NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

INTERVENTIONAL PROCEDURES PROGRAMME

Interventional procedure overview of photodynamic therapy for Barrett's oesophagus

Barrett's oesophagus is a condition in which the internal lining of the gullet (oesophagus) becomes damaged by long-term leaking of the stomach contents back into the gullet, known as 'reflux'. Some patients with Barrett's oesophagus may go on to develop cancer of the oesophagus. In photodynamic therapy, the patient is injected with a drug that makes the affected lining of the oeosophagus sensitive to light. Some hours after this a laser light source is passed down into the oesophagus where it is used to start a reaction that destroys the abnormal lining of the oesophagus, with the aim of preventing the progression to cancer.

Introduction

The National Institute for Health and Clinical Excellence (NICE) has prepared this overview to help members of the Interventional Procedures Advisory Committee (IPAC) make 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 in December 2009.

Procedure name

- Photodynamic therapy for Barrett's oesophagus

Specialty societies

- The Association of Upper Gastrointestinal Surgeons of Great Britain and Ireland
- British Society of Gastroenterology

Description

Indications and current treatment

Barrett's oesophagus is a premalignant condition characterised by the abnormal partial replacement of the squamous epithelium (lining) of the oesophagus by a type of columnar epithelium found elsewhere in the gastrointestinal tract. Typically these changes occur in segments of the lower oesophagus, at varying lengths.

The condition is thought to be asymptomatic, although the patient may have a history of heartburn, as there is a strong association of Barrett's oesophagus with gastro-oesophageal reflux disease (GORD).

The epithelium in patients with Barrett's oesophagus may be of normal microscopic appearance (metaplasia) or may have abnormal cellular architecture (either low- or high-grade dysplasia [LGD and HGD respectively]). In some patients, Barrett's oesophagus may progress through a series of stages (from metaplasia to LGD and then HGD) to oesophageal adenocarcinoma – a cancer with a poor prognosis.

The risk of progression to oesophageal adenocarcinoma is difficult to predict accurately. Overall, the risk of cancer progression is highest for patients with HGD, lower for patients with LGD, and even lower for patients with metaplastic-only Barrett's oesophagus. However, 'regression' from HGD to LGD as well as from LGD to metaplasia is also known to occur in some patients. There is uncertainty about the rate of progression (for example, from LGD to HGD), as well as the rate of 'regression' (for example, from HGD to LGD). In addition, accurate classification of Barrett's oesophagus into these distinct histopathological types requires multiple biopsy sampling and specialist histopathological expertise. There is the possibility of diagnostic misclassification due to biopsy sampling error and biopsy interpretation.

The management of patients with Barrett's oesophagus is determined by their dysplasia status. For patients with metaplastic (non-dysplastic) Barrett's oesophagus or LGD, periodic endoscopic surveillance and re-biopsy is traditionally recommended, with the aim of detecting potential progression to HGD or cancer early.

In contrast, for patients with HGD, management options include either very frequent (3-monthly) endoscopic surveillance and re-biopsy or oesophagectomy. (The rationale for oesophagectomy is that some patients with HGD may also have intra-mucosal adenocarcinoma lesions in parts of their oesophagus which were missed at biopsy sampling.)

For HGD patients, during the last 10 years, a series of non-surgical, endoscopic treatments have also been developed. These include endoscopic mucosal resection and ablative modalities, including photodynamic therapy (PDT), argon plasma coagulation (APC), laser ablation, cryotherapy, multipolar electrocoagulation and radiofrequency (RF) ablation. The aim of

ablative treatment is to destroy the Barrett's epithelium, leaving a surface that is subsequently re-epithelialised with squamous epithelium.

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, resulting in a photochemical reaction and the formation of high-energy oxygen molecules, leading to tumour necrosis.

Treatment is carried out as an inpatient procedure with the patient under intravenous sedation. In each treatment session, light is usually applied to a maximum Barrett's oesophagus segment length of approximately 7 cm to avoid toxicity. A second treatment session can be conducted if the Barrett's segment length exceeds 7 cm.

Skin photosensitivity, as a result of the uptake of the sensitising drug to the skin, can last for up to 30 days. Patients are recommended to avoid exposure to bright light from any source, especially direct sunlight during that period.

Literature review

Rapid review of literature

The medical literature was searched to identify studies and reviews relevant to PDT for Barrett's oesophagus. Searches were conducted of the following databases, covering the period from their commencement to 2 March 2010: MEDLINE, PREMEDLINE, EMBASE, Cochrane Library and other databases. Trial registries and the Internet were also searched. No language restriction was applied to the searches (see appendix C for details of search strategy). Relevant published studies identified during consultation or resolution that are published after this date may also be considered for inclusion.

The following selection criteria (table 1) were applied to the abstracts identified by the literature search. Where selection 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 were included. Emphasis was placed on identifying good quality studies. Abstracts were excluded where no clinical outcomes were reported, or where the paper was a review, editorial, or a laboratory or animal study. Conference abstracts were also excluded because of the difficulty of appraising study methodology, unless they reported specific adverse events that were not available in the published literature.
Patient	Patients with 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.

List of studies included in the overview

This overview is based on approximately 613 patients from six randomised controlled trials (RCTs) and one non-randomised trial.

Other studies that were considered to be relevant to the procedure but were not included in the main extraction table (table 2) have been listed in appendix A.

Table 2 Summary of key efficacy and safety findings on photodynamic therapy for Barrett's oesophagus

Abbreviations used: ALA, 5-aminolevulinic acid; APC, argon plasma coagulation; BO, Barrett's oesophagus; COPD; chronic obstructive pulmonary disease; EMR, endoscopic mucosal resection; HGD, high-grade dysplasia; ITT, intention to treat; LGD, low-grade dysplasia; MI, myocardial infarction; OM, omeprazole; POR, porfimer sodium; RCT, randomised controlled trial

<table>
<tr><th>Study details</th><th>Key efficacy findings</th><th>Key safety findings</th><th>Comments</th></tr>
<tr>
<td>Overholt BF (2005)[1]
Overholt BF (2007)[2]
Bronner MP (2009)[3]

RCT
UK, Canada, USA, France
Recruitment period: 1998–1999
Study population: patients with histologically-proven HGD
n = 208 (138 PDT with POR and OM vs 70 OM only)
Mean age: 66 years (PDT+OM) vs 67 years (OM only)
Sex: 85%

Patient selection criteria: minimum 18 years old, women with childbearing potential had to practice birth control and test negative for pregnancy on urine test; Exclusion criteria: any cancer other than nonmelanoma within last 5 years, prior oesophageal PDT,</td>
<td>Number of patients analysed: 203 (132 vs 69) for initial phase[1] and 61 (48 vs 13) for long-term phase[2]
Complete absence of HGD in initial 2-year phase (132 vs 69) (ITT analysis)[1]
<table>
<tr><th></th><th colspan="2">No. with ablation (%)</th><th></th></tr>
<tr><th>Follow-up (months)</th><th>PDT n = 138</th><th>OM n = 70</th><th>p value</th></tr>
<tr><td>6</td><td>73 (53)</td><td>18 (39)</td><td>0.0002</td></tr>
<tr><td>12</td><td>98 (71)</td><td>21 (30)</td><td><0.0001</td></tr>
<tr><td>18</td><td>104 (75)</td><td>25 (36)</td><td><0.0001</td></tr>
<tr><td>Overall ablation*</td><td>106 (77)</td><td>27 (39)</td><td><0.0001</td></tr>
</table>
*defined as complete absence of HGD on endoscopy at any timepoint (this includes patients who later had recurrence)

Complete absence of all Barrett's types (metaplasia and dysplasia) at 2-year follow-up (with ITT analysis)
<table>
<tr><th></th><th colspan="2">No. with ablation (%)</th><th></th></tr>
<tr><th>Follow-up (months)</th><th>PDT n = 138</th><th>OM n = 70</th><th>p value</th></tr>
<tr><td>Metaplasia +dysplasia</td><td>72 (52)</td><td>5 (7)</td><td>< 0.0001</td></tr>
<tr><td>Dysplasia</td><td>81 (59)</td><td>10 (14)</td><td>< 0.0001</td></tr>
</table>
Complete absence of HGD in 5-year phase (48 vs 13)[2]
There were no changes in proportion of responders after 5 years because only 1 patient had an additional PDT course. There was also a significantly shorter period in the time to complete response in the PDT group (113 vs 551 days;</td>
<td>Complications within 2-year follow-up[1]
<table>
<tr><th>Event</th><th>% (no.)</th></tr>
<tr><td>Photosensitivity reaction within 90 days**</td><td>69</td></tr>
<tr><td>Stricture***</td><td>36 (49)</td></tr>
<tr><td>Vomiting*</td><td>32</td></tr>
<tr><td>Noncardiac chest pain*</td><td>20</td></tr>
<tr><td>Pyrexia *</td><td>20</td></tr>
<tr><td>Dysphagia*</td><td>19</td></tr>
<tr><td>Constipation*</td><td>13</td></tr>
<tr><td>Dehydration*</td><td>12</td></tr>
<tr><td>Nausea*</td><td>11</td></tr>
<tr><td>Hiccups*</td><td>10</td></tr>
</table>
These events did not occur in the OM group. Time of events not reported unless otherwise specified.
*% given out of 138 patients

**usually sunburn-like affecting face, head and neck. All resolved but one left with motion impairment from keloid scars.
***16 during first, 29 during second, and 4 during third course of treatment; all managed successfully with dilatation (but dilatation-related perforation in 1 requiring oesophagectomy)

Events of severe intensity were similar in groups:16% vs 15% (65% vs 2% were related to the treatment).

