), constipation (13%), dehydration (12%), nausea (11%), and hiccups (10%). In the omeprazole arm, no major events were reported. The photosensitivity reactions generally occurred within 90 days after the initial porfimer sodium injection, and affected exposed areas such as the face, hands, and neck. The photosensitivity reactions observed were mild (69%), moderate (24%), and severe (7%). Eventually, all photosensitivity reactions resolved, although one patient was left with scarring that resulted in motion impairment. The formation of

esophageal strictures occurred most frequently during the second course of treatment, with 16 (of 132) forming in the first, 29 (of 90) in the second, and 4 (of 42) in the third.

Quality of life outcomes were not reported in this randomized trial.

Table 1. Treatment outcomes, randomized controlled trial

Study	Interventions	N	Median follow-up (months)	Complete ablation of high-grade dysplasia (%)	Strictures (%)	Progression to cancer (%)
Overholt BF et al (5)	PDT with porfimer sodium plus omeprazole	138	24.2	77 (106/138)	36 (n=49)	13 (n=18)
	Omeprazole alone	70	18.6	39 (27/70) p<0.0001	0	28 (n=20) p=0.006

Note: N, number.

Efficacy Outcomes – Case Series and Retrospective, and Survey Studies

Only two of the remaining five trials obtained reported on the results of patients with high-grade dysplasia associated with Barrett's esophagus separately from patients with early adenocarcinoma (6,7) (Table 2).

In the trial by Overholt et al (6), one to three courses of PDT was administered to a total of 100 patients (one course, 61 patients; 2 courses, 15 patients; three courses, 3 patients), 73 of whom had Barrett's with high-grade dysplasia. Complete ablation of Barrett's tissue was found in 43 of 73 patients after PDT, which was verified by biopsy. Eight of these patients were treated with PDT alone, and the other 35 also had thermal ablation performed with a Nd:YAG laser to remove residual Barrett's tissue remaining post-PDT. Eighty-eight percent of all high-grade dysplasia was removed by the combined PDT/Nd:YAG laser treatment. Follow-up reported a 97% adenocarcinoma prevention rate, as two of the 73 patients later developed biopsy confirmed carcinoma. At the time of trial reporting, survival remained at 100%.

In the trial by Wolfsen et al (7), a single course of PDT was delivered to a total of 102 patients, 69 of whom had high-grade dysplasia associated with Barrett's esophagus. Complete ablation of high-grade dysplasia associated with Barrett's esophagus was achieved in 52% of patients (36 of 69 patients). Considering all patients, PDT ablated dysplasia or early carcinoma in 96% of all patients (98 of 102 patients). Of the four patients not cured of dysplasia by PDT, three were cured by later esophagectomy, and one patient eventually died from metastatic adenocarcinoma.

Table 2. Treatment outcomes, case series, retrospective, and survey studies

Study	Interventions	N	Median follow-up (months)	Dysplasia Reduction %	Strictures (%)	Survival (%)
Overholt BF et al 1999 (6) [USA]	PDT with porfimer sodium, followed by thermal ablation with Nd:YAG laser	73	19 (mean) (range, 4 to 84)	90.4	46.6	100
Wolfsen HC et al 2004 (7) [USA]	PDT with porfimer sodium	69	20.4	52.2	21.7	NR for HGD pts with BE; 99% for all patients

Note: N, number; PDT, photodynamic therapy; Nd:YAG, Neodymium-doped Yttrium Aluminum Garnet thermal laser; NR, not reported; HGD, high-grade dysplasia; BE, Barrett's esophagus.

