NATIONAL INSTITUTE FOR CLINICAL EXCELLENCE

INTERVENTIONAL PROCEDURES PROGRAMME

Interventional procedures overview of photodynamic therapy for high-grade dysplasia for Barrett's oesophagus

Introduction

This overview has been prepared to assist members of the Interventional Procedures Advisory Committee in making recommendations about the safety and efficacy of an interventional procedure. It is based on a rapid review of the medical literature and specialist opinion. It should not be regarded as a definitive assessment of the procedure.

Date prepared

This overview was prepared by NICE in November 2003.

Procedure name

- Photodynamic therapy for high-grade dysplasia.

Specialty societies

- Association of Upper Gastrointestinal Surgeons of Great Britain and Ireland
- British Society of Gastroenterology
- Association of Cancer Physicians (Royal College of Physicians)

Description

Indications

Barrett's oesophagus (Barrett's) is a condition characterised by an abnormal lining of the oesophagus, which occurs in patients with a long history of heartburn and gastro-oesophageal reflux disease.

In a minority of people Barrett's oesophagus may progress through a series of stages (dysplasia) to cancer. High-grade dysplasia is the stage which immediately precedes the occurrence of cancer, but it is not possible to predict how soon cancer will develop. The grade of dysplasia and the length of Barrett's oesophagus are thought to be the most important risk factors for progression to cancer [2].

Over the last few years there has been a substantial increase in number of new cases (incidence) of Barrett's oesophagus.

Current treatments and alternatives

Oesophagectomy is the most radical treatment option for high-grade dysplasia, because removal of the whole oesophagus means that the risk of progression to cancer is removed. However, oesophagectomy is a major operation with the potential for morbidity and mortality. Some patients are unfit for surgery of this kind and others are reluctant to accept this treatment.

Less invasive treatments include laser ablation, endoscopic mucosal resection and photodynamic therapy. All aim to ablate the specialised columnar epithelium which is affected by dysplasia and to promote the regeneration of normal squamous epithelium.

The patients treated by oesophagectomy and by the less invasive techniques are therefore likely to be different, so direct comparisons of the results of the treatment may not be appropriate. In addition, the aims of the treatments are different – oesophagectomy aims at cure, while the less invasive methods simply ablate dysplastic tissue, but need to be followed by surveillance to try to detect further dysplasia or progression to cancer.

What the procedure involves

Photodynamic therapy involves the administration of a photosensitising agent by intravenous injection. The agent is then activated by the application of light to the selected area, usually with a low-power laser. It absorbs the energy from the light and this results in formation of a high-energy oxygen molecules. These molecules interact with the tissue, leading to tumour necrosis by a photochemical rather than a thermal effect [3.]

Treatment can be performed on an outpatient basis and is usually applied to approximately 7 cm of the Barrett's oesophagus at a time to avoid toxicity. A second treatment session can be conducted if the Barrett's exceeds this length of oesophagus.

Skin photosensitivity, as a result of the uptake of the sensitiser to the skin, is quite long lasting and patients are recommended to avoid exposure to bright light from any source, especially direct sunlight. The labelling of the photosensitiser used in this procedure includes information on precautions that should be taken to avoid exposure of skin and eyes to bright light.

Photodynamic therapy for Barrett's oesophagus has involved a number of photosensitising agents, including porfimer sodium, aminolevulinic acid (ALA) and temoporfin. Porfimer sodium is the only one of these agents commercially available in the UK for use in Barrett's oesophagus.

Efficacy

The evidence on efficacy is based predominately on three uncontrolled reports and one unpublished randomised trial. Results of all four reports indicate that the majority of patients (77–98%) have a downgrading of dysplasia status following the procedure from high-grade dysplasia to Barrett's oesophagus without dysplasia. Elimination of Barrett's oesophagus was achieved in around 42% (25/60)–98% (47/48) of patients; however residual disease was often ablated by lasers.

One study of 103 patients, 80 of whom had high-grade dysplasia, reported a survival rate of 77.5%. In an extended follow up of 65 of these 80 patients, three (4.6%)

developed carcinoma at a mean follow up of 58 months. Initial results from the unpublished randomised controlled trial indicate that at 24 months 13.8% (18/130) of patients treated with photodynamic therapy progressed to cancer compared with 28.6% (20/70) of patients receiving medication. The study is still ongoing and these are preliminary findings, so caution should be exercised in interpreting these results.

