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Photodynamic Therapy for the Treatment of Barrett's Esophagus: A Systematic Review and Economic Evaluation

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Purpose of the report

This assessment was undertaken at the request of Alberta Health and Wellness for their consideration of photodynamic therapy (PDT) as a publicly funded treatment for Barrett's esophagus.

Barrett's esophagus is a benign condition, usually caused by long-term gastroesophageal reflux disease. In some individuals the abnormal Barrett's tissue develops precancerous cells (dysplasia). Barrett's esophagus with high grade dysplasia is associated with a higher risk of developing one type of esophageal cancer (esophageal adenocarcinoma). Interventions to remove the dysplastic tissue are intended to reduce this risk. Photodynamic therapy is one of several less invasive, endoscopic treatment options for Barrett's esophagus that offer an alternative to surgical removal of the esophagus (esophagectomy).

This review assesses the evidence on the safety and effectiveness of photodynamic therapy for the treatment of Barrett's esophagus with high grade dysplasia in comparison to esophagectomy and other endoscopic treatments for this condition. It also examines the social and economic considerations for the provision of PDT in comparison to alternate treatments.

A companion review examines the evidence on photodynamic therapy and other treatments for early esophageal cancer.

Questions & answers for policy makers

1. What is the potential role of photodynamic therapy (PDT) in the management of Barrett's esophagus with dysplasia in adults?

Photodynamic therapy is one of several endoscopic treatment options for patients who have Barrett's esophagus with dysplasia. It is used as a first-line treatment for some patients and also as a supplementary treatment in patients with residual or recurrent Barrett's with dysplasia despite other treatments. As with other endoscopic and ablative treatments for Barrett's esophagus with dysplasia, PDT offers a less invasive alternative to esophagectomy (surgical removal of the esophagus). **[See pages 25-28.]**

2. In comparison with alternate treatments (endoscopic therapies (i.e., endoscopic mucosal resection, cryosurgery, radiofrequency ablation, laser ablation, multipolar electrocoagulation and argon plasma coagulation) and surgery (i.e., esophagectomy)), what is the safety of PDT for Barrett's esophagus?

Adverse events associated with PDT vary depending on the photosensitizer drug used. The most common adverse events associated with porfimer sodium were photosensitivity and stricture.

Photosensitivity and stricture were much less common in patients treated with PDT using aminolevulinic acid (ALA), but ALA is not licensed by Health Canada for this indication. No deaths, perforations, or bleeds were reported in studies of PDT for Barrett's esophagus using porfimer sodium. There was 1 patient death reported in the studies of PDT using ALA, but this was due to cardiac arrhythmia.

No deaths were reported in the studies of other endoscopic, ablative treatments for Barrett's esophagus. Non-fatal adverse events such as perforation, bleeding and stricture were also reported with some of the alternate treatments. Overall, the safety profile of PDT seems to be similar to that of other ablative techniques.

By comparison, esophagectomy is associated with a higher (albeit small) mortality rate of 1.2%, and has a greater risk of major adverse events, including anastomotic leaks, pulmonary and cardiovascular complications. **[See pages 36-37.]**

3. In comparison with alternate treatments, what is the effectiveness or efficacy of PDT for Barrett's esophagus?

Photodynamic therapy appears to be as effective as other endoscopic treatments in removing abnormal esophageal tissue. The available evidence does not show a clear superiority of one endoscopic treatment over another or indicate which sub-groups of Barrett's patients might benefit most from one or another of these treatments. Current experience in Alberta indicates that PDT is often used in addition to, rather than as a substitute for, other endoscopic therapies. **[See pages 37-44.]**

4. What are the patient factors related to outcomes?

Patients with Barrett's esophagus who have higher degrees of dysplasia and more diffuse dysplasia, have a greater risk for developing esophageal cancer. But, not all patients with high grade dysplasia develop cancer, and in some patients the condition may not progress, and may even regress. Current diagnostic methods cannot reliably indicate which patients will develop esophageal cancer or which patients with Barrett's would benefit most from treatment. **[See pages 20-24.]**

5. What are the known challenges to using PDT for Barrett's esophagus?

Staff training is one of the challenges associated with photodynamic therapy. Some physician training is needed, although the administration of PDT is not technically difficult. The main issue is the training needed for nursing staff to ensure procedures are in place to protect the patient from exposure to light sources. The photosensitivity restrictions, which apply for about 30 days with the photosensitizer porfimer sodium, may be a burden for some patients and their families. **[See pages 37, 45, 69-70.]**

6. Is PDT for Barrett's esophagus less costly than standard procedures, and, if not, do the benefits of using PDT outweigh its cost?

Compared to esophagectomy, PDT therapy is less costly and is associated with fewer major adverse events. Photodynamic therapy appears to be slightly more expensive than most of the other endoscopic therapies for Barrett's esophagus, but the difference in costs between the endoscopic therapies is relatively inconsequential. Of all the endoscopic therapies, radiofrequency ablation (RFA) appears to offer the best value for money, but evidence on long-term outcomes (in particular, rates of Barrett's recurrence and progression to cancer) with RFA and other endoscopic therapies is lacking. **[See pages 46-68.]**

Executive summary

Introduction:

Barrett's esophagus is a benign condition that usually develops as a result of long-term gastroesophageal reflux disease. Although Barrett's esophagus is benign and often symptomless, individuals with Barrett's esophagus have a higher risk for developing a type of esophageal cancer called esophageal adenocarcinoma. Esophageal cancer is a relatively rare cancer, but its incidence, and the incidence of Barrett's esophagus appear to be increasing. This may reflect more frequent use of endoscopy and awareness of the condition. It may also be associated with rising rates of obesity and the link between obesity and gastroesophageal reflux disease.

Surveillance and treatment of Barrett's esophagus are preventive measures intended to reduce the risk of developing esophageal cancer. However, there is some uncertainty regarding treatments at the precancerous stage (Barrett's esophagus with high grade dysplasia). Several endoscopic treatments are now available. For some patients these new endoscopic treatments offer an alternative to surgical esophagectomy, but the superiority of one treatment over another is not clear.

Photodynamic therapy (PDT) uses a photosensitizing drug that is activated by a laser to ablate abnormal tissue. Porfimer sodium (Photofrin®) is the only photosensitizing drug that has been approved for use by Health Canada for treating Barrett's esophagus with high grade dysplasia. The drug costs $2,200 per 75 mg vial. Most patients will require 2-3 vials per treatment (based on a dosage of 2 mg/kg of body weight). In Alberta, PDT is used at the Foothills Hospital, in Calgary, and at the Royal Alexandra Hospital, in Edmonton.

This report reviews the safety and effectiveness of PDT for Barrett's esophagus with dysplasia, compared to surgical removal of the esophagus (esophagectomy) and to endoscopic techniques: endoscopic mucosal resection, radiofrequency ablation, argon plasma coagulation, multipolar electrocoagulation, laser ablation and cryoablation. The report also compares the costs of PDT to other techniques, and examines the potential economic and social implications of its use in Alberta.

Methods:

Two separate literature searches were undertaken for this assessment. The first search focused on PDT for the treatment of Barrett's esophagus; no date limits were applied. The second search focused on the alternative treatments and included literature from 2003 to date. A total of 97 studies were included in the review; 11 of the studies were comparative and 86 were non-comparative.

A comprehensive economic decision model was also developed as part of this assessment. The model used cost and treatment information from the published literature, industry, Alberta Health and Wellness, the Alberta Cancer Board, and consultation with clinical experts.

Safety and effectiveness:

The most common adverse events with PDT using porfimer sodium were strictures and photosensitivity. Strictures were also seen with most of the other endoscopic approaches and with esophagectomy. One patient death (due to cardiac arrhythmia) was reported in the studies of PDT using the photosensitizer ALA. No deaths were reported with any of the other endoscopic treatments. A few patients (<1%) who received argon plasma coagulation (APC) or laser ablation, had major bleeds that required transfusion. In comparison, esophagectomy had a pooled mortality rate of 1.2%, and was associated with more major adverse events.

The three main measures of effectiveness examined were: complete eradication of Barrett's esophagus, recurrence of Barrett's esophagus, and progression to esophageal cancer. No one technology dominated insofar as these effectiveness measures are concerned. In fact, there are wide ranges of effectiveness. This is partly due to the heterogeneity of study designs, and the variability in the reporting of results. There is a lack of good quality evidence upon which to define the "gold standard" for managing this condition.

Economic considerations:

Photodynamic therapy uses a photosensitizing drug, porfimer sodium (Photofrin®) which costs $2,200 per 75 mg vial. Using the recommended dosage of 2 mg per kg of body weight, a typical PDT treatment will require at least 2 vials of porfimer sodium, at a cost of $4,400 per patient. This does not include the laser and other costs involved with administering photodynamic therapy.

The literature searches identified 5 published economic evaluations. Once again, the study results varied. In some cases, the authors reached different conclusions regarding the incremental cost-effectiveness of different pairs of technologies for treating Barrett's esophagus. These models are somewhat simplistic and they do not reflect actual clinical practice where several treatment alternatives are available, and where it is likely that patient and physician preferences significantly influence treatment choices.

In the decision model developed for this assessment, a patient with high grade dysplasia begins their treatment with one of several possible technologies. Depending on various factors (such as, outcome with this treatment or limits on the number of repeat treatments), the patient may subsequently be treated with one or more of the other therapies. The base case analysis with this model shows that all of the interventions have incremental cost-effectiveness ratios (ICERs) below conventional thresholds. However, esophagectomy offers considerably worse value than the other technologies with an estimated $11,504/QALY. Radiofrequency ablation appears to offer the best value at $1,783/QALY, followed by multipolar electrocoagulation at $1,863/QALY.

In comparison to other endoscopic treatments, photodynamic therapy is relatively poor in value at an estimated $3,985/QALY.

Esophagectomy clearly offers the worst value, but the results for other treatments suggest that there is not a good efficiency rationale for restricting clinical choice between endoscopic treatment options, particularly as the use of a combination of endoscopic treatments may improve treatment outcomes.

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Abbreviations

AH&W	Alberta Health & Wellness
ALA	aminolevulinic acid
APC	argon plasma coagulation
ARDS	acute respiratory distress syndrome
ARS	anti-reflux surgery
BE	Barrett's esophagus
BMI	body mass index
CIM	cardia intestinal metaplasia
CR	complete response
CRBE	complete response of Barrett's esophagus
CRHG	complete response of high grade dysplasia
DVT	deep vein thrombosis
EAC	esophageal adenocarcinoma
EMR	endoscopic mucosal resection
ERCP	endoscopic retrograde cholangiopancreatography
ESD	endoscopic submucosal dissection
ESO	esophagectomy
EUS	endoscopic ultrasound
GERD	gastroesophageal reflux disease
GI	gastrointestinal
HGD	high grade dysplasia
HpD	hematoporphyrin derivative
HRQL	health-related quality of life
ICER	incremental cost-effectiveness ratio
IM	intestinal metaplasia
IMC	Intramucosal carcinoma
IV	intravenous
KTP	potassium titanyl phosphate laser
LES	lower esophageal sphincter
LGD	low grade dysplasia
MPEC	multipolar electrocoagulation
mTHPC	meta-tetrahydroxyphenylchlorin
Nd:YAG	neodymium doped yttrium aluminum garnet laser
NR	non-response
OM	omeprazole (drug)
PDT	photodynamic therapy
PPI	proton pump inhibitor (drug)
PR	partial response
QALY	quality adjusted life year

RCT	randomized controlled trial
RFA	radiofrequency ablation
SCC	squamous cell carcinoma

Glossary

Ablation: removal (e.g., of tissue).
Aminolevulinic acid: a photosensitizing drug used in photodynamic therapy.
Anastomosis: a surgical connection, usually between two tubular or hollow parts of the body (e.g., blood vessels, intestines, stomach, esophagus).
Argon plasma coagulation: use of argon gas and a monopolar electrical current to stop bleeding and ablate tissue.
Arrhythmia: irregular heartbeat.
Barrett's esophagus (also called Barrett esophagus or oesophagus, Barrett syndrome, Barrett's epithelium, Barrett's metaplasia): abnormal tissue (intestinal metaplasia) that replaces the normal lining of the esophagus; usually caused by long term gastroesophageal reflux disease.
Biopsy: removal of tissue samples for pathological examination to determine the presence or extent of disease.
Budget impact analysis: the estimated costs to a particular health care budget of adopting and using a new technology.
Cardia: the lower esophageal sphincter; the junction of the esophagus and stomach.
Coagulation: in the context of ablation procedures (rather than to stop bleeding), coagulation involves the use of thermal or electrical energy to destroy tissue.
Columnar epithelium: the specialized cells (better able to withstand exposure to stomach acids) that line the stomach and intestine.
Cryoablation (also called cryotherapy or cryosurgery): the use of liquid nitrogen or carbon dioxide gas to freeze and destroy tissue.
Dysphagia: difficulty in swallowing.
Dysplasia (also called intraepithelial neoplasia): precancerous, abnormal cells.
Emphysema: difficulty breathing, a type of chronic obstructive pulmonary disease.
Endoscope: a flexible, lit tube with a tiny camera that transmits images to a screen. In upper gastrointestinal endoscopy the endoscope is inserted through the mouth and down the esophagus to allow visualization of the esophagus, stomach and the upper part of the small intestine (duodenum).
Endoscopic mucosal resection: the surgical resection of abnormal tissue through an endoscope; typically used to remove lesions <2 cm, or for piece-by-piece removal of larger lesions; EMR is also used to diagnose and stage disease.
Endoscopic submucosal dissection: a technique used to remove larger (>2cm) lesions in the gastrointestinal tract.
Endoscopic ultrasound: the use of an ultrasound transducer and an endoscope to obtain more detailed images of the gastrointestinal tract; used for diagnosis, staging and tissue sampling.
Endoscopy: the use of an endoscope to see inside the body; endoscopy is also used to perform endoscopic procedures, such as biopsy or endoscopic mucosal resection.
Epigastric: in the area of the stomach or upper abdomen.
Epithelium: layers of cells covering external body surfaces or lining internal organs.

Esophageal adenocarcinoma: a type of esophageal cancer originating in abnormal glandular cells that have replaced the normal tissue at the lower end of the esophagus.
Esophagectomy: surgical removal of all or part of the esophagus.
Esophagitis: inflammation of the esophagus, usually caused by gastroesophageal reflux disease.
Esophagus (also called the gullet): part of the digestive system connecting the mouth to the stomach.
Fundoplication: a surgical procedure where the top of the stomach is wrapped around the esophageal sphincter and secured to strengthen the sphincter and prevent reflux; used to treat severe GERD and hiatus hernia.
Gastroesophageal junction: where the esophagus joins the stomach.
Gastroesophageal reflux disease (GERD, also called gastro-oesophageal reflux disease or GORD): frequent, chronic regurgitation of stomach contents that damages the lining of the esophagus and may cause symptoms that affect quality of life.
Goblet cells: epithelial cells that produce mucus; normally found in the lining of the stomach and intestines, their presence in the esophagus denotes the intestinal metaplasia of Barrett's esophagus.
Hematemesis: vomiting blood.
Hypotension: low blood pressure.
Incremental cost-effectiveness ratio: the additional cost of an intervention compared to the less expensive intervention (or no intervention), divided by the difference in effect or patient outcome (e.g., QALY).
Intestinal metaplasia: intestinal cells that replace the normal squamous cells lining the esophagus; their presence in the esophagus indicates Barrett's esophagus.
Intraepithelial neoplasia: see dysplasia.
Intramucosal carcinoma: cancer cells in the epithelium that have not yet spread into the submucosal layer.
Lower esophageal sphincter: the valve at the lower end of the esophagus, at the junction of the esophagus and stomach.
Metaplasia: where abnormal cells replace the tissue normally found in that part of the body.
Mucosa: a mucous secreting membrane that forms one layer of the lining of the esophagus and intestines.
Multipolar electrocoagulation: a thermal ablative technique.
Muscularis propria: the muscular layer of the esophageal lining, below the submucosa.
Odynophagia: pain when swallowing.
Photodynamic therapy: a treatment used for some types of cancer, skin conditions and age-related macular degeneration; it uses a photosensitizing drug followed by exposure to a light source to destroy tissue.
Photosensitivity: sensitivity to light.
Pleural effusion: excess fluid around the lungs.
Porfimer sodium: a photosensitizing drug used in photodynamic therapy.
Proton pump inhibitors: a class of drugs that reduce the production of stomach acids; used to treat peptic ulcers and gastroesophageal reflux disease.

Quality-adjusted life year: a measure of health care outcomes that adjusts gains (or losses) in years of life subsequent to an intervention by the quality of life during those years.
Radiofrequency ablation: the use of microwave energy to ablate tissue.
Reflux: in gastroesophageal reflux this means the backwards flow of food and digestive fluids from the stomach into the esophagus.
Squamous cells: flat, scaly cells.
Squamous cell carcinoma: a type of esophageal cancer that begins in the squamous cells (the normal tissue lining the esophagus).
Stenosis: abnormal constriction or narrowing of a vessel, canal or cavity in the body.
Stricture: narrowing caused by scar tissue; esophageal strictures may cause difficulty in swallowing.
Subcutaneous: below the skin.
Submucosa: a layer of the lining of the esophagus that is below the mucosa and deep mucosa, and above the muscularis propria.

Part 1: Introduction & background

Barrett's esophagus

The esophagus is often described as a muscular tube. It connects the mouth to the stomach and is part of the digestive system (Figure 1). Sphincters (valves) at each end of the esophagus open and close to allow the passage of food and prevent regurgitation of stomach contents. If the muscles that control the sphincter at the junction of the esophagus and stomach malfunction, acidic digestive fluid flows back up from the stomach into the esophagus, lungs and mouth. This causes what is commonly called heartburn or acid indigestion, or in medical terminology, gastroesophageal reflux.

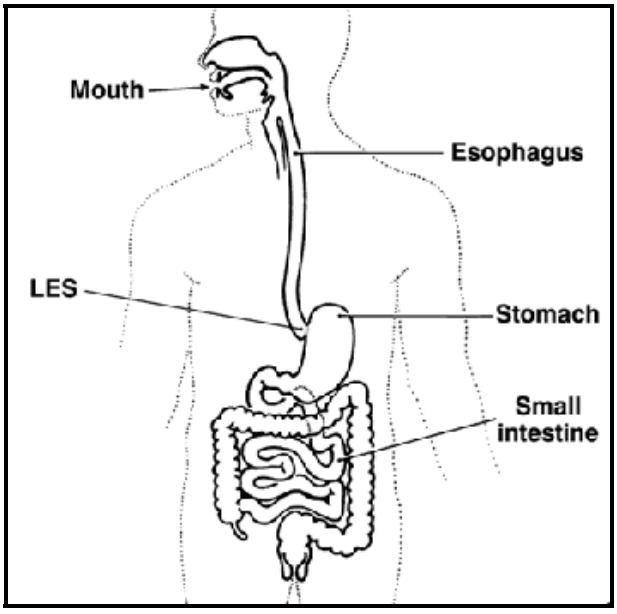


Figure 1. The digestive system.
(*Image courtesy of the US National Institutes of Health*.)

Most people have occasional gastroesophageal reflux. It is usually caused by lifestyle factors such as obesity, smoking, consuming too much alcohol or caffeine, or eating certain foods. Mild gastroesophageal reflux can be relieved with changes to diet, weight loss and smoking cessation, and with the use of over-the-counter antacids. More severe reflux may require prescription drugs, such as proton pump inhibitors, or in some cases, surgery (e.g., fundoplication) to strengthen the lower esophageal sphincter. Frequent, chronic gastroesophageal reflux is called gastroesophageal reflux disease (GERD).

In some individuals with gastroesophageal reflux disease, long-term exposure to digestive fluids causes abnormal cells to grow in the epithelium (lining) of the esophagus, near the junction with the stomach. The abnormal tissue is usually referred to as intestinal metaplasia, though

other types of abnormal cells may also be present. The condition itself is called Barrett's esophagus.[1]

Barrett's esophagus is not life threatening and it is often asymptomatic, but over time the Barrett's tissue (intestinal metaplasia) may develop precancerous cells. The precancerous cells are called dysplasia. Individuals with Barrett's esophagus have a slightly increased risk for developing a type of esophageal cancer known as esophageal adenocarcinoma.[1-3] One US study found a risk of esophageal adenocarcinoma of approximately 0.4% per person-year in individuals with Barrett's esophagus, compared with a risk of 0.07% in those with GERD, but without Barrett's.[4] The risk of developing esophageal cancer increases in relation to the "severity, frequency and duration of GERD symptoms".[5]

Risk factors for Barrett's esophagus

Barrett's esophagus is more common in Caucasian men over the age of 50, and in individuals with chronic upper gastrointestinal disorders, such as esophagitis, hiatus hernia, and long-term gastrointestinal reflux disease.[3 6,7] Obesity is associated with an increased risk for gastrointestinal reflux disease (GERD), and for esophageal cancer, but a recent meta-analysis found only an indirect association between increased BMI (body mass index) and the development of Barrett's esophagus.[8,9]

Diagnosis of Barrett's esophagus

Individuals with Barrett's esophagus may have symptoms of gastroesophageal reflux (such as heartburn), or respiratory symptoms (such as coughing), but they are often asymptomatic.[1] As a result, many individuals are never diagnosed with this condition and the number of patients diagnosed is an underestimate of the true prevalence of the disease.[10] Barrett's esophagus is usually detected during endoscopy to investigate chronic gastroesophageal reflux disease. The abnormal Barrett's tissue is dark red, in contrast to the pale, normal epithelium of the esophagus.

Although it can be seen endoscopically, tissue biopsy is needed for a definitive diagnosis of the intestinal metaplasia (the presence of goblet cells) that signify Barrett's esophagus. But, there is significant variation in the accuracy of the diagnosis of Barrett's, and in the ability to distinguish the level of dysplasia. This may lead to both under- and over-diagnosis, and treatment of this condition.[11,12]

Endoscopic ultrasound (EUS) gives more detailed images of the layers of tissue within the wall of the esophagus, and improves the accuracy of diagnosis and appropriate treatment by showing submucosal involvement. If the endoscopic ultrasound shows no submucosal involvement in patients with high grade dysplasia, the less invasive, endoscopic therapies, rather than major surgery (esophagectomy), might be appropriate.[13]

Barrett's esophagus may be categorized into long segment, short segment and cardia intestinal metaplasia (CIM). Long segment Barrett's esophagus refers to intestinal metaplasia which is ≥3 cm long; short segment Barrett's is intestinal metaplasia tissue that is <3cm long, and cardia intestinal metaplasia describes abnormal tissue limited to the cardia (the lower esophageal sphincter area at the junction of the esophagus and stomach).[10]

Further categories are used to describe the presence or extent of dysplasia:

- **Negative for dysplasia** indicates Barrett's esophagus without the presence of atypical cells.
- **Indeterminant or indefinite for dysplasia** is used when inflammation of the esophagus (esophagitis) makes it difficult to determine the presence or extent of dysplasia.
- **Low grade dysplasia** refers to Barrett's esophagus where some cells show atypical changes, but the glandular tissue is still normal.
- **High grade dysplasia** indicates an advanced stage of dysplasia where most cells show atypical development and the glandular cells are also irregular or abnormal.[14]

Barrett's esophagus may progress to dysplasia or esophageal cancer, as shown in Figure 2, but it does not always follow a predictable pattern. Most people with Barrett's esophagus do not develop dysplasia or esophageal cancer, and in some individuals the metaplasia or dysplasia may disappear or regress.[11,15,16]

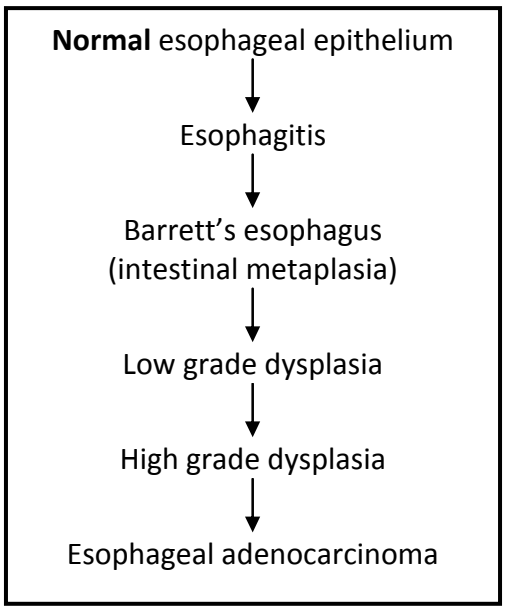


Figure 2. Progression of esophageal changes.
(Adapted from Shalauta MD & Saad R. Barrett's esophagus.)[17]

Prevalence of Barrett's esophagus

Gastroesophageal reflux

In the 1996 DIGEST survey of 1,036 Canadians, 28.6% (296 individuals) reported having substantial upper gastrointestinal symptoms (defined as moderate to severe symptoms including heartburn, nausea, vomiting, abdominal pain, regurgitation, etc.) at least once per week. Heartburn was the most common symptom - reported by 52.3% of those with chronic gastrointestinal disorders.[18]

Barrett's esophagus

Between 10% to 20% of individuals with chronic GERD may develop Barrett's esophagus.[1,19] The Canadian Adult Dyspepsia Empirical Therapy Prompt Endoscopy study included people who had visited primary care practitioners due to symptoms of upper gastrointestinal pain or discomfort (such as heartburn and acid regurgitation), that had persisted for at least 3 months. Of the 1,040 study participants who had endoscopies, 53 patients (5%) were thought to have Barrett's esophagus. However, biopsies confirmed the diagnosis of Barrett's esophagus (based on the presence of intestinal metaplasia) in only 25 of these patients (2.4%). The authors concluded that in Canadian primary care patients with chronic dyspepsia the prevalence of Barrett's esophagus, confirmed by biopsy, was about 2%.[3]

Many individuals with GERD and Barrett's esophagus are either asymptomatic or do not seek medical care for their reflux symptoms, thus the prevalence of these conditions is probably underestimated.[18] A US study of 110 asymptomatic veterans (mostly male) over the age of 50 found that 27 (25%) of the study participants had Barrett's intestinal metaplasia.[7] A recent Canadian commentary suggests that an estimated prevalence of 2% to 6% for Barrett's esophagus in the general population may be reasonable.[20]

Based on Alberta billing data for the year 2006-2007 about 2,000 people were diagnosed with Barrett's esophagus. The billing codes do not distinguish between diagnoses of Barrett's esophagus with or without dysplasia, or those with low or high grade dysplasia. A US study estimated that between 7% to 8% of patients with Barrett's have some degree of dysplasia (see below).[19] Thus, an estimated 150 of the 2,000 Alberta patients diagnosed with Barrett's esophagus in 2006-2007 may have had dysplasia.