Four patients in the PDT group withdrew because of</td>
<td>Follow-up issues:
• Endoscopy with biopsy at first visit and then every 3 months until four consecutive quarterly follow-up biopsies were negative; then biannually until 60-month follow-up (or until treatment failure).
• There was a significant loss to follow-up:
- 81/132 vs 20/70 completed the initial phase (2 year follow-up). Others had cancer progression (18 vs 20), HGD progression (19 vs 20), death not related to treatment or BO (2 vs 1) and other (18 vs 9) (no more details given) (however, the 2005 study reported that 78 vs 26 completed the initial phase).
- Of the 61 who</td>
</tr>
</table>

Abbreviations used: ALA, 5-aminolevulinic acid; APC, argon plasma coagulation; BO, Barrett's oesophagus; COPD; chronic obstructive pulmonary disease; EMR, endoscopic mucosal resection; HGD, high-grade dysplasia; ITT, intention to treat; LGD, low-grade dysplasia; MI, myocardial infarction; OM, omeprazole; POR, porfimer sodium; RCT, randomised controlled trial

Study details	Key efficacy findings	Key safety findings	Comments
oesophageal stricture unresponsive to dilation, oesophageal ulcer >1 cm, oesophageal or gastric varices, contraindications to analgesia, endoscopy or OM, class III/IV cardiovascular disease, significant acute or chronic illness, porphyria or porphyrin hypersensitivity, blood cell counts < 2.5 X 10^9/L, platelet count < 50 x 10^9/L, haemoglobin < 90 g/L, haematocrit < 27%, > 1.5 upper normal limit for normalized ratio of prothrombin time, serum creatinine, serum bilirubin and > 2.5 upper normal limit for aspartate aminotransferase or alanine aminotranferase or alkaline phosphatase. Technique: maximum 3 PDT courses over 5 years with at least 3 months between courses; 2.0 mg/kg PHO injection with balloon application of light (630 nm, 130 J/cm) 40–50 hours later; second application of light (without balloon; 50 J/cm)	p < 0.0001). By the end of the 5-year follow-up, there was a significantly greater probability of maintaining a complete absence of HGD in those with PDT vs those with OM (48% vs 4%; p < 0.0001). ***Development of cancer*** (ITT analysis) 15% (21/138) PDT and 29% (20/70) OM developed cancer during the 5-year follow-up period (p = 0.027). There were no significant differences between these groups in age, gender, race, smoking and endoscopy conditions. Of those in the PDT group, 9 were previously classified as having had complete HGD ablation while 12 did not. Of those in the OM group, 1 had achieved complete eradication of HGD at an earlier follow-up. (the management and outcomes for these patients was not reported; the authors report that no patient died from causes related to Barrett's or the treatment)	stroke, lung cancer, perforation during dilatation (reported above) and anxiety. Three life-threatening events unrelated to treatment occurred in the OM group: 2 cerebrovascular incidents and 1 MI. **Death**. There were a total of 3 deaths. Each death was unrelated to treatment and each occurred within the first 2 years of follow-up. - 2 in PDT group 14 and 16 months after (cardiac arrest after bypass surgery and metastatic breast cancer) - 1 from stroke in a patients with cardiovascular disease in OM group **Complications after 5-year follow-up**[2] There were no long-term effects of stricture formation or photosensitivity. Three patients with asymptomatic stricture but were stricture free at latest follow-up. ***Presence of squamous growth***[3] A separate publication from the same study cohort of patients reported results of testing the Barrett's epithelium and Barrett's glands below this overgrowth for neoplasia at four consecutive quarterly follow-ups and then biannually for 5 years.	entered the long-term phase, 51 completed 5-year follow-up (41 vs 10). Others had cancer progression (3 PDT+OM), HGD progression (1 vs 1) or 'other reasons' (3 vs 2) (no more details given). **Study design issues**: • Multi-centre (30) study with pathologist blinding only • Recruitment and randomisation processes not described • 485 patients were screened but 208 were eligible. Of those randomised, 7 did not complete treatment (6 PDT and 1 OM): this was because 3 withdrew consent, biopsy specimens showed LGD in one and adenocarcinoma in another, 1 had anxiety and the patient randomised

Abbreviations used: ALA, 5-aminolevulinic acid; APC, argon plasma coagulation; BO, Barrett's oesophagus; COPD; chronic obstructive pulmonary disease; EMR, endoscopic mucosal resection; HGD, high-grade dysplasia; ITT, intention to treat; LGD, low-grade dysplasia; MI, myocardial infarction; OM, omeprazole; POR, porfimer sodium; RCT, randomised controlled trial

<table>
<tr><th>Study details</th><th>Key efficacy findings</th><th>Key safety findings</th><th>Comments</th></tr>
<tr>
<td>96–120 hours after injection only on parts missed; 20 mg of OM daily for both groups

Follow-up: 2 years (initial phase) and 5 years (long-term phase)

Conflict of interest/source of funding: the trial was funded at each site by Axcan; primary author has shared patent rights on device used in trial; one author is an employee of Axcan and holds shares of Axcan stock; four other authors have either previous consultancy with Axcan, received honoraria, own small number of shares in Axcan or been paid fees for statistical analysis by Axcan.</td>
<td></td>
<td>
<table>
<tr><th></th><th colspan="2">Pre-treatment</th><th colspan="2">Post-treatment</th></tr>
<tr><th></th><th>PDT n=138</th><th>OM n=70</th><th>PDT n=132</th><th>OM N=67</th></tr>
<tr><td>No. with overgrowth (%)</td><td>8 (5.8)</td><td>2 (2.9)</td><td>39 (30)</td><td>22 (33)</td></tr>
<tr><td>No of biopsies</td><td>304 7</td><td>158 1</td><td>23 498</td><td>10 160</td></tr>
<tr><td>Per patient</td><td>22.2</td><td>22.6</td><td>178. 0</td><td>151.6</td></tr>
<tr><td>Squamous overgrowth (%)</td><td>9 (0.3)</td><td>2 (0.1 3)</td><td>114 (0.5)</td><td>130 (1.3)</td></tr>
<tr><td>Squamous overgrowth areas per patient</td><td>0.50 (2.2)</td><td>0.26 (1.6)</td><td>0.48 (1.3)</td><td>0.66 (1.4)</td></tr>
</table>
No significant difference between proportion of patients with squamous overgrowth, per biopsy or per patient. There were significantly more biopsies performed per patient in those treated by PDT.
</td>
<td>to OM had oesophagectomy.
• The study had an initial phase (24 months) and then a long-term phase lasting 5 years but only 61 patients (36% [48/132} and 18.6% [13/70] of those randomised and 60 vs 65% of those who completed initial phase) chose to continue into the long-term phase. Patients stayed in the same group originally randomised to.
• ITT analysis of those randomised to each group.
Study population issues:
• There was no significant difference in age, sex, race, smoking history, or BO characteristics between groups at baseline in either stage of the trial.</td>
</tr>
</table>

Abbreviations used: ALA, 5-aminolevulinic acid; APC, argon plasma coagulation; BO, Barrett's oesophagus; COPD; chronic obstructive pulmonary disease; EMR, endoscopic mucosal resection; HGD, high-grade dysplasia; ITT, intention to treat; LGD, low-grade dysplasia; MI, myocardial infarction; OM, omeprazole; POR, porfimer sodium; RCT, randomised controlled trial

Study details	Key efficacy findings	Key safety findings	Comments
			• In PDT group: 132 patients had at least one dose, 68% (90/132) of these had a second course and 47% (42/90) of these had a third. **Other issues**: • There are three publications from this trial cohort which are included here. • The authors used the term 'squamous growth' (or neosquamous) to describe 'buried glands'.

Abbreviations used: ALA, 5-aminolevulinic acid; APC, argon plasma coagulation; BO, Barrett's oesophagus; COPD; chronic obstructive pulmonary disease; EMR, endoscopic mucosal resection; HGD, high-grade dysplasia; ITT, intention to treat; LGD, low-grade dysplasia; MI, myocardial infarction; OM, omeprazole; POR, porfimer sodium; RCT, randomised controlled trial

<table>
<tr><th>Study details</th><th>Key efficacy findings</th><th>Key safety findings</th><th>Comments</th></tr>
<tr>
<td>Kelty CJ (2004)[4]

RCT
UK
Recruitment period: not reported
Study population: patients from larger cohort of patients with histologically confirmed non-dysplastic BO enrolled in endoscopic screening program
n = 72 (35 PDT vs 37 APC)
Median age: 61 PDT, 59 APC
Sex: 81% male

Patient selection criteria: not reported

Technique: outpatient procedure with intravenous sedation, 30mg/kg of ALA, 4–6 hours later endoscopy, application of light with balloon applicator allowing treatment of proximal 3 cm segment with endoscopic guidance</td>
<td>Number of patients analysed: 68 (34 PDT vs 34 APC)

Complete response
Complete response was defined as macroscopic reversal of columnar segment to squamous epithelium (to the level of the gastro-oesophageal junction) viewed on endoscopy.
<table>
<tr><th></th><th>PDT</th><th>APC</th><th>p value</th></tr>
<tr><td>Complete response</td><td>50% (17/34)</td><td>97% (33/34)</td><td>< 0.0 001</td></tr>
<tr><td>Median no. of treatments</td><td>2 (1–4)</td><td>3 (1–5)</td><td>Not signifi cant</td></tr>
</table>
Of the patients with no complete response in the PDT group, all exhibited a partial response (evidence of squamous re-epithelialisation – either regression of the length of Barrett's segment towards gastro-oesophageal junction or formation of squamous islands within the Barrett's segment).
Shorter BO segment length was significantly associated with successful treatment (successful treatment was not defined).
Microscopic response
Histological analysis confirmed squamous re-epithelialisation in the treated areas and columnar metaplasia in the non-responding areas.
Results from blood tests
Four patients developed mild elevation of liver function tests but these were asymptomatic.</td>
<td>Complications
<table>
<tr><th>Events in those treated with PDT</th><th>No. (%)</th></tr>
<tr><td>Nausea and vomiting [a]</td><td>11 (32)</td></tr>
<tr><td>Photosensitivity reaction [b]</td><td>5 (14.7)</td></tr>
<tr><td>Hypotension not requiring intervention</td><td>2 (5.8)</td></tr>
<tr><td>Angina after 2 days [c, d]</td><td>1(2.9)</td></tr>
<tr><td>Fever and painful swallowing after 4 days</td><td>1(2.9)</td></tr>
<tr><td>Oesophageal stricture [e]</td><td>1 (2.9)</td></tr>
</table>
[a] this occurred more frequently in patients with higher ALA dose (n = 5 with 60 mg/kg)
[b]all were mild (involved erythema and pain in light-exposed skin); not related to dose or timing
[c] in a patient with history of ischaemic disease
[d] successfully treated with oral analgesia and discharged 2 days later
[e] this patient was unable to complete treatment; this was written as a reason for loss to follow-up. Later in the safety section, it reports that there were no strictures (the reason for this discrepancy is unclear)
Buried columnar glands
Biopsy revealed the presence of buried glands in 24% (4/17) of patients treated with PDT and 21% (7/33) patients treated with APC (not significant; no other details given).</td>
<td>Follow-up issues:
• Patients were contacted about side effects after the first day.
• Endoscopy and biopsy at 4 weeks, 6, 12, and 24 months.
• 4 patients did not complete treatment (1 died of pancreatic carcinoma, 1 could not attend regularly because of COPD, 1 developed oesophageal stricture, 1 withdrew for social reasons).

Study design issues:
• Computer randomisation to 5 groups.
• No blinding reported.
• Of 150 patients approached, 72 agreed to be involved.
• The analysis was not by ITT (i.e. including patients</td>
</tr>
</table>

Abbreviations used: ALA, 5-aminolevulinic acid; APC, argon plasma coagulation; BO, Barrett's oesophagus; COPD; chronic obstructive pulmonary disease; EMR, endoscopic mucosal resection; HGD, high-grade dysplasia; ITT, intention to treat; LGD, low-grade dysplasia; MI, myocardial infarction; OM, omeprazole; POR, porfimer sodium; RCT, randomised controlled trial

Study details	Key efficacy findings	Key safety findings	Comments
(635 nm, 68mW/cm2, 85 J/cm2); patients told to avoid bright light for 24 hours (APC patients each had 2 cm strips coagulated at a time); patients in both groups discharged with oral analgesia and maintained on daily 40 mg of OM. Median follow-up: **12 months** Conflict of interest/source of funding: primary author was supported by Yorkshire Cancer Research and BUPA, DUSA Pharmaceuticals provided the ALA used in the study.			who did not complete treatment). **Study population issues**: • Exclusion criteria not reported. • Patients in the two groups were of similar age and gender and were followed-up over a similar period.