Evidence from two small uncontrolled reports suggested that oesophageal dysmotility worsened following treatment.

One Specialist Advisor stated that a proportion of patients undergoing this procedure will have undetected advanced carcinomas, which will be beyond the reach of the therapy.

Safety

Oesophageal strictures and cutaneous reactions associated with the photosensiter are the most commonly reported complications following photodynamic therapy. Oesophageal strictures are the most significant of these complications, with the published studies reporting that 23% (11/48) – 34% (34/100) of patients developed oesophageal strictures after the procedure. It is unclear whether the incidence of oesophageal strictures is associated with the number of treatment sessions that patients receive.

Skin reactions also occurred in around a third of patients undergoing photodynamic therapy. These included mild, moderate and severe reactions, with 3 (3/100)–15% (7/48) of patients experiencing severe photosensitivity reactions requiring medical treatment.

Oesophageal perforation, pleural effusions and atrial fibrillation were also reported complications, with an incidence of around 3–4%.

The Specialist Advisors listed the main adverse events as photosensitivity and development of strictures. One Advisor stated that underlying malignancy may continue to grow unobserved because of the superficial healing of the Barrett's oesophagus. One Advisor noted that some patients will develop a pleural effusion, and that atrial fibrillation had been reported in a patient with ischaemic heart disease.

Literature reviews

Rapid review of literature

The medical literature was searched to identify studies and reviews relevant to photodynamic therapy for high-grade dysplasia for Barrett's oesophagus. Searches were conducted via the following databases from commencement to October 2003: MEDLINE, PREMEDLINE, EMBASE, Cochrane Library and Science Citation Index. Trial registries and the Internet were also searched. No language restriction was applied to the searches.The literature search identified 272 non-duplicate abstracts on photodynamic therapy for high-grade dysplasia for Barrett's oesophagus.
The following selection criteria (Table 1) were applied to the abstracts identified by the literature search. Where these criteria could not be determined from the abstracts the full paper was retrieved.

Table 1 Inclusion criteria for identification of relevant studies

Characteristic	Criteria
Publication type	Clinical studies included. Efficacy: Emphasis was placed on identifying good quality comparative studies. Safety: Emphasis was placed on Registries and case reports were also considered. Studies were excluded where no clinical outcomes were reported; or where the paper was a review, editorial, technical or animal study. Abstracts were excluded because of the difficulty of appraising methodology.
Patient	Patients with high-grade dysplasia from Barrett's oesophagus
Intervention/test	Photodynamic therapy
Outcome	Articles were retrieved if the abstract contained information relevant to the safety and/or efficacy.
Language	Non-English-language articles were excluded unless they were thought to add substantively to the English-language evidence base.

Excluded studies

Studies were predominately excluded because they reported on patients with oesophageal cancer, or used another photosensitiser (primarily ALA).

List of studies included in the overview

This overview is based on 11 studies, including the unpublished results of three clinical trials submitted to the US Food and Drug Authority (FDA).

Nine studies are included in the efficacy section of this document. Nine studies are also reviewed in relation to the safety of this procedure, including two studies that specifically reported on complications following this procedure [4,5].

To date, published studies assessing efficacy as a primary endpoint have all been uncontrolled. One randomised controlled trial was identified that investigated whether oral steroids would reduce the incidence of stricture formation. This is included in the safety section.

Existing Reviews on the Procedure

No completed reviews were identified. A Cochrane protocol on the treatment of Barrett's oesophagus is listed in the Cochrane library. This review will consider endoscopic ablative therapies, including photodynamic therapy.

Abbreviations:

PDT – photodynamic therapy;
HGD – high grade dysplasia;
LGD – low grade dysplasia;
BE Barrett's epithelium;
T1 – tumour stage 1;
T2 – tumour stage 2;
SQ: normal squamous epithelium;
CR – complete response;
TS – treatment success;
TF – treatment failure;
O – omprazole;
ITT - intent to treat;
E -evaluable

Table 2 Summary of key efficacy and safety findings from published papers.