The incidence of Barrett's esophagus seems to be increasing. This could be due to a greater use of endoscopy and awareness of this condition.[11] It may also be associated with rising obesity rates and the effect of obesity on gastroesophageal reflux, although a direct link between obesity and Barrett's esophagus has not yet been shown.[8,9]

Barrett's esophagus with dysplasia

Most individuals with Barrett's esophagus will not develop dysplasia. A retrospective pathology review of 790 cases of Barrett's esophagus at 3 US hospitals found that 686 cases (86.9%) were

negative for dysplasia, 47 cases (5.9%) were indefinite for dysplasia, 37 cases (4.7%) had low grade dysplasia, and 20 cases (2.5%) had high grade dysplasia.[19] Patients who have Barrett's esophagus with high grade dysplasia are those most at risk for developing esophageal adenocarcinoma.

Esophageal adenocarcinoma risk in Barrett's esophagus
A review of English language studies of esophageal cancer risk in individuals with Barrett's esophagus found the estimates ranged from 0% to almost 3% per patient year, and that the smaller studies had much higher estimates of esophageal cancer risk.[21] As a result, the published literature may overestimate the risk of esophageal cancer. Although their study was not intended to determine true cancer risk, the peak of the funnel plot graph of study results indicated an incidence of about 0.5% per patient year.[21]

A 2008 meta-analysis found that when only the larger, higher-quality studies were included the estimated risks of progression to esophageal cancer and high grade dysplasia dropped to 0.39% per year for esophageal cancer, and 0.77% per year for cancer and high grade dysplasia.[22] Men had twice the rate of progression to cancer as women. The authors concluded that, with the lower estimates of cancer risk, the cost-effectiveness of endoscopic surveillance for patients with Barrett's will depend on whether such surveillance can target those most at risk.[22]

In a retrospective study of 60 patients who had esophagectomies for Barrett's esophagus with high grade dysplasia (HGD, n=41) or intramucosal carcinoma (IMC, n=19), the overall rate of submucosal invasive carcinoma was 6.7% (n=4). Patients with high grade dysplasia had a submucosal invasion rate of 5%; patients with intramucosal carcinoma had a submucosal invasion rate of 11%.[23] This rate of submucosal invasive carcinoma is considerably lower than what the authors found reported in the literature (e.g., a range of 13% to 75%, often cited as a mode of 40%). They concluded that "with adequate sampling and staging, patients with BE with HGD and IMC, especially those without endoscopically visible lesions, can potentially be treated by nonsurgical (local) therapies".[23]

Burden of Barrett's esophagus

Patient burden

Individuals with Barrett's esophagus report a decreased quality of life similar to that of people with chronic gastroesophageal reflux disease.[24] In a US study of 107 patients with Barrett's esophagus and 104 patients with gastroesophageal reflux disease, both groups scored below average on all domains of the SF-36 (a standardized questionnaire used to measure overall health) in comparison to published norms for an age-matched group without Barrett's or GERD.[24]

Dutch researchers who surveyed patients with Barrett's found that 60% of the 180 survey respondents considered endoscopy "burdensome".[25] Moreover, the patients were more distressed before undergoing endoscopy than while awaiting the biopsy results afterwards, indicating that they found the procedure itself stressful.

Health care costs

Because they are so common, upper gastrointestinal disorders, including gastroesophageal reflux disease, are associated with substantial health care costs – for physician visits, diagnostic tests, and the prescription drugs used to treat or prevent symptoms.[18,26] Diagnostic testing for Barrett's esophagus involves both endoscopy and biopsy. Both procedures are also used to monitor Barrett's patients, particularly those with dysplasia. Indirect costs, such as work absenteeism and reduced productivity, are also higher in individuals with chronic upper gastrointestinal disorders.[18]

Studies from the US and Europe report similar estimates of costs associated with gastroesophageal reflux disease and Barrett's esophagus, with the largest portion of direct health care costs attributed to prescription drugs, in particular, to the costs of proton pump inhibitors (PPIs).[27] One US study of the direct costs associated with Barrett's esophagus found that drug therapies constituted about 67% of total direct costs, and that of these drug costs, over 75% were for proton pump inhibitors.[28] Endoscopies were responsible for over 85% of the procedural costs associated with Barrett's esophagus, followed by pathology costs. In 1999, the final year of the study, the average number of endoscopies per patient, per year was 1.03. The authors estimated that overall costs for patients with Barrett's esophagus were about 21.2% higher than for patients treated for gastroesophageal reflux disease.[28]

Management of Barrett's esophagus

Surveillance

Surveillance endoscopy is used to monitor patients with Barrett's esophagus to try to detect, and when necessary treat, any progression of metaplasia to dysplasia or esophageal cancer. But whether surveillance is beneficial is still controversial, and patients should be informed of the potential benefits and the risks involved.[29]

Recent American College of Gastroenterology guidelines recommend surveillance but indicate that there is currently only Grade C evidence (case series or poor quality cohort studies) to support this practice. The recommended frequency of surveillance depends on the presence or extent of dysplasia, and on other factors, such as the individual's life expectancy and preferences.[29] The guidelines recommend that patients with Barrett's esophagus and no evidence of dysplasia receive 2 endoscopies with biopsy during the first year. If no dysplasia is found endoscopy should be repeated every 3 years.[29] Patients with low grade dysplasia should

receive a follow-up endoscopy with biopsy within 6 months, and annually thereafter, until there is no evidence of dysplasia at 2 consecutive checkups. For patients with high grade dysplasia the guidelines advocate a repeat endoscopy with biopsy within 3 months to check for adenocarcinoma, endoscopic resection to remove dysplasia, and continued surveillance or intervention every 3 months as appropriate, or until 3 consecutive endoscopies have demonstrated complete ablation.[29]

Esophagectomy

Esophagectomy is the surgical removal of all or part of the esophagus. A section of the stomach is then pulled into the chest and surgically joined to form a replacement for the esophagus. Esophagectomy is intended to prevent progression to cancer in patients who have Barrett's esophagus with high grade dysplasia, and as a cure for patients with early stage esophageal cancer. But, not all patients with high grade dysplasia will develop esophageal cancer.

Esophagectomy is a major surgical procedure with high complication and mortality rates.[30,31] Mortality rates range from 1% to 20%.[31-33] Complications associated with esophagectomy include infections, pneumonia, myocardial infarction, heart failure, pulmonary embolism, stenosis, and chronic digestive disorders. Although esophagectomy may be performed using different surgical techniques, the superiority of one surgical approach over another has not been shown.[31] The recent use of minimally invasive surgical techniques may reduce mortality and complication rates.[31,34]

Frail, elderly patients or those with other health conditions may not be considered candidates for esophagectomy. Less invasive, endoscopic treatments may be options for some of these patients.

Endoscopic treatments for Barrett's esophagus

The treatments described below are performed endoscopically using various devices. The main intent is to prevent esophageal cancer by destroying the abnormal tissue and allowing regrowth of normal esophageal tissue. Depending on the extent of dysplasia, patients may need several treatment sessions, follow-up endoscopies and biopsies. A combination of treatments may be used, for example, endoscopic mucosal resection, which has the advantage of providing tissue samples for biopsy, followed by an ablative treatment. Patients typically receive long term drug therapy to control acid reflux and prevent further damage to the esophagus.[29]

Endoscopic mucosal resection

Endoscopic ultrasound (EUS) is used to determine if the abnormal tissue is within the mucosal layer of the esophageal wall and suitable for treatment with endoscopic mucosal resection (EMR).[35] In endoscopic mucosal resection the abnormal mucosal and submucosal layers of the

esophageal wall are cut out and removed through an endoscope. The tissue is raised by injecting a solution (such as saline) beneath it, or by applying suction, and then removed using a cap, snare, or ligator device. It is typically used to remove smaller lesions (<2 cm in size); larger lesions can be removed in sections, but this may miss some abnormal tissue, and make it difficult to determine pathological staging.[31,36]

Endoscopic mucosal resection is also used as a diagnostic or staging technique to establish the depth of dysplasia or cancer and determine the appropriate treatment course. Endoscopic submucosal dissection (ESD) is used for the removal of larger (>2 cm) lesions in the gastrointestinal tract. The abnormal tissue is marked using electrocautery, a solution is injected to lift the tissue, and the lesion is cut out with an electrocautery knife.[36]

Argon plasma coagulation

Argon plasma coagulation (APC) uses a monopolar electrical current, powered by a generator, to ablate tissue. The depth of tissue destruction is determined by the power level, the duration of treatment and the distance between the probe and the targeted tissue.[31] Several treatment sessions are usually needed.

Cryoablation

Another ablative treatment, cryoablation (also called cryotherapy or cryosurgery) uses liquid nitrogen or freezing carbon dioxide gas. The nitrogen or gas is sprayed onto the targeted tissue through an open-tipped catheter. The spray freezes the lesion and the tissue is allowed to thaw before the process is repeated. The “freeze and thaw” cycle destroys the tissue. The procedure can be performed on an outpatient basis.[37]

Laser ablation

Lasers can also be used to produce heat for thermal ablation of tissue. The depth of tissue destruction depends on the type of tissue and the kind of laser or wavelength used. For example, argon, potassium titanium phosphate (KTP) and neodymium: yttrium-aluminium-garnet (Nd:YAG) lasers can penetrate tissue to depths of between 1 mm to 4 mm.[38]

Multipolar electrocoagulation

Multipolar electrocoagulation (MPEC) is an ablative treatment that uses heat generated by a high frequency current. The current passes from one electrode to another on the tip of the probe and through small areas of tissue.[39] Depending on the probe used, multipolar electrocoagulation can be used for ablating (or cutting) tissue, or to stop bleeding.

Photodynamic therapy

When certain chemicals (photosensitizers) are exposed to light and oxygen they produce a chemical reaction that causes cell death. In photodynamic therapy (PDT) the patient receives a photosensitizer drug. After an interval to allow optimal uptake of the drug the abnormal tissue is exposed to light of a particular wavelength. In esophageal PDT the light source (e.g., a laser or a fiber optic light diffuser), is delivered via a catheter, to activate the drug and destroy the abnormal tissue.

Porfimer sodium (Photofrin®) is the only photosensitizer approved for systemic use in the treatment of Barrett's esophagus with high grade dysplasia and esophageal cancer in Canada. Porfimer sodium is administered intravenously, typically, about 2 days before the light is applied. The drug is cleared from most of the body within a few days, but some tissues (tumours, skin, eyes) remain light sensitive for 4 to 6 weeks. Patients must avoid direct sunlight and bright lights during this period.[40]

Another photosensitizing drug, aminolevulinic acid (ALA, Levulan®), is only used for topical PDT treatments in Canada (for example, in the treatment of certain skin conditions), but has been used in clinical trials for systemic treatments. ALA may have certain advantages over porfimer sodium, including higher and quicker uptake in the mucosal layer of the esophagus, and a shorter half life, with a correspondingly shorter period of photosensitivity for patients.[40]

Other photosensitizing agents are used in photodynamic therapy for different conditions, for example, verteporfin (Visudyne®) for age-related macular degeneration, and temoporfin (mTHPC, Foscan®) which is marketed in Europe for the treatment of head and neck cancers. New photosensitizers, such as HPPH (Photochlor®, Roswell Park Cancer Institute) are under investigation for esophageal, lung, and other cancers.[41] Some of these newer agents are more targeted photosensitizers, intended to be taken up only by the abnormal cells, and offering deeper tissue penetration.

Radiofrequency ablation

Radiofrequency (RF) ablation uses microwave energy to ablate Barrett's tissue. A balloon catheter is used to measure the size of the inner diameter of the esophagus after which a balloon ablation catheter with electrodes around the tip is inserted. The balloon is inflated and the radiofrequency energy is activated to destroy the tissue around the circumference. Focal ablation is also used to target smaller lesions.

Status of photodynamic therapy & other treatments for Barrett's esophagus in Canada

Market status

Porfimer sodium (Photofrin®) received a Health Canada Notice of Compliance in the 1990s. Axcan Pharma Inc. holds the current Canadian licenses for the product. Photofrin is licensed in Canada as an antineoplastic photosensitizing drug. Licensed indications include its use in photodynamic therapy for the treatment of obstruction and palliation of dysphagia due to esophageal cancer, and in the ablation of high grade dysplasia in patients with Barrett's esophagus.[42]

Other photosensitizing drugs, such as aminolevulinic acid (ALA, Levulan®, DUSA Pharmaceuticals, Inc.) and meso-tetrahydroxyphenylchlorin (mTHPC), have been used in some studies of photodynamic therapy for Barrett's esophagus, but these agents have not been licensed in Canada for this indication.

The Diomed 630 PDT Laser (Angiodynamics UK Ltd / Diomed Inc.) used as a light source for photodynamic therapy, received a Health Canada medical device licence in 2001.[43] Other light sources have been used, but the Diomed system is specifically licensed for use with porfimer sodium and for gastrointestinal applications.[40]

Esophagectomy is a surgical procedure and as such it does not require Health Canada licensing. The HALO radiofrequency generator (BARRX Medical, Inc.), and other components of the HALO 360 and HALO 90 radiofrequency ablation systems (ablation catheters and sizing balloons) have received Health Canada medical device licenses.[43] Radiofrequency generators from other manufacturers are also licensed in Canada (e.g., Valleylab, Medtronic). Argon plasma coagulation units and accessories from several manufacturers (e.g.,Erbe Elektromedizin, Valleylab) are licensed by Health Canada.[43] Cryoablation units for other endoscopic surgical procedures are licensed in Canada, but these units are not licensed for use in treating Barrett's esophagus or esophageal cancer.[43]

Diffusion of photodynamic therapy

According to Axcan Pharma, the Canadian distributor of Photofrin®, several Canadian centres offer photodynamic therapy. These are shown in Table 1 below.

Table 1. Photodynamic therapy centres in Canada

Province	Centre
British Columbia	- Royal Jubilee Hospital, Victoria
Alberta	- Foothills Hospital, Calgary - Royal Alexandra Hospital, Edmonton
Ontario	- Hamilton Regional Cancer Centre, Hamilton - St. Michael's Hospital, Toronto - Toronto General Hospital, Toronto - Ottawa General Hospital, Ottawa
Quebec	- Montreal General Hospital, McGill University Health Centre (MUHC), Montreal - Centre Hospitalier de l'Université de Montréal (CHUM, Notre Dame site), Montreal* - Centre Hospitalier Universitaire du Québec (CHUQ), Quebec City

Note: does not include centres that use PDT for eye or skin treatments; *Not yet operational.
Information supplied by Axcan Pharma.

Part II: Safety & efficacy of photodynamic therapy for Barrett's esophagus in comparison to other management strategies

Research questions

The main question to be addressed by this review was:

- What is the potential role of photodynamic therapy (PDT) in the management of Barrett's esophagus in adults?

Specific questions to be addressed were:

- In comparison with alternate treatments (esophagectomy, endoscopic surgical resection and other ablative technologies):
    - what is the safety of PDT for Barrett's esophagus?
    - what is the effectiveness or efficacy of PDT for Barrett's esophagus?
    - what are the patient factors related to outcomes?
    - what are the known challenges to using PDT for Barrett's esophagus?

Methods

This report is based on a systematic review of the published literature on PDT and alternative therapies for the treatment of Barrett's esophagus with dysplasia. Advice from a clinical expert in this field was also sought throughout the project. The methods used to develop the economic model are described in Part IV.

Literature search

Two separate literature searches were undertaken for this assessment. The first search focused on PDT for the treatment of Barrett's esophagus and esophageal cancer. (Because the published studies often included patients with either condition a single search was used to avoid duplication.) This search was run in July 2008, with additional monthly updates (using PubMed) to capture new studies throughout the project with a cut off date of January 2009. No date limits were applied. Search results from an earlier, scoping review of PDT for cancer were also reviewed.[44] The second search focused on alternatives to PDT for the treatment of Barrett's esophagus with dysplasia: surveillance, endoscopic mucosal resection, radiofrequency ablation, argon plasma coagulation, cryosurgery and esophagectomy, and additional alternatives for the treatment of early stage esophageal cancer: radiation therapy and chemotherapy. The alternative treatments search was first run in September 2008, to cover a three-year period (2006 to 2008), then again in December 2008 to expand coverage to a five-year period (2003 to 2008).

The search strategies for the searches are shown in Appendix A. The numbers shown in Figure 3 are totalled results from both searches. The American Society of Clinical Oncology and Digestive Disease Week meetings abstracts, Cancer Care Ontario, guidelines and clinical trials web sites

were searched, and the reference lists of relevant papers were checked for additional studies. The Canadian supplier of porfimer sodium, Axcan Pharma, was contacted for cost and prescribing information on their product. The investigators working on the Cochrane Collaboration systematic review of *Surgery versus radical endotherapies for early cancer and high grade dysplasia in Barrett's oesophagus,* and the UK Centre for Reviews and Dissemination's review on photodynamic therapy for Barrett's esophagus and various types of cancer provided updates on the status of their reviews. The principal researchers involved in several of the ongoing clinical trials in this area were also contacted regarding the status of their trial results.

Selection of relevant studies

A bibliographic software program (Reference Manager®) was used to remove duplicate references and manage bibliographic citations. The search results (titles, and abstracts where available) were reviewed by 2 researchers. The full papers of potentially relevant studies were retrieved for review and assessed using the criteria shown in the table below. Non-English language studies were excluded unless they had an English language abstract that provided sufficient detail on patients and outcomes. Editorials, opinion pieces and review articles were also excluded.

Table 2. Criteria for including studies in this review

Parameter	Inclusion criteria	Exclusion criteria
Study design	Randomized or controlled (e.g., pseudo-randomized or quasi-randomized) trials Non-randomized clinical trials Retrospective, prospective, or concurrent cohort studies Case or clinical series	Editorials & opinion pieces Review articles
Participants	Patients diagnosed with Barrett's esophagus	Patients diagnosed with esophageal cancer or other conditions
Interventions	Photodynamic therapy Esophagectomy Endomucosal resection Other ablative treatments (cryoablation, laser ablation, argon plasma coagulation, multipolar electrocoagulation,radiofrequency ablation)	
Comparators	Same as interventions above	
Outcomes	Adverse events Response to treatment (% of dysplasia eradicated) Recurrence Progression to esophageal cancer	Note: In studies that included patients with Barrett's esophagus and early cancer, only those for which it was possible to separate patients with Barrett's were included.

Synthesis & critical appraisal of selected studies

Two reviewers extracted information from the studies using a standard, pre-tested data abstraction form and a set of decision rules. The form contained elements to assess the purpose and methods of each study (Table 3). When required, missing data were sought from the study's author. Because of the heterogeneity of studies it was not possible to use meta-analysis software to pool data.

The quality of each study was appraised using the Oxford Centre for Evidence-based Medicine Levels of Evidence and Grades of Recommendation for Studies of Therapy (see Appendix H). This is a validated and widely used scale that allows comparisons to be made across different study designs.

Table 3. Summary of data abstraction form elements

Parameter	Description of information collected
Cancer/cell type	BE; dysplasia
Study design	Setting; study type; treatment(s) used; length of follow-up
Patients	Number of patients by treatment group; age; gender; length of Barrett's; inclusion/exclusion criteria; prior treatments
Intervention	Details of the treatment; number of patients who underwent each treatment; co-interventions
Outcomes	Complete and partial response; survival; recurrence; progression to cancer; reduction in length of Barrett's; adverse events

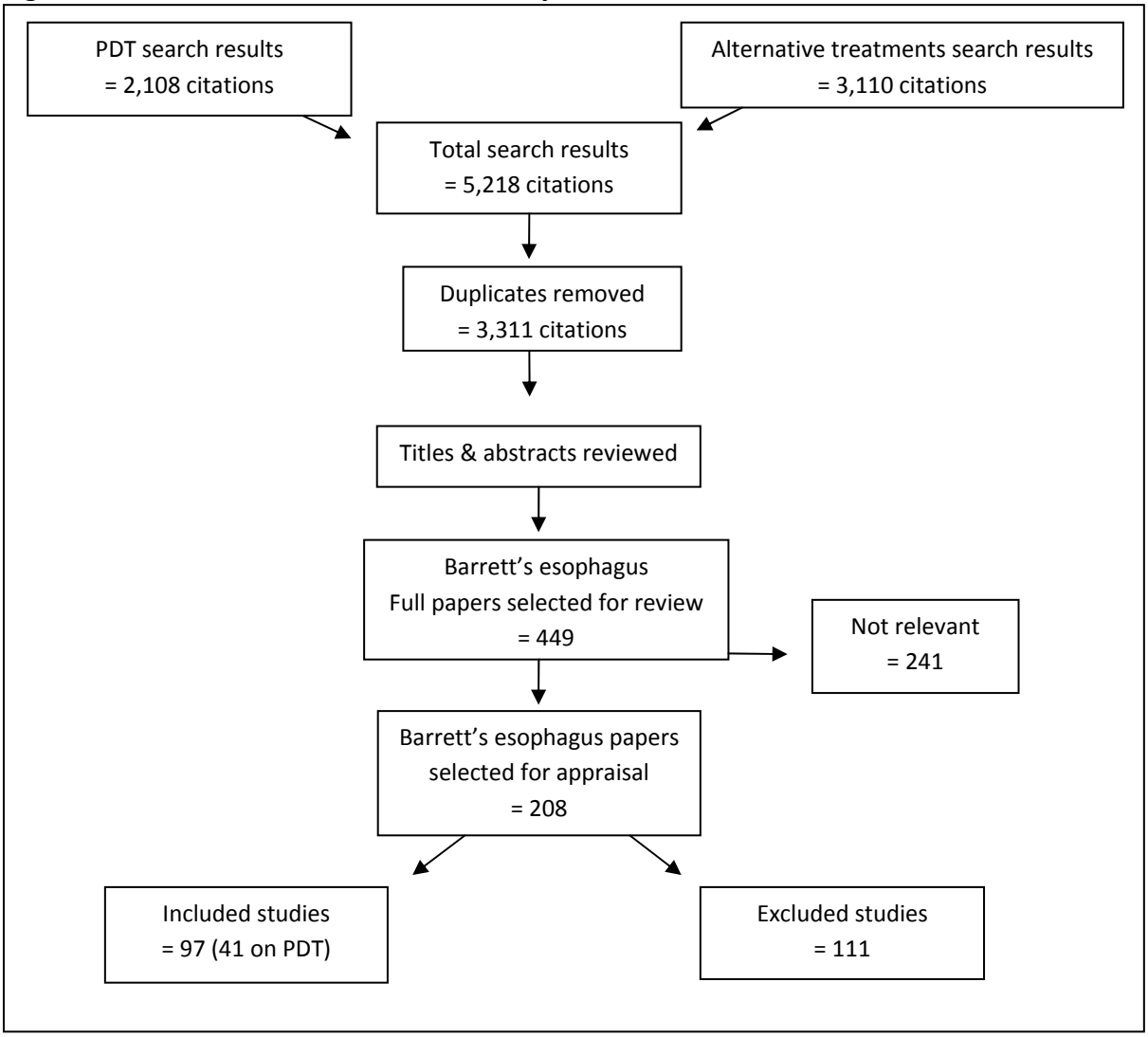
Data analysis

Information collected from studies was summarized in tabular form to more easily identify trends or patterns in findings across studies. Results from individual studies were pooled, using weighted mean values, to generate summary estimates for each of the outcomes of interest.

Results

Over 400 potentially relevant papers were selected from the literature search results for full review (see Figure 3). Of these, 97 studies met the inclusion criteria. The included studies are summarized in Appendix B, Tables B1 through B8. The excluded studies and the reasons for their exclusion are listed in Appendix C, Table C1.

Figure 3. Literature search results and study selection



Description of included studies

This review is based on 97 studies with a total of 3,209 patients (see Appendix B, Tables B1 to B8). All but 8 of the studies involved endoscopic therapies, the majority of which were ablative techniques: argon plasma coagulation (APC), cryoablation, laser, multipolar electrocoagulation (MPEC), photodynamic therapy (PDT) and radiofrequency ablation (RFA). Most studies of ablative techniques (88%) were non-comparative.

Photodynamic therapy was used in about half of the studies, but most of these were non-comparative studies. The PDT studies used different photosensitizers and dosages: porfimer sodium (11 studies), ALA at 30 mg/kg (5 studies) and ALA at 60 mg/kg (10 studies). The studies generally included patients with high grade dysplasia who were followed for a period ranging from 2 months to over 60 months. Four of the studies were randomized controlled trials (RCTs) that compared PDT to APC.

Of the remaining studies on endoscopic techniques, about half discussed APC in patients with Barrett's esophagus, but no dysplasia. Follow-up periods were comparable to those in the studies of PDT. Six studies were RCTs, including the 4 already mentioned of APC vs PDT and 2 studies of APC vs. MPEC. One cohort study compared APC to esophagectomy or surveillance.

For the other endoscopic treatments, 2 single arm clinical trials of cryoablation, both of which had relatively short follow-up periods (12 months) were included. The 6 studies of EMR involved patients with high grade dysplasia. Two of these were cohort studies, 1 comparing EMR to PDT or EMR combined with PDT, and the other comparing EMR to surgery or surveillance. Follow-up times ranged from 3 months to 120 months. All 7 studies of laser ablation, were non-comparative. Most studies were of patients with Barrett's esophagus who were followed for between 1.5 and 28 months.

Although 2 of the 6 studies of MPEC included were RCTs, which compared MPEC to APC, none involved patients with high grade dysplasia. The evidence was limited to patients with Barrett's esophagus only. Most of the 11 studies of RFA involved patients with Barrett's only; 1 was a cohort study comparing RFA to PDT.

Esophagectomy (surgery) was assessed in 8 studies, and outcomes were reported on a total of 198 patients with high grade dysplasia. But, various surgical approaches were used in the studies, and the follow-up periods ranged from 12 to 120 months.

Table 4. Key characteristics & overall description of included studies

	Treatment	Number of studies*	Comparative studies*	Non-comparative studies	Number of patients	Patients with HGD	Patients with BE only
Endoscopic	APC	26	7	19	792	53	739
	Cryoablation	2	0	2	31	21	10
	Combined EMR+PDT	2	0	2	6	6	0
	EMR	6	2	4	38	38	0
	Laser	7	0	7	88	6	82
	MPEC	6	2	4	129	0	129
	PDT	41	8	33	1,464	1,040	424
	RFA	11	1	10	463	292	171
	Total*	92	11	81	3,011	1,456	1,555
Surgical	Esophagectomy	8	3	5	198	198	0
Total*		97	11	86	3,209	1,654	1,555

*These totals include comparative studies that are included under each separate treatment modality.
APC=argon plasma coagulation; BE=Barrett's esophagus; EMR=endoscopic mucosal resection; HGD=high grade dysplasia; MPEC=multipolar electrocoagulation; PDT=photodynamic therapy; RFA=radiofrequency ablation.