Abbreviations used: ALA, 5-aminolevulinic acid; APC, argon plasma coagulation; BO, Barrett's oesophagus; COPD; chronic obstructive pulmonary disease; EMR, endoscopic mucosal resection; HGD, high-grade dysplasia; ITT, intention to treat; LGD, low-grade dysplasia; MI, myocardial infarction; OM, omeprazole; POR, porfimer sodium; RCT, randomised controlled trial

<table>
<tr><th>Study details</th><th>Key efficacy findings</th><th>Key safety findings</th><th>Comments</th></tr>
<tr>
<td>Panjehpoor M (2000)[5]
(in original overview)
RCT
USA
Recruitment period: not reported
Study population: patients with LGD, HGD or T1 or T2 tumours (43 HGD, 10 LGD, 3 intramucosal, 4 submucosal)
n = 60 (30 PDT vs 30 PDT plus oral prednisone)
Age: not reported
Sex: 83% male

Patient selection criteria: not reported

Technique: outpatient procedure, Photofrin + light application with a 5 or 7 cm windowed balloon (those with LGD had 175 J/cm and those with HGD or nodular disease had 200 J/cm), followed by OM postoperatively (narcotics were given if chest discomfort); prednisone was given 1</td>
<td>Number of patients analysed: 60 (30 PDT vs 30 PDT plus oral prednisone)
Procedure efficacy
<table>
<tr><th>Outcome</th><th>Patients</th></tr>
<tr><td>Elimination of HGD</td><td>96% (41/43)</td></tr>
<tr><td>Elimination of Barrett's with no dysplasia</td><td>33.9%* (21/62)</td></tr>
<tr><td>Elimination of Barrett's mucosa</td><td>42% (25/60)</td></tr>
<tr><td>Elimination of cancer (in patients who presented originally with cancer)</td><td>100% (7/7)</td></tr>
</table>
*% calculated by analyst
The following are numbers of patients in each group with each diagnosis before the procedure and at follow-up:
<table>
<tr><th></th><th colspan="2">PDT alone</th><th colspan="2">PDT + steroids</th></tr>
<tr><td></td><td>Pre-op</td><td>At follow-up</td><td>Pre-op</td><td>At follow-up</td></tr>
<tr><td>LGD</td><td>5</td><td>7</td><td>5</td><td>5</td></tr>
<tr><td>HGD</td><td>23</td><td>0</td><td>20</td><td>2</td></tr>
<tr><td>T1</td><td>2</td><td>0</td><td>1</td><td>0</td></tr>
<tr><td>T2</td><td>0</td><td>0</td><td>4</td><td>0</td></tr>
</table>
If residual BO was detected on follow-up, thermal ablation was used on small segments and PDT on large segments (all but 6 were treated with thermal ablation; 6 in each group were treated with a second PDT treatment; it was not stated at which times these subsequent treatments were done).

Length of BO</td>
<td>Stricture formation
The following strictures occurred within 1 month after the operation (stricture was defined as dysphagia and the inability to pass an endoscope through the lumen):
<table>
<tr><th></th><th>No. with stricture (%)</th></tr>
<tr><td>All patients</td><td>20 (33.3)</td></tr>
<tr><td>PDT only</td><td>9 (30)*</td></tr>
<tr><td>PDT+OM</td><td>11 (36.7)</td></tr>
</table>
*Two of these patients have a history of stricture.
In those treated with a second course, more strictures occurred in patients who had overlapping treatment fields.
The study did not report how the strictures were managed or when they occurred.</td>
<td>Follow-up issues:
1 patient was lost to follow-up and another discontinued prednisone so both were excluded from the analysis. These patients were not included in the analysis, which was therefore not by ITT, see below.
Follow-up endoscopies 2–3 days after procedure. For patients with T1 and T2 cancer, four-quadrant biopsies every 3 months. Biopsies every 6 months for all other patients.
Study design issues:
The purpose of this study is to see the effect of oral steroids on stricture formation.
Block randomisation was used.</td>
</tr>
</table>

Abbreviations used: ALA, 5-aminolevulinic acid; APC, argon plasma coagulation; BO, Barrett's oesophagus; COPD; chronic obstructive pulmonary disease; EMR, endoscopic mucosal resection; HGD, high-grade dysplasia; ITT, intention to treat; LGD, low-grade dysplasia; MI, myocardial infarction; OM, omeprazole; POR, porfimer sodium; RCT, randomised controlled trial

Study details	Key efficacy findings	Key safety findings	Comments
hour after treatment and for 2 days (60 mg) and reduced to 10mg every 2 days. Mean follow-up: **9.8 months** Conflict of interest/source of funding: Photofrin, cylindrical diffusers and PDT balloons were provided by QLT Phototherapeutics	<table><tr><th></th><th>Reduction in BO segment length (cm)</th><th>p value</th></tr><tr><td>PDT alone</td><td>5.93 to 0.8</td><td>< 0.0001</td></tr><tr><td>PDT + steroids</td><td>6.8 to 1.48</td><td>< 0.0001</td></tr><tr><td>All</td><td>6.36 to 1.14</td><td>< 0.0001</td></tr></table>		• No ITT analysis (2 patients not included in analysis). • Endoscopists were blind to patient group. **Study population issues**: • Patients treated with only PDT included 5 LGD, 23 HGD, 2 T1, 0 T2; respective numbers were 5 LGD, 20 HGD, 1 T1, and 4 T2 for the other group. • Those who received steroids had a longer BO segment than those who had PDT alone. **Other issues**: • This study was the only RCT in the previous overview.

Abbreviations used: ALA, 5-aminolevulinic acid; APC, argon plasma coagulation; BO, Barrett's oesophagus; COPD; chronic obstructive pulmonary disease; EMR, endoscopic mucosal resection; HGD, high-grade dysplasia; ITT, intention to treat; LGD, low-grade dysplasia; MI, myocardial infarction; OM, omeprazole; POR, porfimer sodium; RCT, randomised controlled trial

<table>
<tr><th>Study details</th><th>Key efficacy findings</th><th>Key safety findings</th><th>Comments</th></tr>
<tr>
<td>Hage M (2004)[6]

RCT
The Netherlands
Recruitment period: 2001–2002
Study population: patients with histologically confirmed BO (32 non-dysplastic, 8 LGD) who had been taking proton pump inhibitors for at least 6 months before treatment
n = 40 (single-dose 100 J/cm2 PDT 13 vs two-dose (20 and 100 J/cm2) PDT 13 vs APC 14)
Mean age: 59
Sex: 77.5% male

Patient selection criteria: patients with either no dysplasia or LGD; Exclusion criteria: intolerance to repeated endoscopy, pregnancy, history of acute porphyria, and concurrent diseases precluding survival during the study period.</td>
<td>Number of patients analysed: 40 (13 PDT with one dose vs 13 with PDT at two doses and 14 APC)
Presence of BO at 6-week follow-up (on biopsy)
<table>
<tr><th></th><th>Single dose PDT n = 13</th><th>Two-dose PDT n = 13</th><th>APC n = 14</th></tr>
<tr><td>No BO</td><td>1 (8%)</td><td>4 (33%)</td><td>5 (36%)</td></tr>
<tr><td>Residual BO</td><td>12</td><td>7</td><td>4*</td></tr>
<tr><td>Sub-squamous BO</td><td>0</td><td>1</td><td>5</td></tr>
</table>
None of these differences were significant
*2 of these patients also had sub-squamous BO
All 23 patients with residual BO at 6 weeks received APC (one session for 20 patients and 2 sessions for 3 patients).
Presence of BO on endoscopy and biopsy at later follow-up
<table>
<tr><th rowspan="3">Follow-up</th><th colspan="6">No. with BO (%)</th></tr>
<tr><th colspan="2">PDT100</th><th colspan="2">PDT20+100</th><th colspan="2">APC</th></tr>
<tr><th>Endoscopic</th><th>Histopathic</th><th>Endoscopic</th><th>Histopathic</th><th>Endoscopic</th><th>Histopathic</th></tr>
<tr><td>6</td><td>0/13 (0)</td><td>1/13 (8)</td><td>0/12 (0)</td><td>0/12 (0)</td><td>1/14 (7)</td><td>3/14 (21)</td></tr>
<tr><td>12</td><td>1/11 (9)</td><td>2/11 (18)</td><td>0/10 (0)</td><td>1/10 (10)</td><td>2/12 (17)</td><td>4/12 (33)</td></tr>
<tr><td>18</td><td>2/8 (25)</td><td>2/8 (25)</td><td>0/8</td><td>1/8 (12)</td><td>2/9 (22)</td><td>3/9 (33)</td></tr>
<tr><td>24</td><td>-</td><td>-</td><td>0/2</td><td>0/2</td><td>-</td><td>-</td></tr>
</table>
</td>
<td>Complications
One patient treated with PDT died 3 days after treatment. The autopsy revealed transmural necrosis without perforation.
<table>
<tr><th></th><th>PDT n=26</th><th>APC n=14</th></tr>
<tr><td>Pain during treatment</td><td>23</td><td>5</td></tr>
<tr><td>Odynophagia</td><td>24</td><td>12</td></tr>
<tr><td>Fever</td><td>8</td><td>2</td></tr>
<tr><td>Nausea and vomiting</td><td>7</td><td>0</td></tr>
<tr><td>Stricture</td><td>0</td><td>1</td></tr>
<tr><td>Elevated liver enzymes*</td><td>20</td><td>0</td></tr>
</table>
*these had normalised 6 weeks after treatment
Nausea and vomiting, pain during the treatment, and elevated liver enzyme levels were each significantly worse in patients treated with PDT ($p < 0.05$ for pain and $p < 0.01$ for others).</td>
<td>Follow-up issues:
Patients were contacted by phone 5 days after treatment; follow-up endoscopy and biopsies at 6 weeks and 6, 12, 18 and 24 months.
The authors did not explicitly report a loss to follow-up. It is unclear if change in denomination relates to loss of follow-up of original cohort, or to differential follow-up between patients recruited at different times.
Study design issues:
Recruitment and blinding not described.
Randomisation was said to have been performed by the trial centre of the Department of Internal Oncology, Erasmus MC Rotterdam and</td>
</tr>
</table>

Abbreviations used: ALA, 5-aminolevulinic acid; APC, argon plasma coagulation; BO, Barrett's oesophagus; COPD; chronic obstructive pulmonary disease; EMR, endoscopic mucosal resection; HGD, high-grade dysplasia; ITT, intention to treat; LGD, low-grade dysplasia; MI, myocardial infarction; OM, omeprazole; POR, porfimer sodium; RCT, randomised controlled trial

Study details	Key efficacy findings	Key safety findings	Comments
Technique: administration of 60 mg/kg ALA, light (630 nm) administered with a balloon once in one group (4 hours later) and twice in the other at 20 J/cm2 and 100 J/cm2 (1 and 4 hours later) (all were kept in dark room for 36 hours after administration of ALA) (APC patients had maximum of 2 treatment sessions per patient at 4 week intervals); all patients had daily 40 mg OM; if BO observed at first follow-up in either group, additional APC was used at a maximum of two sessions at 4 week intervals. Follow-up: **12 months** Conflict of interest/source of funding: the primary author was financially supported by the Revolving Fund of the Erasmus MC University Medical Centre Rotterdam.	There was no significant differences between groups		patients were stratified for the presence of dysplasia or LGD. No other details given. • APC was used to treat any patient with macroscopic BO presenting at first follow-up in any group. **Study population issues**: • The authors reported that there were no significant demographical differences between groups.