Adverse Effects

The adverse effects observed in the trials varied, but included: esophageal stricture (6,7,8), atrial fibrillation (6,7), chest pain (6,10), dysphasia (6,10), odynophasia (10), severe sunburn-like reactions (6,7), esophageal perforation (7), and constipation (10) (Table 3). Only one trial reported any observed deaths (6), although none of the three deaths were related to either the Barrett's esophagus or the PDT (1 death from cryptococcal meningitis, 1 death from complication from pulmonary disease, and 1 death from myocardial infarction). One of the trials obtained did not report on the adverse effects (8). The main adverse effect of concern with PDT therapy is the development of esophageal strictures, which have been reported as ranging from 18% to 37% of patients (9), while the two trials reviewed range from 16.7% (9) to 46.6% (6). Strictures resulting from PDT have an appearance similar to the strictures formed as a result of external beam radiation therapy (7). Strictures appear endoscopically as areas of blanched, thickened, and inelastic mucosa (7). To restore stable lumen patency, studies (7,9) reported multiple dilations may be required (a median of five was reported in one trial (7)) using Savary (7), American (7), or Safeguide (9) dilators, either with or without the use of fluoroscopic guidance.

Table 3. Adverse effects.

Study	Esophageal stricture (%)	Atrial fibrillation (%)	Chest pain (%)	Dysphasia or Odynophasia (%)	Severe sunburn-like reactions (%)	Esophageal Perforation (%)	Constipation (%)
Overholt et al, 1999 (6)	46.6 (15 severe)	6 (of the first 50)	NR	NR	1.5	NR	NR
Wolfsen et al, 2004 (7)	21.7	1.5	NR	NR	18	1.5	NR
Ban et al, 2004 (8)	NR	NR	NR	NR	NR	NR	NR
Panjehpour et al, 2005 (9)	115J/cm: 22.0 105J/cm:16.7 95J/cm:29.4 85J/cm:26.3	NR	NR	NR	NR	NR	NR
Hemminger et al, 2002 (10)	NR	NR	12.5	75	NR	NR	19

Note: NR, not reported.

Quality of Life and Patient Satisfaction

None of the trials obtained explicitly reported any data on quality of life; however, the patient satisfaction survey reported by Hemminger et al (10) provides useful data related to quality of life. In this survey study, 16 respondents (of 18 total patients surveyed) previously treated with first-line PDT for the ablation of high-grade dysplasia associated with Barrett's esophagus were contacted at a later date and asked about their treatment experiences. The survey sample was comprised of five females and 11 males, with a median age of 75 years (range 52 to 87 years). Of the two patients who did not complete the satisfaction survey, one was mentally incompetent, and the other was in congestive heart failure. Both of these patients were female. The median survey follow-up time was 27 months (range 5 to 45 months). The survey was designed to measure acute and chronic PDT adverse reactions as well as overall patient satisfaction, and the main results follow. For patient perceptions of worst PDT effect, 75% of all patients reported dysphagia/odynophagia, 12.5% reported chest pain, and 12.5% reported there were no adverse effects. The most common medication used to control symptoms post-PDT was hydrocodone bitartrate plus acetaminophen, reported by 75% of all patients. Patients reported a median duration of sensitivity to sunlight of six weeks (range 4 to 24 weeks). Two patients reported experiencing severe sunburns that required a hospital visit, eight patients reported severe sunburns that did not require a hospital visit, and six patients reported either mild or no sunburn reactions. Although this was a highly selective patient population, when asked if they would choose PDT again if they were given the choice of PDT or surgery, 100% of all patients reported that they would still choose PDT.

V. INTERPRETIVE SUMMARY

The early treatment of Barrett's esophagus with PDT in an attempt to prevent the possible later development of adenocarcinoma is clinically compelling. Presently, the best evidence in favour of PDT with porfimer sodium for these patients is the RCT reported by Overholt et al (5), which showed superiority for PDT treatment over treatment with omeprazole alone for both complete ablation of HGD associated with Barrett's esophagus and the later development of