Quality of included studies

Overall, the quality of the evidence reviewed was low. Only 11 of 97 studies were comparative, and of these, 5 studies were observational (i.e., cohort studies). Because the allocation of patients to each treatment group was not controlled bias may have been introduced. Furthermore, the methods were often poorly reported, with information missing or inconsistently reported across patient groups.

Although 6 high quality RCTs were identified, the evidence was limited to 2 comparisons: APC vs MPEC and APC vs PDT. The studies included only a small number of patients and had only short follow-up periods.[45] A meta-analysis could not be performed because the types of patients and the treatment protocols varied across studies.

Most of the included studies were non-comparative case series or single-arm clinical trials. Across studies of PDT, the protocols employed, outcomes measured, and follow-up periods varied. This was also the case with the studies of other ablative techniques, where the number of treatment sessions differed and patients frequently received interventions in addition to the study treatment. For example, EMR was typically performed during endoscopies to confirm diagnosis of dysplasia, regardless of the treatment under investigation. And, if a treatment failed, patients often received other interventions. This was usually not taken into account when outcomes were reported. Consequently, the findings from these studies should be interpreted with caution.

Safety

Photodynamic therapy (PDT)

The type and frequency of adverse events reported for PDT varied with the photosensitizing agent used (see Appendix D, Table D1). In studies of PDT using porfimer sodium, no deaths, perforations, or bleeds were observed. The most common adverse events were photosensitivity (41%) and strictures (29%). Across all studies of PDT with ALA (30 mg/kg), no deaths, perforations, or bleeds were observed, no strictures were reported, and only a few patients experienced photosensitivity reactions. One patient undergoing PDT with ALA (60mg/kg) died of cardiac arrhythmia. In all studies of ALA, regardless of dose, the most commonly reported side effects were nausea and vomiting.

Other endoscopic techniques

No deaths were reported in any of the studies of other endoscopic therapies reviewed (see Appendix D, Tables D2 to D7). Significant, but non-fatal, complications, such as esophageal perforation, were seen mainly in patients who received APC (see Appendix D, Table D2). A small proportion of patients who underwent APC, EMR, RFA, laser ablation, or MPEC experienced bleeding that could be managed endoscopically (see Appendix D, Tables D2 to D7). Major bleeds requiring transfusion were reported with both APC and laser ablation. However, for both therapies, the incidence of these adverse events was small (< 1%).

Most studies involving ablative therapies reported cases of strictures. The highest rates were found in studies of PDT with porfimer sodium. They were fewer reports of strictures in studies of laser ablation, APC, MPEC, and RFA. No strictures were observed in patients undergoing EMR or cryoablation.

Chest pain and dysphagia or odynophagia were among the most commonly noted adverse events in studies of APC, cryoablation, and MPEC.

Esophagectomy

Across studies of esophagectomy, the pooled mortality rate was 1.2% (see Appendix D, Table D8). Esophagectomy was associated with more significant side effects, ranging from anastomotic leaks, and pulmonary or cardiovascular complications, to delayed gastric emptying. The stricture rate for esophagectomy was lower than that for PDT, but higher than those of the other treatments.

None of the studies reviewed assessed the relationship between adverse events and clinician experience.

Efficacy / effectiveness

Evidence of clinical benefit with photodynamic therapy and comparators

There are critical deficiencies in the current evidence base on treatments for Barrett's esophagus. The published studies do not give a clear indication of the superiority of one treatment over another and for which sub-groups of Barrett's patients.

Complete eradication of Barrett's esophagus or high grade dysplasia

Photodynamic therapy (PDT)

Barrett's esophagus

Ten of the 41 studies (see Appendix B, Table B1, Appendix E, Table 1) assessed reported the extent to which patients with Barrett's esophagus had a complete response (i.e., total eradication of metaplastic tissue) in 2 to 3 months after treatment with PDT using porfimer sodium or ALA (at 30 mg/kg or 60 mg/kg doses). Of patients who received porfimer sodium, 49.2% achieved a complete response after an average of 1.4 treatment sessions. For ALA, the complete response was lower (38.0%), regardless of the dose.

Regarding the efficacy or effectiveness of PDT relative to other treatments, 1 comparative study of porfimer sodium versus argon plasma coagulation (APC) was found that reported on complete response. Two months after treatment, there was a complete response in 15.4% of patients in both the PDT and the APC arm. Two RCTs of PDT with ALA were found, both of which had APC as the comparator, and reported outcomes at 2 to 3 months. In one of these, which used an ALA dose of 30 mg/kg, the complete response rate in the APC group was almost

double that of the PDT group. In the other study, which used ALA at a dose of 60 mg/kg, the complete response rates were similar.

In one cohort study comparing radiofrequency ablation (RFA) to PDT, no statistically significant difference in complete response between groups was found.

High grade dysplasia

Twenty two of the 41 studies assessed the extent to which high grade dysplasia was eradicated through PDT with porfimer sodium or ALA (see Appendix B, Table B1; Appendix E, Table E2). However, only 8 of these provided data on complete response at 2 or more months post-treatment. In the 2 porfimer sodium trials, 79.2% of patients achieved complete response, compared to 79.6% in the 6 trials of ALA. However, because the ALA doses varied across trials (30 mg/kg to 60 mg/kg), and the number of PDT sessions were different as well, it is difficult to draw any further conclusions.

Only 2 studies assessed the relative efficacy or effectiveness of PDT in patients with high grade dysplasia. The first, an RCT of PDT using porfimer sodium compared to argon plasma coagulation (APC), found no statistically significant difference in complete response rates between treatment groups. The second, a cohort study that involved 3 treatment groups: 1) PDT with ALA at 60 mg/kg, 2) endoscopic mucosal resection (EMR), and 3) both (EMR followed by PDT with ALA at 60 mg/kg), also reported no statistically significant difference between groups.

Other endoscopic techniques

Argon plasma coagulation (APC)

Nineteen studies reported on complete response within 3 months of treatment. In the 4 comparative trials, complete response was achieved in 70% of patients, compared to 54% in the comparator arm, which included PDT. The pooled weighted average complete response rate in the non-comparative studies was, however, 88.5% But patients who received argon plasma coagulation (APC) had more treatment sessions than those who received any of the comparator treatments (see Appendix B, Table B2; Appendix E, Table E3).

There was little information on complete response in patients included in studies using APC for eradicating high grade dysplasia. In the one study that provided such information within 3 months of treatment, the complete response rate was 85.7%.

Cryoablation

Evidence of the efficacy or effectiveness of cryoablation for Barrett's was limited to a single, non-comparative study in which metaplastic tissue was eradicated in 82% of patients after approximately 5 treatment sessions (see Appendix B, Table B3; Appendix E, Table E5). No information on treatment failures was reported. Findings were comparable to those from the single study of cryoablation in high grade dysplasia patients. Approximately 89% of patients

achieved a complete response through 4 sessions. Once again, non-response rates were not presented.

Thus, as with argon plasma coagulation (APC), complete response rates and the average number of sessions per patient were greater with cryoablation than with PDT.

Endoscopic mucosal resection (EMR)

Only 1 case study reported on outcomes within 3 months. In this case, the patient had a complete response (see Appendix B, Table B4; Appendix E, Table E7). In the 4 non-comparative studies, Barrett's was eradicated in 25% of patients over an average of 1.9 treatment sessions. In 2 of these comparative studies, all but 1 of 13 patients had complete responses.

Radiofrequency ablation (RFA)

Of the 11 studies (1 of which was comparative), only 4 (all non-comparative) reported on response within the first 3 months (see Appendix B, Table B7; Appendix E, Table E12). Complete response was achieved in 73.6% of patients. However, on average, it took more than 2 sessions per patient to achieve this. Only one study of RFA for high grade dysplasia was identified (see Appendix E, Table E13). It reported a complete response in 90% of patients after a single treatment session, a value considerably higher than that demonstrated after 1 PDT treatment in the non-comparative studies reviewed.

Laser ablation

Five of the 7 non-comparative studies using laser ablation for Barrett's esophagus reported on outcomes within 3 months (see Appendix B, Table B5; Appendix E, Table E9). Pooled complete response rate from these studies was 79.0%. Multiple sessions were needed to achieve this, ranging from a mean of 3 to 6.5 across studies. One study examined the use of laser ablation for high grade dysplasia, reporting a complete response in all patients after 6.5 treatment sessions (see Appendix E, Table E10).

Multipolar electrocoagulation (MPEC)

Two of the 7 MPEC studies (one comparative against argon plasma coagulation (APC), and the other non-comparative) reported outcomes within the first 3 months (see Appendix B, Table B6; Appendix E, Table E11). In the RCT, complete response within this time frame was similar between MPEC (88.5%) and APC (81.0%). In the non-comparative study of MPEC, the complete response rate was 56.0%. Again, multiple treatment sessions were required to achieve these results.

Esophagectomy

No studies reported the extent to which Barrett's esophagus or high grade dyplasia was completely eradicated in patients who underwent esophagectomy (see Appendix B, Table B8). (Although esophagectomy removes most of the esophagus, there is a possibility that the remaining tissue may harbour remnants of abnormal tissue.)

Recurrence

Photodynamic therapy (PDT)

Barrett's esophagus

None of the 41 studies of PDT with porfimer sodium examined recurrence of Barrett's esophagus following a complete response (see Appendix B, Table B1; Appendix E, Table E1). Only one study of PDT with ALA (at 30 mg/kg) assessed recurrence, reporting 0% recurrence of Barrett's esophagus following complete response during 24 months of follow-up.

High grade dysplasia

In the 2 studies that examined recurrence rates in patients who received PDT with porfimer sodium, high grade dysplasia recurred in almost half the patients (42%) (see Appendix B, Table B1; Appendix E, Table E2). No studies of PDT with ALA provided information on recurrence.

Argon plasma coagulation (APC)

The proportion of patients in which Barrett's esophagus recurred appeared to be considerably smaller with APC than with PDT. In the 8 studies reporting recurrence, Barrett's esophagus recurred in approximately 17% of patients. The findings were similar for patients with high grade dysplasia (see Appendix B, Table B2; Appendix E, Tables E3 and E4).

Cryoablation

None of the cryoablation studies assessed recurrence (see Appendix B, Table B3; Appendix E, Table E5).

Endoscopic mucosal resection (EMR)

No information on recurrence in patients who underwent EMR for Barrett's esophagus was found (see Appendix B, Table B4; Appendix E, Table E7). One EMR study of patients with high grade dysplasia assessed recurrence, reporting values comparable to those for argon plasma coagulation (APC) (approximately 17%).

Laser ablation

Two studies assessed recurrence in patients whose Barrett's esophagus had been completely eradicated (see Appendix B, Table B5, Appendix E, Table E10). The findings were similar to those for PDT, with Barrett's recurring in 45% of patients. None of the studies of laser ablation of high grade dysplasia presented information on recurrence.

Multipolar electrocoagulation (MPEC)

None of the studies of MPEC assessed recurrence (see Appendix B, Table B6, Appendix E, Table E11).

Radiofrequency ablation (RFA)

Two studies of RFA for Barrett's esophagus found no recurrence of metaplastic tissue in patients who initially had a complete response (see Appendix B, Table B7; Appendix E, Table

E12). However, none of the RFA studies involving patients with high grade dysplasia provided information on recurrence (see Appendix E, Table E13).

Esophagectomy

None of the studies assessed recurrence of high grade dysplasia in the remaining esophageal tissue post-esophagectomy (see Appendix B, Table B8).

Progression to esophageal cancer

Photodynamic therapy (PDT)

Barrett's esophagus

Two studies reported on progression to cancer. In one, using ALA, none of the 8 patients had progressed to cancer 18 to 30 months post-treatment. In the other PDT study, there was no cancer detected in patients who were followed up for 5 years after treatment (see Appendix B, Table B1, Appendix F, Table F1).

High grade dysplasia

Based on findings from the 4 non-comparative studies of PDT with porfimer sodium that assessed progression from high grade dysplasia to cancer, approximately 10% of patients developed esophageal cancer (see Appendix B, Table B1, Appendix F, Table F2). Similar results were demonstrated in the 2 studies of PDT with ALA at 60 mg/kg, with cancer occurring in 11% of patients. None of the studies of PDT with ALA at 30 mg/kg examined disease progression.

Argon plasma coagulation (APC)

None of the non-comparative studies of APC in patients with Barrett's esophagus assessed disease progression, but those involving patients with high grade dysplasia did (see Appendix B, Table B2, Appendix F, Tables F3 and F4). Results were similar to PDT, with cancer developing in approximately 14% of patients. Findings from the single RCT, which compared APC to multipolar electrocoagulation (MPEC) in patients with Barrett's esophagus, suggested that there was no difference in disease progression between the 2 treatments.

Cryoablation

Progression to cancer was not assessed in any of the cryoablation studies (see Appendix B, Table B3).

Endoscopic Mucosal Resection (EMR)

Of studies assessing EMR in patients with Barrett's esophagus or high grade dysplasia, only one provided information on progression to cancer (see Appendix B, Table B4, Appendix F, Table F5). It involved patients with high grade dysplasia, none of whom developed cancer during a 12-month follow-up period.

Laser ablation

In the one laser ablation study that examined progression to cancer in patients with Barrett's esophagus, 5.6 % of patients developed esophageal cancer, a proportion slightly lower that that reported with PDT (see Appendix B, Table B5, Appendix F, Tables F6 and F7). With the exception of a single case report, no studies involving patients with high grade dysplasia assessed disease progression.

Multipolar electrocoagulation (MPEC)

None of the non-comparative studies of MPEC presented information on disease progression in patients with Barrett's esophagus or high grade dysplasia (see Appendix B, Table B6). But, as mentioned previously, 1 RCT comparing argon plasma coagulation (APC) to MPEC found no difference between treatment groups in the proportion of Barrett's patients who developed cancer.

Radiofrequency ablation (RFA)

Based on findings from the single relevant study, progression to cancer occurred in 2% of patients with high grade dysplasia who received RFA (see Appendix B, Table B7, Appendix F, Table F9).

Esophagectomy

Studies of esophagectomy were limited to patients with high grade dysplasia. According to the results of the 3 studies that examined disease progression, approximately 7% of patients went on to develop cancer, a value comparable to that reported for PDT (see Appendix B, Table B8, Appendix F, Table F8).

Summary of earlier health technology assessments of PDT for Barrett's esophagus

Several agencies have examined the evidence on photodynamic therapy for Barrett's esophagus.[15,30,46-49] The 2 most recent assessments are the California Technology Assessment Forum review, in 2005, and the National Institute for Health and Clinical Excellence (NICE) guidance issued in 2004.[15,30]

The California assessment concluded that, based on evidence from uncontrolled studies, photodynamic therapy for high grade dysplasia may be efficacious. However, adequate evidence to meet their criteria for safety, effectiveness and improvement in health outcomes was lacking.[30]

The NICE guidance concluded that photodynamic therapy seemed to be effective in removing high grade dysplasia in Barrett's esophagus, but that there was insufficient evidence that it prevented the development of esophageal cancer.[15] The NICE guidance also recommended that clinicians inform their patients about the uncertainties surrounding this therapy for Barrett's

esophagus; monitor the outcomes of patients who receive this treatment, and, consider having their patients participate in randomized clinical trials that are underway.

Cancer Care Ontario conducted a review of the evidence on the role of photodynamic therapy in the treatment of Barrett's esophagus with high grade dysplasia.[48] This 2006 guideline recommended that PDT should be considered a treatment option for patients with Barrett's esophagus with high grade dysplasia who were not able or were unwilling to undergo esophagectomy. However, the guideline did not assess the role of other endoscopic therapies.

A 2009 Cochrane Collaboration systematic review that compared esophagectomy to endoscopic therapies for early esophageal cancer and Barrett's with high grade dysplasia concluded that:

"...there are no randomised controlled trials to compare management options in this vital area, therefore trials should be undertaken as a matter of urgency. Current use of endotherapies in the care of patients with early cancer or high grade dysplasia of Barrett's oesophagus should be at the recommendation of the multi-disciplinary team involved in individual care. Properly conducted randomised controlled trials comparing surgery with endotherapies should be conducted before any conclusions can be drawn."[39]

Other assessments in progress

Two UK assessments are underway and expected to be published within the next year:

- the Centre for Reviews and Dissemination systematic review on PDT for Barrett's esophagus and various types of cancers is expected to be published in 2010.[50]
- The National Institute for Health and Clinical Excellence (NICE) guidance on ablative therapies for the treatment of Barrett's esophagus should be released in 2010.[51]

Important trials are also ongoing in the US and UK. These trials will address some of the gaps in the current evidence on the natural history of Barrett's esophagus, the benefits of surveillance, and the effectiveness of drug therapy to prevent progression to cancer.

- The Barrett's Esophagus Study (BEST) trial is examining the factors that affect the prevalence and incidence of low grade dysplasia, high grade dysplasia and esophageal cancer in patients with Barrett's esophagus.[52]
- The Aspirin Esomeprazole Chemoprevention (AspECT) trial is assessing whether long-term reflux suppression with a proton pump inhibitor, combined with aspirin, can prevent the development of esophageal cancer in patients with Barrett's esophagus.[53]

- A second UK trial, the Barrett's Oesophagus Surveillance Study (BOSS) trial is comparing the impact of endoscopic surveillance to no surveillance on mortality and the the development of esophageal cancer.[54]

Unfortunately, it will be some years before the final results of these trials are known.

Part III: Social & ethical implications of photodynamic therapy for Barrett's esophagus

No studies have assessed quality of life measures before and after photodynamic therapy for Barrett's esophagus. The long period of photosensitivity (4 to 6 weeks) with porfimer sodium may be burdensome for patients and their families, but how much of a burden is not known. For younger patients, the restrictions due to photosensitivity might also mean time off work, reduced productivity, and possibly loss of income. Studies of patients' preferences for the various treatment options and for endoscopic surveillance are also lacking.

The 2004 National Institute for Health and Clinical Excellence (NICE) guidance advises clinicians to inform their patients about the uncertainties of the long term effects of PDT.[15,55] The natural progression and regression of Barrett's esophagus and dysplasia are also not fully known. And, current screening technologies cannot adequately identify those most at risk for developing esophageal cancer – particularly in patients with no or low grade dysplasia.

Photodynamic therapy is provided in specialist, tertiary care centres. As with other types of specialty care, patients in rural or remote areas of Alberta may have more difficulty accessing this treatment.

Part IV: Economic and fiscal considerations

Research questions

The main question to be addressed in the economic component of this assessment was:

- Is photodynamic therapy for Barrett's esophagus less costly than standard procedures, and, if not, do the benefits of using PDT outweigh its cost?

Specifically, the economic analysis was to include:

- Unit cost estimates, including physician billings, hospitalization or facility operational costs, other service costs and capital costs, for the procedure as well as related health services
- Costs of services avoided within a reasonable period of time
- Cost comparisons (effectiveness or utility analyses) of new technology in comparison to standard technology
- Estimates of patient and public demand, including prevalence and incidence of condition(s); utilization rates of standard or alternative treatments, where data exist; and estimates of the use of the new technology taking into account service capacity, where feasible, as well as appropriate clinical indicators for use
- Total costs based on utilization estimates
- Potential for transfer of service and funds from existing services being replaced or reduced in usage, as well as the impact on the health system of such transfers, if possible.

Methods

Literature search

Published economic evaluations of PDT for treating Barrett's esophagus were obtained from the broader literature searches for the project (see Appendix A). Additional searches were run using the bibliographic databases PubMed and EconLit as a further check for published studies. The keywords used for this search were "ablative therapy", "photodynamic therapy", "Barrett's esophagus", "cost OR costs OR costing", "economics", "cost-benefit analysis" and "cost analysis".

Selection of relevant studies

Inclusion criteria used for this economic review were: relevant English language publications, published within the last 6 years.

Critical appraisal

The economic studies were appraised using the criteria developed by Drummond et al.[56] These criteria assess both the validity of the study results and the appropriateness of the methodological approach used. The critical appraisal tool includes ten questions that allow the assessor to evaluate the rigor with which the methodology was undertaken and whether the results were appropriately reported. Each question is answered using 1 of 3 possible responses ("Yes", "No" or "Can't tell"). The results of the economic evaluations were then abstracted from each paper.

Results

A total of 38 studies were identified through the literature search. Of these, 5 met the inclusion criteria and were retrieved for detailed review.[57-61]

Review of existing economic analyses

Results of the critical appraisal of the 5 studies using Drummond's criteria are shown in Table 5. Two of these studies met the criteria fully.[57,61] The other 3 studies met most of the criteria.[58-60] Overall, the areas of strength were the appropriately posed analysis questions, comprehensive coverage of costs and consequences, the use of appropriate physical units, the use of discounting, the presentation of incremental analysis, and discussions of uncertainty. Areas of weakness were the inadequate descriptions of alternative treatments, poorly established evidence of treatment effectiveness, and the presentation and discussion of the findings of the analyses.

Table 5. Critical appraisal of economic studies of PDT for Barrett's esophagus

Author (year) country	Well defined analysis question	Comprehensive description of alternatives	Established program effectiveness	Identified all relevant costs and consequences	Accurately measured costs and consequences	Accurately valued costs and consequences	Discounting of costs and consequences	Incremental analysis of costs and consequences	Allowance for uncertainty in costs and consequences	Comprehensive presentation and discussion
Comay D, et al[57] (2007) Canada	Y	Y	Y	Y	Y	Y	Y	Y	Y	N
Hur C, et al[58] (2003) US	Y	Y	?	?	?	N	Y	Y	Y	N
Inadomi JM et al.[59] (2009) US	Y	N	?	Y	Y	Y	Y	Y	Y	Y
Ragunath K, et al[60] (2005) UK	Y	Y	Y	Y	Y	Y	?	Y	?	Y
Vij R et al[61] (2004) US	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y

Y: Yes, criteria met ; **N:** No, criteria not met; **?:** Can't tell from the information provided in the study.
Criteria developed by Drummond et al.[56]

Summary of published economic analyses

There are relatively few published economic evaluations of PDT for treating Barrett's esophagus. This may be because the use of PDT is a fairly new treatment for HGD in Barrett's esophagus, although it has been used for some time in the treatment of other conditions. The limited number of cost-effectiveness studies may also reflect the fact that treating Barrett's esophagus itself is a recent concern. Improved diagnostic tools, increased surveillance, and a better understanding of disease progression, along with an apparent increase in the incidence of esophageal adenocarcinoma may partly explain the recent focus on treatments for HGD in Barrett's esophagus.

The results of the economic evaluations are summarized in Table 6. Four of the analyses reviewed in this paper have either not included a "do nothing" approach, or it has been left to the reader to "assume" which approach is the "do nothing" comparator (often this is the "surveillance only" approach).[57,58,60,61] Comay et al acknowledge the presence of other

treatment modalities and provide rationale for the lack of comparators.[57] One analysis compares several ablative techniques in combination.[59]

Most of the studies reported incremental cost-effectiveness ratios (ICERs). An ICER specifies how much it would cost to gain one additional "quality-adjusted life year" (QALY). The QALY combines the length of life gained as a result of an intervention with the quality of that life, and is often used to compare the cost-effectiveness of competing interventions or technologies.

Various measures are used to determine utility scores attributed to the comparators, including direct utility scores obtained from patients, utility scores from "similar" conditions, and utility scores from the literature. This variability has contributed to the limited "generalizability" of results from the different studies.

Only one of the papers reviewed took a "societal perspective", but it has significant methodological flaws associated with cost and consequence validation.[57] An analysis from the societal perspective is more complex and time consuming, but it does provide useful information and may be useful considering the condition being assessed. Photodynamic therapy, and most of the other endoscopic approaches for treating HGD in Barrett's esophagus, are mainly outpatient procedures, and much of the post-treatment care will be either "self-provided" or provided by family members. Taking account of indirect costs may significantly alter the procedure's costs; either negatively or positively. In addition, esophagectomy is a major surgical procedure requiring post-operative hospitalization and recovery. Return to work, for example, may be expedited with the use of endoscopic procedures, therefore further reducing their social costs compared to esophagectomy.

Several of the papers reviewed dealt inadequately with the issue of discounting. While most papers provided for a 3% discount rate only one paper justified this rate.[60] Discounting is necessary to account for future cost and benefit streams and when a percentage value is provided it should be justified. Comay et al justified the discount rate they used as in accordance with "Canadian guidelines", which is appropriate given the context of a Canadian analysis.[57] Had the other studies used a similar approach the validity and reliability of the economic analyses would have improved.

All the studies found that when comparing PDT, surveillance, and esophagectomy for patients with Barrett's esophagus with HGD, PDT was the more cost-effective treatment modality. Ragunath et al noted that PDT outperformed argon plasma coagulation in terms of effectiveness, but that the added effectiveness came with an additional monetary cost.[60,60] In fact, in 2 of the studies comparing PDT to surveillance and esophagectomy, direct costs were higher with PDT than with the comparators.[58,61] The other 2 papers are more recent and both report a lower monetary cost for PDT compared to esophagectomy.[57,60] These 2 studies included surveillance as part of the PDT treatment follow-up, and a possible explanation for the cost differences may be the reduced costs of follow-up surveillance.

Incremental cost-effectiveness ratios from these studies are shown in Table 6. It is difficult to reach any conclusions regarding the use of PDT in comparison to other treatments for dysplasia in Barrett's esophagus. First, the costs per QALYs calculated from the data of Inadomi et al for HGD and LGD are very high.[59] This is because the differential QALY gain is very small (0.02 and 0.5), while there is a significant difference in cost. In this case, a cost minimization analysis would conclude that APC would be the better option. While the table indicates that PDT (with associated surveillance) has been compared to several viable treatment options for this condition the results appear both in favour of PDT (PDT dominant) and against PDT (higher dollar values per QALY attained). This diversity is seen across studies that compare the same comparator treatments. For example, Comay et al found PDT to be dominant over esophagectomy, whereas Vij et al report PDT to be considerably more expensive for the QALYs gained.[57,61]

A possible explanation for these findings lies in the model designs presented in each study. While the treatment of esophageal dysplasia may not be complex, the condition itself and the resulting possible treatment outcomes can be complex. Treatments can have several outcomes, including: complete response, partial response, minimal or no response, or disease progression. And, the natural history of Barrett's esophagus must also include the possibilities of relapse, regardless of the initial response. For example, a complete response may revert back to dysplasia at some point, at which time treatment must be re-initiated. Furthermore, disease progression will complicate the treatment process and add subsequent costs.

A model that is designed to assess costs for treatment options must consider the variety of all treatment modalities used. It is not uncommon for the same patient to be treated multiple times for their condition and treatment may include several treatment modalities. A model designed to assess effectiveness and cost-effectiveness must be complex and comprehensive to capture the vagaries of the disease, its natural history and the various treatment options. The models presented in these studies lack both complexity and comprehensiveness and do not adequately inform decision makers.