Abbreviations used: ALA, 5-aminolevulinic acid; APC, argon plasma coagulation; BO, Barrett's oesophagus; COPD; chronic obstructive pulmonary disease; EMR, endoscopic mucosal resection; HGD, high-grade dysplasia; ITT, intention to treat; LGD, low-grade dysplasia; MI, myocardial infarction; OM, omeprazole; POR, porfimer sodium; RCT, randomised controlled trial

<table>
<tr><th>Study details</th><th>Key efficacy findings</th><th>Key safety findings</th><th>Comments</th></tr>
<tr>
<td>Ackroyd R (2000)[7]

RCT
USA and the Netherlands
Recruitment period: 1995
Study population: patients with histologically confirmed LGD BO receiving acid suppression medication and OM
n = 36 (18 PDT vs 18 placebo)
Median age: 56
Sex: 83% male

Patient selection criteria: BO of at least 3 cm, receiving OM

Technique: all patients treated as day cases; PDT with 30 mg/kg ALA with endoscopy performed 4 hours later under intravenous sedation and analgesia, light administered with fibre with a diffuser tip (514nm, 120 mW/cm2) for 500 seconds per 3 cm length in 2 treatments</td>
<td>Number of patients analysed: 36 (18 PDT vs 18 placebo)

Operative success
89% (16/18) of 18 of patients treated by PDT had macroscopic evidence of regression at follow-up.
30% difference in the groups in median area regression (not otherwise described; 95% CI 20–40%)
<table>
<tr><th></th><th>PDT (n=18)</th><th>Placebo (n=18)</th><th>p value</th></tr>
<tr><td>No. with macroscopic response (%)</td><td>16 (89)*</td><td>2 (11)**</td><td>< 0.001</td></tr>
<tr><td>Average percentage of area reduction</td><td>30%</td><td>0%</td><td>< 0.001</td></tr>
<tr><td>No. with residual dysplasia (%)</td><td>2 (11)</td><td>12 (67)</td><td>< 0.001</td></tr>
</table>
*These results were confirmed on biopsy, revealing normal squamous mucosa with no evidence of squamous dysplasia or underlying columnar epithelium. There was also no evidence of dysplasia in the area treated by PDT.
** on biopsy, also appearance of normal squamous epithelium; 12 of 18 cases still had LGD, but 6 had no evidence of dysplasia.</td>
<td>Complications
All patients treated with PDT experienced chest pain which persisted for 3 to 5 days and was aggravated by coughing or swallowing. Three were treated with analgesia.

One patient developed mild skin rash on the day after treatment because of exposure to sunlight but this resolved in 48 hours without treatment.

No patients were reported to have had dysphagia.</td>
<td>Follow-up issues:
Follow-up endoscopy at 1, 6, 12 and 24 months by 2 blind observers; 6 biopsies taken at 6, 12 and 24 months.
Study design issues:
70 patients assessed, 45 confirmed, 36 agreed to take part (9 did not: 5 for family reasons and 4 wanting to see therapeutic benefit before agreeing to multiple endoscopic examinations).
Appropriate patients were sought from endoscopic and histopathologic records.
Randomisation done with series of sealed envelopes opened by pharmacy staff.
Double blinded.
BO was only ablated to a maximum of 6 cm.</td>
</tr>
</table>

Abbreviations used: ALA, 5-aminolevulinic acid; APC, argon plasma coagulation; BO, Barrett's oesophagus; COPD; chronic obstructive pulmonary disease; EMR, endoscopic mucosal resection; HGD, high-grade dysplasia; ITT, intention to treat; LGD, low-grade dysplasia; MI, myocardial infarction; OM, omeprazole; POR, porfimer sodium; RCT, randomised controlled trial			
Study details	**Key efficacy findings**	**Key safety findings**	**Comments**
(distal and proximal; to a maximum of 6 cm, even if residual BO); allowed to eat and drink when able, remained at hospital until dark and instructed to stay out of bright light for 24 hours, remained on daily 20 mg of OM (placebo group received a placebo in place of ALA and then had laser endoscopy with sedation). Follow-up: **59 to 61 months** Conflict of interest/source of funding: supported by a grant from a health authority.			**Study population issues**: • Groups were demographically similar in age and sex. • Exclusion criteria not given. **Other issues**: • This study was not included in the original overview, probably because the original overview was on HGD and this study only included patients with LGD. • In the discussion section, the authors report that PDT usually resulted in streaks or patches of columnar epithelium rather than complete circumferential ablation. They hypothesised that this could be because of mucosal folds which were not eradicated by the 'solid state' applicator.

Abbreviations used: ALA, 5-aminolevulinic acid; APC, argon plasma coagulation; BO, Barrett's oesophagus; COPD; chronic obstructive pulmonary disease; EMR, endoscopic mucosal resection; HGD, high-grade dysplasia; ITT, intention to treat; LGD, low-grade dysplasia; MI, myocardial infarction; OM, omeprazole; POR, porfimer sodium; RCT, randomised controlled trial

<table>
<tr><th>Study details</th><th>Key efficacy findings</th><th>Key safety findings</th><th>Comments</th></tr>
<tr>
<td>Ragunath K (2005)[8]
RCT
UK
Recruitment period: not reported
Study population: patients with histologically confirmed dysplastic BO (23 LGD, 3 HGD)
n = 26 (13 PDT vs 13 APC)
Median age: 60
Sex: 81% male
Patient selection criteria: BO ≥ 3 cm. Excluded patients were those with comorbidities, known to have oesophageal malignancy of any form, previous oesophageal resection, previous mucosal ablative therapy or EMR, with tongue-shaped BO lesions rather than circumferential, known to have prophyria, pregnant, trying to get pregnant or not using contraception, intolerance to endoscopy.
Technique: 2 mg/kg Photofrin administered, 48 hours later (with</td>
<td>Number of patients analysed: 26 (13 PDT vs 13 APC)

Median length of BO segment eradicated
<table><tr><th>Follow-up</th><th>PDT</th><th>APC</th></tr><tr><td>4 months</td><td>57% (3 cm)</td><td>65% (3 cm)</td></tr><tr><td>12 months</td><td>60% (3 cm)</td><td>56% (2.5 cm)</td></tr></table>
Number of patients with dysplasia eradicated (on endoscopy and biopsy)
<table><tr><th>Follow-up</th><th>4 month eradication</th><th>12 month eradication</th></tr><tr><td>PDT (all)</td><td>77% (10/13)</td><td>Same</td></tr><tr><td>PDT (LGD)</td><td>73% (8/11)</td><td>Same</td></tr><tr><td>PDT (HGD)</td><td>100% (2/2)</td><td>Same</td></tr><tr><td>APC (all)</td><td>62% (8/13)</td><td>67% (6/9)</td></tr><tr><td>APC (LGD)</td><td>50% (6/12)</td><td>73% (8/11)</td></tr><tr><td>APC (HGD)</td><td>100% (1/1)</td><td>n/a</td></tr></table>*
The difference in eradication between the groups at 4 months was significant (p = 0.03) and remained so at 12 months.
At 12 months, the percentage of Barrett's eradication was:
56% APC
61% PDT</td>
<td>Complications
Almost all patients in the study had minimal discomfort swallowing solid food for a few days.
Severe side effects occurred in 31% (4/13) of patients treated by PDT and 23% (3/13) of patients treated by APC.
<table><tr><th></th><th>PDT</th><th>APC</th></tr><tr><td>Oesophageal stricture*</td><td>15% (2/13)</td><td>15% (2/13)</td></tr><tr><td>Severe chest pain</td><td>0</td><td>8% (1/13)</td></tr><tr><td>Photosensitivity** </td><td>15% (2/13)</td><td>0</td></tr></table>*required dilatation
**required analgesics and soothing cream
(time of occurrence of events not reported)
One patient treated with PDT who failed to have eradication of LGD at 4 months was found to have buried glands and adenocarcinoma beneath the neosquamous epithelium at 12-month follow-up. The patient was successfully treated with oesophagectomy.</td>
<td>Follow-up issues:
• Follow-up endoscopy and biopsy at 4 and 12 months assessed by more than one endoscopist.
• 4 patients in the APC group were not followed up at 12 months: 3 with LGD were lost to follow-up (no other details provided) and 1 with HGD who had eradicated dysplasia was deemed unfit for endoscopy because of the development of other serious comorbidities.

Study design issues:
• 33 patients were identified from endoscopy and histopathology records for inclusion in the study but 3 were excluded due to significant comorbidity, 3 with HGD chose to have</td>
</tr>
</table>

Abbreviations used: ALA, 5-aminolevulinic acid; APC, argon plasma coagulation; BO, Barrett's oesophagus; COPD; chronic obstructive pulmonary disease; EMR, endoscopic mucosal resection; HGD, high-grade dysplasia; ITT, intention to treat; LGD, low-grade dysplasia; MI, myocardial infarction; OM, omeprazole; POR, porfimer sodium; RCT, randomised controlled trial

Study details	Key efficacy findings	Key safety findings	Comments
sedation), laser light (630 nm, 840 mW, 200 J/cm) administered with balloon in 3 cm segments, patients were given PPIs, daily 30 mg lansoprazole for 3 months and instructed to avoid direct sunlight for 4–8 weeks, repeat endoscopy after 48 hours and then discharged (APC in one or more sessions depending on length and patient tolerability with interval of 2–4 weeks with maximum 6 sessions). Follow-up: **12 months** Conflict of interest/source of funding: Axcan and Wyeth funded the research.	(significance level, numerator and denominator not reported)		APC. • Computer generated randomisation. • Blinding not reported. • Patients with HGD also underwent preoperative endoscopy ultrasound to rule out submucosal invasive cancer. **Study population issues**: • The PDT group had a greater median age compared to the APC group (65 vs 58), had one more patient with HGD (2 vs 1) and more females (3 vs2) but there were no tests to see if these differences were significant.

Abbreviations used: ALA, 5-aminolevulinic acid; APC, argon plasma coagulation; BO, Barrett's oesophagus; COPD; chronic obstructive pulmonary disease; EMR, endoscopic mucosal resection; HGD, high-grade dysplasia; ITT, intention to treat; LGD, low-grade dysplasia; MI, myocardial infarction; OM, omeprazole; POR, porfimer sodium; RCT, randomised controlled trial

<table>
<tr><th>Study details</th><th>Key efficacy findings</th><th>Key safety findings</th><th>Comments</th></tr>
<tr>
<td>Prasad K (2004)[9]

Non randomised trial
UK
Recruitment period: 1994–2004
Study population: patients with histologically confirmed HGD who presented at the Mayo Clinic for management of their Barrett's oesophagus.

n = 199 (129 PDT vs 70 oesophagectomy)
Median age: 63 years
Sex: 80% male
Patient selection criteria:
Exclusion criteria: patients with evidence of carcinoma on histopathologic assessment.