Study details	Key efficacy outcomes	Key safety findings	Comments
Overholt et al (2003) [6] Study design: uncontrolled USA November 1993 – July 2001 103 patients • 80 high grade dysplasia (HGD) • 14 low grade dysplasia (LGD) • 9 cancer (CA) Mean age: 64.9 years • 69 patients 1 PDT session • 29 patients 2 PDT session • 5 patients 3 PDT session • 82 patients were followed through the study (65 HGD) (patients were excluded – death, surgery and lost to follow up) Mean follow up: 50.7 months (range 2–122 months)	Clinical response following PDT (intent-to-treat) **Treatment success (TS)** — **High grade** — **All** No dysplasia - no Barrett's — 43 (53.8%) — 56 (54.4%) No dysplasia - Barrett's — 19(23.8%) — 23 (22.3%) Total — 62(77.5%) — 79(76.7%) **Treatment failure (TF)** — **High grade** — **All** TF (persistence of disease) — 2 — 2 TF (disease progression) — 1 — 1 TF (death) — 7 — 13 TF (surgery) — 7 — 7 TF (lost to follow-up) — 1 — 1 Out of those patients who had died, high grade dysplasia and Barrett's oesophagus were eliminated in 3, high grade dysplasia had reduced to low grade dysplasia (LGD) in 1 patient and 2 patients had persistent high grade dysplasia. 1 patient with cancer died from cardiac failure. **Extended follow-up (mean 58 months):** Subsquamous cancer developed in 3/65 patients (4.6%) with HGD after PDT. Two patients were re-treated with PDT and at the time of writing were free of cancer. 6/80 (7.5%) developed carcinoma during follow-up (3 patients during extended follow-up, 2 patients in surgery group, 1 patient as a treatment failure). **Length of Barrett's mucosa (all patients)** Length had been reduced by a mean 6.92 cm (range 1–22 cm) **Survival** (high grade dysplasia) Intent to treat — Per protocol 77.5% — 80.0% Kaplan – Meier curves presented (limited information on patients with HGD)	**General complications** Oesophageal strictures developed in 18% of the 82 patients with 1 PDT session and 50% with 2 PDT sessions. Overall frequency of strictures was 30%	Nd:YAG laser was used to ablate small islands of residual Barrett's mucosa on 3-month or longer-term endoscopies. All patients were maintained on acid-suppressive therapy with proton pump inhibitors. HGD confirmed by 2 histopathologists. Follow-up endoscopies were performed – four quadrant biopsy every 2 cm. Primary endpoint: elimination of dysplasia. In some cases percentages in text of paper are calculated on 82 patients (rather than 103 patients). Complications reported for all patients (unable to separate patients with HGD).