Table 6. Incremental cost-effectiveness ratios (ICERs) of PDT for Barrett's esophagus vs alternative treatments

Study	PDT vs SURV	PDT + SURV vs RFA + SURV	PDT + SURV vs APC + SURV	PDT + SURV vs ESO	PDT + ESO vs ESO
Comay D, et al[57] (2007) **Canada**	CDN$879 /QALY	-	-	**PDT dominant**	
Hur C, et al[58] (2003) **US**	US $12,363 /QALY	-	-	PDT vs ESO US$3,273 /QALY	
Inadomi JM, et al [59] (2009) **US**	**HGD** -	**HGD RFA dominant**	**HGD** US$249,260/QALY	**HGD PDT dominant**	**HGD** -
	LGD -	**LGD RFA dominant**	**LGD** US$1,331,450/QALY-	**LGD** $72,750/QALY	**LGD** -
Ragunath K, et al [60] (2005) **UK**	-	-	- APC dominant at 4 months - PDT cost $621/inch reduction in Barrett's at 12 months	-	
Vij R, et al[61] (2004) **US**	-	-	-	US$47,459/QALY	If HGD after PDT US$17,520 /QALY

APC = argon plasma coagulation; ESO = esophagectomy; HGD = high grade dysplasia; ICERs = incremental cost effectiveness ratios; LGD = low grade dysplasia; PDT = photodynamic therapy; QALY = quality-adjusted life year; RFA = radiofrequency ablation; SURV =endoscopic surveillance. Dominant means cheaper & more effective (i.e., more QALYs for less $)

Development of the economic model

Existing decision models for PDT generally assume that a patient receives only one intervention, e.g., PDT or esophagectomy. The model developed for this project allows for the use of multiple treatment modalities which may be used at one or several points in the treatment pathway, depending on disease stage, recurrence rate and patient, as well as physician, preferences. In the model, patients are either monitored with endoscopic surveillance or are treated with argon plasma coagulation, cryoablation, endoscopic mucosal resection, laser ablation, multipolar electrocoagulation, photodynamic therapy or radiofrequency ablation or with esophagectomy. Patients are then monitored by scheduled endoscopies, the frequency of which is determined by current disease state as well as recent history. The failure of any of the endoscopic therapies, either initially or due to high-grade dysplasia recurrence, is followed by the application of one of the other endoscopic therapies. This process continues until all endoscopic therapies have been tried, at which point failure of the last endoscopic treatment precipitates an esophagectomy. By evaluating each treatment in this manner, cost and efficacy/effectiveness comparisons were made in the context of complementary and overlapping technologies.

A Markov model was constructed using TreeAge Pro software. In this model, patients diagnosed with Barrett's esophagus are treated initially with argon plasma coagulation, cryoablation, endoscopic mucosal resection, laser ablation, multipolar electrocoagulation, photodynamic therapy, radiofrequency ablation or esophagectomy. Patients can undergo transitions between different health states depending on the natural history of the disease and the efficacy of the treatment received. The health states represented in the model include: no Barrett's, Barrett's without dysplasia, Barrett's with low grade dysplasia, Barrett's with high grade dysplasia, early stage esophageal cancer, late stage esophageal cancer and death. Patients with high grade dysplasia and those with an incomplete response following treatment (high or low grade dysplasia) may undergo additional ablative therapies. Ablative treatment options remain available until cancer is diagnosed, an esophagectomy is performed, or the patient dies.

The effect of misdiagnosis on cost and effectiveness of patient care is also incorporated in this model, by making treatment outcomes dependent on the actual health state while making treatment choice dependent on the perceived health state of the patient. Since the perceived health state is evaluated at every endoscopy and treatment, the model allows for the correction of misdiagnosis.

The model uses clinical data from the synthesis of clinical studies described earlier in this report, supplemented by expert opinion (when published data was inadequate), and cost data provided by Alberta Health & Wellness. These data are presented in the Table 7 and Table 8.

The model for Barrett's esophagus assumes the following as the base case scenario:

- All patients start with Barrett's esophagus with high grade dysplasia.

- The first treatment a patient may receive is one of: endoscopic surveillance only, argon plasma coagulation, cryoablation, endoscopic mucosal resection, laser ablation, multipolar electrocoagulation, photodynamic therapy, radiofrequency ablation or esophagectomy.
- In the case of endoscopic surveillance, patients receive diagnostic endoscopies until a diagnosis of cancer. The frequency of the endoscopies is based on the American College of Gastroenterology guidelines.[29] The schedule depends on the past health state and frequency of endoscopies, as well as on the current health state.
- For each ablative therapy, a patient receives one or more treatment sessions. Each session occurs in a separate 3 month period and the number of sessions is randomly determined based on the average number of sessions for each modality as reported in the literature.
- Following successful ablative treatment, or if the maximum number of ablative treatments has been reached, patients undergo endoscopic surveillance based on the American College of Gastroenterology guidelines.[29] Additional ablative retreatment,

using a different modality selected from those not yet tried, is performed with a new diagnosis of Barrett's with dysplasia.

- If a patient receives an initial ablative treatment and it fails, additional ablative treatments are available, with the proviso that each ablative treatment is only selected once.
- The additional ablative treatment is randomly determined from the pool of ablative therapies that have not been tried. The number of sessions for each additional ablative therapy is randomly determined based on the average number of session for each modality as reported in the literature.
- The maximum number of ablative treatments (allowing for multiple sessions of each treatment) is 7, the total number of ablative therapies in the model.
- Esophagectomy is available after failure of ablative therapy.
- After esophagectomy, performed as either the initial treatment strategy or as a result of the failure of the ablative treatment strategy, patients undergo endoscopic surveillance based on the American College of Gastroenterology guidelines.[29]
- Following esophagectomy, the model continues until a diagnosis of cancer or death occurs.

Table 7. Summary of variables included in the economic model

Model variable	Value	Range	Reference (Level of evidence※)
Annual rates of disease progression			
GERD to Barrett's	0.1	0.01 – 0.25%	[62](2c) [63](2b)
No dysplasia to low grade dysplasia	0.039	0.028 – 0.060	[16](2a) [64](2b) [65](2b)
Low grade dysplasia to high grade dysplasia	0.025	0.005 – 0.05	[65](2b) [66](2b) [67](2c)
No dysplasia to high grade dysplasia	0.009	0.006 – 0.01	[64](2b) [68](2c) [65](2b)
No dysplasia to cancer	0.005	0.0020 – 0.020	[11](5) [59](#) [68](2b)
Low grade dysplasia to cancer	0.006	0.002 – 0.05	[16](2a) [66](2b) [67](2c)
High grade dysplasia to cancer	0.099	0.077 - 0.131	[16](2a) [69](2b)
Annual rates of disease regression			
No dysplasia to no Barrett's	0.021	0.001 – 0.024	[62](2c) [70]2b)
Low grade dysplasia to no dysplasia	0.11	0.089 – 0.14	[67](2c) [62](2c)
High grade dysplasia to low dysplasia	0.08	0.04 – 0.13	[70](2b) [69](2b)
High grade dysplasia to no dysplasia	0.09	0.01 – 0.15	[69](2b) [67,70](2b)
Rates of misdiagnosis			
Low grade dysplasia called high grade dysplasia	0.083	0.010 – 0.10	[71](2b) [72](5) [73](2b) [74](4)
Low grade dysplasia called cancer	0.050	0.010 – 0.10	[71](2b) [72](5) [73](2b) [74](4)
Low grade dysplasia called Barrett's	0.15	0.010 – 0.25	[71](2b) [72](5) [73](2b) [74](4)
High grade dysplasia called Barrett's	0.00	0.000 – 0.001	[71](2b) [72](5) [73](2b) [74](4)
High grade dysplasia called low grade dysplasia	0.12	0.01 – 0.20	[71](2b) [72](5) [73](2b) [74](4)
High grade dysplasia called cancer	0.11	0.010 – 0.20	[71](2b) [72](5) [73](2b) [74](4)
Cancer called low grade dysplasia	0.050	0.010 – 0.20	[71](2b) [72](5) [73](2b) [74](4)
Cancer called high grade dysplasia	0.18	0.010 – 0.20	[71](2b) [72](5) [73](2b) [74](4)
Cancer called Barrett's	0.00	0.000 – 0.001	[71](2b) [72](5) [73](2b) [74](4)

Table 7. Summary of variables included in the economic model

Model variable	Value	Range	Reference (Level of evidence※)
Efficacy of treatment for Barrett's			
Argon plasma coagulation			
Complete eradication of Barrett's	0.87	0.60 – 1.0	Table E3
Complete eradication of dysplasia	0.86	0.71 – 1.0	Table E4
Recurrence	0.17	0.071 – 0.21	Tables E3, E4
Progression to cancer	0.14	0.0 - 0.40	Tables F3, F4
Stricture	0.049	0.0 – 0.23	Table D2
Perforation	0.01	0.0 – 0.02	Table D2
Mortality from surgery to repair perforation	0.080	0.05 – 0.15	[75](4) [76](4) [77](4) [78](4)
Number of treatment sessions	2.6	1 - 6	Table B2
Cryoablation			
Complete eradication of Barrett's	0.82	0.73 – 0.91	Table E5
Complete eradication of dysplasia	0.89	0.75 – 1.0	Table E6
Recurrence	0.22	0.0 – 0.47	Tables E5, E6
Progression to cancer	0.060	0.030 – 0.080	Not reported
Stricture	0.0	0.0 - 0.031	[79](4), Table D3
Perforation	0.094	0.0 – 0.20	Table D3
Mortality from surgery to repair perforation	0.080	0.05 – 0.15	[75](4) [76](4) [77](4) [78](4)
Number of treatment sessions	4.5	1 - 8	Table B3
Endoscopic mucosal resection			
Complete eradication of Barrett's	0.84	0.67 – 1.0	Table E7
Complete eradication of dysplasia	0.93	0.86 – 1.0	Table E8
Recurrence	0.11	0.038 – 0.17	Tables E7, E8
Progression to cancer	0.14	0.13 – 0.16	Table F5
Stricture	0.057	0.043 – 0.27	Table D4
Perforation	0.019	0.0 – 0.046	Table D4
Mortality from surgery to repair perforation	0.080	0.05 – 0.15	[75](4) [76](4) [77](4) [78](4)
Number of treatment sessions	1.9	1 - 4	Table B4
Laser ablation			
Complete eradication of Barrett's	0.82	0.61 – 1.0	Table E9
Complete eradication of dysplasia	1.0	0.0 – 1.0	Table E10
Recurrence	0.18	0.13 – 0.26	Tables E9, E10
Progression to cancer	0.056	0.0 – 0.11	Tables F6, F7
Stricture	0.058	0.0 – 0.125	Table D5
Perforation	0.048	0.0 – 0.095	Table D5
Mortality from surgery to repair perforation	0.080	0.05 – 0.15	[75](4) [76](4) [77](4) [78](4)
Number of treatment sessions	4.5	1 - 6	Table B5
Multipolar electrocoagulation			
Complete eradication of Barrett's	0.89	0.85 – 0.96	Table E11
Complete eradication of dysplasia	0.89	0.85 – 0.96	*
Recurrence	0.050	0.0013 – 0.10	[80](4)
Progression to cancer	0.060	0.00 – 0.12	Table B6

Table 7. Summary of variables included in the economic model

Model variable	Value	Range	Reference (Level of evidence※)
Stricture	0.028	0.0 – 0.040	Table D6
Perforation	0.0	0.0 – 0.020	Table D6
Mortality from surgery to repair perforation	0.080	0.05 – 0.15	[75](4) [76](4) [77](4) [78](4)
Number of treatment sessions	3	2 - 7	Table B6
Photodynamic therapy			
Complete eradication of Barrett's	0.46	0.14 – 0.50	Table E1
Complete eradication of dysplasia	0.79	0.0 – 0.96	Table E2
Recurrence	0.11	0.07 – 0.14	Tables E1, E2
Progression to cancer	0.093	0.083 – 0.10	Tables F1, F2
Stricture	0.30	0.0 – 0.37	Table D1
Perforation	0.029	0.0 – 0.086	[81](4)
Mortality from surgery to repair perforation	0.080	0.05 – 0.15	[75](4) [76](4) [77](4) [78](4)
Number of treatment sessions	1.5	1 - 3	Table B1
Radiofrequency ablation			
Complete eradication of Barrett's	0.74	0.22 – 0.93	Table E12
Complete eradication of dysplasia	0.74	0.22 – 0.93	Table E13*
Recurrence	0.020	0.0 – 0.040	**
Progression to cancer	0.022	0.0 – 0.045	Table F9
Stricture	0.005	0.0 – 0.007	Table D7
Perforation	0.003	0.0 – 0.006	‡
Mortality from surgery to repair perforation	0.080	0.05 – 0.15	[75](4) [76](4) [77](4) [78](4)
Number of treatment sessions	2.5	1 - 5	Table B7
Esophagectomy			
Complete resection	1.0	0.82 – 1.0	Table B8
Recurrence	0.030	0.0 – 0.18	Table B8
Progression to cancer	0.05	0.0 – 0.25	[82](2b)
Stricture	0.080	0.0 – 0.13	Table D8
Mortality from surgery	0.016	0.00 – 0.020	Table D8
Health state utilities			
Gastroesophageal Reflux Disease	0.95	0.88 – 1.0	[83](2c)
Barrett's			
No dysplasia	0.95	0.78 - 0.98	[84](4) [85](2c)
Low grade dysplasia	0.85	0.82 - 0.88	[85](2c)
High grade dysplasia	0.77	0.74 – 0.81	[85](2c)
Esophageal cancer			
Early stage	0.79	0.61 – 0.87	[86](2c) [87,88](2c)
Late stage	0.55	0.47 – 0.60	[86,89](2c)
Endoscopic techniques			
Intense surveillance			[84](4)
Argon plasma coagulation			
< 4 weeks post treatment	0.93	0.78 - 0.99	[84](4)†
> 4 weeks post treatment	0.93	0.78 - 0.99	[84](4)†

Table 7. Summary of variables included in the economic model

Model variable	Value	Range	Reference (Level of evidence א)
Cryoablation			
< 4 weeks post treatment	0.93	0.78 - 0.99	[84](4)†
> 4 weeks post treatment	0.93	0.78 - 0.99	[84](4)†
Endoscopic mucosal resection			
< 4 weeks post treatment	0.93	0.78 - 0.99	[84](4)†
> 4 weeks post treatment	0.93	0.78 - 0.99	[84](4)†
Laser ablation			
< 4 weeks post treatment	0.93	0.78 - 0.99	[84](4)†
> 4 weeks post treatment	0.93	0.78 - 0.99	[84](4)†
Multipolar electrocoagulation			
< 4 weeks post treatment	0.93	0.78 - 0.99	[84](4)†
> 4 weeks post treatment	0.93	0.78 - 0.99	[84](4)†
Photodynamic therapy			
< 4 weeks post treatment	0.92	0.55 - 0.99	[84](4)†
> 4 weeks post treatment	0.92	0.55 - 0.99	[84](4)†
Radiofrequency ablation			
< 4 weeks post treatment	0.93	0.78 - 0.99	[84](4)†
> 4 weeks post treatment	0.93	0.78 - 0.99	[84](4)†
Esophagectomy			
3 months	0.72	0.69 - 0.73	[86](2c) [88](2c)
6 months	0.77	0.61 - 0.83	[90](2c) [88,91](2c)
9 months	0.80	0.77 – 0.83	[88](2c)
12 months	0.86	0.85 – 0.87	[88](2c)
3 years	0.73	0.71 – 0.76	[87,90](2c)

א See Appendix H for levels of evidence table; # Study is a cost-utility analysis so levels of evidence not applicable

* Assumes a response rate equivalent to that for eradication of Barrett's, since no information for dyplasia could be found

† Based on published utility scores for PDT. Assumes a higher minimum utility in patients who are not photosensitive during the first 4 weeks post treatment

δ personal communication (C. Wong, March 2009)

** Assumes same value as that for progression to cancer

Table 8. Estimated per procedure costs of treatment alternatives

Treatment costs (per session)	Base case value (2006 Cdn dollars)	Range (2006 Cdn dollars)	Reference (Level of evidence ✕)
Endoscopic surveillance	$638		[92,93](2c)§
Argon plasma coagulation			
Amortized fixed cost of laser source assuming 1000 procedures over 5 years	$26	$19 – $31	[94](3a)
Hospital costs and physician fees	$1,326		[92,93](2c)δ
Probe	$197	$171 - $303	[94](3a)
Total cost	$1,549		
Cryoablation			
Amortized fixed cost of laser source assuming 1000 procedures over 5 years	$27	$10 - $218	[94](3a)
Hospital costs and physician fees	$1,326		[92,93](2c)δ
Single use ablation catheter	$644	$358 - $930	[94](3a)
Total cost	$1,997		
Endoscopic mucosal dissection			
Hospital costs and physician fees	$1,326		[92,93](2c)δ
Injection needle, specialized knife and tissue collection kits	$254	$210 - $299	[36](3a)†
Total cost	$1,580		
Laser ablation			
Amortized fixed cost of laser source assuming 1000 procedures over 5 years	$95	$86 - $101	‡
Hospital costs and physician fees	$1,326		[92,93](2c)δ
Fiber	$650	$500 - $800	‡
Total cost	$2,071		
Multipolar electrocoagulation			
Amortized fixed cost of laser source assuming 1000 procedures over 5 years	$18	$11 - $25	[94](3a)
Hospital costs and physician fees	$1,326		[92,93](2c)δ
Probes	$317	$260 - $370	[94](3a)
Total cost	$1,661		
Photodynamic therapy			
Amortized fixed cost of laser source assuming 1000 procedures over 5 years	$95	$86 - $101	[40](3a) [57](3a)
Hospital costs and physician fees	$1,326		[92,93](2c)δ
Light diffusion catheter, centering balloon, fiber optic diffuser, and porfimer sodium††	$5,100	$4,200 - $6,600	Axcan, [40](3a) [57](3a)
Total cost	$6,521		
Radiofrequency ablation			
Amortized fixed cost of laser source assuming 1000 procedures over 5 years	$24	$14 - $34	[94](3a)
Hospital costs and physician fees	$1,326		[92,93](2c)δ
Centering balloon and ablation balloon	$1,185	$992 - $1,378	[94](3a)
Total cost	$2,535		
Esophagectomy			

Hospital costs and physician fees	$34,481	$23,951 - $129,735	AH&W administrative data

א See Appendix H for levels of evidence table

* Values adjusted for inflation using the Consumer Price Index and converted from US to Cdn dollars using Bank of Canada historical exchange rates for 2006 and inflation http://www.bankofcanada.ca/en/review/autumn06/r06-4-ed.html

§ Based on average cost of upper gastrointestinal endoscopy reported in the Health Costing in Alberta: 2006 Annual Report[92] and the physician fee code for esophagoscopy in the 2009 Schedule of Medical Benefits for Alberta[93]

δ Assumes cost equal to that of an ERCP (personal communication, C. Wong, March 2009) reported in the Health Costing in Alberta: 2006 Annual Report[92]

† Assumes costs equivalent to EMR since no cost information could be found

‡ Personal communication (W. Austin, April 2009)

AH&W=Alberta Health and Wellness

†† Porfimer sodium costs $2,200 per 75 mg vial (Axcan Pharma Inc.). A typical patient requires 2-3 vials per treatment based on a dosage of 2 mg/kg of body weight.

Results

Economic model

A baseline model was constructed using the mean values extracted from the literature, if available, or from expert opinion, if necessary. The model creates 100,000 consecutive 50-year old patients, with gender randomly determined. Each patient is "treated" in parallel using each of the comparator therapies as the initial treatment. The true patient health state is evaluated every three months, whereas the diagnosed (perceived) health state is evaluated during treatment and endoscopic surveillance only. Treatment decisions are based on the perceived health state and the randomly determined treatment outcomes, including all cause mortality, are based on the true health state. Treatment effectiveness, based on the utility of living in the current state, and costs are calculated every three months and their discounted values (3%) are accumulated. The results of the base case analysis are presented in Table 9.

The table shows the average discounted cost and effectiveness for each of the comparators. In addition, the incremental cost-effectiveness ratios (ICERs) are shown using surveillance as the baseline standard of care. For each comparator, the ICER specifies how much it would cost to gain one additional "quality-adjusted life year" (QALY) when compared to surveillance. The QALY integrates of the length of life gained as a result of an intervention with the quality of life resulting from the intervention, and is often used to compare the cost-effectiveness of competing interventions or technologies.

Table 9. Incremental cost-effectiveness ratios (ICERs)

	Cost ($)	Outcome (QALY)	ICER	Cost/QALY
SURV	6,239	4.59		$1,359
RFA	17,367	10.83	1,783	$1,604
MPEC	15,759	9.70	1,863	$1,625
EMR	13,486	7.58	2,424	$1,779
APC	15,073	7.62	2,916	$1,978
Laser	20,829	9.46	2,996	$2,202
Cryo	20,325	8.75	3,386	$2,323
PDT	20,426	8.15	3,985	$2,506
ESO	39,600	7.49	11,504	$5,287

APC=argon plasma coagulation; Cryo=cryosurgery; EMR=endoscopic mucosal resection; ESO=esophagectomy; Laser=laser ablation; MPEC=multipolar electrocoagulation; PDT=photodynamic therapy; RFA=radiofrequency ablation; SURV=surveillance

Baseline costs, outcomes and incremental cost-effectiveness ratios for the treatment of Barrett's esophagus with high-grade dysplasia. All of the comparator therapies produce more health gain (QALYs) than surveillance but all therapies are also more expensive than

surveillance. The ICERs range from $1,783/QALY for radiofrequency ablation to $11,504 / QALY for esophagectomy, well within what is commonly deemed as an "acceptable" ICER range.

The base case analysis indicates that radiofrequency ablation, multipolar electrocoagulation and laser ablation are the most cost-effective endoscopic therapies, with each therapy yielding approximately 5 additional quality-adjusted life years. The remaining endoscopic therapies were as effective as esophagectomy, with the exception of cryoablation, which was more effective than esophagectomy, but less effective than best therapies.

Radiofrequency ablation appears to yield the largest health gain (10.83 QALYs) in this model. However, this could be because of the relatively short follow-up of patients in the RFA studies, because RFA is a relatively new treatment for Barrett's esophagus. A recurrence rate of 2% / year and a progression to cancer rate 2.2% has been used based on this short follow up. However, it is likely that more patients will develop cancer with time. Using an estimate of 10% for recurrence (which is closer to the event rate observed with PDT), the number of QALYs from RFA drops to 8.4 QALYs.

In this base case analysis, all of the interventions have ICERs below conventional thresholds. However, esophagectomy offers considerably worse value than the other technologies. Apart from ruling out esophagectomy, the results suggest that there is not a good efficiency rationale for constraining clinical options in this area. If the recurrence rate with RFA turns out to be as good as the early literature suggests it will provide the best value for money.

Probabilistic sensitivity analysis

The inherent uncertainty in the parameter estimates complicates the interpretation of the results of any complex model. One method for dealing with this uncertainty is to use deterministic sensitivity analysis. That is, each of the parameters is systematically varied between two extremes and many iterations of the model are run with each change. While this method does yield insight into the range of outcomes which could be expected with changes in the parameters, it does not give us a good sense of the probability that we would experience any of the outcomes. In addition, there are likely to be interactions between the various parameters which cannot be accounted for in a deterministic sensitivity analysis. Both of these problems can be addressed using a probabilistic sensitivity analysis, where model parameters are defined as distributions rather than as fixed values.[95] With each iteration of the model, a new random sample of each parameter is taken. Over many iterations, the value for each parameter averages out to the mean estimate. However, since all parameter distributions are resampled every iteration, the effects of parameter variability and parameter interactions are propagated through the model on each run. Over many iterations, this generates a cost and effectiveness surface for each therapy. Average cost and effectiveness for each therapy can be

calculated over all trials and incremental cost-effectiveness ratios can be determined. In addition, the incremental cost-effectiveness ratios can be calculated for each individual trial. Then, for a given cost / effectiveness ceiling, the fraction of each therapy which is cost-effective can be calculated. By varying the cost / effectiveness ceiling, so-called cost-effectiveness acceptability curves (CEAC) are generated. CEACs plot the percentage of simulations where the technology of interest was both cost-effective compared to standard care and below a given Cost / QALY ceiling ratio. This curve can be interpreted as the probability that the technology of interest will be cost effective at a given Cost / QALY level.[95]

For this analysis, it is assumed that the "true" value of a parameter lies somewhere within the range of values taken from the literature. Thus, all variables were modeled as Beta distributions using the minimum, maximum and mean values taken from the literature (where available) or estimated (where not available, as indicated). First, all variables were normalized so that the minimum value was 0.0 and the maximum value was 1.0. This was done by subtracting the minimum value from each of the minimum, mean and maximum values and then dividing these numbers by the new, adjusted maximum value. For example, the minimum and maximum values for the Cost of Disposables for PDT were $4,200 and $6,600 with a mean value of $5,100. This yields

Normalized Minimum Value= ($4,200 - $4,200) / ($6,600 - $4,200) = 0.0

Normalized Mean Value = ($5,100 - $4,200) / ($6,600 - $4,200) = 0.375

Normalized Maximum Value= ($6,600 - $4,200) / ($6,600 - $4,200) = 1.0

These values are then used to generate a Beta distribution, a distribution with 2 parameters, α and β. Estimates of α and β can be determined from the mean and the variance of the parameter using the method of moments[95], where

$\alpha = [(\text{mean})^2 * (1 - \text{mean}) / \text{variance}] - \text{mean}$

$\beta = \alpha * (1 - \text{mean}) / \text{mean}$

To simplify the modeling process, we have estimated the variance using the assumption that the Beta distribution approximates a normal distribution, with 95% of the distribution laying within +/- 1.96 standard deviations from the mean. Thus we estimated the variance for each variable as

$\text{Variance} \approx [(\text{Normalized Mean} - 0) / 1.96]^2$ for variables with a Normalized Mean <= 0.5

$\text{Variance} \approx [(1 - \text{Normalized Mean}) / 1.96]^2$ for variables with a Normalized Mean > 0.5

The Beta(α, β) distribution for each parameter is given in following tables along with the maximum, minimum and mean values used to generate the distributions. Values were calculated during each model iteration as

Variable value = Minimum value + Beta distribution * (Maximum value - Minimum value)

e.g. Cost of disposables, PDT = $4,200 + Random draw from Beta(2.03, 3.38) * ($6,600 - $4,200)

For some highly skewed variables (e.g. Cost of esophagectomy), the distributions were constructed after first taking the logarithm of the variable values. This was taken into account when calculating each random sample of the parameter during the probabilistic sensitivity analysis.