Technique: photosensitiser, administration of light 48 hours later (630 nm, 200 J/cm) with a balloon (12 were treated with a balloon with 5–7 cm</td>
<td>Number of patients analysed: 199 (129 PDT vs 70 oesophagectomy)

Outcomes after PDT
<table>
<tr><th>Outcome</th><th>% of patients</th></tr>
<tr><td>HGD eradication at 1 year</td><td>88 (114/129)</td></tr>
<tr><td>HGD eradication at 3 years</td><td>86 (111/129)</td></tr>
</table>
33 patients had failure (HGD was detected within 12 months of the first PDT session) so were re-treated with PDT and/or EMR which lead to elimination of HGD in 70% (23/33).
Recurrence of HGD (HGD detected after 12 months from first PDT session) occurred in 10. These patients were treated with EMR and/or multipolar electrocoagulation resulting in 60% (6/10) eradication of HGD (the study did not report that these patients required oesophagectomy).
Development of cancer
<table>
<tr><th></th><th>PDT</th><th>oesophagectomy</th></tr>
<tr><td>% with cancer</td><td>6.2% *(8/129)</td><td>12.8% ** (9/70)</td></tr>
</table>
*6 in the first 12 months and 2 within 18 months; 5 had intramucosal carcinoma (all successfully treated: 4 with oesophagectomy and one with EMR) and 3 had submucosal cancer (all had oesophagectomy); none had metastatic lymphadenopathy and all were alive at last follow-up.
**these were detected in the resected surgical specimen (all had preoperatively been determined to be HGD); 4 had intramucosal cancer and 5 had submucosal cancer; endoscopic ultrasonography was performed in 8 of the 9 patients; none had metastatic lymphadenopathy and all were alive at last follow-up.</td>
<td>Complications
The authors report oesophageal stricture to be 27% (35/131) in another publication which included these patients. These required a median of 4 dilations; most were successful but one patient had a perforation after dilation so had a oesophagectomy
<table>
<tr><th></th><th>PDT (n = 129)</th><th>Oesophagectomy (n = 70)</th></tr>
<tr><td>Anastomotic stricture</td><td>0</td><td>12.6% (9)</td></tr>
<tr><td>Severe chest pain</td><td>0</td><td>8% (1/13)</td></tr>
<tr><td>Photosensitivity *</td><td>60% (77)</td><td>0</td></tr>
<tr><td>Surgical complications</td><td></td><td>12.6% (9)</td></tr>
</table>
* 91% (70/77) of these had mild erythema, 6 had localised blistering treated with topic therapy, and one needed oral corticosteroids
(time of occurrence of events not reported)
All-cause mortality
<table>
<tr><th></th><th>PDT</th><th>oesophagectomy</th></tr>
<tr><td>Overall</td><td>9% (11/129)</td><td>8.5% (6/70)</td></tr>
</table>
(this was over the total follow-up)
Reasons for death in the PDT group:
7 lung cancer
3 heart failure
1 pulmonary embolism</td>
<td>Follow-up issues:
Endoscopic surveillance and biopsy (and EMR if indicated) every 3 months for 2 years and then every 6 months for 1–2 years if HGD was eliminated. If persistent HGD, follow-up every 3 months for 2 years; if LGD present, then every 6 months; if nondysplastic BO at 2 years, than annual follow-up.
No reported loss to follow-up.
Study design issues:
PDT group was prospective but those who had oesophagectomy were identified retrospectively from the Mayo Clinic Pathology database.
Histological specimens were taken from either</td>
</tr>
</table>

<table>
<tr><td colspan="4">Abbreviations used: ALA, 5-aminolevulinic acid; APC, argon plasma coagulation; BO, Barrett's oesophagus; COPD; chronic obstructive pulmonary disease; EMR, endoscopic mucosal resection; HGD, high-grade dysplasia; ITT, intention to treat; LGD, low-grade dysplasia; MI, myocardial infarction; OM, omeprazole; POR, porfimer sodium; RCT, randomised controlled trial</td></tr>
<tr><th>Study details</th><th>Key efficacy findings</th><th>Key safety findings</th><th>Comments</th></tr>
<tr>
<td>windows and 130 J/cm); a second endoscopy was performed in those treated between 1992 and 1998 24–48 hours after the procedure to detect untreated areas but this was later not found necessary; all patients had proton pump inhibitors twice daily after PDT.

Follow-up: 59 months (PDT) and 61 months (oesophagectomy) (approximately 5 years)

Conflict of interest/source of funding: not reported</td>
<td>Kaplan-Meier analysis

There was no significant difference between the groups in overall survival.

Using a Kaplan-Meier curve, cancer-free survival is lower in the PDT group but there is no statistical significant difference between the two.
<table>
<tr><th></th><th>Hazard ratio (95% CI)</th><th>p value</th></tr>
<tr><td>Overall patient survival adjusting for covariates</td><td>1.31 (0.41–4.17)</td><td>0.653</td></tr>
<tr><td>Overall patient survival adjusting for propensity score</td><td>1.25 (0.38–4.10)</td><td>0.714</td></tr>
<tr><td>Cancer-free survival adjusting for all covariates</td><td>2.45 (0.85–7.12)</td><td>0.099</td></tr>
<tr><td>Cancer-free survival adjusting for propensity score</td><td></td><td>0.102</td></tr>
</table>
*covariates included age, sex, length of BO, age-adjusted Charlson comorbidity index</td>
<td>In the oesophagectomy:

3 pneumonia
1 postoperative complication
1 malignant astrocytoma
1 metastatic transitional cell cancer

Total mortality was 19% (5/26) in those treated with a hematoporphyrin derivative and 5.8% (6/103) of those treated with porfimer sodium.</td>
<td>biopsy or EMR; if patients had EMR (usually for focal endoscopically visible lesions), they waited 4 weeks before PDT was performed.
• 26 patients were treated with 4 mg/kg of a hematoporphyrin derivative as the photosensitiser and the rest received 2 mg/kg Photofrin. No other details were given on this derivative (for example if it was prepared in a laboratory).
• Treatment for residual HGD was PDT and/or EMR if occurred before 12 months after first PDT and EMR and/or multipolar electrocoagulation if occurred after 12 months.
Study population issues:
• Patients in PDT</td>
</tr>
</table>

Abbreviations used: ALA, 5-aminolevulinic acid; APC, argon plasma coagulation; BO, Barrett's oesophagus; COPD; chronic obstructive pulmonary disease; EMR, endoscopic mucosal resection; HGD, high-grade dysplasia; ITT, intention to treat; LGD, low-grade dysplasia; MI, myocardial infarction; OM, omeprazole; POR, porfimer sodium; RCT, randomised controlled trial			
Study details	**Key efficacy findings**	**Key safety findings**	**Comments**
			group were older than the surgical group, had a shorter segment of BO, more cardiac disease and had a higher Charlson comorbidity index ($p < 0.008$, < 0.003, 0.001, and 0.0001 respectively).

Efficacy

Eradication of Barrett's metaplasia and dysplasia

High-grade dysplasia

An RCT of 208 patients with HGD reported the absence of HGD in 75% (104/138) of patients treated with PDT and omeprazole compared to 36% (25/70) of those treated with omeprazole alone at 18-month follow-up ($p < 0.0001$; intention-to-treat analysis). These trend was consistent at 5-year follow-up with 48% and 4% respectively, still having no HGD ($p < 0.0001$)[2].

The same study reported absence of dysplasia in 59% (81/138) of patients treated with PDT and 14% (10/70) of patients treated with omeprazole and an absence of all types of Barrett's oesophagus (metaplasia and dysplasia) in 52% (72/138) and 7% (5/70) respectively, at 2-year follow-up ($p < 0.0001$)[2].

An RCT of 60 patients which compared 30 patients treated with PDT with 30 patients treated with PDT and oral steroids reported the elimination of HGD in 96% (41/43) of patients at a mean 9.8 months of follow-up[5].

A non-randomised trial of 199 patients with HGD which compared 129 patients treated with PDT with 70 treated with oesophagectomy reported eradication of HGD in 86% (111/129) in those treated with PDT at 3 year follow-up. There was a recurrence of HGD in 10 patients after 12 months, so these patients were treated with either EMR or multipolar electrocoagulation with the result that 60% (6/10) had eradication of HGD[9].

Low-grade dysplasia or non-dysplastic Barrett's oesophagus

In an RCT of 72 patients with non-dysplastic Barrett's oesophagus a complete response (defined as reversal of columnar to squamous epithelium) was obtained in 50% (17/34) of patients treated with PDT and 97% (33/34) of patients treated with APC at 12-month follow-up ($p < 0.0001$)[4].

In the RCT of 60 patients, in which 43 had HGD, 10 had LGD and 7 had either intramucosal or submucosal tumours, dysplasia was eliminated in 34% (21/62) and all types of Barrett's mucosa (dysplasia and metaplasia) were eliminated in 42% (25/60) at a mean 9.8 months of follow-up. At the same follow-up, cancer had been eliminated in all 7 patients who originally presented with cancer[5].

An RCT of 40 patients with non-dysplastic Barrett's oesophagus (32) or LGD (8), residual Barrett's oesophagus was detected histologically in 92% (12/13) of patients treated with a single dose of PDT, 54% (7/13) of patients treated with two-dose PDT and 29% (4/14) of patients treated with APC at 6-week follow-up. All patients with residual Barrett's oesophagus were treated with APC. At 12-month follow-up, 18% (2/11), 10% (1/10), and 33% (4/12) of patients

respectively, had histologically-shown presence of Barrett's oesophagus [6]. (None of these differences were significant.)

An RCT of patients with LGD showed that 89% (16/18) of patients treated with PDT and 11% (2/18) of those with placebo showed macroscopic evidence of regression, which was confirmed with a biopsy at between 59 and 61 months of follow-up ($p < 0.001$). There were significantly more patients with residual dysplasia in the placebo group (67% [12/18]) than in the group treated with PDT (0%)[7].

An RCT of patients with dysplastic Barrett's oesophagus (23 with LGD and 3 with HGD) reported eradication of dysplasia in 77% (10/13) of patients treated with PDT compared to 62% (8/13) of those treated with APC ($p = 0.03$). At 12 months, this difference was still significant (PDT: 77% [10/13] and APC: 67% [6/9]; 4 patients in the APC group were lost to follow-up)[8].

Progression to cancer

In the RCT of 208 patients, 15% (21/138) of patients treated with PDT and omeprazole and 29% (20/70) of patients treated with omeprazole alone developed cancer during the 5-year follow-up period[2].

In the non-randomised trial of 199 patients, 6% (8/129) of patients treated with PDT developed carcinoma (6 in first 12 months and 2 within 18 months) and 13% (9/70) of patients treated by oesophagectomy were found to have carcinoma in the resected surgical specimens. The 8 carcinoma patients with carcinoma development in the PDT group were successfully treated (7 with oesophagectomy and 1 with EMR). All patients were free from metastatic lymphadenopathy and were alive at the last follow-up[9].

Safety

Death

The RCT of 40 patients reported that 1 patient treated with PDT died 3 days after treatment. The autopsy revealed transmural necrosis without perforation, but the reason for the death was not known[6].

Stricture formation

Oesophageal stricture occurred in 36% (49/138)[1], 3% (1/34)[4], 33% (20/60)[5], 15% (2/13) [8], and 27% (35/131) [9] of patients. One occurred in a patient who was then unable to complete treatment and the other occurred after treatment (exact time of occurrence not reported). Most were treated successfully with dilatation but 2 patients (1 from the RCT of 208 patients and 1 from the non-randomised trial of

199 patients) were reported to have had a perforation after dilatation, requiring oesophagectomy[1,9].