Study details	Key efficacy outcomes	Key safety findings	Comments
Overholt et al (1999) [7] Study design: uncontrolled USA 100 patients • 73 high grade dysplasia (HGD) • 14 low grade dysplasia (LGD) • 12 tumour stage 1 • 1 tumour stage 2 • 73 patients one PDT session • 22 patients two PDT sessions • 5 patients 3 PDT session Mean age: 66 years (range 33–83 years) Mean follow up: 19 months (range 4-84 months)	**Clinical response following PDT** **HDG LGD T1 T2 n** **Pre** 73 14 12 1 100 **Post** Cancer 0 0 3 0 3 HGD 7 1 0 0 8 LGD 8 0 1 0 9 No dysplasia 56 13 8 1 78 No Barrett's 32 7 4 0 43 (not mutually exclusive categories) 78/100 (78%) patients had conversion of dysplastic/malignant Barrett's mucosa without dysplasia. 56/73 (77%) HGD patients had no evidence of dysplasia and 64/73 (88%) had no evidence of having high-grade dysplasia (56+8) 32 HGD patients (44%) had no evidence of Barrett's after treatment. Not reported: survival	**General complications** • 34 patients (34%) developed oesophageal strictures • 11 patients (11%) required multiple dilations for these strictures (severe) • 3 patients (3%) atrial fibrillations (2 requiring hospitalisation) • 3 patients (3%) developed significant cutaneous erythema and oedema after sun exposure • 1 patient (1%) developed severe cutaneous blisters • Majority of patients had small unilateral or bilateral pleural effusions. • 2 patients required thoracentesis 3 patients died of medical conditions not related to Barrett's oesophagus or to PDT	Consecutive **Unclear whether same patients as those in the later paper. (6)** Nd:YAG laser was used to ablate small islands of residual Barrett's mucosa on 3-month or longer-term endoscopies. Histological confirmation of condition. All patients treated with proton pump inhibitors. Follow-up endoscopies were performed – four quadrant biopsy every 2 cm. Complications reported for all patients (unable to separate patients with HGD). Correlation between length of segment and development of stricture. Complications reported for both people with HGD and adenocarcinoma.
Wolfsen et al (2002) [8] Study design: uncontrolled retrospective. 48 patients (34 high grade, 14 cancer) Median age: 72	**Complete ablation of Barrett epithelium** (1 treatment session) All patients: 27/48 (56%) Patients with HGD: 19/34 (56%) **Complete ablation after argon plasma coagulator (for residual disease)** All patients 47/48 (98%)	**General complications** • 11 patients (23%)oesophageal stricture • 7 patients (15%) severe photosensitivity that required medical therapy • 1 patient (4%) onset of atrial fibrillation • 1 patient (4%) recurrent	HGD confirmed by 2 histopathologists. Argon beam laser was used to ablated small islands of residual Barrett's mucosa on 3-month or longer-term endoscopies.

Study details	Key efficacy outcomes	Key safety findings	Comments
(range 47–85) Median BE segment: 5 cms (range 2–15) Median follow up: 18.5 months (range 1-56 months) 34 HGD Median age: 72 (range 47-85) Median BE segment: 6 cms (range 2-15) Median follow up 18.5 months (1–56 months)	1 patient had to undergo curative oesophagectomy (patients had superficial adenocarcinoma) **Kaplan-Meier analysis** Event defined as either death or resection 1 death (metastatic lung cancer) 1 oesophagectomy	congestive heart failure • 1 patient (4%) chest pain from perforation	Follow-up endoscopy performed 1–3 days after treatment. After photosensitivity period patients returned for second endoscopy. Then had surveillance endoscopy every 3 to 6 months - four quadrant biopsy every 1 cm. Correlation between length of segment and incomplete ablation. Correlation between length of segment and development of stricture. Complications reported for both people with HGD and adenocarcinoma.
Panjehpoor et al (2000) [9] Study design: RCT/uncontrolled. USA 60 patients • 43 HGD • 30 PDT (6 patients 2 sessions) • 30 PDT plus oral prednisone (4 patients two session, 2 patients 3 sessions) Mean follow up: 9.8 months (range 3–18 months	**Histological results** **PDT Alone** Pre/Post; **PDT + steroid** Pre/Post; **Overall** Pre/Post **SQ** 0/13; 0/12; 0/25 **BE** 0/10; 0/11; 0/21 **LGD** 5/ 7; 5/5; 10/12 **HGD** 23/0; 20/2; 43/2 **TI** 2/0; 1/0; 3/0 **T2** 0/0; 4/0; 4/0 SQ: normal squamous epithelium High-grade dysplasia was eliminated in 41/43 (96%) patients (23+18) Barrett's mucosa was eliminated in 25/60 (42%) patients. **Average length reduction of Barrett's mucosa** PDT alone: 5.93 cm to 0.8cms p<0.0001 PDT+ steroid: 6.8cm to 1.48 cm p<0.0001 Overall: 6.36cm to 1.14cm p<0.0001	**Oesophageal strictures** **No of patients with strictures** PDT alone 1 session 7 Re-treatment 3 PDT +steroids 1 session 8 Re-treatment 3 2 patients in the PDT alone group had a history of stricture formation 1 patient in the PDT+ steroids group had a history of stricture formation. All strictures occurred within 1 month of PDT treatment.	RCT – however all patients received PDT – study question is about effect of oral steroids on stricture formation (so for the purpose of efficacy regarded as a uncontrolled trial). 2 patients excluded from the analysis (originally 62; lost to follow up, discontinued medication) Follow-up endoscopies were performed – four quadrant biopsy every 2 cm. Patients unable to separate high-grade group results.