Table 10. Probabalistic sensivity analysis - Costs

Parameter	Distribution	Minimum Value	Maximum Value	Mean Value
Cost of esophagectomy[1]	Beta(2.8, 10.17)	23951	129735	34481
Cost of disposables, APC	Beta(2.89, 11.77)	171	303	197
Cost of disposables, CRYO	Beta(1.42, 1.42)	358	930	644
Cost of disposables, EMR	Beta(1.45, 1.48)	210	299	254
Cost of disposables, LASER	Beta(1.42, 1.42)	500	800	650
Cost of disposables, MPEC	Beta(1.62, 1.51)	260	370	317
Cost of disposables, PDT	Beta(2.03, 3.38)	4200	6600	5100
Cost of disposables, RFA	Beta(1.42, 1.42)	992	1378	1185
Fixed cost, APC	Beta(2.55, 1.82)	19	31	26
Fixed cost, CRYO[1]	Beta(2.28, 4.8)	10	218	27
Fixed cost, EMR[2]	Beta(1.42, 1.42)	19	31	26
Fixed cost, LASER	Beta(2.86, 1.9)	86	101	95
Fixed cost, MPEC	Beta(1.42, 1.42)	11	25	18
Fixed cost, PDT	Beta(2.86, 1.9)	86	101	95
Fixed cost, RFA	Beta(1.42, 1.42)	14	34	24
Hospital and physician fees, APC[3]	Beta(1.42, 1.42)	663	1989	1326
Hospital and physician fees, CRYO[3]	Beta(1.42, 1.42)	663	1989	1326
Hospital and physician fees, EMR[3]	Beta(1.42, 1.42)	663	1989	1326
Hospital and physician fees, LASER[3]	Beta(1.42, 1.42)	663	1989	1326
Hospital and physician fees, MPEC[3]	Beta(1.42, 1.42)	663	1989	1326
Hospital and physician fees, PDT[3]	Beta(1.42, 1.42)	663	1989	1326
Hospital and physician fees, RFA[3]	Beta(1.42, 1.42)	663	1989	1326
Cost of surgery to repair perforation[4]	Beta(2.80, 10.17)	23951	129735	34481
Cost of dilation of treat stricture[3]	Beta(1.42, 1.42)	319	957	638
Cost of visit with endoscopy[3]	Beta(1.42, 1.42)	319	957	638

[1]Distributions were constructed after first taking the logarithm of the variable values. [2]Costs not available. Values were estimated to be equal to that of "Fixed cost, APC"; [3]Cost variability not available. Maximum and minimum values represent mean value +/- 50%. [4]Costs not available. Costs were assumed to be the same as for esophagectomy.

Table 11. Probabilistic sensivity analysis - Probabilities, rates and treatment effects

Parameter	Distribution	Minimum Value	Maximum Value	Mean Value
Probability of eradication of Barrett's, APC	Beta(4.71, 2.27)	0.6	1	0.87
Probability of eradication of Barrett's, CRYO	Beta(1.42, 1.42)	0.73	0.91	0.82

Probability of eradication of Barrett's, EMR	Beta(1.59, 1.49)	0.67	1	0.84
Probability of eradication of Barrett's, ESO[1]	Beta(6.49, 2.5)	0.82	1	0.95
Probability of eradication of Barrett's, LASER	Beta(1.87, 1.61)	0.61	1	0.82
Probability of eradication of Barrett's, MPEC	Beta(2.08, 3.64)	0.85	0.96	0.89
Probability of eradication of Barrett's, PDT	Beta(26.43, 3.3)	0.14	0.5	0.46
Probability of eradication of Barrett's, RFA	Beta(6.97, 2.55)	0.22	0.93	0.74
Probability of eradication of dysplasia, APC	Beta(1.61, 1.5)	0.71	1	0.86
Probability of eradication of dysplasia, CRYO	Beta(2.18, 1.71)	0.75	1	0.89
Probability of eradication of dysplasia, EMR	Beta(1.42, 1.42)	0.86	1	0.93
Probability of eradication of dysplasia, ESO[2]	Beta(6.49, 2.5)	0.82	1	0.95
Probability of eradication of dysplasia, LASER[2]	Beta(1.87, 1.61)	0.61	1	0.82
Probability of eradication of dysplasia, MPEC[2]	Beta(2.08, 3.64)	0.85	0.96	0.89
Probability of eradication of dysplasia, PDT	Beta(13.87, 2.98)	0	0.96	0.79
Probability of eradication of dysplasia, RFA	Beta(6.97, 2.55)	0.22	0.93	0.74
Probability of death resulting from esophagectomy	Beta(11.49, 2.87)	0	0.02	0.016
Probability of misdiagnosing high-grade dysplasia as low-grade dysplasia	Beta(2.48, 1.8)	0.01	0.2	0.12
Probability of misdiagnosing high-grade dysplasia as no dysplasia[1]	Beta(3.36, 30.22)	0	0.001	0.0001
Probability of misdiagnosing high-grade dysplasia as cancer	Beta(1.72, 1.55)	0.01	0.2	0.11
Probability of misdiagnosing low-grade dysplasia as high-grade dysplasia	Beta(12.57, 2.93)	0.01	0.1	0.083
Probability of misdiagnosing low-grade dysplasia as no dysplasia	Beta(2.55, 1.82)	0.01	0.25	0.15
Probability of misdiagnosing low-grade dysplasia as cancer	Beta(1.69, 2.11)	0.01	0.1	0.05
Probability of misdiagnosing cancer as high-grade dysplasia	Beta(28.32, 3.33)	0.01	0. 20	0.18
Probability of misdiagnosing cancer as low-grade dysplasia	Beta(2.82, 10.58)	0.01	0.2	0.05
Probability of misdiagnosing cancer as no dysplaisa[1]	Beta(3.36, 30.22)	0	0.001	0.0001
Probability of esophageal perforation during APC	Beta(1.42, 1.42)	0	0.02	0.01
Probability of esophageal perforation during CRYO	Beta(1.57, 1.77)	0	0.2	0.094
Probability of esophageal perforation during EMR	Beta(1.84, 2.62)	0	0.046	0.019
Probability of esophageal perforation during LASER	Beta(1.48, 1.45)	0	0.095	0.048
Probability of esophageal perforation during MPEC[1]	Beta(1.42, 1.42)	0	0.02	0.01
Probability of esophageal perforation during PDT	Beta(2.21, 4.34)	0	0.086	0.029
Probability of esophageal perforation during RFA	Beta(1.42, 1.42)	0	0.006	0.003
Probability of death due to surgery to repair perforation	Beta(2.39, 5.57)	0.05	0.15	0.08
Probability of stricture following APC	Beta(2.81, 10.38)	0	0.23	0.049
Probability of stricture following CRYO[1]	Beta(3.06, 15.92)	0	0.031	0.005
Probability of stricture following EMR	Beta(3.54, 53.9)	0.043	0.27	0.057
Probability of stricture following ESO	Beta(3.17, 1.98)	0	0.13	0.08
Probability of stricture following LASER	Beta(1.6, 1.84)	0	0.125	0.058
Probability of stricture following MPEC	Beta(5.57, 2.39)	0	0.04	0.028
Probability of stricture following PDT	Beta(12.54, 2.93)	0	0.37	0.3
Probability of stricture following RFA	Beta(6.15, 2.46)	0	0.007	0.005

[1]Variability data not available. Mean value estimated. [2]Variability data not available. Values estimated to be equal to the respective probabilities of the eradication of Barrett's.

Table 12. Probabilistic sensitivity analysis - Rates and treatment parameters

Parameter	Distribution	Minimum Value	Maximum Value	Mean Value
Endoscopic therapies tried before esophagectomy[1]	Beta(1.42, 1.42)	1	7	4
Proportion of male patients	Beta(9.68, 2.77)	0.5	1	0.889
Average treatments / patient, APC	Beta(2.29, 4.87)	1	6	2.6
Average treatments / patient, CRYO	Beta(1.42, 1.42)	1	8	4.5
Average treatments / patient, EMR	Beta(2.39, 5.57)	1	4	1.9
Average treatments / patient, LASER	Beta(5.57, 2.39)	1	6	4.5
Average treatments / patient, MPEC	Beta(2.87, 11.49)	2	7	3
Average treatments / patient, PDT	Beta(2.63, 7.89)	1	3	1.5
Average treatments / patient, RFA	Beta(2.03, 3.38)	1	5	2.5
Yearly rate of progression to cancer following APC	Beta(2.15, 3.99)	0	0.4	0.14
Yearly rate of progression to cancer following CRYO	Beta(2.86, 1.9)	0.03	0.08	0.06
Yearly rate of progression to cancer following EMR	Beta(2.23, 4.46)	0.13	0.16	0.14
Yearly rate of progression to cancer following ESO[2]	Beta(2.87, 11.49)	0	0.25	0.05
Yearly rate of progression to cancer following LASER	Beta(1.52, 1.46)	0	0.11	0.056
Yearly rate of progression to cancer following MPEC	Beta(1.42, 1.42)	0	0.12	0.06
Yearly rate of progression to cancer following PDT	Beta(2.64, 1.85)	0.083	0.1	0.093
Yearly rate of progression to cancer following RFA	Beta(1.47, 1.54)	0	0.045	0.022
No Barrett's to Barrett's no dysplasia, yearly rate.	Beta(2.03, 3.38)	0.01	0.25	0.1
No dysplasia to low-grade dysplasia, yearly rate.	Beta(2.18, 4.16)	0.028	0.06	0.039
No dysplasia to high-grade dysplasia, yearly rate.	Beta(7.89, 2.63)	0.006	0.01	0.009
No dysplasia to cancer, yearly rate.	Beta(3.03, 15.17)	0.002	0.02	0.005
Low-grade dysplasia to high-grade dysplasia, yearly rate.	Beta(1.69, 2.11)	0.005	0.05	0.025
Low-grade dysplasia to cancer, yearly rate.	Beta(3.44, 37.82)	0.002	0.05	0.006
High-grade dysplasia to cancer, yearly rate.	Beta(1.87, 2.72)	0.077	0.131	0.099
Yearly rate of recurrence of high-grade dysplasia following APC	Beta(6.06, 2.45)	0.071	0.21	0.17
Yearly rate of recurrence of high-grade dysplasia following CRYO	Beta(1.58, 1.79)	0	0.47	0.22
Yearly rate of recurrence of high-grade dysplasia following EMR	Beta(1.97, 1.64)	0.038	0.17	0.11
Yearly rate of recurrence of high-grade dysplasia following ESO	Beta(3.03, 15.17)	0	0.18	0.03
Yearly rate of recurrence of high-grade dysplasia following LASER	Beta(1.98, 3.17)	0.13	0.26	0.18
Yearly rate of recurrence of high-grade dysplasia following MPEC	Beta(1.45, 1.49)	0.0013	0.1	0.05
Yearly rate of recurrence of high-grade dysplasia following PDT	Beta(2.36, 1.77)	0.07	0.14	0.11
Yearly rate of recurrence of high-grade dysplasia following RFA	Beta(1.42, 1.42)	0	0.04	0.02
Yearly regression rate, high-grade dysplasia to low-grade dysplasia	Beta(1.69, 2.11)	0.04	0.13	0.08
Yearly regression rate, high-grade dysplasia to low-grade dysplasia	Beta(2.36, 1.77)	0.01	0.15	0.09
Yearly regression rate, low-grade dysplasia to low-grade dysplasia	Beta(1.85, 2.64)	0.089	0.14	0.11
Yearly regression rate, no dysplasia to no Barrett's	Beta(21.4, 3.21)	0.001	0.024	0.021

[1]Variability data not available. Mean value estimated

[2]Variability data not available. Minimum value set to 0.

Table 13. Probabilistic sensitivity analysis - Utilites

Parameter	Distribution	Minimum Value	Maximum Value	Mean Value
Utility following APC	Beta(6.15, 2.46)	0.78	0.99	0.93
Utility of living with Barrett's with high-grade dysplasia	Beta(1.77, 2.36)	0.74	0.81	0.77
Utility of living with Barrett's with low-grade dysplasia	Beta(1.42, 1.42)	0.82	0.88	0.85
Utility of living with Barrett's without dysplasia	Beta(17.65, 3.12)	0.78	0.98	0.95
Utility following CRYO	Beta(6.15, 2.46)	0.78	0.99	0.93
Utility following EMR	Beta(6.15, 2.46)	0.78	0.99	0.93
Utility of living with early-stage cancer	Beta(5.29, 2.35)	0.61	0.87	0.79
Utility at 3 months following esophagectomy	Beta(7.89, 2.63)	0.69	0.73	0.72
Utility at 9 months following esophagectomy	Beta(1.42, 1.42)	0.77	0.83	0.8
Utility at 6 months following esophagectomy	Beta(6.72, 2.52)	0.61	0.83	0.77
Utility at 12 months following esophagectomy	Beta(1.42, 1.42)	0.85	0.87	0.86
Utility at 36 months following esophagectomy	Beta(1.9, 2.86)	0.71	0.76	0.73
Utility following LASER	Beta(6.15, 2.46)	0.78	0.99	0.93
Utility of living with late-stage cancer	Beta(3.17, 1.98)	0.47	0.6	0.55
Utility following MPEC	Beta(6.15, 2.46)	0.78	0.99	0.93
Utility of living without Barrett's	Beta(2.55, 1.82)	0.88	1	0.95
Utility of palliative care	Beta(1.42, 1.42)	0.25	0.43	0.34
Utility following PDT	Beta(16.23, 3.07)	0.55	0.99	0.92
Utility of living with recurrent cancer	Beta(1.42, 1.42)	0.32	0.5	0.41
Utility following RFA	Beta(6.15, 2.46)	0.78	0.99	0.93
Utility following endoscopy[1]	Beta(30.22, 3.36)	0.9	1	0.99

[1]Variability data not available. Minimum value was estimated at 0.9. Mean value was estimated at 0.99.

Table 14. Probabilistic sensitivity analysis - Average costs, effectiveness & ICERS

Treatment	Cost	QALY	ICER
Surv	6852	5.01	
RFA	18718	10.81	2044
MPEC	17017	9.48	2273
EMR	15017	7.11	3876
APC	17506	7.37	4502
LASER	23146	8.52	4634
CRYO	21675	8.18	4677
PDT	22678	7.56	6203
ESO	40402	7.53	13295

Average costs, effectiveness and incremental cost-effectiveness ratios (ICER) from 100,000 runs of the model using probabilistic sensitivity analysis. The ICERs were calculated from the difference in average cost divided by the difference in average effectiveness (measured as quality-adjusted life years) between the comparator therapy and the baseline therapy, surveillance.

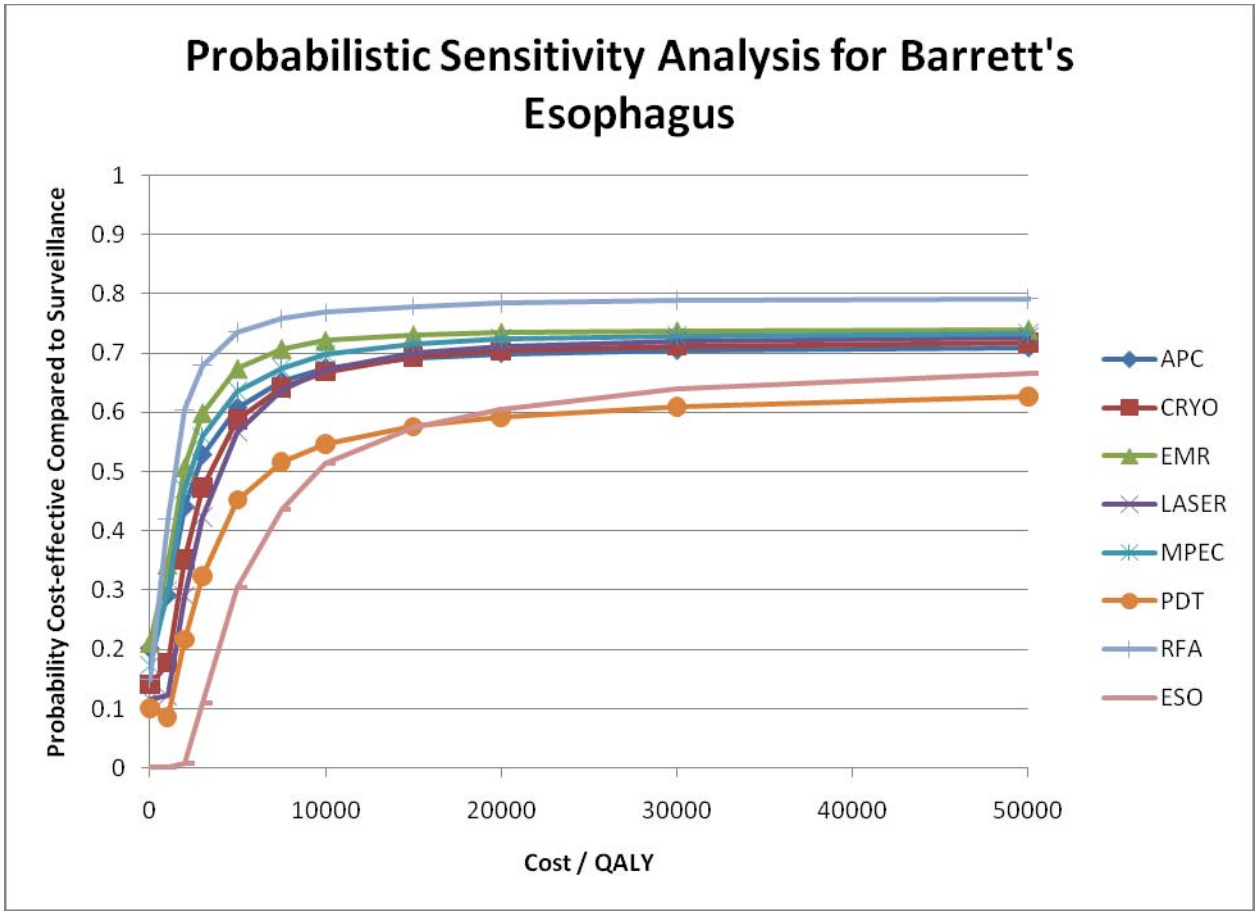


Figure 4. Probabilistic sensitivity analysis for treatments of Barrett's esophagus

Uncertainty in the model was explored by defining the model parameters as distributions rather than fixed values. For this analysis, it is assumed that the "true" value for each of the parameters was distributed around the mean value and between the lowest and highest values found from the literature search. The figure shows the results after 100,000 runs. For each run of the model, incremental cost and incremental effectiveness were calculated for each therapy using surveillance as the comparator. The data points represent the percentage of the simulations where the therapy was both cost-effective compared to surveillance and below a given Cost / QALY ceiling ratio. The intercept of each curve on the Probability Cost-effective axis represents the percentage of simulations where the therapy was cheaper than surveillance. The plateau value observed for each curve with increasing Cost / QALY represents the percentage of simulations where the therapy was more effective than surveillance.

The average costs and effectiveness seen with the probabilistic sensitivity analysis did not change the conclusions taken from the baseline case that all comparator therapies are both more effective and more expensive than surveillance. By aggregating the results of individual trials, the probability that any particular treatment was cost-effective for a given patient can be considered. These results show that as the cost / QALY ceiling increases, all of the comparators became more probable than not to be cost-effective on an individual basis, with the 50-50 point for each therapy at or below $10,000 / QALY.

Budget impact analysis

A budget impact analysis estimates the potential costs to a particular health care budget (provincial government, regional health authority, hospital, etc.) of adopting and using a new technology. This includes an analysis of how the incorporation of the new technology with existing treatments (as a replacement for, or in addition to existing treatments) will affect the overall costs of treating the condition.[96]

A budget impact analysis for the province of Alberta was conducted to estimate the potential costs of adopting and using PDT for the treatment of Barrett's esophagus with low or high grade dysplasia. Importantly, it was assumed that patients with Barrett's but no dysplasia would not receive PDT.

To estimate the number of patients in Alberta who may be treated for Barrett's with dysplasia in a fiscal year, two information sources were used: 1) Alberta Health and Wellness billing data and 2) published literature. First, all individuals with an outpatient or inpatient visit coded as K227 (Barrett's esophagus) using the ICD-10-CA system during the 2006/2007 fiscal year were identified. Since there is no specific code for Barrett's with dysplasia, rates from the published literature were used to estimate the proportion of patients with Barrett's who had low or high grade dysplasia. Using this approach, the number of patients with Barrett's in Alberta who had a diagnosis of Barrett's in 2006/2007 was estimated to be 2,000. Of these patients, 7% to 8%

were assumed to have Barrett's with dysplasia, based on a published, hospital-based study from the US. In the absence of billing data for PDT, the per case cost of a PDT treatment was estimated to be $6,521. This value was based on information obtained from literature, discussions with local specialists, and information from the manufacturer (Table 8). Therefore, if one assumes that all 150 Albertan patients receive treatment with PDT for Barrett's with dysplasia, the annual total cost would be $978,150. This is considered to be a conservative estimate. Given the lack of a clearly defined treatment pathway for Barrett's, it is not possible to determine in which patients PDT would be used in addition to other treatments, and in which patients PDT would replace other treatments.

Part V: Policy considerations

Implications of the clinical evidence:
The clinical studies reviewed for this report have been heterogeneous in the types of patients, stage of Barrett's esophagus, and the treatment(s) used. Moreover, the methodologies used and study reporting are relatively poor. Most the literature reports on the use of PDT or esophagectomy, and there is relatively little on the other newer ablative treatments, such as radiofrequency ablation and cryoablation. Photodynamic therapy has been shown to produce outcomes comparable to the other ablative techniques; however, typically this is achieved with a single PDT session as compared to multiple sessions of other ablative therapies. There is insufficient evidence to conclude that one ablative technology is more appropriate than another and for which patients. The literature on esophagectomy shows that it cannot be considered as being completely curative, since recurrences and progression to cancer after this surgery have been reported.

Current clinical practice:
The published studies show that patients are typically not treated with a single technology. In some cases the same treatment is applied a number of times, and a different treatment may be used if an earlier treatment fails. Because several of these technologies are relatively new, it is likely that this practice will continue. At present, there is no "gold standard" ablative treatment. In Edmonton, PDT for treating Barrett's esophagus was introduced over a year ago, and RFA more recently. Both of these have been integrated into the operations of the endoscopy suite at the Royal Alexandra Hospital where the procedures are done on an outpatient basis. Although PDT was introduced earlier in Calgary, the procedure is still performed as an inpatient procedure. For physicians, photodynamic therapy is not a particularly challenging procedure to perform. However, additional nursing staff training is required to ensure the photosensitivity procedures are in place. (Personal communication: Dr. Clarence Wong).

Patient preference:
Published evidence from patients with Barrett's esophagus indicates that there is a preference for endoscopic treatment over esophagectomy. However, which treatment patients prefer among the ablative options is not clear. One factor that differentiates PDT from the other ablative techniques is the photosensitivity that results from the treatment. With porfimer sodium (the only PDT agent available in Canada for Barrett's esophagus treatment), patients need to be protected from light for 4 weeks. The burden of this on patients and their familes has not been assessed; this might influence the uptake of PDT.

Funding issues:
The prevalence of Barrett's esophagus has been increasing over the past decade, and there is no reason to expect this trend to change. In Alberta, almost 2,000 patients had a diagnosis of Barrett's in 2006/07, of whom about 150 would be expected to have dysplasia. The average annual (conservative) cost of treating each patient was $6,521, for a total cost of

approximately one million dollars. This does not include the cost of drug therapy (PPIs), which all of these patients receive.

Given the absence of specific billing codes in Alberta for each ablative technique, it is difficult to estimate their actual use and cost in patients with Barrett's esophagus. It seems unlikely that the availability of PDT and the other ablative therapies will create a bigger patient pool. At the same time, it is not clear whether the existing pool of patients will receive increased service intensity (with the use of more ablative treatments per patient). This could result in increased expenditures. Nonetheless, the use of the ablative treatments may reduce the number of esophagectomies.

Part VI: Conclusions

This review examined PDT and 7 other interventions for the treatment of Barrett's esophagus with dysplasia. The safety profile of PDT is comparable to the other endoscopic therapies, but esophagectomy had higher mortality rates and higher rates of major adverse events. Clinical effectiveness (measured by complete eradication of dysplasia, recurrence of dysplasia and progression to cancer) ranged widely for each technology, due mainly to the heterogeneity of study designs and the variability in the reporting of results. Consequently, no one endoscopic therapy appears to dominate over another on the basis of clinical effectiveness.

The economic model developed for this project shows that all of the interventions have incremental cost-effectiveness ratios that are below conventionally accepted thresholds. The analysis indicates that, except for esophagectomy, which is the most costly (due mainly to hospitalization costs), the other therapies are relatively similar as far as value for money is concerned. As such, there is no good efficiency rationale for choosing one over another; in fact, a combination of endoscopic techniques may improve outcomes and value for money.