In the RCT of 208 patients, dysphagia was reported 19% (number not given)[1] and odynophagia was reported in 92% (24/26) [6] of patients in the non-randomised trial of 199 patients.

Photosensitivity

Photosensitivity reactions occurred in 69% (numerator and denominators not given)[1], 15% (5/34)[4], 15% (2/13)[8], and 60% (77/129)[9] of patients. This usually involved mild erythema and sometimes localised blistering.

Buried glands

A later publication from the RCT of 208 patients reported no significant difference between the proportion of patients with buried glands between patients treated with PDT and patients treated with omeprazole only[3].

The RCT of 72 patients reported that buried glands were discovered in 24% (4/17) patients treated with PDT compared to 21% (7/33) of patients treated with APC, but this difference was not significant[4].

The RCT of 26 patients reported that 1 patient who had persistent LGD after PDT was found to have a buried gland and adenocarcinoma beneath the neosquamous epithelium 12 months after surgery. This patient was successfully treated with oesophagectomy[8].

Other

The RCT of 72 patients reported hypotension not requiring treatment in 6% (2/32) of patients. The same study reported angina after 2 days, which was successfully treated with oral analgesia in 3% (1/32) of patients[4].

Validity and generalisability of the studies

- The previous overview was based on 7 case series including 260 patients and an unpublished RCT of 60 patients (now included in this overview[5]) with a maximum follow-up of 50.7 months. This overview now includes 6 RCTs and a non-randomised trial including a total of 643 patients[1], 3 studies included at least 5 years of follow-up[1,5,7].

- The original guidance specified the need for randomised trials, longer term follow-up and demonstrable efficacy in decreasing progression to cancer in addition to its ability to downgrade dysplasia.
- The previous overview included patients treated for HGD only. The indication was expanded by the Committee during scoping for the review of this procedure to include all levels of Barrett's oesophagus.
- The overview contains two studies including patients with HGD only[1,7], two including patients with various Barrett's oesophagus histological types (HGD and LGD; one of these included 7 with intra- and sub-mucosal cancer)[3,6], one with patients with both LGD and non-dysplastic Barrett's oesophagus [4] and one with only patients with non-dysplastic Barrett's oesophagus [2].
- The previous overview excluded studies using ALA. Studies using this photosensitiser have now been included in this overview, but this overview only includes literature on ALA which has been published since October 2003 (since this is the end date from the previous literature search).

Existing assessments of this procedure

There were no published assessments from other organisations identified at the time of the literature search.

Related NICE guidance

Below is a list of NICE guidance related to this procedure. Appendix B gives details of the recommendations made in each piece of guidance listed.

Interventional procedures

- Photodynamic therapy for high-grade dysplasia in Barrett's oesophagus. NICE interventional procedures guidance 82 (2004). Available from www.nice.org.uk/IPG82
- Thoracoscopically assisted oesophagectomy. NICE interventional procedures guidance 189 (2006). Available from www.nice.org.uk/IPG189

Specialist Advisers' opinions

Specialist advice was sought from consultants who have been nominated or ratified by their Specialist Society or Royal College. The advice received is their individual opinion and does not represent the view of the society.

John Wayman, Sami Shimi, Association of Upper Gastrointestinal Surgeons for Great Britain and Ireland, Laurence Lovat, British Society of Gastroenterology.

- Comparators include oesophagectomy, radiofrequency ablation, EMR. One Adviser highlighted that PDT is only appropriate in patients unfit for surgery so in practice, the comparator is 'do nothing' or monitor regularly with endoscopy. The same Adviser stated that PDT may be best suited to patients with diffuse HGD, whereas endoscopic mucosal resection may be best suited to patients with focal HGD lesions.
- The main efficacy outcome is reversal of dysplasia or prevention of dysplasia into adenocarcinoma. Reversal of metaplasia is also an important outcome.
- One Adviser highlighted that surgeons are hesitant to use PDT in the presence of high-grade dysplasia because of the possibility of underlying invasive cancer which was missed by biopsy.
- The Advisers listed anecdotal evidence to include pain and inflammation, which may form ulceration initially and subsequent scarring and narrowing, death, hypotension and prolonged hypotension after the use of PDT with ALA.
- Theoretical events include perforation, death or decompensation in patients with cirrhosis of the liver, stricture, skin and retinal damage due to photosensitisation.

Patient Commentators' opinions

NICE's Patient and Public Involvement Programme were unable to obtain patient commentary for this procedure.

Issues for consideration by IPAC

- See validity and generalisability section above.
- There is an RCT in the UK which is currently recruiting participants.
- Photodynamic therapy for Barrett's oesophagus has involved a number of photosensitising agents, including porfimer sodium and ALA, which are both licensed to be used for PDT. There were some reports on the safety of specific photosensitisers, but these were considered to be concerns with the use of

photosensitising agents in general and not to be related with the interventional aspects of PDT for Barrett's oesophagus –therefore those outcomes were not included in the main Table in the Overview. Some studies of this nature are included in Appendix A.

References

1. Overholt BF, Lightdale CJ, Wang KK et al. (2005) Photodynamic therapy with porfimer sodium for ablation of high-grade dysplasia in Barrett's esophagus: international, partially blinded, randomized phase III trial. Gastrointestinal Endoscopy 62:488–98.

2. Overholt BF, Wang KK, Burdick JS et al. (2007) Five-year efficacy and safety of photodynamic therapy with Photofrin in Barrett's high-grade dysplasia. Gastrointestinal Endoscopy 66:460–68.

3. Bronner MP, Overholt BF, Taylor SL et al. (2009) Squamous overgrowth is not a safety concern for photodynamic therapy for Barrett's esophagus with high-grade dysplasia. Gastroenterology 136:56–64.

4. Kelty CJ, Ackroyd R, Brown NJ et al. (2004) Endoscopic ablation of Barrett's oesophagus: a randomized-controlled trial of photodynamic therapy vs. argon plasma coagulation. Alimentary Pharmacology & Therapeutics 20:1289–96.

5. Panjehpour M, Overholt BF, Haydek JM et al. (2000) Results of photodynamic therapy for ablation of dysplasia and early cancer in Barrett's esophagus and effect of oral steroids on stricture formation. The American Journal of Gastroenterology 95:2177–84.

6. Hage M, Siersema PD, van Dekken H et al. (2004) 5-aminolevulinic acid photodynamic therapy versus argon plasma coagulation for ablation of Barrett's oesophagus: a randomised trial. Gut 53:785–90.

7. Ackroyd R, Brown NJ, Davis MF et al. (2000) Photodynamic therapy for dysplastic Barrett's oesophagus: a prospective, double blind, randomised, placebo controlled trial. Gut 47:612–17.

8. Ragunath K, Krasner N, Raman VS et al. (2005) Endoscopic ablation of dysplastic Barrett's oesophagus comparing argon plasma coagulation and photodynamic therapy: a randomized prospective trial assessing efficacy and cost-effectiveness. Scandinavian Journal of Gastroenterology 40:750–58.

9. Prasad GA, Wang KK, Buttar NS et al. (2007) Long-term survival following endoscopic and surgical treatment of high-grade dysplasia in Barrett's esophagus. Gastroenterology 132:1226–33.

Appendix A: Additional papers on photodynamic therapy for Barrett's oesophagus

The following table outlines the studies that are considered potentially relevant to the overview but were not included in the main data extraction table (table 2). It is by no means an exhaustive list of potentially relevant studies.

Article	Number of patients/follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
Ackroyd R, Brown N, Vernon, D et al. (1999) 5-Aminolevulinic acid photosensitization of dysplastic Barrett's esophagus: a pharmacokinetic study. Photochemistry and photobiology 70:656–662.	Case series n = 35 (LGD)	Side effects of ALA administration included malaise, headache, photosensitivity, alopecia, transient derangement of liver function, nausea and vomiting.	Larger studies are included in table 2.
Ackroyd R, Kelty CJ, Brown NJ et al. (2003) Eradication of dysplastic Barrett's oesophagus using photodynamic therapy: long-term follow-up. Endoscopy 35:496–501.	Case series n = 40 (LGD) median follow-up = 53 months	88% (35) had macroscopic reduction in area with columnar epithelium and dysplasia eradicated at 1 month. This was maintained in all except 1 patient with a late carcinoma 3 years later.	Larger studies are included in table 2.
Behrens A, May A, Gossner L et al. (2005) Curative treatment for high-grade intraepithelial neoplasia in Barrett's esophagus. Endoscopy 37:999–1005.	Case series n = 27 (all with high-grade intra-epithelial neoplasia) Follow-up = 36 months	Complete remission in 97.7% (43/44) and no complications. 6 patients (17.1%) had recurrent or metachronous lesion within the follow-up period.	Larger studies are included in table 2.
Eickhoff A, Jakobs R, Weickert U et al. (2006) Long-Segment early squamous cell carcinoma of the proximal esophagus: curative treatment and long-term follow-up after 5-aminolevulinic acid (5-ALA)-photodynamic therapy. Endoscopy 38:641–3.	Case report n = 1 Follow-up = 23 months	Description of treatment in a long segment of squamous cell carcinoma. No recurrence in follow-up.	Larger studies are included in table 2.
Etienne J, Dorme N, Bourg-Heckly G et al. (2004) Photodynamic therapy with green light and m-tetrahydroxyphenyl chlorin for intramucosal adenocarcinoma and high-grade dysplasia in	Case series n = 12 (7 HGD, 7 IMC) Follow-up = 34 months	14 lesions successful treated in 12 patients One stricture	Larger studies are included in table 2.

Barrett's esophagus. Gastrointestinal Endoscopy 59:880–-9.			
Foroulis CN and Thorpe JA. (2006) Photodynamic therapy (PDT) in Barrett's esophagus with dysplasia or early cancer. European Journal of Cardio-Thoracic Surgery 29:30–4.	Case series n = 31 (15 HGD, 10 HGD and IMC 6 submucosal/limited T2 adenocarcinoma) Follow-up = 14 months	Patients who refused or were unfit for oesophagectomy were treated. PDT was effective at ablation. Main complications were oesophagitis (16.1%), photoreactions (12.9%) and stricture (6.3%).	Larger studies are included in table 2.
Gill KR, Wolfsen HC, Preyer NW et al. (2009) Pilot study on light dosimetry variables for photodynamic therapy of Barrett's esophagus with high-grade dysplasia. Clinical Cancer Research 15:1830–6.	Case series n = 11 Follow-up = 6–8 weeks	Oesophageal thickness is strong predictor of treatment outcomes.	Larger studies are included in table 2.
Globe J, Smythe A, Kelty CJ et al. (2006) The effect of photodynamic therapy (PDT) on oesophageal motility and acid clearance in patients with Barrett's oesophagus. Journal of Photochemistry & Photobiology B:17–22.	Case series n = 12	No significant differences in oesophageal motility between areas treated by PDT and not treated.	Larger studies are included in table 2.
Hage M, Siersema PD, Vissers KJ et al. (2006) Genomic analysis of Barrett's esophagus after ablative therapy: persistence of genetic alterations at tumor suppressor loci. International Journal of Cancer 118:155–160.	Case series n = 29	Outcomes were mostly molecular. Elimination of Barrett's oesophagus in 76% of patients.	Larger studies are included in table 2.
Hur C, Wittenberg E, Nishioka NS et al. (2005) Patient preferences for the management of high-grade dysplasia in Barrett's esophagus. Digestive Diseases & Sciences 50:116–25.	Case series n = 20 (HGD)	Assessed patient preferences in management of HGD Barrett's oesophagus.	Larger studies are included in table 2.
Kashtan H, Umansky M, Birkenfeld S et al. (2002) Photodynamic therapy of Barrett's esophagus with dysplasia using systemic aminolevulinic acid and a non-laser light source.	Case series n = 8 (7 LGD, 1 HGD) Follow-up = 30 months	No major side effects or strictures. Partial squamous regeneration in 3/8 patients 14 days after PDT. No dysplasia in 4/8.	Larger studies are included in table 2.