Study details	Key efficacy outcomes	Key safety findings	Comments
Wolfsen et al (2002) [4] • 72 patients • 21 patients with oesophagus with high grade dysplasia or T1N0Mo adenocarcinoma • 51 patients with gastro-oesophageal cancer	**Not the aim of the study (not reported)**	**Cutaneous complications** 22 patients (31%) developed cutaneous complications – 7 with high grade dysplasia Most complications were phototoxic reactions involving erythema, blistering, swelling and pain or sun-exposed area. **2 other complications were reported**. 1 patient with mucosal adenocarcinoma developed severe herpes zoster 1 patient developed a protracted case of erythema multiforme-type drug reaction.	Study only looked at cutaneous complications. Complications were reported for all patients that received photodynamic therapy. Presentation of symptoms did not vary seasonally.
Overholt et al (1997) [5] 12 patients undergoing photodynamic therapy. Patients had dysplasia or early oesophageal adenocarcinoma. 5 patients had coronary artery disease 1 patient was a heart transplant patient. Cardiac enzymes measured pre-treatment and 24, 48 and 72 hours after treated. Electrocardiograms were obtained before and 48 hours after treatment	**Not the aim of the study (not reported)**	**Cardiac complications** All patients experienced moderate chest pain and dysphagia (5-7 days following procedure) 1 patient experienced atrial fibrillation occurring during the 48 hour endoscopic follow-up	Study only looked at cardiac complications. Patients noted to be consecutive. Patients were evaluated using cardiac enzymes and electrocardiograms following oesophageal PDT. Limited information. Authors note that the long term follow-up on these patients is part of an ongoing clinical trial.
Malhi-chowla et al (2001) [10] 23 patients • 10 with Barrett's oesophagus • 13 with carcinoma.	**Oesophageal dysmotility** Pre / Post Normal motility 11 (48%) / 6 (26%) Infective motility 6 (26%) / 7 (30%) Aperistalsis 6 (26%) / 10 (43%)	Not the aim of the study (not reported)	Study only looked at oesophageal dysmotility.
De Vault et al (2002) [11] 17 patients	**Oesophageal dysmotility** Pre / Post Normal motility 12 (70%) / 8 (26%) Infective motility 4 (24%) / 5 (30%) Aperistalsis 1 (6%) / 4 (43%)	Not the aim of the study (not reported)	Abstract – limited information. Study only looked at oesophageal dysmotility.

Abbreviations: PDT – photodynamic therapy; HGD – high grade dysplasia; LGD – low grade dysplasia; BE Barrett's epithelium; T1 – tumour stage 1; T2 – tumour stage 2; SQ: normal squamous epithelium; CR – complete response; TS – treatment success; TF – treatment failure;

Table 3 Summary of key efficacy findings from unpublished papers

The manufacturer of the photosensitiser agent has submitted the results of three clinical trials (phase I) to the US Food and Drugs Authority [12]. These results have been summarised below.

Study details	Key efficacy outcomes	Key safety outcomes	Comments
PHOBAR 01 trial Randomised controlled trial All patients had HGD • 138 patients to PDT + omeprazole (PDT+O) • 70 patients to omprazole (O) only Follow up: 2–3.6 years ITT: Intent to treat	**Clinical response after 24 months** (E: evaluable) **PDT+ O** / **O** **CR1** 72 (55.4%) / 5 (7.2%) **CR2** 9 (6.9%) / 5 (7.2%) **CR3** 25 (19.2%) / 17 (24.6%) **CR1+2+3 (E)** 106 (81.5%) / 27 (39.1%) **CR1+2+3 (ITT**) 106 (76.8%) / 27 (38.6%) **No response** 24 (18.5%) / 42 (60.9%) Significant differences between the two groups in terms of no of patients CR1+2+3 $p < 0.0001$ **No of patients who progressed to cancer by clinical response (24 months)** **PDT+ O** / **O** **CR1+2+3 (E)** 6/106 (5.7%) / 1/27 (3.7%) **No response** 12/24 (50%) / 19/42 (45.2%) **Total** 18/130 (13.8%) / 20/70 (28.6%)	See below	Multicentre Partially blinded 130 evaluable (E) in PDT+ O arm 69 evaluable (E) O arm. CR1 – complete response return to normal SE CR2 – SE with some areas of metaplasia CR3 – SE with some areas LGD, indefinite dysplasia or metaplasia.
TCSC 93-07 Patients randomised to two light doses 44 HGD	**Clinical response** • Number of patients with HGD who achieved CR: 41/44 (93%) • Number of patients with HGD who progressed to cancer 11/86 (13%) (includes patients in 96-01) – 12 months	See below	Patients had HGD, LGD, localised adenocarcinoma and BE with dysplasia or carcinoma.