adenocarcinoma. However, an RCT comparison between surgery alone and PDT with porfimer sodium for these patients has yet to be published. The remaining data are currently limited to two case-series studies, and both report high-grade dysplasia ablation rates lower than 60% (6,7) with a single course of treatment. In one of the trials (6) PDT alone only ablated the dysplasia in eight of 73 patients (11%), while the remaining 35 patients required the additional treatment of Nd:YAG laser to ablate the high-grade dysplasia. Also, the adverse effects observed with PDT using porfimer sodium are significant (e.g. stricture formation, light sensitivity) and are potentially fatal (e.g. esophageal perforation). The development of dysphagia secondary to stricture formation following PDT cannot be ignored. It is also possible that following PDT ablation, normal squamous tissue may grow over any remaining Barrett's tissue, which could possibly develop into an adenocarcinoma, while remaining hidden to endoscopic inspection for malignant conversion. Considering this, the role of PDT with porfimer sodium in the ablation of high-grade dysplasia associated with Barrett's esophagus remains unclear, especially as it's efficacy in comparison to the standard treatment of surgery is unknown.

Despite this, PDT provides some benefits over surgery alone. In the studies reviewed, PDT with porfimer sodium has a post-treatment mortality rate approaching zero, while surgical interventions report post-treatment mortality rates ranging from 6% to 14% (6), however, newer studies report that post-operative mortality with surgery alone also approaches zero (12). One benefit with PDT using porfimer sodium is that treatment may be given in multiple courses with minimal time between cycles (5,11) (see Appendix 1).

It is recommended that for patients who are not candidates for surgery, either due to contraindications or patient preference, in the primary treatment of high-grade dysplasia associated with Barrett's esophagus, PDT with porfimer sodium could be considered.

VI. RECOMMENDATIONS AND EVIDENCE

Recommendations

- For patients with high-grade dysplasia associated with Barrett's esophagus and who are willing and able to tolerate surgery, surgery alone should be the first treatment of choice.
- For patients with high-grade dysplasia associated with Barrett's esophagus with contraindications to surgery, or who choose not to receive surgery, there are randomized controlled trial data confirming that photodynamic therapy (PDT) with porfimer sodium followed by laser light shows superiority over omeprazole alone in the ablation of high-grade dysplasia. Therefore, PDT with porfimer sodium could be considered a treatment option for these patients.

See Appendix 1 for recommended regimens and dosages, and Appendix 2 for the regimens and dosages used in the included trials.

Evidence

- One randomized controlled trial involving 208 patients comparing photodynamic therapy with porfimer sodium plus omeprazole versus omeprazole alone showed benefits for photodynamic therapy with porfimer sodium in both the complete ablation of high-grade dysplasia ($p<0.0001$) and the later development of adenocarcinoma ($p<0.006$).
- Two case-series of 100 patients (including 73 patients with high-grade dysplasia associated with Barrett's esophagus) and 102 patients (including 69 patients with high-grade dysplasia associated with Barrett's esophagus) using photodynamic therapy with porfimer sodium were able to remove 59% and 52% of high-grade dysplasia associated with Barrett's esophagus.
- Adverse effects associated with photodynamic therapy using porfimer sodium

include esophageal strictures, perforation, photosensitivity, and mucosal overgrowth over remaining Barrett's epithelium.

Future Research

Future studies investigating PDT in the ablation of high-grade dysplasia associated with Barrett's esophagus should focus on answering the following three clinically important questions:

1. *Is red laser light the optimum in the treatment of high-grade dysplasia associated with Barrett's esophagus?*
   Porfimer sodium is typically activated by red light (630 nm) to facilitate deeper tissue penetration, but green laser light (532 nm) may be more efficacious in destroying Barrett's tissue as green laser light has much shallower penetration (6), which could potentially destroy the Barrett's tissue leaving deeper, unaffected tissues intact.
2. *Is porfimer sodium the best choice for the photosensitizing agent in PDT treatment of high-grade dysplasia associated with Barrett's esophagus?*
   For example, aminolevulinic acid (ALA), a newer, less studied photosensitizing agent, is an oral drug that may show benefits over porfimer sodium, as ALA only causes mucosal damage when activated (6), which, like the possible benefit of green laser light described above, could potentially destroy the Barrett's tissue leaving deeper, unaffected tissues intact. However, as high-grade dysplasia can involve intramucosal and submucosal tissue, porfimer sodium activated by red laser light may provide additional benefits over ALA, but they should be compared in a head-to-head randomized and controlled study.
3. *Finally, if stricture development (mild or severe only) is related to the light dose administered as suggested by the Panjehpour et al trial (9), then what is the optimum light dose that should be used to minimize the development of strictures?*