A phase I/II study. Gastrointestinal Oncology 4:153–7.			
Keeley SB, Pennathur A, Gooding W et al. (2007) Photodynamic therapy with curative intent for Barrett's esophagus with high grade dysplasia and superficial esophageal cancer. Annals of Surgical Oncology 14:2406–10.	Case series n = 50 (13 HGD, 6 IMC, 16 T1 N0, 14 T2 N0, 1 sT3) Follow-up = 28.1 months	32% (16) were alive and without recurrence at publication, 30% (15) had residual or recurrent disease and have had PDT, 38% died of recurrent oesophageal cancer.	Larger studies are included in table 2.
Kelty CJ, Ackroyd R, Brown NJ et al. (2004) Comparison of high- vs low-dose 5-aminolevulinic acid for photodynamic therapy of Barrett's esophagus. Surgical Endoscopy 18:452–8.	RCT n = 25 Follow-up = 1 month	This study randomised patients to different doses and periods of light application. The mean reduction in area of Barrett's oesophagus was 30%. Safety events were reported in the study by the same author in table 2 (which indicate that these may be the same patients).	Patients are likely to be included in Kelty (2004) in table 2.
Lovat LB, Jamieson NF, Novelli MR et al. (2005) Photodynamic therapy with m-tetrahydroxyphenyl chlorin for high-grade dysplasia and early cancer in Barrett's columnar lined esophagus. Gastrointestinal Endoscopy 62:617–23.	Case series n = 19 (7 HGD, 12 early oesophageal cancer)	One procedure-related death with bare-tipped fibre 2 strictures	Larger studies are included in table 2.
Mackenzie GD, Jamieson NF, Novelli MR et al. (2008) How light dosimetry influences the efficacy of photodynamic therapy with 5-aminolaevulinic acid for ablation of high-grade dysplasia in Barrett's esophagus. Lasers in Medical Science 23:203–10.	Non-randomised trial n = 24 (HGD) Follow-up = 45 months	Patients received different doses. No skin photosensitivity or oesophageal strictures.	Larger studies are included in table 2.
Malhi-Chowla N, Wolfsen HC, DeVault KR. (2001) Esophageal dysmotility in patients undergoing photodynamic therapy. Mayo Clinic Proceedings 76:987–9.	Case series n = 23 (10 with BO, 13 carcinoma)	Normal oesophageal dysmotility decreased from 48% (11) to 26% (6) after the procedure. Infective motility rose from 26% (6) to 30% (7) Aperistalsis rose from 26% (6) before the procedure to 43% (10)	Larger studies are included in table 2.

		after the procedure	
Mino-Kenudson M, Ban S, Ohana M et al. (2007) Buried dysplasia and early adenocarcinoma arising in barrett esophagus after porfimer-photodynamic therapy. American Journal of Surgical Pathology 31:403–9.	Case series n = 52 (19 HGD, 28 IMC, 5 invasive adenocarcinoma) Follow-up = 29.3 months	Buried neoplasm in 1 patient before PDT and 13 patients after.	Larger studies are included in table 2.
Moghissi K, Dixon K, and Campbell A. (2008) Adeno-carcinoma of the pharyngo-oesophageal junction and cervical oesophagus in a patient with an oesophagus lined entirely by columnar epithelium report of a case treated by photodynamic therapy (PDT). Photodiagnosis & Photodynamic Therapy 5:224–7.	Case report n = 1 (adenocarcinoma)	PDT was used as palliation for dysphagia. Patient died after 9 months from carcinomatosis and oesophago-airway fistula.	Larger studies are included in table 2.
Moghissi K, Dixon K, Stringer M et al. (2009) Photofrin PDT for early stage oesophageal cancer: Long term results in 40 patients and literature review. Photodiagnosis and photodynamic therapy 6:159–66.	Case series n = 40 (35 adenocarcinoma, 5 squamous cell carcinoma) Median follow-up = 76.1 months	No operative or 30-day mortality 3 and 5 year survival: 72.5% and 53.8% [24 patients died between 2 and 150 month follow-up (cause of death not reported)] No serious complications Skin photosensitivity in 2 and stricture requiring dilatation in 3 patients.	Larger studies are included in table 2.
Overholt BF, Panjehpour M, and Halberg DL. (2003) Photodynamic therapy for Barrett's esophagus with dysplasia and/or early stage carcinoma: long-term results. Gastrointestinal Endoscopy 58:183–8.	Case series n = 103 (14 LGD, 80 HGD, 9 cancer) Follow-up = 50.65 months	82 patients lost to follow-up Mean length of Barrett's oesophagus decreased by 6.92 cm. ITT success rates were 92.9%, 77.5%, 44.4% for LGD, HGD and carcinoma, respectively.	Larger studies are included in table 2.
Overholt BF, Panjehpour M, Haydek JM. (1999) Photodynamic therapy for Barrett's esophagus: follow-up in 100 patients. Gastrointestinal Endoscopy 49:1–7.	Case series n = 100 (73 HGD, 14 LGD, 12 T1, 1 T2) Follow-up = 19 months	78% (78/100) had conversion of dysplastic or malignant Barrett's oesophagus to Barrett's oesophagus with no dysplasia	Larger studies are included in table 2.
Overholt BF, Panjehpour M, Ayres M. (1997) Photodynamic therapy for Barrett's esophagus:	Case series n = 12 (dysplasia or early adenocarcinoma)	Cardiac complications were reported. All patients had moderate chest pain and	Larger studies are included in table 2.

cardiac effects. Lasers in Surgery & Medicine 21:317–20.		dysphagia 5–7 days after the procedure. One patient had atrial fibrillation in the 48 hours after follow-up.	
Pacifico RJ, Wang KK, Wongkeesong LM et al. (2003) Combined endoscopic mucosal resection and photodynamic therapy versus esophagectomy for management of early adenocarcinoma in Barrett's esophagus. Clinical Gastroenterology & Hepatology 1:252–7.	Non-randomised trial n = 88 (24 EMR/PDT vs 64 oesophagectomy) Follow-up = 12 months PDT/EMR and 19 months oesophagectomy	Oesophagectomy group had higher procedure-related complication rate ($p < 0.001$). 83% (20/24) and all patients in oesophagectomy group were cancer free at follow-up	Larger studies are included in table 2.
Panjepour M, Overholt BF, Phan MN et al. (2005) Optimisation of light dosimetry for photodynamic therapy of Barrett's esophagus: efficacy vs. incidence of stricture after treatment. Gastrointestinal endoscopy 61:13–18.	Non-randomised trial n = 113 Follow-up = 3 months	Study to test dose de-escalation. At 115 J/cm, 15.3% had severe strictures compared with 5.3% and 5.6% at lower doses. Residual HGD in 17% of patients at 115 J/cm and 33.3%, 29.4%, and 31.6% at 105, 95, and 85 J/cm, respectively.	Randomised study designs included in table 2.
Pech O, Gossner L, May A et al. (2005) Long-term results of photodynamic therapy with 5-aminolevulinic acid for superficial Barrett's cancer and high-grade intraepithelial neoplasia. Gastrointestinal Endoscopy 62:24–30.	Case series n = 55 Follow-up = 63.6 months	Study had results from patients treated by endoscopic resection, PDT, both resection and PDT and APC. Complete response in 96.6% of all patients.	Larger studies are included in table 2.
Pech O, Behrens A, May A et al. (2008) Long-term results and risk factor analysis for recurrence after curative endoscopic therapy in 349 patients with high-grade intraepithelial neoplasia and mucosal adenocarcinoma in Barrett's oesophagus. Gut 57:1200–6.	Case series n = 66 (35 high-grade intraepithelial neoplasia, 31 adenocarcinoma) Median follow-up = 37 months	97% (34/35) with high-grade intraepithelial neoplasia had complete response; complete response was100% in those with adenocarcinoma 1 and 10 patients, respectively had recurrence 7 died during follow-up (not all tumour-related)	Larger studies are included in table 2.
Peters F, Kara M, Rosmolen W et al. (2005) Poor results of 5-aminolevulinic acid-photodynamic therapy for residual high-grade dysplasia and early	Case series n = 19 Median follow-up = 19 months	In all patients treated (including 13 by endoscopic resection and 3 by APC), 26/28 patients were treated successfully	Larger studies are included in table 2.

cancer in barrett esophagus after endoscopic resection. Endoscopy 37:418–24.			
Peters FP, Kara MA, Rosmolen WD et al. (2005) Endoscopic treatment of high-grade dysplasia and early stage cancer in Barrett's esophagus. Gastrointestinal Endoscopy 61:506–14.	Case series n = 20 (HGD) Median follow-up = 30 months	Mild complications in 4/26 procedures Success rate: 75% (15/20) All patients had residual Barrett's oesophagus after PDT; recurrence of HGD occurred in 4	Larger studies are included in table 2.
Prasad GA, Wang KK, Buttar NS et al. (2007) Predictors of stricture formation after photodynamic therapy for high-grade dysplasia in Barrett's esophagus{A figure is presented}. Gastrointestinal Endoscopy 65:60–6.	Case series n = 131 (HGD)	27% (35/131) developed stricture. Risk factors included a history of prior oesophageal stricture, prior EMR performance, more than one 1 PDT application in one session.	Larger studies are included in table 2.
Reed MF, Tolis J, Edil BH et al. (2005) Surgical treatment of esophageal high-grade dysplasia. Annals of Thoracic Surgery 79:1110–5.	Case series n = 42 (HGD)	2 patients had recurrent HGD or invasive adenocarcinoma.	Larger studies are included in table 2.
Savoy AD, Wolfsen HC, Raimondo M et al. (2008) The role of surveillance endoscopy and endosonography after endoscopic ablation of high-grade dysplasia and carcinoma of the esophagus. Diseases of the Esophagus 21:108–13.	Case series n = 67 (HGD) Median follow-up = 16 months	Recurrent or residual adenocarcinoma in 4 patients 2 deaths: 1 related to disease progression and 1 not related.	Larger studies are included in table 2.
Schembre DB, Huang JL, Lin OS et al. (2008) Treatment of Barrett's esophagus with early neoplasia: a comparison of endoscopic therapy and esophagectomy. Gastrointestinal Endoscopy 67:595–601.	Retrospective comparative case series n = 2 APC vs 18 EMR+APC vs 20 PDT+APC vs 22 EMR+PDT+APC vs 32 oesophagectomy	Cancer developed in 6% of those treated endotherapeutically vs non treated with oesophagectomy.	The mixture of interventions makes it difficult to interpret the efficacy of PDT alone.
Shah AK, Wolfsen HC, Hemminger LL et al. (2006) Changes in esophageal motility after porfimer sodium photodynamic therapy for Barrett's dysplasia and mucosal carcinoma. Diseases of the Esophagus 19:335–9.	Case series n = 47 (HGD; 6 did not complete study)	Abnormal oesphageal motility in 30% (14/47) Longer segments had significant larger deterioration in function	Larger studies are included in table 2.