Appendices

Appendix A - Literature searches

Part 1. Photodynamic therapy (PDT) for the treatment of Barrett's esophagus or esophageal cancer
Searches run July 2008

1. PubMed
Total = 606 references

Search	Most Recent Queries	Time	Result
#25	Search #24 OR #23	13:39:50	606
#24	Search #22 Limits: Humans	13:23:42	585
#23	Search #22 AND (in process [sb] OR publisher [sb])	13:23:03	21
#22	Search #11 AND #21	13:22:38	659
#21	Search #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20	13:22:06	80948
#20	Search "Barrett's oesophagus"	13:21:02	803
#19	Search "oesophageal cancer*"	13:20:49	1403
#18	Search "esophageal cancer*"	13:20:41	7523
#17	Search Barrett's	13:20:32	4330
#16	Search "barrett epithelium"	13:20:26	32
#15	Search "barrett syndrome"	13:20:18	28
#14	Search esophagus	13:20:08	64117
#13	Search esophageal neoplasms	13:20:04	32717
#12	Search barrett esophagus	13:19:56	4295
#11	Search #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10	13:19:18	62377
#10	Search temoporfin	13:18:40	238
#9	Search hematoporphyrin derivative	13:18:33	1936
#8	Search dihematoporphyrin ether	13:18:17	801
#7	Search porphyrins	13:17:52	41066
#6	Search aminolevulinic acid	13:17:33	5031
#5	Search "photodynamic therapies"	13:17:19	19
#4	Search "photodynamic therapy"	13:17:11	6742
#3	Search photosensitizing agents	13:16:56	21357
#2	Search hematoporphyrin photoradiation	13:16:44	760
#1	Search photochemotherapy	13:16:34	9492

2. The Cochrane Library (issue 3, 2008)
Total = 37 refs
""photodynamic therapy" OR photochemotherapy OR hematoporphyrin photoradiation OR photosensitizing agents **in** Title, Abstract or Keywords **and** barrett esophagus OR esophageal neoplasms OR esophagus OR barrett's OR "oesophageal cancer*" OR "esophageal cancer*" **in** Title, Abstract or Keywords
Cochrane Reviews [0] | Other Reviews [0] | Clinical Trials [23] | Methods Studies [0] | Technology Assessments [7] | Economic Evaluations [7] | Cochrane Groups [0]

3. UK Centre for Reviews & Dissemination (DARE, NHS EED, HTA) databases
Total =17 refs

(photodynamic OR photochemotherapy OR photosensitizing OR aminolevulinic acid OR porphyrins OR hematoporphyrin OR dihematoporphyrin ether OR temoporfin) AND (Barrett esophagus OR esophageal neoplasms OR esophagus OR Barrett's OR esophageal OR oesphageal): 17 documents found

4. EMBASE (EMBASE 1988 to 2008 Week 30)

Total =784 refs

#	Searches	Results
1	photodynamic therapy.mp. or exp Photodynamic Therapy/	8786
2	limit 1 to human	6235
3	exp PHOTOCHEMOTHERAPY/	1255
4	limit 3 to human	1096
5	exp Hematoporphyrin Derivative/	914
6	limit 5 to human	572
7	exp HEMATOPORPHYRIN/	497
8	limit 7 to human	254
9	exp Aminolevulinic Acid/	2931
10	limit 9 to human	2058
11	exp PORPHYRIN/	7870
12	limit 11 to human	3265
13	exp Photofrin II/	557
14	limit 13 to human	329
15	exp TEMOPORFIN/	282
16	limit 15 to human	213
17	exp PHOTOFRIN/ or exp PHOTOFRIN I/	1219
18	limit 17 to human	887
19	exp "Tetrakis(3 Hydroxyphenyl)Chlorin"/	144
20	limit 19 to human	101
21	2 or 4 or 6 or 8 or 10 or 12 or 14 or 16 or 18 or 20	10509
22	exp Barrett Esophagus/	5230
23	limit 22 to human	4931
24	exp ESOPHAGUS/ or exp ESOPHAGUS CANCER/ or exp ESOPHAGUS CARCINOMA/	28191
25	limit 24 to human	24988
26	23 or 25	27097
27	21 and 26	784

5. CINAHL

Total = 64 refs

S3	S2 and S1	Search modes - Boolean/Phrase	64
S2	barrett esophagus or esophageal neoplasms or esophagus or barrett's or (oesophageal OR oesophagus)	Search modes - Boolean/Phrase	2970
S1	photodynamic therapy or (photochemotherapy OR hematoporphyrin radiation OR photosensitizing agents OR "photodynamic therapy")	Search modes - Boolean/Phrase	550

6. Web of Knowledge

Total = 598 refs

Topic=("photodynamic therapy" OR photochemotherapy OR hematoporphyrin OR aminolevulinic) AND Topic=("barrett's esophagus" OR "esophageal neoplasms" OR "esophageal cancer*" OR "barrett syndrome" OR "barrett's oesophagus") Timespan=All Years. Databases=SCI-EXPANDED, SSCI, A&HCI.

7. EconLit
Total = 2 refs
Photodynamic OR PDT

Part 2. Alternative treatments for Barrett's esophagus and early stage esophageal cancer

Initial searches run September 2008 (covering period 2006 to 2008)
Additional search to extend timelines, databases & terms run in December 2008
Limits: Human, English language, 5 years (2003-2008)

1. PubMed
Total = 565 refs

Search	Most Recent Queries	Time	Result
#120	Search #114 OR #117 OR #119 Limits: Publication Date from 2006 to 2009	16:42:20	565
#119	Search #115 AND in process [sb] Limits: Publication Date from 2006 to 2009	16:38:19	78
#117	Search #115 AND technology assessment, biomedical	16:28:41	3
#115	Search #106 OR #107 OR #108 OR #109 OR #110 OR #111 OR #112 Limits: Publication Date from 2006 to 2009	13:26:06	2479
#114	Search #106 OR #107 OR #108 OR #109 OR #110 OR #111 OR #112 Limits: Publication Date from 2006 to 2009, Humans, Clinical Trial, Meta-Analysis, Practice Guideline, Randomized Controlled Trial, Clinical Trial, Phase III, Clinical Trial, Phase IV, Comparative Study, Controlled Clinical Trial, Evaluation Studies, Multicenter Study, English	13:24:38	484
#113	Search Limits: Publication Date from 2006 to 2009, Humans, Clinical Trial, Meta-Analysis, Practice Guideline, Randomized Controlled Trial, Clinical Trial, Phase III, Clinical Trial, Phase IV, Comparative Study, Controlled Clinical Trial, Evaluation Studies, Multicenter Study, English	13:24:01	169892
#112	Search #62 AND #105 Limits: Publication Date from 2006 to 2009	13:22:56	548
#111	Search #62 AND #102 Limits: Publication Date from 2006 to 2009	13:22:48	986
#110	Search #62 AND #98 Limits: Publication Date from 2006 to 2009	13:22:42	826
#109	Search #62 AND #95 Limits: Publication Date from 2006 to 2009	13:22:36	84
#108	Search #62 AND #89 Limits: Publication Date from 2006 to 2009	13:22:30	62
#107	Search #62 AND #81 Limits: Publication Date from 2006 to 2009	13:22:25	1094
#106	Search #62 AND #71 Limits: Publication Date from 2006 to 2009	13:22:06	690
#105	Search #103 OR #104	13:20:50	202292
#104	Search radiotherapy	13:20:42	202292
#103	Search radiotherapy, adjuvant	13:20:38	21020
#102	Search #99 OR #100 OR #101	13:20:00	1614671
#101	Search chemotherapy	13:19:50	1614671
#100	Search chemotherapy, adjuvant	13:19:43	33306
#99	Search drug therapy	13:19:36	1549020
#98	Search #96 OR #97	13:19:15	5654
#97	Search oesophagectomy	13:19:05	5654
#96	Search esophagectomy	13:18:56	5654
#95	Search #90 OR #91 OR #92 OR #93 OR #94	13:17:36	162985
#94	Search coagulation	13:17:18	121432
#93	Search "laser thermocoagulation"	13:17:11	10
#92	Search "argon plasma coagulation"	13:17:02	458

#91 Search laser therapy	13:16:53	48421
#90 Search laser coagulation	13:16:48	8082
#89 Search #82 OR #83 OR #84 OR #85 OR #86 OR #87 OR #88	13:16:13	44178
#88 Search "radiofrequency ablation"	13:15:52	4548
#87 Search "radio frequency ablation"	13:15:44	329
#86 Search "radiofrequency catheter ablation"	13:15:34	1705
#85 Search "rf ablation"	13:15:21	1123
#84 Search radio waves	13:15:13	12388
#83 Search electrocoagulation	13:15:07	30812
#82 Search catheter ablation	13:15:00	13383
#81 Search #72 OR #73 OR #74 OR #75 OR #76 OR #77 OR #78 OR #79 OR #80	13:13:48	40104
#80 Search "submucosal resection"	13:13:05	82
#79 Search "submucosal dissection"	13:12:55	216
#78 Search EMR	13:12:45	1890
#77 Search "mucosal resection"	13:12:38	958
#76 Search intestinal mucosa/surgery	13:12:28	1247
#75 Search esophageal neoplasms/surgery	13:12:08	8892
#74 Search barrett esophagus/surgery	13:11:59	641
#73 Search mucous membrane/surgery	13:11:49	4968
#72 Search microsurgery	13:11:33	24072
#71 Search #63 OR #64 OR #65 OR #66 OR #67 OR #68 OR #69 OR #70	13:06:43	459788
#70 Search "endoscopic ultrasound"	13:06:11	1845
#69 Search monitoring [ti]	13:05:59	51520
#68 Search surveillance [ti]	13:05:52	17269
#67 Search ultrasonography	13:05:42	257945
#66 Search endosonography	13:05:35	5873
#65 Search esophagoscopy	13:05:25	10030
#64 Search mass screening	13:04:59	98748
#63 Search population surveillance	13:04:51	42193
#62 Search #54 OR #55 OR #56 OR #57 OR #59 OR #60 OR #61	13:04:03	36537
#61 Search "oesophageal cancer*"	13:03:28	1413
#60 Search "esophageal cancer*"	13:03:20	7579
#59 Search esophageal neoplasms	13:03:11	32876
#57 Search Barrett's	13:02:29	4367
#56 Search "barrett epithelium"	13:02:05	33
#55 Search "barrett syndrome"	13:01:56	28
#54 Search barrett esophagus	13:01:32	4338

Dec. 2, 2008
Total = 1156 refs

Search	Most Recent Queries	Time	Result
#71	Search #69 AND (case-control studies [mh] OR follow-up studies [mh] OR retrospective studies [mh]) Limits: Publication Date from 2003/01/01 to 2008/12/31, Humans, English	14:10:54	95
#69	Search #54 Limits: Publication Date from 2003/01/01 to 2008/12/31, Humans, Clinical Trial, English	14:04:04	504
#68	Search #8 AND #53 Limits: Publication Date from 2006/01/01 to 2008/12/31, Humans, Clinical Trial, Meta-Analysis, Practice Guideline, Randomized Controlled Trial, Case Reports, Clinical Trial, Phase I, Clinical Trial, Phase II, Clinical Trial, Phase III, Clinical Trial, Phase IV, Comparative Study, Controlled Clinical Trial, Evaluation Studies, Multicenter Study, Validation Studies, English	13:59:02	1
#67	Search #63 NOT (#64 OR #65 OR #66)	13:52:50	121
#66	Search #63 Limits: Publication Date from 2005/01/01 to 2005/12/31	11:11:44	346
#65	Search #63 Limits: Publication Date from 2004/01/01 to 2004/12/31	11:10:14	301
#64	Search #63 Limits: Publication Date from 2003/01/01 to 2003/12/31	11:07:01	294
#63	Search #57 OR #59 OR #60	10:53:01	1059
#60	Search #54 AND in process [sb]	10:44:20	120
#59	Search #8 AND #53 Limits: Humans, Clinical Trial, Meta-Analysis, Practice Guideline, Randomized Controlled Trial, Case Reports, Clinical Trial, Phase I, Clinical Trial, Phase II, Clinical Trial, Phase III, Clinical Trial, Phase IV, Comparative Study, Controlled Clinical Trial, Evaluation Studies, Multicenter Study, Validation Studies, English	10:39:44	6
#57	Search #54 Limits: Publication Date from 2003/01/01 to 2005/12/31, Humans, Clinical Trial, Meta-Analysis, Practice Guideline, Randomized Controlled Trial, Case Reports, Clinical Trial, Phase I, Clinical Trial, Phase II, Clinical Trial, Phase III, Clinical Trial, Phase IV, Comparative Study, Controlled Clinical Trial, Evaluation Studies, Multicenter Study, Validation Studies, English	10:37:07	933
#55	Search #54 AND technology assessment, biomedical	10:28:39	6
#54	Search #8 AND (#17 OR #26 OR #34 OR #40 OR #43 OR #47 OR #50 OR #53)	10:28:04	19312
#53	Search #51 OR #52	10:26:13	27911
#52	Search cryotherapy	10:26:05	19926
#51	Search cryosurgery	10:26:00	9944
#50	Search #48 OR #49	10:25:36	204617
#49	Search radiotherapy	10:25:27	204617
#48	Search radiotherapy, adjuvant	10:25:20	21400
#47	Search #44 OR #45 OR #46	10:25:02	1633803
#46	Search chemotherapy	10:24:48	1633803
#45	Search chemotherapy, adjuvant	10:24:43	33912
#44	Search drug therapy	10:24:35	1567010
#43	Search #41 OR #42	10:24:20	5735
#42	Search oesophagectomy	10:24:05	5735
#41	Search esophagectomy	10:23:54	5735
#40	Search #35 OR #36 OR #37 OR #38 OR #39	10:23:35	164484
#39	Search coagulation	10:23:21	122464

#38	Search "laser thermocoagulation"	10:23:11	11
#37	Search "argon plasma coagulation"	10:23:03	475
#36	Search laser therapy	10:22:51	48943
#35	Search laser coagulation	10:22:45	8158
#34	Search #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33	10:22:29	44911
#33	Search "radiofrequency ablation"	10:22:04	4668
#32	Search "radio frequency ablation"	10:21:56	336
#31	Search "radiofrequency catheter ablation"	10:21:44	1728
#30	Search "rf ablation"	10:21:32	1153
#29	Search radio waves	10:21:26	12612
#28	Search electrocoagulation	10:21:21	31266
#27	Search catheter ablation	10:21:15	13710
#26	Search #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25	10:20:51	39031
#25	Search "submucosal resection"	10:20:28	82
#24	Search "submucosal dissection"	10:20:20	230
#23	Search "mucosal resection"	10:20:10	971
#22	Search intestinal mucosa/surgery	10:19:59	1263
#21	Search esophageal neoplasms/surgery	10:19:49	8958
#20	Search barrett esophagus/surgery	10:19:37	649
#19	Search mucous membrane/surgery	10:19:26	5036
#18	Search microsurgery	10:19:15	24338
#17	Search #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16	10:18:42	466399
#16	Search "endoscopic ultrasound"	10:18:15	1902
#15	Search monitoring [ti]	10:18:01	52356
#14	Search surveillance [ti]	10:17:39	17564
#13	Search ultrasonography	10:17:30	261149
#12	Search endosonography	10:17:24	5997
#11	Search esophagoscopy	10:17:12	10097
#10	Search mass screening	10:17:02	100339
#9	Search population surveillance	10:16:55	43160
#8	Search #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7	10:16:31	36951
#7	Search "oesophageal cancer*"	10:15:57	1432
#6	Search "esophageal cancer*"	10:15:46	7685
#5	Search esophageal neoplasms	10:15:40	33201
#4	Search Barrett's	10:15:32	4453
#3	Search "barrett epithelium"	10:15:16	33
#2	Search "barrett syndrome"	10:15:07	28
#1	Search barrett esophagus	10:14:55	4394

2. Cochrane Library (issue 4 , 2008)
Total = 286 refs

Barrett esophagus (in title, abstract or keywords) OR esophageal neoplasms (in title, abstract or keywords), limited to 2003 to 2008, in all Cochrane databases
= 6 Cochrane reviews; 12 other reviews, 196 clinical trials, 1 methods studies, 26 technology assessments, 45 economic evaluations.

3. Centre for Reviews and Dissemination (CRD): HTA, NHS EED, DARE databases
Total = 23 refs
barrett esophagus OR "barrett's oesophagus" OR "barrett's esophagus" OR esophageal neoplasms OR "esophageal cancer*" OR "oesophageal cancer*" RESTRICT YR 2006 2009
Dec. 8, 2008
Total = 38 refs
barrett esophagus OR "barrett's oesophagus" OR "barrett's esophagus" OR esophageal neoplasms OR "esophageal cancer*" OR "oesophageal cancer*" RESTRICT YR 2003 2005

4. EMBASE 1988 – 2008 (Week 49) Dec. 8, 2008
Total =1042 references

Results	Search Type	Display
1	*Barrett Esophagus/dt, si, dm, th, rt, su [Drug Therapy, Side Effect, Disease Management, Therapy, Radiotherapy, Surgery]	1091
2	*Esophagus Cancer/dt, dm, su, rt, si, th [Drug Therapy, Disease Management, Surgery, Radiotherapy, Side Effect, Therapy]	3568
3	*Esophagus Carcinoma/dt, dm, su, rt, si, th [Drug Therapy, Disease Management, Surgery, Radiotherapy, Side Effect, Therapy]	3156
4	1 or 3 or 2	7646
5	limit 4 to (human and English language and yr="2003 - 2009")	2455
6	comparative study/ or controlled study/ or case control study/ or controlled clinical trial/	2803977
7	exp Case Study/	4035
8	exp Practice Guideline/	143169
9	Meta Analysis/	34296
10	8 or 6 or 7 or 9	2945737
11	10 and 5	1042

Appendix B - Evidence tables: included studies

Table B 1. Studies of photodynamic therapy (PDT) for Barrett's esophagus with/without dysplasia

Study authors (year published)	Cancer / Cell Type	Study Design	Patients	Intervention	Outcome Measures	Findings	Study quality
ALA 15mg/kg administered orally							
Comparative studies							
None							
Non-comparative studies							
Ortner MA, et al (2001)[97]	BE (7 patients) BE + LGD (7 patients)	Clinical trial Single centre Prospective *Countries:* Germany *Length of follow-up:* Mean: 32.6 months Range: 12 to 48 months	*Number of patients:* 14 *Gender:* Male: 12 Female:2 *Age:* Mean: 61.8 yrs *Prior treatments:* none reported *Length of Barretts:* not reported *Inclusion criteria:* none notable *Exclusion criteria:* Allergy to omeprazole Porphyria Previous esophageal cancer HGD Contraindications for endoscopy Clotting disturbances Pregnant or lactating	PDT *Drug:* 5-ALA *Dose:* 15mg/kg *Route of administration:* topical *Light source*: argon dye laser @632nm *Light dose:* 90 to 120 J/cm^2 *Time to photoactivation:* 1.5 to 2 hours *Treatment time:* not recorded *Number of sessions:* Mean: 1.4 sessions / patient *Co-interventions:* Omeprazole 80 mg/day for 2 months	*Outcomes:* Complete response of BE Complete response of LGD Partial response of BE *Adverse events*	*Outcomes:* Complete response of BE: - at 3 months: 3/14 patients (21%) - at 6 months: 4/14 patients (29%) Complete response of LGD: - at 3 months: 4/7 patients (57%) - at 6 months: 5/7 patients (71%) Partial response of BE: - at 3 months: 11/14 patients (79%) - at 6 months: 10/14 patients (71%) *Adverse events:* Chest pain and dysphagia: 2/13 patients (15%) Photosensitivity: 3/13 patients (23%) Strictures: 0/13 patients (0%) Hepatotoxicity: 0/13 patients (0%)	4
Ortner M, et al (1997)[98]	BE	Case series Single centre	*Number of patients:* 9 *Gender:* not reported *Age:* not reported	PDT *Drug:* 5-ALA *Dose:* 14 to 16 mg/kg	*Outcomes:* Complete response of BE	*Outcomes:* Complete response of BE at 2 months: 4/9 patients (44%)	4

Table B 1. Studies of photodynamic therapy (PDT) for Barrett's esophagus with/without dysplasia

Study authors (year published)	Cancer / Cell Type	Study Design	Patients	Intervention	Outcome Measures	Findings	Study quality
		Countries: Germany *Length of follow-up:* 2 months	*Prior treatments:* none reported *Length of Barretts:* not reported *Inclusion criteria:* none notable *Exclusion criteria:* none notable	*Route of administration:* topical spray *Light source*: argon dye laser @ 632nm *Light dose:* 180J/cm^2 *Time to photoactivation:* 1.5 to 2 hours *Treatment time:* 180 to 300 seconds *Number of sessions:* 1 session / patient *Co-interventions:* Omeprazole 40 mg 4 times daily for 2 months	Partial response of BE Non-response of BE *Adverse events*	Partial response of BE at 2 months: 3/9 patients (33%) Non-response of BE at 2 months: 2/9 patients (22%) *Adverse events:* Chest pain: occasionally Dysphagia, mild: occasionally	
ALA 30mg/kg administered orally							
Comparative studies							
Kelty CJ, et al. (2004)[45]	BE	RCT Single centre Prospective PDT vs. APC *Countries:* UK *Length of follow-up*: 24 months	*Number of patients:* 72 (PDT Group:35 patients; APC Group: 37 patients) <u>PDT Group</u> *Gender:* Male: 28 Female: 7 *Age:* Median: 61 yrs Range: 33 to 83 yrs <u>APC Group</u> *Gender:* Male: 30 Female: 7 *Age:* Median: 59 yrs Range: 28 to 79 yrs *Prior treatments:* none	PDT vs. APC <u>PDT Group</u> *Drug:* 5-ALA *Dose:* 30 mg/kg *Route of administration:* oral *Light source*: diode laser @ 633 nm *Light dose:* 85 J/cm^2 *Time to photoactivation:* 4 to 6 hours post ALA *Treatment time:* not reported *Number of sessions:* Median: 5 sessions Range: 1 to 5 sessions Max allowed: 5 sessions <u>APC Group</u> *Gas flow:* 2L/minute	*Outcomes:* Complete response of BE (assessed through endoscopy and 4 quadrant biopsy every 2 cm) Partial response of BE Number of treatments to achieve complete response of BE	*Outcomes:* Complete response of BE at 4 weeks: -PDT Group: 17/34 patients (50%) -APC Group: 33/34 patients (97%) Partial response of BE: -PDT Group: 17/34 patients (50%) -APC Group: 1/34 patients (3%) Number of treatments to achieve complete response of BE: <u>PDT Group</u> Median: 2 treatments Range: 1 to 4 treatments	1

Table B 1. Studies of photodynamic therapy (PDT) for Barrett's esophagus with/without dysplasia

Study authors (year published)	Cancer / Cell Type	Study Design	Patients	Intervention	Outcome Measures	Findings	Study quality
			reported *Length of Barretts:* PDT Group Median: 4 cm Range: 2 to 15 cm APC Group Median: 4 cm Range: 2 to 8 cm *Inclustion criteria:* none notable *Exclusion criteria:* none notable	*Power:* 65 watts *Number of sessions:* Median: 3 sessions Range: 1 to 5 sessions Max allowed: 5 sessions *Co-interventions:* none reported	*Adverse events*	APC Group Median: 3 treatments Range: 1 to 5 treatments *Adverse events:* PDT Group Nausea / vomiting: 11/34 patients (32%) Photosensitivity: 5/34 patients (15 %) Hypotension: 2/34 patients (6%) Chest pain: 1/34 patients (3%) Odynophagia: 1/34 patients (3%) Dysphagia secondary to strictures: 0/34 patients (0%) Elevated liver enzymes, mild: 4/34 patients (12%) Buried glands (4 week follow-up): 4/17 patients (24%) APC Group Nausea / vomiting; photosensitivity; hypotension; chest pain; elevated liver enzymes, mild: 0/34 patients (0%) Odynophagia: 32/34 patients (94%) Dysphagia secondary to strictures: 1/34 patients (3%) Buried glands (4 week follow-up): 7/33 patients (21%)	
Non-comparative studies							
Akroyd R, et al (2003)[99]	BE + LGD	Case series Single centre Prospective	*Number of patients:* 40 *Gender:* Male: 36	PDT *Drug:* ALA *Dose:* 30 mg/kg	*Outcomes:* Complete response of LGD	*Outcomes:* Complete response of LGD -at 1 month: 40/40 patients	4

Table B 1. Studies of photodynamic therapy (PDT) for Barrett's esophagus with/without dysplasia

Study authors (year published)	Cancer / Cell Type	Study Design	Patients	Intervention	Outcome Measures	Findings	Study quality
		Countries: UK *Length of follow-up:* Median: 53 months Range: 18 to 68 months	Female: 4 *Age:* Median: 61 yrs Range: 34 to 86 yrs *Prior treatments:* not reported *Length of Barretts:* Median: 6 cm Range: 3 to 18 cm *Inclusion criteria:* none notable *Exclusion criteria:* none notable	*Route of administration:* oral *Light source*: copper vapour laser @514nm *Light dose:* 60 J/cm^2 *Time to photoactivation:* 4 hours *Treatment time:* not reported *Number of sessions:* 1 session / patient *Co-interventions:* Omeprazole 20-40 mg/day Endoscopy at 1, 6, 12 months	Reduction of BE area *Adverse events*	(100%) -at 24 months: 38/38 patients (100%) -at 60 months: 15/15 patients (100%) Reduction of BE area: Median: 30% Range: 0 to 90% *Adverse events:* Buried glands: 1/40 patients (2.5%) Strictures: 0/40 patients (0%) Discomfort, duration ≤ 3 days: most patients Nausea and vomiting ≤ 24 hours: most patients Photosensitivity, mild (patient exposed to direct sun for several hours): 1/40 patients (2.5%)	
Ackroyd R, et al (1999)[100]	BE + LGD (3 patients) BE + HGD (4 patients)	Case series Single centre Prospective *Countries:* UK *Length of follow-up:* 28 months	*Number of patients:* 7 *Gender:* Male: 5 Female: 2 *Age:* Mean: 68.3 yrs Range: 49 to 83 yrs *Prior treatments:* not reported *Length of Barretts:* not reported *Inclusion criteria:* none	PDT *Drug:* ALA *Dose:* 30 mg/kg *Route of administration:* oral *Light source*: copper vapour laser @514nm or 630nm *Light dose:* Mean: 80 J/cm^2 Range: 50 to 100 J/cm^2 *Time to photoactivation:* 4 hours *Treatment time:* not reported	*Outcomes:* Complete response of BE Complete response of HGD Complete response of LGD	*Outcomes:* Complete response of BE -at 1 month: 1/7 patients (14%) -at 24 months: 1/7 patients (14%) Complete response of HGD -at 1 month: 4/4 patients (100%) -at 24 months: 4/4 patients (100%) Complete response of LGD -at 1 month: 3/3 patients	4

Table B 1. Studies of photodynamic therapy (PDT) for Barrett's esophagus with/without dysplasia

Study authors (year published)	Cancer / Cell Type	Study Design	Patients	Intervention	Outcome Measures	Findings	Study quality
* Information extracted for BE or HGD patients only			notable *Exclusion criteria:* none notable	*Number of sessions:* 1 session / patient *Co-interventions:* Omeprazole 20 mg/day	Reduction of BE area Survival *Adverse events:* No BE or HGD specific information available.	(100%) -at 24 months: 3/3 patients (100%) Reduction of BE area at 1 month: Mean: 44 % Range: 10 to 100% Survival -at 1 month: 7/7 patients (100%) -at 24 months: 7/7 patients (100%)	
Ackroyd R, et al (1999)[101] * * Information extracted for BE or HGD patients only	BE + LGD (1 patient) BE + HGD (4 patients)	Case series Single centre *Countries:* UK *Length of follow-up:* not reported	*Number of patients:* 5 *Gender:* not reported *Age:* not reported *Prior treatments:* not reported *Length of Barretts:* not reported *Inclusion criteria:* none notable *Exclusion criteria:* none notable	PDT *Drug:* ALA *Dose:* 30 mg/kg *Route of administration:* oral *Light source*: copper vapour laser @514nm *Light dose:* 1000J/cm^2 *Time to photoactivation:* 4 hours *Treatment time:* 1000 seconds of laser activation *Number of sessions:* 1 session / patient *Co-interventions:* none reported	*Outcomes:* Complete response of HGD Complete response of LGD Reduction in BE area *Adverse events:* none	*Outcomes:* Complete response of HGD at unknown follow-up: 4/4 patients (100%) Complete response of LGD at unknown follow-up: 1/1 patients (100%) Reduction in BE area: Mean: 48 % Range: 10 to 70 %	4
Mackenzie G, et al (2005)[102]*	BE + HGD	RCT Single centre Prospective	*Number of patients:*16 *Gender:* not reported *Age:* not reported	<u>PDT with red light</u> *Drug: 5*-ALA *Dose:* 30 mg/kg *Route of administration:*	*Outcomes:* Number of sessions reporting complete response of dysplasia	*Outcomes:* Number of sessions reporting complete response of dysplasia:	4