Related Guidelines

- Practice Guideline Report #2-11: *Neoadjuvant or Adjuvant Therapy for Resectable Esophageal Cancer*.
- Practice Guideline Report #2-12: *Combined Modality Radiotherapy and Chemotherapy in the Non-Surgical Management of Localized Carcinoma of the Esophagus*.

VII. CONFLICTS OF INTEREST

Neither of the authors declared any conflicts of interest.

VIII. ACKNOWLEDGEMENTS

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For a complete list of the Gastrointestinal Cancer Disease Site Group members, please visit the CCO website at http://www.cancercare.on.ca/.

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Appendix 1. Recommended dosing information for the use of porfimer sodium in Barrett's esophagus with high-grade dysplasia.

Porfimer sodium administration

The first stage of PDT is IV injection of porfimer sodium at 2mg/kg of body weight. Porfimer sodium is available in either 15 mg or 75 mg vials. Porfimer sodium should be reconstituted with 5% dextrose solution to a final concentration of 2.5 mg of porfimer sodium per mL and administrated as a single slow IV injection over three to five minutes.

Laser light administration

The second stage of PDT is illumination with laser light 40-50 hours following porfimer sodium injection. Light from the laser is delivered to the Barrett's segment with an OPTIGUIDE™ fibre optic diffuser at a continuous wavelength of 630±3 nanometres. The size and type of fibre optic diffuser tip used will depend on the Barrett's segment location and size (see Table 1). Approximately 40-50 hours after porfimer sodium injection, laser light should be applied by the OPTIGUIDE™ diffuser through a centering balloon.

Table 1. OPTIGUIDE™ diffuser and centering balloon combinations.

Barrett's segment length (cm)	OPTIGUIDE™ size (cm)	Balloon window size (cm)
6-7	9	7
4-5	7	5
1-3	5	3
Note: any Barrett's segment treated with PDT should include normal tissue margins of at least three millimetres at the proximal and distal ends.		

The light dose administered should be 130 J/cm of diffuser length using the OPTIGUIDE™. Therapeutic intensities range from 175-270 mW/cm of diffuser. Figure 1 provides the formula for determining the light dose to be administered.

Figure 1. Light dose calculation.

$$\text{Light dose (J/cm)} = \frac{\text{Power output from diffuser (W)} * \text{treatment time (seconds)}}{\text{Diffuser length (cm)}}$$

Table 2. OPTIGUIDE™ power output and treatment times required to deliver 130 J/cm of diffuser length in patients with Barrett's esophagus and high-grade dysplasia.

Balloon window length (cm)	Diffuser length (cm)	Light intensity (mW/cm)	Required power output from diffuser (W)	Treatment time (seconds)	Treatment time (minutes:seconds)
3	5	270	1.35	480	8:00
5	7	270	1.90	480	8:00
		200	1.40	650	10:50
7	9	270	2.44	480	8:00
		200	1.80	650	10:50
Note: required power output from diffuser is to be measured by immersing the diffuser into the cuvet in the power meter and slowly increasing the laser power.					

Patients with high-grade dysplasia associated with Barrett's esophagus may receive a second light application 96-120 hours after injection. If need be, up to two additional courses may be given separated by a minimum of 90 days.

Patients with a Barrett's segment greater than 7 cm should have the remaining untreated length of Barrett's esophagus treated with a second PDT course at least 90 days later.