Sylantiev C, Schoenfeld N, Mamet R et al. (2005) Acute neuropathy mimicking porphyria induced by aminolevulinic acid during photodynamic therapy. Muscle & Nerve 31:390–3.	Case report n = 1	Report of acute neuropathy in a patient treated with ALA.	Larger studies are included in table 2.
Upton MP, Nishioka NS, Ransil BJ et al. (2006) Multilayered epithelium may be found in patients with Barrett's epithelium and dysplasia or adenocarcinoma. Digestive Diseases & Sciences 51:1783–90.	Case series n = not clear in study	Multilayered epithelium was found in some patients after therapy.	Larger studies are included in table 2.
van Hillegersberg R, Haringsma J, Ten Kate FJ et al. (2003) Invasive carcinoma after endoscopic ablative therapy for high-grade dysplasia in Barrett's oesophagus. Digestive Surgery 20:440–4.	Multiple case report n = 2 (HGD)	Report of 2 patients who had invasive carcinoma after being treated with PDT (1 patient was also treated with EMR).	Larger studies are included in table 2.
Weiss AA, Wiesinger HA, and Owen D. (2006) Photodynamic therapy in Barrett's esophagus: results of treatment of 17 patients. Canadian Journal of Gastroenterology 20:261–264.	Case series n = 17 (HGD or early adenocarcinoma) Mean follow-up = 21 months	Complete eradication of HGD or adenocarcinoma in 60% (15).	Larger studies are included in table 2.
Wolfsen HC, Hemminger LL, Raimondo M et al. (2004) Photodynamic therapy and endoscopic mucosal resection for Barrett's dysplasia and early esophageal adenocarcinoma. Southern Medical Journal 97:827–30.	Case series n = 3 (HGD) Follow-up = 46, 13 and 6 months	Patients were treated with both EMR and PDT.	Larger studies are included in table 2.
Wolfsen HC, Hemminger LL, Wallace MB et al. (2004) Clinical experience of patients undergoing photodynamic therapy for Barrett's dysplasia or cancer. Alimentary Pharmacology and Therapeutics 20:1125–31.	Case series n = 102 (69 HGD and 33 adenocarcinoma) Follow-up = 1.6 years	Complete ablation with one course in 56%. Stricture requiring dilatation in 20% (20).	Larger studies are included in table 2.
Wolfsen HC and Hemminger LL. (2006) Salvage photodynamic	Case series n = 7 (patients with inoperable persistent	All patients developed stricture requiring dilation.	Larger studies are included in table 2.

therapy for persistent esophageal cancer after chemoradiation therapy. Photodiagnosis and Photodynamic Therapy 3:11–4.	mucosal carcinoma after chemoradiation therapy) Follow-up = 30 months	2 who had squamous cell carcinoma had recurrent disease. The other 5 which had Barrett's carcinoma are disease free (but 1 died of metastatic colon cancer).	
Wolfsen HC, Ng CS. (2002) Cutaneous consequences of photodynamic therapy. Cutis 69:140–2.	Case series n = 72 (21 HGD or T1N0Mo adenocarcinoma, 51 with gastro-oesophageal cancer)	31% (22) had cutaneous complications (7 with HGD) which were mostly phototoxic reactions involving erythema, blistering, swelling and pain or sun-exposed areas). 1 patient developed severe herpes zoster and another developed a protracted case of erythema multiforme-type drug reaction	Larger studies are included in table 2.
Wolfsen HC, Woodward TA, Raimondo M. (2002) Photodynamic therapy for dysplastic barrett esophagus and early esophageal adenocarcinoma. Mayo Clinic Proceedings 77:1176–81.	Case series n = 48 patients (34 HGD, 14 cancer)	Complete ablation of BO in 56% (27/48) and 56% of those with HGD (19/34). Patients with residual disease were treated with PAC; 98% (47/48) had ablation once this was completed.	Larger studies are included in table 2.
Yachimski P, Puricelli WP, and Nishioka NS. (2008) Patient predictors of esophageal stricture development after photodynamic therapy. Clinical Gastroenterology & Hepatology 6:302–8.	Case series n = 116 (59 HGD and 57 intramucosal carcinoma or T1)	Stricture happened in 16% (19/116). It was higher after a second PDT compared with just one PDT. There was no association with age, gender, BMI, or prior EMR.	Larger studies are included in table 2.
Yachimski P, Puricelli WP, and Nishioka NS. (2009) Patient predictors of histopathologic response after photodynamic therapy of Barrett's esophagus with high-grade dysplasia or intramucosal carcinoma. Gastrointestinal Endoscopy 69:205–12.	Same patients as above. Follow-up = 12 months	70% had ablation of HGD and/or cancer and 39% of Barrett's epithelium was ablated. Patients with intramucosal carcinoma were not less likely to experience elimination of HGD or cancer.	Larger studies are included in table 2.

Appendix B: Related NICE guidance for photodynamic therapy for Barrett's oesophagus

Guidance	Recommendations
Interventional procedures	**Photodynamic therapy for high-grade dysplasia in Barrett's oesophagus. NICE interventional procedures guidance 82 (2004).** 1.1 Current evidence on the safety of photodynamic therapy for high-grade dysplasia in Barrett's oesophagus appears adequate to support the use of this procedure. Photodynamic therapy appears efficacious in downgrading dysplasia in Barrett's oesophagus, when used for the treatment of high-grade dysplasia (a premalignant lesion). However, its efficacy in preventing the progression of Barrett's oesophagus to invasive cancer is not clear. 1.2 Clinicians wishing to undertake photodynamic therapy for high-grade dysplasia in Barrett's oesophagus should take the following actions. • Inform the clinical governance leads in their Trusts. • Inform patients, as part of the consent process, about the uncertainty of influencing their long-term prognosis and provide them with clear written information. Use of the Institute's Information for the Public is recommended. • Audit and review clinical outcomes of all patients having photodynamic therapy for high-grade dysplasia in Barrett's oesophagus. 1.3 Publication of long-term efficacy outcomes will be useful in reducing the current uncertainty. Randomised trials are in progress and clinicians are encouraged to consider entering patients into these (www.cancerhelp.org.uk/trials/trials/default.asp). The Institute may review the procedure upon publication of further evidence. 1.4 This guidance is limited to the procedure using pharmaceuticals licensed for photodynamic therapy of oesophageal dysplasia. **Circumferential epithelial radiofrequency ablation for Barrett's oesophagus. NICE interventional procedures guidance 310 (2007).** 1.1 Evidence on the safety and efficacy of circumferential epithelial radiofrequency (RF) ablation for Barrett's oesophagus is currently inadequate. The evidence is limited in quantity and duration of follow-up and fails to justify the treatment of non-dysplastic Barrett's oesophagus. Therefore this procedure should only be used in the context

	of research. 1.2 Further research should specify clearly the grade of Barrett's oesophagus being treated and should include arrangements for long-term follow-up (for example, 5 years). The Institute may review the procedure upon publication of further evidence. **Thoracoscopically assisted oesophagectomy. NICE interventional procedures guidance 189 (2006).** 1.1 Current evidence on the safety and efficacy of thoracoscopically assisted oesophagectomy appears adequate to support the use of this procedure, provided that normal arrangements are in place for consent, audit and clinical governance. 1.2 This procedure is technically demanding, and surgeons undertaking it should have special expertise and specific training in laparoscopic and thoracoscopic surgical techniques and should perform their initial procedures with an experienced mentor. 1.3 Patient selection and management should be carried out in the context of a multidisciplinary team that has a regular practice in open oesophagectomy. 1.4 Clinicians should submit data to the Minimally Invasive Gastro-Oesophageal Cancer Surgery (MIGOCS) National Database (www.e-dendrite.com/databases.htm) or the Association of Upper Gastrointestinal Surgeons of Great Britain and Ireland (AUGIS) data set (www.augis.org/news/default.html).

Appendix C: Literature search for photodynamic therapy for Barrett's oesophagus

Databases	Date searched	Version/files
Cochrane Database of Systematic Reviews – CDSR (Cochrane Library)	02/03/2010	February 2010
Database of Abstracts of Reviews of Effects – DARE (CRD website)	02/03/2010	N/A
HTA database (CRD website)	02/03/2010	N/A
Cochrane Central Database of Controlled Trials – CENTRAL (Cochrane Library)	02/03/2010	February 2010
MEDLINE (Ovid)	02/03/2010	1950 to February Week 3 2010
MEDLINE In-Process (Ovid)	02/03/2010	March 01, 2010
EMBASE (Ovid)	02/03/2010	1980 to 2010 Week 08
CINAHL (NLH Search 2.0 or EBSCOhost)	02/03/2010	N/A
BLIC (Dialog DataStar)	02/03/2010	N/A

Trial sources searched on 07 08 09

- National Institute for Health Research Clinical Research Network Coordinating Centre (NIHR CRN CC) Portfolio Database
- Current Controlled Trials *meta*Register of Controlled Trials – *m*RCT
- Clinicaltrials.gov

Websites searched on : 07 08 2009

- National Institute for Health and Clinical Excellence (NICE)
- Food and Drug Administration (FDA) - MAUDE database
- Australian Safety and Efficacy Register of New Interventional Procedures – Surgical (ASERNIP – S)
- Australia and New Zealand Horizon Scanning Network (ANZHSN)
- Conference websites
- General internet search

The following search strategy was used to identify papers in MEDLINE. A similar strategy was used to identify papers in other databases.

1	exp Barrett Esophagus/
2	(Barret$ adj3 (Esophag$ or Oesophag$ or Syndrom$)).tw.
3	barret$.tw.
4	(Dysplas$ adj3 (Esophag$ or Oesophag$ or Syndrom$)).tw.

5	dysplasi$.tw.
6	or/1-5
7	Photochemotherapy/
8	(Photo$ adj3 (dynamic$ or chemotherap$ or radiat$)).tw.
9	PDT.tw.
10	photofimer$.tw.
11	photofrin$.tw.
12	Photosensitizing Agents/
13	(Photosensitiz$ adj3 agent$).tw.
14	porfrin$.tw.
15	Hematoporphyrins/
16	Hematoporphy$.tw.
17	Aminolevulinic Acid/
18	ALA.tw.
19	Dihematoporphyrin Ether/
20	(Dihematoporph$ adj3 ether$).tw.
21	or/7-20
22	6 and 21
23	Animals/
24	Humans/
25	23 not (23 and 24)
26	22 not 25
27	200310$.ed.
28	200311$.ed.
29	200312$.ed.
30	2004$.ed.
31	2005$.ed.
32	2006$.ed.

33	2007$.ed.
34	2008$.ed.
35	2009*.ed.
36	or/27-35
37	36 and 26