Table B 1. Studies of photodynamic therapy (PDT) for Barrett's esophagus with/without dysplasia

Study authors (year published)	Cancer / Cell Type	Study Design	Patients	Intervention	Outcome Measures	Findings	Study quality
* Patients thought to be included in Mackenzie et al. (2007) [103] (see Group C)		PDT (red light) vs. PDT (green light) *Countries:* not reported *Length of follow-up:* not reported	<u>PDT Red Light</u> *Number of patients:* not reported <u>PDT Green Light</u> *Number of patients:* not reported *Prior treatments:* EMR of nodular dysplasia in 4 patients *Length of Barretts:* not reported *Inclusion criteria:* none notable *Exclusion criteria:* none notable	oral *Light source*: 600nm laser *Light dose:* not reported *Time to photoactivation:* 4 hours *Treatment time:* not reported *Number of sessions:* Mean: 2.15 sessions / patient <u>PDT with green light</u> *Light source*: 520 to 570nm laser *Number of sessions*: Mean 2.15 sessions / patient Other details as above *Co-interventions:* Treatments preceded by EMR	*Adverse events:* none	-Red light: 4/17 sessions (24%) -Green light: 1/19 sessions (5%)	
ALA 40mg/kg administered orally							
Comparative studies							
None							
Non-comparative studies							
Peters F, et al (2005)[104]	BE + HGD	Case series Single centre *Countries:* Netherlands *Length of follow-up:* Mean: 30 months Range: 22 to 31 months	*Number of patients*: 16 patients *Gender:* Male: 12 Female: 4 *Age:* Mean: 69 yrs Range: 59 to 74 yrs *Prior treatments:* Diagnostic EMR for focal	PDT *Drug:* ALA *Dose:* 40 mg/kg *Route of administration:* oral *Light source*: KTP/Nd:Yag laser @ 600 nm *Light dose:* 100J/cm^2 *Time to photoactivation:* not reported *Treatment time:* not	*Outcomes:* Complete response of HGD (assessed through endoscopy with 4 quadrant biopsies every 2 cm) *Adverse events*	*Outcomes:* Complete response of dysplasia at: - at 3 months: 14 /18 patients (78%) - at 30 months: 10/18 patients (56%) *Adverse events:* Hematemesis: 1/20 patients	4

Table B 1. Studies of photodynamic therapy (PDT) for Barrett's esophagus with/without dysplasia

Study authors (year published)	Cancer / Cell Type	Study Design	Patients	Intervention	Outcome Measures	Findings	Study quality
			lesions *Length of Barretts: n*ot reported *Inclusion criteria:* Ineligible for or refused surgery *Exclusion criteria:* none notable	reported *Number of sessions:* Mean: 1 session / patient Range: 1 to 2 sessions / patient *Co-interventions:* Ranitidine 300 mg @ night for 1st week Omeprazole 40 mg twice daily for first week Esomeprazole 40 mg twice daily from 2nd week on		(5%) Hypotension: 2/20 patients (10%) Atrial fibrillation: 1/20 patients (5%) Buried glands (at mean =30 months): 8/15 patients (53%)	
Van Hillegerberg R, et al (2003)[105]	BE + HGD	Case report Single centre Retrospective *Countries:* Netherlands *Length of follow-up:* Mean: 6 months Range: 5 to 8 months	*Number of patients:* 2 *Gender:* Male: 1 Female: 1 *Age:* Mean: 65 yrs Range: 61 to 69 yrs *Prior treatments:* PPI, unspecified (1/2 patients) *Length of Barretts*: not reported *Inclusion criteria:* none notable *Exclusion criteria:* none notable	PDT *Drug:* ALA *Dose:* 40 mg/kg *Route of administration:* oral *Light source*: laser @630nm *Light dose:* 70 to 100J/cm^2 *Time to photoactivation:* 3.3 to 5.9 hours *Treatment time:* not reported *Number of sessions:* Mean: 2 sessions / patient Range: 1 to 3 sessions *Co-interventions:* High dose PPI Ranitidine 150 mg as needed.	*Outcomes:* Complete response of BE (assessed through endoscopy with random biopsies) Complete response of HGD (assessed through endoscopy with random biopsies) Progression to cancer *Adverse events*	*Outcomes:* Complete response of BE at 3 months: 0/2 patients (0%) Complete response of HGD at 3 months: 0/2 patients (0%) Progression to cancer at 6 months: 2/2 patients (100%) *Adverse events:* Nausea and vomiting: 1/2 patients (50%)	4
ALA 60mg/kg administered orally							
Comparative studies							
Behrens A, et	BE + HGD	Cohort study	*Number of patients:* 44	PDT vs. EMR vs. PDT +	*Outcomes:*	*Outcomes:*	4

Table B 1. Studies of photodynamic therapy (PDT) for Barrett's esophagus with/without dysplasia

Study authors (year published)	Cancer / Cell Type	Study Design	Patients	Intervention	Outcome Measures	Findings	Study quality
al. (2005)[106]		Single centre Prospective PDT vs. EMR vs. PDT + EMR *Countries:* Germany *Length of follow-up:* Mean: 38 months Range: 7 to 61 months	(PDT Group: 27 patients; EMR Group: 14 patients; PDT+EMR: 3 patients) *Gender:* Male: 38 Female: 6 *Age:* Mean:61 yrs Range: 33 to 79 yrs <u>PDT Group</u> *Number of patients:* 27 patients *Gender:* not reported *Age:* not reported <u>EMR Group</u> *Number of patients:* 14 patients *Gender:* not reported *Age:* not reported <u>PDT + EMR Group</u> *Number of patients:* 3 patients *Gender:* not reported *Age:* not reported *Prior treatments:* none reported *Length of Barretts:* not reported *Inclusion criteria:* none notable	EMR <u>PDT Group</u> Patients with microscopic / histologic HGD *Drug:* 5-ALA *Dose:* 60 mg/kg *Route of administration:* oral *Light source*: dye laser @ 630 to 635nm *Light dose:* not reported *Time to photoactivation:* 4 to 6 hours *Treatment time:* not reported *Number of sessions:* Mean: 1 session/patient Range: 1 to 4 sessions / patient <u>EMR</u> *Technique:* EMR with ligation, or cap and snare *Injection:* none *Number of treatments:* not reported <u>PDT + EMR Group</u> Details as above. *Co-interventions:* Omeprazole 40 mg IV twice daily or Pantoprazole 40 mg IV twice daily	Complete response of HGD Recurrence of HGD Progression to cancer *Adverse events:*	Complete response of dysplasia … … at 1 month (after 1 treatment session): -All patients: 39/43 patients (91%) -PDT Group: 26/27 patients (96%) -EMR Group: 13/14 patients (93%) -PDT + EMR Group: 2/3 patients (67%) … at 38 months (mean) (after 1 to 4 sessions) -All patients: 29/35 patients (83%) Recurrence of HGD at 38 months (mean): 4/35 patients (11%) Progression to cancer at 38 months (mean): 2/35 patients (6%) *Adverse events:* <u>PDT Group</u> Vomiting, severe: 1/27 patients (4%) Nausea: 14/27 patients (52%) <u>EMR Group</u>	

Table B 1. Studies of photodynamic therapy (PDT) for Barrett's esophagus with/without dysplasia

Study authors (year published)	Cancer / Cell Type	Study Design	Patients	Intervention	Outcome Measures	Findings	Study quality
			Exclusion criteria: none notable				
Hage M, et al. (2004)[107]	BE BE+LGD	RCT Prospective PDT vs. APC *Countries:* Netherlands *Length of follow-up:* 24 months	Number of patients: 40 (PDT100 Group: 13 patients; PDT20+100 Group: 13 patients; APC Group: 14 patients) <u>PDT100 Group:</u> *Gender:* Male: 10 Female: 3 *Age:* Median: 57 yrs Range: 52 to 72 yrs <u>PDT20+100 Group:</u> *Gender:* Male: 10 Female: 3 *Age:* Median: 61 yrs Range: 57 to 69 yrs <u>APC Group:</u> *Gender:* Male: 11 Female: 3 *Age:* Median: 60 yrs Range: 41 to 69 yrs *Prior treatments:* PPI, unspecified *Length of Barretts:* Median: 3 cm	<u>PDT100 Group:</u> *Drug:* 5-ALA *Dose:* 60 mg/kg *Route of administration:* oral *Light source*: diode laser @ 633 nm *Light dose:* 100 J/cm^2 *Time to photoactivation:* 4 hours post ALA *Treatment time:* not reported *Number of sessions:* not reported <u>PDT20+100 Group:</u> *Drug:* 5-ALA *Dose:* 60 mg/kg *Route of administration:* oral *Light source*: diode laser @ 633 nm *Light dose:* 20 J/cm^2 one hour post ALA + 100 J/cm^2 4 hours post ALA *Time to photoactivation:* 4 hours post ALA *Treatment time:* not reported *Number of sessions:* not reported <u>APC Group:</u>	*Outcomes:* Complete response of BE (assessed *endoscopically*) Complete response of BE (assessed *histologically* through 4 quadrant biopsies every 2 cm) *Adverse events*	*Outcomes:* Complete response of BE by endoscopy at 6 weeks: -PDT100 Group: 1/13 patients (8%) -PDT20+100 Group: 5/13 patients (38%) -APC Group: 7/14 patients (50%) (PDT100 vs. PDT20+100: p<0.005) (PDT20+100 vs. APC: not significant) (PDT100 vs. APC: = p<0.05) Complete response of BE – histological at 6 weeks: -PDT100 Group: 1/13 patients (8%) -PDT20+100 Group: 4/13 patients (31%) -APC Group: 5/14 patients (36%) (no significant differences) *Adverse events:* <u>PDT Groups</u> Pain during treatments: 23/26 patients (89%) Odynophagia: 24/26 patients (92%) Fever: 8/26 patients (31%) Nausea/vomiting: 7/26	1

Table B 1. Studies of photodynamic therapy (PDT) for Barrett's esophagus with/without dysplasia

Study authors (year published)	Cancer / Cell Type	Study Design	Patients	Intervention	Outcome Measures	Findings	Study quality
			Range: 2 to 5 cm *Inclusion criteria:* none notable *Exclusion criteria:* Acute porphyria; pregnancy; intolerance to endoscopy; inter-current diseases with an adverse impact on survival	*Gas flow:* 2L/minute *Power:* 65 watts *Number of sessions:* 2 2/3 of the lesion ablated in the 1st session and the rest in the second *Co-interventions:* Omeprazole 40mg/day		patients (27%) Sudden death (presumably from cardiac arrhythmia): 1/26 patients (4%) Strictures: 0/26 patients (0%) Elevated liver enzymes: 20/26 patients (77%) Buried glands: 1/26 patients (4%) <u>APC Group</u> Pain during treatments: 5/14 patients (36%) Odynophagia: 12/14 patients (86%) Fever: 2/14 patients (14%) Nausea/vomiting: 0/14 patients (0%) Sudden death (presumably from cardiac arrhythmia): 0/14 patients (0%) Strictures: 1/14 patients (7%) Elevated liver enzymes: 0/14 patients (0%) Buried glands: 7/14 patients (50%)	
Zoepf T, et al. (2003)[108]	BE + HGD BE + LGD	RCT Single centre Prospective PDT vs. APC *Countries:* Germany *Length of follow-up*:	*Number of patients:* 20 (PDT Group: 10 patients; APC Group: 10 patients) *Gender:* not reported *Age:* Mean: 68 yrs Range 44 to 77 yrs *Prior treatments:* none reported	PDT vs. APC <u>PDT</u> *Drug:* 5-ALA *Dose:* 60 mg/kg *Route of administration:* oral *Time to photoactivation:* not reported *Light source:* diode laser @ non-reported wavelength	*Outcomes:* Reduction in length of BE *Adverse events*	*Outcomes:* Reduction in length of BE "after treatment": <u>PDT</u> Mean: 90% Range: 0 to 100% <u>APC</u> Mean 90% Range: 50 to 100% *Adverse events:*	1

Table B 1. Studies of photodynamic therapy (PDT) for Barrett's esophagus with/without dysplasia

Study authors (year published)	Cancer / Cell Type	Study Design	Patients	Intervention	Outcome Measures	Findings	Study quality
		PDT Median: 27 months Range: 12 to 42 months APC Median: 24 months Range: 4 to 46 months	*Length of Barretts:* PDT Mean: 3.5 cm Range: 3 to 12 cm APC Mean: 4.0 cm Range: 3 to 7 cm *Inclusion criteria:* none notable *Exclusion criteria:* none notable	*Light dose:* 150J/cm^2 *Treatment time:* not reported *Number of sessions / patient:* Mean: 2 sessions / patient Range: 1 to 5 sessions / patient APC *Power:* 70 watts *Gas flow:* not reported *Treatment time:* not reported *Number of sessions / patient:* Mean: 4 sessions / patient Range: 2 to 9 sessions / patient *Co-interventions:* none reported		PDT Nausea / vomiting: 10/10 patients (100%) Dysphagia, transient 4/10 patients (40%) Photosensitivity: 0/10 patients (0%) Mediastinal emphysema: 0/10 patients (0%) APC Nausea / vomiting: 0/10 patients (0%) Dysphagia, transient: 3/10 patients (30%) Photosensitivity: 0/10 patients (0%) Mediastinal emphysema: 1/10 patients (10%)	
Non-comparative studies							
Barr H, et al. (1996) [109]	BE+HGD	Case series Single-centre *Countries:* UK *Length of follow-up:* Range: 26 to 44 months	*Number of patients:* 5 *Gender:* Male: 3 Female: 2 *Age:* Median: 74 years Range: 56 to 81 years *Length of Barretts:* not reported *Prior treatments:* none reported *Inclusion criteria:* none	PDT *Drug:* ALA *Dose:* 60 mg/kg *Route of administration:* oral *Light source*: laser @ 630nm *Light dose:* 90 to 150 J/cm^2 *Time to photoactivation:* 4 *Treatment time:* not reported *Number of sessions:* 1 session/patient	*Outcomes:* Partial response of dysplasia (defined as any squamous re-epithelialization) (method of assessment not reported) *Adverse events:*	*Outcomes:* Partial response of dysplasia post treatment: 5/5 patients (100%) *Adverse events:* Buried glands: 2/5 patients (40%)	4

Table B 1. Studies of photodynamic therapy (PDT) for Barrett's esophagus with/without dysplasia

Study authors (year published)	Cancer / Cell Type	Study Design	Patients	Intervention	Outcome Measures	Findings	Study quality
			notable *Exclusion criteria:* none notable	*Co-interventions:* Omeprazole, 40mg/day			
Gossner L, et al (1999)[110]* * Information extracted for BE or HGD patients only	BE + HGD	Case series Single centre *Countries:* Germany *Length of follow-up:* Mean: 5.4 months Range: 1 to 11 months	*Number of patients:* 10 *Gender:* Male: 9 Female: 1 *Age:* Mean: 69.6 yrs ± 7.91 yrs *Prior treatments:* none reported *Length of Barretts:* Mean: 5.1 cm Range: 0.5 to 10 cm *Length of dysplasia:* Range: 27 to 36 cm *Inclusion criteria:* Severe dysplasia or early EAC Ineligible for surgery *Exclusion criteria:* none notable	PDT *Drug:* 5-ALA *Dose:* 60 mg/kg *Route of administration:* oral *Light source*: dye laser (KTP/YAG) @ 635nm *Light dose:* 150 J/cm^2 @ 100mW/cm^2 *Time to photoactivation:* 4 to 6 hours *Treatment time:* not reported *Number of sessions:* Mean: 2.2 sessions / patient *Co-interventions:* Omeprazole 20 to 40 mg post treatment	*Outcomes:* Complete response of BE (assessed through endoscopy with 4 quadrant biopsy over the "whole length" of BE) Partial response of BE Complete response of HGD *Adverse events:* No BE or HGD specific information available.	*Outcomes:* Complete response of BE at 5.4 months (mean): 0/10 patients (0%) Partial response of BE: 10/10 patients (100%) Complete response of dysplasia at 5.4 months (mean): 10/10 patients (100%)	4
Gossner L, et al (1999)[111]	HGD	Case report Single centre Prospective *Countries:* Germany *Length of follow-up:*	*Number of patients*: 2 *Gender:* Male: 1 Female: 1 *Age:* Range: 48 to 79 yrs *Prior treatments:* not reported	PDT *Drug:* 5-ALA *Dose:* 60 mg/kg *Route of administration:* oral *Light source*: KTP:YAG laser @ 635nm *Light dose:* 150J/cm^2 *Time to photoactivation:*	*Outcomes:* Complete response of HGD Survival *Adverse events*:	*Outcomes:* Complete response of HGD at 2 days: 2/2 patients (100%) Survival at 10.5 months (mean): 2/2 patients (100%) Adverse events:	4

Table B 1. Studies of photodynamic therapy (PDT) for Barrett's esophagus with/without dysplasia

Study authors (year published)	Cancer / Cell Type	Study Design	Patients	Intervention	Outcome Measures	Findings	Study quality
		Mean: 10.5 months Range: 10 to 11 months	*Length of Barretts:* not reported *Inclusion criteria:* Ineligible for or refused surgery *Exclusion criteria:* none notable	not reported *Treatment time:* not reported *Number of sessions:* not reported *Co-interventions:* none reported		Perforation: 0/2 patients (0%) Stricture: 0/2 patients (0%)	
Kashtan H, et al (2002)[112]	BE + LGD (7 patients) BE + HGD (1 patient)	Clinical trial Single centre Prospective *Countries:* Israel *Length of follow-up:* Range: 18 to 30 months	*Number of patients:* 8 *Gender:* Male: 7 Female: 1 *Age:* Mean: 70.6 yrs Range: 52 to 84 yrs *Prior treatments:* none reported *Length of Barretts:* not reported *Inclusion criteria:* none notable *Exclusion criteria:* Photosensitivity, impaired liver function tests; porphyria	PDT *Drug:* 5 ALA *Dose:* 60 mg/kg *Route of administration:* oral *Light source*: xenon lamp @ 580 to 720nm and 1250 to 1600nm *Light dose:* 100J/cm^2 *Time to photoactivation:* not reported *Treatment time:* not recorded *Number of sessions:* 1 *Co-interventions:* none reported	*Outcomes:* Complete response of BE Complete response of HGD Complete response of LGD Progression to cancer *Adverse events*	*Outcomes:* Complete response of BE at 18 to 30 months: 3/8 patients (38%) Complete response of HGD at 18 to 30 months: 0/1 patients (0%) Complete response of LGD at 18 to 30 months: 4/7 patients (57%) Progression to cancer at 18 to 30 months: 0/8 patients (0%) *Adverse events:* Photosensitivity: 6/8 patients (75%) Nausea and vomiting: 4/8 patients (50%)	4
Macrae FA, et al (2004)[113]	BE + HGD	Case series Retrospective *Countries:* Australia *Length of follow-*	*Number of patients:* 8 *Gender:* not reported *Age:* not reported *Prior treatments:* not reported	PDT *Drug:* 5-ALA *Dose:* 60 mg/kg in 3 divided doses *Route of administration:* oral *Light source*: KTP laser @	*Outcomes:* Complete response of HGD Progression to cancer	*Outcomes:* Complete response of dysplasia at 5 to 98 months: 3/8 patients (37.5%) Progression to cancer at 5 to 98 months: 1/8 patients	4

Table B 1. Studies of photodynamic therapy (PDT) for Barrett's esophagus with/without dysplasia

Study authors (year published)	Cancer / Cell Type	Study Design	Patients	Intervention	Outcome Measures	Findings	Study quality
		up: Range: 5 to 98 months	*Length of Barretts:* not reported *Inclusion criteria:* none notable *Exclusion criteria:* none notable	628nm *Light dose:* 150J/cm^2 *Time to photoactivation:* 18 hours from 1st dose *Treatment time:* not reported *Number of sessions:* 1 session / patient *Co-interventions:* none reported	Survival *Adverse events*	(12.5%) Survival at 5 to 98 months: 8/8 patients (100%) *Adverse events:* Strictures: 1/8 patients (12.5%) Photosensitivity: common	
Mellidez JC, et al (2005)[114] * Patients thought to be included in Mackenzie et al (2007) [103] (See group A)	BE + HGD	Case series Single centre Prospective *Countries:* not reported *Length of follow-up:* not reported	*Number of patients:* 13 (PDT Red Light: 8 patients; PDT Green light: 4 patients) <u>Red light group</u> *Gender:* not reported *Age:* not reported <u>Green light group</u> *Gender:* not reported *Age:* not reported 1 additional patient lost to follow-up, treatment allocation unknown. *Prior treatments:* none reported *Length of Barretts:* not reported *Inclusion criteria:* none notable *Exclusion criteria:* none	PDT *Drug:* ALA *Dose:* 60 mg/kg *Route of administration:* oral *Light source*: red light laser or green light laser *Light dose:* not reported *Time to photoactivation:* 4 hours *Treatment time:* not reported *Number of sessions:* not reported *Co-interventions:* Preceded by EMR	*Outcomes:* Complete response of HGD -Red light -Green light Reduction in area of columnar mucosa -Red light -Green light *Adverse events*	*Outcomes:* Complete response of dysplasia at unknown follow-up: -Red light: 7/8 patients (87.5%) -Green light: 2/4 patients (50%) Difference is statistically significant Reduction in area of columnar mucosa at unknown follow-up: -Red light: 59% -Green light: 7% *Adverse events:* GI bleed: 1/13 patients (8%)	4

Table B 1. Studies of photodynamic therapy (PDT) for Barrett's esophagus with/without dysplasia

Study authors (year published)	Cancer / Cell Type	Study Design	Patients	Intervention	Outcome Measures	Findings	Study quality
			notable				
HpD 1.5mg/kg administered intravenously							
Comparative studies							
None							
Non-comparative studies							
Laukka MA, et al (1995)[115]	BE + LGD (4 patients) BE + HGD (1 patient)	Case series Single centre *Countries:* US *Length of follow-up:* Range: 2 to 12 months	*Number of patients:* 5 *Gender:* Male: 4 Female: 1 *Age:* Median: 69 yrs Range: 56 to 80 yrs *Prior treatments:* none reported *Length of Barretts:* Mean: 9.8 cm Range: 7 to 13 cm *Inclusion criteria:* none notable *Exclusion criteria:* Pregnancy; lactation; allergy to omeprazole, or contraindications to endoscopy	PDT *Drug:* HpD *Dose:* 1.5 mg/kg *Route of administration:* IV *Light source*: argon pumped dye laser @ 630nm *Light dose:* 175J/cm^2 *Time to photoactivation:* not reported *Treatment time:* 6 minutes / 2cm segment *Number of sessions:* 1 session / patient *Co-interventions:* Omeprazole 20 mg for 6 months	*Outcomes:* Complete response of BE (assessed through endoscopy with 4 quadrant biopsies every 2 cm) Complete response of HGD Mean reduction in length of BE *Adverse events*	*Outcomes:* Complete response of BE at 2 months: 0/5 patients (0%) Complete response of HGD at 2 to 12 months: 1/1 patient (100%) Mean reduction in length of BE at 2 months: 24% (range: 10 to 50%) *Adverse events:* Nausea: 2/5 patients (40%) Anorexia: 2/5 patients (40%) Photosensitivity: 2/5 patients (40 %) Buried glands: observed	4
Wang KK, et al (1999)[116]	BE (23 patients) BE + LGD (32 patients) BE + HGD (9 patients)	RCT Single centre Prospective *Countries:* US *Length of follow-up:* Mean: 25 months ± 2	*Number of patients:* 75 (PDT Group: 55 patients; Control Group: 20 patients) *Gender:* Male: 61 Female: 14 *Age:* Mean: 61 yrs ± 1 yr	PDT <u>PDT Group</u> *Drug:* HpD *Dose:* 1.5 to 2.0 mg/kg *Route of administration:* IV *Light source*: argon pumped dye laser @ 630nm	*Outcomes:* Complete response of BE (assessed through endoscopy with 4 quadrant biopsy every 1 cm) Reduction in treated BE	*Outcomes:* Complete response of BE at unknown follow-up: -PDT Group: 7/55 patients (13%) -Control Group: 0/20 patients (0%) ($p<0.05$)	4

Table B 1. Studies of photodynamic therapy (PDT) for Barrett's esophagus with/without dysplasia

Study authors (year published)	Cancer / Cell Type	Study Design	Patients	Intervention	Outcome Measures	Findings	Study quality
		months	PDT Group *Number of patients:* 55 *Gender:* not reported *Age:* not reported Control Group *Number of patients:* 20 *Gender:* not reported *Age:* not reported *Prior treatments:* none reported *Length of Barretts:* not reported *Inclusion criteria:* none notable *Exclusion criteria:* none notable	*Light dose:* 175 to 200 J/cm^2 *Time to photoactivation:* 48 hours *Treatment time:* not reported *Number of sessions:* Mean:: 1 session / patient Control Group not reported *Co-interventions:* none reported	length *Adverse events*	Reduction in treated BE length at unknown follow-up: -PDT Group: 7±1 cm to 4 ±1 cm -Control Group: 6±1 cm to 6±1 cm *Adverse events:* Photosensitivity: common Odynophagia: common Strictures: 0/54 patients (0%)	
Wang KK, et al (1999)[117] * Information extracted for BE or HGD patients only	BE (9 patients) BE + LGD (30 patients) BE + HGD (11 patients)	Clinical trial Single centre Prospective *Countries:* US *Length of follow-up:* Mean: 24 months ± 3 months	*Number of patients:* 50 *Gender:* not reported *Age:* not reported *Prior treatments:* none reported *Length of Barretts:* Mean 6cm ±1 cm *Inclusion criteria:* none notable *Exclusion criteria:* none notable	PDT *Drug:* hematoporphyrin derivative (HpD) *Dose:* 1.75 to 4.0 mg/kg *Route of administration:* IV *Light source*: not reported *Light dose:* 175 to 200J/cm^2 *Time to photoactivation:* 48 hours *Treatment time:* not reported *Number of sessions:* 1 session / patient	*Outcomes:* Progression to HGD from BE or LGD Length of Barretts *Adverse events:* none	*Outcomes:* Progression to HGD from BE or LGD 24 months (mean): 4/39 patients (10%) Length of Barretts: -Pre-PDT: mean 6cm ± 1 cm - at 3 months: mean 3 cm ± 1 cm	4

Table B 1. Studies of photodynamic therapy (PDT) for Barrett's esophagus with/without dysplasia