Study details	Key efficacy outcomes	Key safety outcomes	Comments
TCSC 96-01 Patients randomised to +/- post-PDT steroids to test effect on stricture formation. 40 HGD	**Clinical response** • Number of patients with HGD who achieved CR: 40/42 (95%) • Number of patients with HDG who progressed to cancer: 11/86 (13%) (includes patients in 93-07) – 12 months	See below	Patients had HGD, LGD, localised adenocarcinoma and BE with dysplasia or carcinoma.
PHOBAR 01 TCSC 93-07 TCSC 96-01 318 patients 133 PHOBAR01 99 TSCA 93-07 86 TSCA 96-01	See above	**Complications** **Acute** (lasting for approx 4 weeks) 47% of patients chest pain 10% abdominal pain 22% fever 39% nausea 34% vomiting 15% odynophagia 24% dysphagia **Skin photosensitivity** 44% of patients 68% had mild reactions 26% had moderate reactions 6% severe reactions (including swelling, erythema, blisters, itching, burning sensations and heat) **Oesophageal strictures** 38.1% patients experienced strictures (endoscopy reports) 29.9% patients experienced strictures (adverse events) 6 patient died (not related to treatment) Some patients had gastrointestinal disorders and dehydration 2 patients had oesophageal perforations.	Safety data presented for all 3 clinical studies who received PDT – including patients with other indications e.g LGD. Incidence of oesophageal stricture depends on whether the data were collected from adverse events response or from endoscopy reports. Note that it would appear that patients who have more than one treatment session more likely to develop stricture.

Abbreviations: PDT – photodynamic therapy; O – omprazole; HGD – high grade dysplasia; LGD – low grade dysplasia; BE Barrett's epithelium; T1 – tumour stage 1; T2 – tumour stage 2; CR – clinical response; ITT - intent to treat; E -evaluable

Validity and generalisability of the studies

- Many of the studies included patients with low-grade dysplasia or cancer as well as patients with high-grade dysplasia. As such in some of these studies it was not possible to separate the results for patients with high-grade dysplasia.

- The actual procedural technique varied among the papers. In comparison to the studies undertaken by Overholt, Wolfsen et al [8] note that their methods included the use of longer light diffusers, mirrored balloon-centering devices and varied light does. There is some suggestion that these methods may reduce the incidence of stricture [13] however the extent of this impact is unclear.

- The studies also varied in that Nd:YAG laser or argon plasma coagulator was used for the ablation of persistent mucosa after PDT.

- Efficacy outcomes have primarily been in respect to elimination of high-grade dysplasia. Few studies have had sufficient follow-up to report on survival or cancer progression rates.

- All studies included in the efficacy section reported that patients had follow-up endoscopies which included four-quadrant biopsies.

Specialist Advisor's opinions

Specialist advice was sought from consultants who have been nominated or ratified by their Specialist society or Royal College.

Deciding what treatment to offer patients with high-grade dysplasia in the Barrett's oesophagus is difficult. Surgery is currently offered but many patients are unfit or unwilling to accept the morbidity associated with this treatment. The option of continued surveillance is also difficult as the cancer may develop undetected and be advanced at presentation.

Potential adverse events include oesophageal strictures and photosensitivity.

Although training is important, the technique is straightforward and can be performed in a standard endoscopy setting.

There is a need for further research, particularly randomised controlled trials.