Note: PDT, photodynamic therapy; IV, intravenous; J/cm, joules per centimetre; W, Watt; mW/cm, milliWatt per centimetre.

Source: Photofrin® [Product Monograph]. Axcan Pharma Inc., Mont-Saint-Hilaire, PQ. [August 11, 2003] (11).

Appendix 2. Dosing by trial.

Overholt BF et al, 2005 (5)
Porfimer sodium 3-5 minute IV injection 2mg/kg, followed 40-50 hours later by laser light at 630 nm using a windowed centering esophageal balloon. The light dose administered was 130 J/cm of diffuser length with the centering balloon. Nodular HGD areas were pretreated with 50 J/cm with a short ≤2.5 cm bare fibre. Approximately 7 cm of Barrett's mucosa was treated in the first session. If deemed necessary by endoscopic examination, a 2nd light application of 50 J/cm was administered 96-120 hours after the initial porfimer sodium application. Patients could receive up to two additional courses of PDT, if given at least three months apart. All patients in both treatment arms also received omeprazole 20 mg twice per day (beginning at least two days prior to porfimer sodium injection in the PDT treatment arm).
Overholt BF et al, 1999 (6)
Porfimer sodium (Photofrin™) IV injection 2mg/kg, followed 48 hours later by laser light at 630 nm from an argon-pumped dye laser (Lambda Plus) or KTP pumped dye laser (Laserscope) endoscopically delivered using a 1.5 to 2.5 cm cylindrical diffuser, or a windowed centering esophageal balloon. Power intensity of the light delivered was 400 mW/cm of diffuser providing an energy density of 100 to 250 J/cm from the diffuser to the tissue.
Wolfsen HC et al, 2004 (7)
Porfimer sodium (Photofrin™) IV injection 2mg/kg, followed both 48h and 72 h later with light from a solid-state diode laser using 2.5-5.0cm cylindrical diffusing fibres used without centering balloons. The energy density of the light dose delivered was 150 and 225 J/cm.
Ban S et al, 2004 (8)
Porfimer sodium (Photofrin™) IV injection at 2 mg/kg for 29 patients, but limited to 150 mg in four patients. In all patients but one, a cylindrical diffuser was used. A single patient was treated with a centering balloon.
Panjehpour et al, 2005 (9)
Porfimer sodium (Photofrin™) IV injection at 2 mg/kg. Three days post-injection 630 nm of light was delivered from a KTP/dye laser (Laserscope) using a cylindrical diffuser inserted into a 20-mm diameter reflective esophageal balloon. A 7-cm or 9-cm cylindrical diffuser was used in a 5-cm or 7-cm windowed balloon, respectively. The first 59 patients were treated with a 115 J/cm light dose, and subsequent patients were treated using a de-escalation regimen with light doses of 105 J/cm (n=18), 95 J/cm (N=17), 85 J/cm (N=19). The power density used in the de-escalation regimens was 270 mW/cm. Supplemental laser light (50 J/cm at a power density of 400 mW/cm) was delivered to areas that exhibited a mild response with a short cylindrical diffuser inserted through the accessory channel of the endoscope.
Hemminger LL et al, 2002 (10)
The dose particulars of the porfimer sodium (Photofrin™) were not disclosed, but it was reported that laser light at 632nm was applied 48 hours after porfimer sodium administration.

Note: IV, intravenous; mg/kg, milligram per kilogram; KTP, potassium-titanyl-phosphate; J/cm, joules per centimetre; mW/cm, milliWatt per centimetre.

Appendix 3. Ongoing trials.

A search of the National Cancer Institute's database of ongoing clinical trials (http://www.cancer.gov/Search/SearchClinicalTrialsAdvanced.aspx) on November 8, 2005 using the search terms given below yielded no listings.

Type of cancer:	Esophageal
Type of trial:	Prevention, Treatment
Status:	Open
Type of intervention:	Photodynamic therapy
Drug:	Porfimer sodium
Phase of trial:	Phase II, Phase III