Issues for consideration by IPAC

There is a UK Barrett's oesophagus registry

The manufacturer involved in this procedure is conducting a 5-year follow-up study of patients treated with the porfimer sodium PDT in the PHOVAR 01 trial in order to evaluate the long-term effect of PDT on high-grade dysplasia of Barrett's oesophagus. Results of this long-term evaluation are expected in 2007.

References

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4 Wolfsen HC, Ng CS. Cutaneous consequences of photodynamic therapy. Cutis 2002; 69(2):140-142.

5 Overholt BF, Panjehpour M, Ayres M. Photodynamic therapy for Barrett's esophagus: cardiac effects. Lasers in Surgery & Medicine 1997; 21(4):317-320.

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7 Overholt BF, Panjehpour M, Haydek JM. Photodynamic therapy for Barrett's esophagus: follow-up in 100 patients.[comment]. Gastrointestinal Endoscopy 1999; 49(1):1-7.

8 Wolfsen HC, Woodward TA, Raimondo M. Photodynamic therapy for dysplastic barrett esophagus and early esophageal adenocarcinoma. Mayo Clinic Proceedings 2002; 77(11):1176-1181.

9 Panjehpour M, Overholt BF, Haydek JM, Lee SG. Results of photodynamic therapy for ablation of dysplasia and early cancer in Barrett's esophagus and effect of oral steroids on stricture formation. American Journal of Gastroenterology 2000; 95(9):2177-2184.

10 Malhi-Chowla N, Wolfsen HC, DeVault KR. Esophageal dysmotility in patients undergoing photodynamic therapy. Mayo Clinic Proceedings 2001; 76(10):987-989.

11 DeVault KR, Wolfsen HC. Esophageal dysmotility in Barrett's esophagus with high grade dysplasia is worsened by photodynamic therapy. American Journal of Gastroenterology 97[9], S24. 2002. Abstract

12 FDA. Summary of the safety and efficacy section for photodynamic therapy. 2003. Available: www.fda.gov

13 Overholt BF, Panjehpour M. Photodynamic therapy for Barrett's esophagus. Gastrointestinal Endoscopy Clinics of North America 1997; 7(2):207-220.

Appendix A: List of relevant studies not included in the summary tables

Study Details	Patients/ Follow-up	Comments
Beejay,U., Riberiro,A., Hourigan, L et al. Photodynamic therapy of high-grade dysplasia/intramucosal carcinoma in Barrett's oesophagus – 30 months follow-up. *Gastrointestinal Endoscopy* (2001). 53: AB144	21 patients 30 months follow-up	Abstract Says 5 patients in [8]
Overholt BF, Panjehpour M. Photodynamic therapy in Barrett's esophagus: Reduction of specialized mucosa, ablation of dysplasia, and treatment of superficial esophageal cancer. *Seminars in Surgical Oncology* 1995; 11(5):372–6.	12 patients	Same authors
Overholt BF, Panjehpour M. Barrett's esophagus: Photodynamic therapy for ablation of dysplasia, reduction of specialized mucosa, and treatment of superficial esophageal cancer. *Gastrointestinal Endoscopy* 1995; 42(1):64–70.	8 patients	Same authors
Overholt B, Panjehpour M, Tefftellar E, Rose M. Photodynamic therapy for treatment of early adenocarcinoma in Barrett's esophagus. *Gastrointestinal Endoscopy* 1993; 39(1):73–6.	2 patients	Same authors

Appendix B: Literature search strategy for Photodynamic therapy for high-grade dysplasia for Barrett's oesophagus

The following search strategy was used to identify papers in Medline. A similar strategy was used to identify papers in EMBASE, Current Contents, PredMedline and all EMB databases.

For all other databases a simple search strategy using the key words in the title was employed.

#	Search history
1	exp BARRETT ESOPHAGUS/
2	barrett oesophagus.mp. or barrett esophagus.mp
3	barrett.tw.
4	(dysplasia adj4 $esophagus).mp. [mp=title, abstract, cas registry/ec number word, mesh subject heading]
5	or/1-4
6	exp Hematoporphyrin Photoradiation/ or exp Photosensitizing Agents/ or exp Photochemotherapy/ or photodynamic.mp.
7	PDT.tw.
8	6 or 7
9	5 and 8