Study authors (year published)	Cancer / Cell Type	Study Design	Patients	Intervention	Outcome Measures	Findings	Study quality
				Co-interventions: Omeprazole 40 mg./ day for one month then 20 mg/day			
mTHPC 0.15mg/kg administered intravenously							
Comparative studies							
None							
Non-comparative studies							
Javaid B, et al (2002)[118]* * Information extracted for BE or HGD patients only	BE + HGD	Clinical trial Single centre Prospective *Countries:* UK *Length of follow-up:* Mean: 12.8 months Range: 4 to 27 months	*Number of patients:* 6 *Gender:* not reported *Age:* not reported *Prior treatments:* none reported *Length of Barretts:* Mean 6.6 cm Range:1.2 to 13 cm *Inclusion criteria:* none notable *Exclusion criteria:* none notable	PDT *Drug:* m-tetrahydroxyphenyl chlorin (mTHPC) *Dose:* 0.15 mg/kg *Route of administration:* IV *Light source*: argon pumped dye laser @ 652nm (4 patients) and Xenon arc lamp @ 652±15 nm (2 patients) *Light dose:* 8 to 20J/cm^2 *Time to photoactivation:* 96 hours *Treatment time:* not reported *Number of sessions:* Mean: 1.5 sessions / patient Range: 1 to 3 sessions *Co-interventions:* PPI, unspecified	*Outcomes:* Complete response of BE (assessed through endoscopy with 4 quadrant biopsies every 2 cm) Partial response of BE (defined as any reduction in BE length <100%) Complete response of HGD Partial response of dysplasia Progression to cancer *Adverse events:* No BE or HGD specific information available.	*Outcomes:* Complete response of BE at 4 weeks: 1/6 patients (17%) Partial response of BE: 3/6 patients (50%) Complete response of dysplasia at 4 weeks: 4/6 patients (67%) Partial response of dysplasia at 4 weeks: 2/6 patients (33%) Progression to cancer at 12.8 months (mean): 0/6 patients (0%)	4
Lovat LL, et al (2005)[119] *	BE + HGD	Case series Single centre *Countries:* UK	*Number of patients:* 7 *Gender:* Male: 7 Female: 0	PDT *Drug:* m-tetrahydroxyphenyl chlorin (mTHPC)	*Outcomes:* Complete response of BE (assessed through endoscopy with 4	*Outcomes:* Complete response of BE at 20.6 months (mean): - Red Light Group: 0/4 patients	4

Table B 1. Studies of photodynamic therapy (PDT) for Barrett's esophagus with/without dysplasia

Study authors (year published)	Cancer / Cell Type	Study Design	Patients	Intervention	Outcome Measures	Findings	Study quality
* Information extracted for BE or HGD patients only		*Length of follow-up:* Mean: 20.6 months Range: 16 to 24 months <u>Red Light Group</u> Mean: 19.8 months Range: 16 to 23 months <u>Green Light Group</u> Mean: 21.7 months Range: 19 to 24 months	*Age:* Range: 61 to 81 yrs <u>Red Light Group</u> *Number of patients:* 4 patients *Gender:* not reported *Age:* not reported <u>Green Light Group</u> *Number of patients:* 3 patients *Gender:* not reported *Age:* not reported *Prior treatments:* PDT (2 patients) EMR (1 patient) Laser (1 patient) *Length of Barretts:* Mean: 2 cm Range: 1 to 4 cm *Inclusion criteria:* Ineligible for or refusing surgery *Exclusion criteria:* none notable	*Dose:* 0.15 mg/kg *Route of administration:* IV *Time to photoactivation:* 3 days *Treatment time:* not reported *Number of sessions:* 1 session <u>Red Light Group</u> *Light source:* diode laser @ 652nm *Light dose:* 75J/cm^2 Other details as above <u>Green Light Group</u> *Light source:* copper vapour laser @ 511 nm *Light dose:* 75J/cm^2 Other details as above *Co-interventions:* none reported	quadrant biopsies every 2 cm) -Red Light Group -Green Light Group Complete response of HGD to BE -Red Light Group -Green Light Group Progression to cancer -Red Light Group -Green Light Group Mortality -All cause -EAC *Adverse events:* No BE or HGD specific information available.	(0%) - Green Light Group: 0/3 patients (0%) Complete response of dysplasia at 20.6 months (mean): - Red Light Group: 3/4 patients (75%) - Green Light Group: 0/3 patients (0%) Progression to cancer at 20.6 months (mean): - Red Light Group: 0/4 patients (0%) - Green Light Group: 1/3 patients (33%) Mortality at 20.6 months (mean): -All cause: 2/7 patients (29%) -EAC: 0/5 patients (0%)	
Porfimer sodium 2mg/kg administered intravenously							
Comparative studies							
Ragunath K, et al. (2005)[60]	BE + HGD BE + LGD	RCT Single centre Prospective	Number of patients: 26 (PDT Group: 13 patients; APC Group: 13 patients)	PDT vs. APC <u>PDT Group</u> *Drug:* porfimer sodium *Dose*: 2 mg.kg	*Outcomes:* Complete response of BE (assessed through endoscopy with 4	*Outcomes:* Complete response of BE: <u>PDT Group</u> - at 4 months: 2/13 patients	1

Table B 1. Studies of photodynamic therapy (PDT) for Barrett's esophagus with/without dysplasia

Study authors (year published)	Cancer / Cell Type	Study Design	Patients	Intervention	Outcome Measures	Findings	Study quality
		PDT vs. APC *Countries*: UK *Length of follow-up:* 12 months	PDT Group *Gender:* Male: 13 Female: 0 *Age:* Mean: 58.1 yrs Range 35 to 79 yrs APC Group *Gender:* Male: 10 Female: 3 *Age:* Mean: 64.9 yrs Range: 41 to 86 yrs *Prior treatments:* not reported *Length of Barretts:* PDT Group Mean: 5.7 cm Range: 3 to 9 cm APC Group Mean: 5.5 cm Range: 3 to 9 cm *Inclusion criteria:* none notable *Exclusion criteria:* Previous or current esophageal malignancy; previous esophagectomy; history of EMR or mucosal ablation treatment; predominantly "tongues"	*Route of administration:* IV *Time to photoactivation:* 48 hours *Light source:* argon pump dye laser @630 nm *Light dose:* 200 J/cm^2 *Treatment time:* not recorded *Number of sessions:* 1 session / patient APC Group *Gas flow:* 1.8L/minute *Power:* 65 watts *Treatment time:* not recorded *Number of sessions:* 1 session / patient *Co-interventions:* Lansoprazole 60 mg/day during treatment then 30 mg/day	quadrant biopsy every 1 cm) Complete response of HGD (assessed through endoscopy with 4 quadrant biopsy every 1 cm) Complete response of LGD (assessed through endoscopy with 4 quadrant biopsy every 1 cm) Complete response of dysplasia Reduction in length of BE	(15%) - at 12 months: 2/13 patients (15%) APC Group - at 4 months: 2/13 patients (15%) - at 12 months: 0/9 patients (0%) Complete response of HGD: PDT Group - at 4 months: 2/2 patients (100%) - at 12 months: 2/2 patients (100%) APC Group - at 4 months: 1/1 patient (100%) - at 12 months: 0/0 patients (0%) Complete response of LGD: PDT Group - at 4 months: 8/11 patients (73%) - at 12 months: 8/11 patients (73%) APC Group - at 4 months: 7/12 patients (58%) - at 12 months: 6/9 patients (67%) Complete response of dysplasia: PDT Group - at 4 months: 10/13 patients	

Table B 1. Studies of photodynamic therapy (PDT) for Barrett's esophagus with/without dysplasia

Study authors (year published)	Cancer / Cell Type	Study Design	Patients	Intervention	Outcome Measures	Findings	Study quality
			as opposed to circumferential BE; history of porphyria; pregnancy or lack of contraception		Progression to cancer *Adverse events*	(77%) - at 12 months: 10/13 patients (77%) <u>APC Group</u> - at 4 months: 8/13 patients (62%) - at 12 months: 6/9 patients (67%) (p=0.03) Reduction in length of BE: <u>PDT Group</u> - at 4 months: 57% reduction - at 12 months: 61% reduction <u>APC Group</u> - at 4 months: 65% reduction - at 12 months: 56% reduction Progression to cancer: <u>PDT Group</u> - at 4 months: 0/13 patients (0%) - at 12 months: 1/13 patients (8%) <u>APC</u> - at 4 months: 0/13 patients (0%) - at 12 months: 0/13 patients (0%) *Adverse events:* <u>PDT Group</u> Strictures: 2/13 patients (15%) Chest pain, odynophagia and fever: 0/13 patients (0%) Photosensitivity: 2/13 patients (15%)	

Table B 1. Studies of photodynamic therapy (PDT) for Barrett's esophagus with/without dysplasia

Study authors (year published)	Cancer / Cell Type	Study Design	Patients	Intervention	Outcome Measures	Findings	Study quality
						Buried glands: 1/13 patients (8%) <u>APC Group</u> Strictures: 3/13 patients (23%) Chest pain, odynophagia and fever: 1/13 patients (8%) Photosensitivity: 0/13 patients (0%) Buried glands: 0/13 patients (0%)	
Non-comparative studies							
Attila T, et al (2005)[120]	BE +HGD	Case series Single centre Retrospective *Countries:* not reported *Length of follow-up:* Mean:43.7 months Range: 2 to 80 months	*Number of patients:* 19 *Gender:* Male: 15 Female: 4 *Age:* Mean: 66.4 yrs ± 7.5 yrs *Prior treatments:* None *Length of Barretts:* Mean: 5.1 cm ± 2.4 cm *Inclusion criteria:* none notable *Exclusion criteria:* none notable	PDT *Drug:* Porfimer sodium *Dose:* 2 mg/kg *Route of administration:* IV *Light source*: laser @630nm *Light dose:* not reported *Time to photoactivation:* 48 to 72 hours *Treatment time:* not reported *Number of sessions:* not reported 2nd PDT or APC done for residual lesions *Co-interventions:* none reported	*Outcomes:* Complete response of BE (assessed through endoscopy with 4 quadrant biopsies every 2cm) Partial response of BE (defined as residual BE islands or tongues) No response of BE (defined as unchanged length of Barretts) Progression to cancer *Adverse events*	*Outcomes:* Complete response of BE: - at 3 months (after 1 PDT session): 5/19 patients (26%) - at 43.7 months (mean) (after PDT + additional therapy): 12/19 patients (63%) Partial response of BE at 3 months (after 1 PDT session): 9/19 patients (47%) No response of BE at 3 months (after 1 PDT session): 5/19 patients (26%) Progression to cancer at 43.7 months (mean): 2/19 patients (10.5%) *Adverse events:* Strictures: 7/19 patients (36.8%)	4
Bronner M, et al (2006)[121]	BE + HGD	RCT Prospective	*Number of patients:* 208 (PDT + OM Group: 138 patients; OM Group:70	PDT <u>PDT + OM</u> *Drug:* porfimer sodium	*Outcomes:* none reported *Adverse events*	*Outcomes:* *Adverse events:*	4

Table B 1. Studies of photodynamic therapy (PDT) for Barrett's esophagus with/without dysplasia

Study authors (year published)	Cancer / Cell Type	Study Design	Patients	Intervention	Outcome Measures	Findings	Study quality
		PDT with omeprazole (OM) vs. OM *Countries:* not reported *Length of follow-up*: 5 yrs	patients) <u>PDT+OM Group</u> *Gender:* not reported *Age:* not reported <u>OM Group</u> *Gender:* not reported *Age:* not reported *Prior treatments:* none reported *Length of Barretts:* not reported *Inclusion criteria:* none notable *Exclusion criteria:* none notable	*Dose:* 2 mg/kg *Route of administration:* IV *Light source*: 630nm laser *Light dose:* not reported *Time to photoactivation:* 40 to 50 hours *Treatment time:* not reported *Number of sessions:* up to 3 PDT sessions at least 90 days apart Omeprazole 20 mg twice daily <u>OM</u> Omeprazole 20 mg twice daily *Co-interventions:* Omeprazole as above		Buried glands <u>PDT + OM Group:</u> 31% of patients 1.2% of biopsies <u>OM Group:</u> 33% of patients 2.2% of biopsies	
Keeley SB, et al (2007)[122]	HGD	Case series Single centre Retrospective *Countries:* US *Length of follow-up:* Mean: 28.1 months Range: 1 to 81 months	*Number of patients:* 13 *Gender:* not reported *Age:* not reported *Prior treatments:* none reported *Length of Barretts:* not reported *Inclusion criteria:* Ineligible for or refusal of surgery *Exclusion criteria:* none	PDT *Drug:* porfimer sodium *Dose:* not reported *Route of administration:* IV *Light source*: red laser @630nm *Light dose:* 300 to 400J/cm^2 *Time to photoactivation:* 48 hours *Treatment time:* not reported *Number of sessions:* >1 (not reported	*Outcomes:* Complete response of HGD Mortality -Overall -Disease related Survival -Overall -Disease related *Adverse events:* No BE or	*Outcomes:* Complete response of HGD at 28.1 months (mean): 5/13 patients (38%) Mortality at 28.1 months (mean): -Overall: 4/10 patients (40%) -Disease related: 0/6 patients (0%) Survival at 28.1 months (mean): -Overall: 6/10 patients (60%) -Disease related: 6/6 patients	4

Table B 1. Studies of photodynamic therapy (PDT) for Barrett's esophagus with/without dysplasia

Study authors (year published)	Cancer / Cell Type	Study Design	Patients	Intervention	Outcome Measures	Findings	Study quality
* Information extracted for BE or HGD patients only			notable	*Co-interventions:* none reported	HGD specific information available.	(100%)	
Overholt BF, et al (2007)[123]	BE + HGD	RCT Multicentre Prospective Omeprazole (OM) vs PDT + OM *Countries:* US, UK, Canada *Length of follow-up:* <u>PDT + OM Group</u> Mean 332 days Range: 48 to 1044 days <u>OM Group</u> Mean: 357 days Range: 63 to 1092 days	Number of patients: 208 (PDT+OM Group: 138 patients; OM Group: 70 patients) <u>PDT + OM Group</u> *Gender:* Male: 117 Female: 21 *Age:* Mean: 66 yrs ± 11 yrs <u>OM Group</u> *Gender:* Male: 59 Female: 11 *Age:* Mean: 67 yrs ± 11 yrs *Inclusion criteria:* none notable *Exclusion criteria:* Cancer other than non-melanoma skin cancer within the last 5 yrs; prior PDT to esophagus; strictures unresponsive to dilation; esophageal ulcers > 1 cm; porphyria; varices; pregnancy	OM vs. PDT + OM <u>PDT + OM</u> 20 mg OM twice daily *Drug:* Porfimer sodium *Dosage:* 2mg/kg *Route of administration:* IV *Time to photoactivation:* 40 to 50 hrs *Light source:* 630 nm KTP dye laser *Total light dose:* 130 J/cm of diffuser length *Treatment time:* Not reported *Number of treatments:* Mean 2 sessions / patient Range: 1 to 3 patients Maximum of 3 treatments at least 3 months apart over 3 years <u>OM Group</u> 20 mg OM twice daily *Co-interventions:* none reported	*Outcomes:* Cumulative proportion of patients ever having a complete response of HGD (assessed through endoscopy with 4 quadrant biopsy every 2 cm) Cumulative probability of maintaining complete response of HGD: (K-M analysis)	*Outcomes:* Cumulative proportion of patients ever having a complete response of HGD: <u>PDT + OM Group</u> - at 6 months: 73/138 patients (53%) - at 12 months: 78/138 patients (71%) - at 18 months 104/138 patients (75%) - at 24 months: 106/138 patients (77%) <u>OM Group</u> - at 6 months: 18/70 patients (26%) - at 12 months: 21/70 patients (30%) - at 18 months: 25/70 patients (36%) - at 24 months: 27/70 patients (39%) Statistically significant difference between groups ($p < 0.0001$) Cumulative probability of maintaining complete response of HGD: <u>PDT + OM Group:</u> - at 6 months: 0.76 - at 12 months: 0.61 - at 18 months: 0.54	4

Table B 1. Studies of photodynamic therapy (PDT) for Barrett's esophagus with/without dysplasia

Study authors (year published)	Cancer / Cell Type	Study Design	Patients	Intervention	Outcome Measures	Findings	Study quality
						- at 24 months: 0.54 - at 5 yrs: 0.48 (p<0.001 vs. OM) <u>OM Group:</u> - at 6 months: 0.35 - at 12 months: 0.16 - at 18 months: 0.16 - at 24 months: 0.13 - at 5 yrs: 0.04 (p<0.001 vs. PDT +OM)	
					Progression to cancer		
					Adverse events	Progression to cancer at 5 years: -PDT+ OM Group: 18/138 patients (13%) -OM Group: 20/70 patients (29%) (p<0.05) *Adverse events:* <u>PDT + OM Group</u> Photosensitivity: 69% Strictures: 36% Hiccups: 10% Vomiting: 32 % Nausea: 11% Chest pain, non-random: 20% Fever: 20% Dysphagia: 19% Constipation: 13% Dehydration 12% <u>OM Group</u>: none reported	
Overholt BF, et al (2003)[124]*	BE + HGD (80 patients) BE + LGD (14 patients)	Clinical trial Single centre Prospective	*Number of patients*: 94 *Gender:* Male: 74 Female: 10	PDT *Drug:* Porfimer sodium *Dose:* 2 mg/kg *Route of administration:*	*Outcomes:* Complete response of BE (assessed through endoscopy with 4	*Outcomes:* Complete response of BE at 3 months: - All patients: 53/94 patients	4

Table B 1. Studies of photodynamic therapy (PDT) for Barrett's esophagus with/without dysplasia

Study authors (year published)	Cancer / Cell Type	Study Design	Patients	Intervention	Outcome Measures	Findings	Study quality
* Information extracted for BE or HGD patients only		*Countries:* US *Length of follow-up:* Mean: 50.7 months Range: 2 to 122 months	*Age:* Mean: 64.9 ± 10.0 yrs *Prior treatments:* none reported *Length of Barretts:* not reported *Inclusion criteria:* Ineligible for surgery *Exclusion criteria:* none notable	IV *Light source*: argon pumped dye laser @ 630 nm *Light dose:* 100-300 J/cm^2 *Time to photoactivation:* 48 hours *Treatment time:* not recorded *Number of sessions:* Median: 1.4 sessions Range: 1 to 3 sessions *Co-interventions:* Omeprazole 20 mg twice daily Nd:YAG ablation of residual BE <1.3 cm offered after 3 months Most patients received Nd:YAG treatment off protocol	quadrant biopsies every 2 cm) - From HGD - From LGD Complete response of HGD Complete response of LGD Cumulative probability of maintaining complete response given complete response* Progression to cancer at 50.7 months (mean) - From HGD - From LGD Survival at 50.7 months - From HGD - From LGD *Adverse events:* No BE or HGD specific information available. *extracted from a K-M survival curve	(56%) - From HGD: 43/80 patients (54%) - From LGD: 10/14 patients (71%) Complete response of HGD at 3 months: 62/80 patients: (78%) Complete response of LGD at 3 months: 13/14 patients (93%) Cumulative probability of maintaining complete response given complete response at 50.7 months (mean): - HGD: approximately 75% - LGD: approximately 43% Progression to cancer at 50.7 months (mean): - From HGD: 2/80 patients (2.5%) - From LGD: 0/14 patients (0%) Survival at 50.7 months (mean): 86/94 patients (91%) - From HGD: 73/80 patients (91%) - From LGD: 13/14 patients (93%)	

Table B 1. Studies of photodynamic therapy (PDT) for Barrett's esophagus with/without dysplasia

Study authors (year published)	Cancer / Cell Type	Study Design	Patients	Intervention	Outcome Measures	Findings	Study quality
Overholt BF (1996, 1997) [125,126]	BE + HGD	Case series Single centre *Countries:* US *Length of follow-up:* not reported	*Number of patients:* 11 *Gender:* Male: 9 Female: 2 *Age:* Mean: 61.9 yrs Range: 42 to 79 yrs *Prior treatments:* not reported *Length of Barretts:* not reported *Inclusion criteria:* none notable *Exclusion criteria:* none notable	PDT *Drug:* Porfimer sodium *Dose:* 2 mg/kg *Route of administration:* IV *Light source*: argon pumped dye laser @ 630nm *Light dose:* 250 J/cm^2 *Time to photoactivation:* 48 hours *Treatment time:* not reported *Number of sessions:* not reported *Co-interventions:* Omeprazole 20 mg twice daily	*Outcomes:* not reported *Adverse events*	*Outcomes:* *Adverse events:* Atrial fibrillation, transient: 0/11 patients (0%) Pleural effusion, small with no symptoms: 10/14 patients (71%)	4
Weiss AA, et al (2006)[127] * * Information extracted for BE or HGD patients only	BE + HGD	Case series Single centre *Countries:* Canada *Length of follow-up:* Mean: 21 months Range: 3 to 55 months	*Number of patients:* 13 *Gender:* Male: 12 Female: 1 *Age:* Mean: 71.6 yrs ± 10.2 yrs *Prior treatments:* none reported *Length of Barretts:* Mean: 5.7 cm 4/13 patients < 3 cm 9/12 patients ≥ 3 cm *Inclusion criteria:* Biopsy proven BE + HGD Ineligible for or refusing	PDT *Drug:* Porfimer sodium *Dose:* 2 mg/kg *Route of administration:* IV *Light source*: KTP dye laser @ 630 nm *Light dose:* 130J/cm^2 *Time to photoactivation:* 48 hours *Treatment time:* not reported *Number of sessions:* not reported *Co-interventions:* PPI, unspecified	*Outcomes:* Complete response of BE Complete response of HGD Partial response of BE Progression to cancer *Adverse events:* No BE or HGD specific information available.	*Outcomes:* Complete response of BE at 21 months (mean): 4/13 patients (31%) Complete response of dysplasia at 21 months (mean): 4/13 patients (31%) Partial response of BE: 8/13 patients (62%) Progression to cancer at 21 months (mean): 4/13 patients (31%)	4

Table B 1. Studies of photodynamic therapy (PDT) for Barrett's esophagus with/without dysplasia

Study authors (year published)	Cancer / Cell Type	Study Design	Patients	Intervention	Outcome Measures	Findings	Study quality
			surgery *Exclusion criteria:* none notable				
Wolfsen HC, et al (2004)[128] * * Information extracted for BE or HGD patients only	BE + HGD	Case series Single centre Retrospective *Countries:* US *Length of follow-up:* 2 years	*Number of patients:* 69 *Gender:* Male: 54 Female: 15 *Age:* Median: 72 *Prior treatments:* Long standing BE surveillance (55 patients) *Length of Barretts:* Median: 5 cm *Inclusion criteria:* none notable *Exclusion criteria:* none notable	PDT *Drug:* Porfimer sodium *Dose:* 2mg/kg *Route of administration:* IV *Light source*: diode laser @ unreported wavelength *Light dose:* 150 to 225J/cm^2 *Time to photoactivation:* 48 hours *Treatment time:* not reported *Number of sessions:* not reported *Co-interventions:* Omeprazole or esomeprazole, 80 to 120 mg/day	*Outcomes:* Complete response of BE from HGD (assessed through endoscopy with 4 quadrant biopsies every 1 cm) *Adverse events:* No BE or HGD specific information available.	*Outcomes:* Complete response of BE from HGD at 6 weeks: 36/69 patients (52%)	4
Yachimski P, et al (2008)[129] * * Information extracted for BE or HGD patients	BE + HGD	Case series Single centre Retrospective *Countries:* US *Length of follow-up:* not reported	*Number of patients:* 59 *Gender:* not reported *Age:* not reported *Prior treatments:* none reported *Length of Barretts:* (among 116 patients): Mean: 6.0 cm ± 3.3 cm *Inclusion criteria:* none notable	PDT *Drug:* porfimer sodium *Dose:* 2 mg/kg *Route of administration:* IV *Light source*: laser @ 630nm *Light dose:* 150 J/cm^2 *Time to photoactivation:* 48 hours *Treatment time:* not reported *Number of sessions:* not	*Outcomes:* None reported *Adverse events*	*Outcomes:* *Adverse events:* Strictures: 8/59 patients (14%)	4

Table B 1. Studies of photodynamic therapy (PDT) for Barrett's esophagus with/without dysplasia

Study authors (year published)	Cancer / Cell Type	Study Design	Patients	Intervention	Outcome Measures	Findings	Study quality
only			*Exclusion criteria:* none notable	reported *Co-interventions:* Omeprazole 80mg/day			
Mixed							
Comparative studies							
Burgarner JM, et al. (2008)[130]	BE	Cohort study Multi-centre Retrospective PDT vs. RFA *Countries*: not stated *Length of follow-up:* not reported	*Number of patients:* (PDT Group: 122 patients; RFA Group: 103 patients) *Gender:* not reported *Age:* not reported *Prior treatments:* PPI, unspecified *Length of Barretts:* not reported *Inclusion criteria:* none notable *Exclusion criteria:* none notable	RFA vs. PDT <u>PDT</u> *Drug:* not reported *Dose:* not reported *Route of administration:* not reported *Light source*: not reported *Light dose:* not reported *Time to photoactivation:* not reported *Treatment time:* not reported *Number of sessions:* not reported <u>RFA</u> *Device:* not reported *Power:* 300W *Dose: n*ot reported *Treatment time:* Not reported *Number of sessions:* Not reported *Co-interventions:* PPI, unspecified	*Outcomes:* Complete response of dysplasia (not HGD), risk ratio Percentage of BE remaining after initial ablation *Adverse events: none*	*Outcomes:* Complete response of dysplasia, risk ratio RFA vs PDT, follow-up unknown: 0.69 (95% CI [0.26, 1.65]) Percentage of BE remaining after initial ablation: -PDT 30% -RFA: 15%	4
Prasad GA, et al. (2007)[131]	BE + HGD	Cohort Study Single centre Retrospective	*Number of patients:* 199 (PDT Group: 129 patients; Esophagectomy Group: 70 patients)	PDT vs. Esophagectomy <u>PDT Group</u> *Drug and dose::* HPD 4 mg/kg – 26 patients	*Outcomes:* Complete response of HGD	*Outcomes:* Complete response of dysplasia: <u>PDT Group</u>	2

Table B 1. Studies of photodynamic therapy (PDT) for Barrett's esophagus with/without dysplasia

Study authors (year published)	Cancer / Cell Type	Study Design	Patients	Intervention	Outcome Measures	Findings	Study quality
		PDT vs Esophagectomy *Countries:* United States *Length of follow-up:* 5 yrs	<u>PDT Group</u> *Gender:* Male: 121 Female: 8 *Age:* 64.5 yrs ± 10.2 yrs <u>Esophagectomy Group</u> *Gender:* Male: 61 Female: 9 *Age:* Mean: 60.5 yrs ± 10.8 yrs *Prior treatments:* none reported *Length of Barretts:* <u>PDT Group</u> Median: 5 cm Range 3 to 8.5 cm <u>Esophagectomy Group</u> Median: 5 cm Range: 5 to 10.5 cm *Inclusion criteria:* none notable *Exclusion criteria:* none notable	Porfimer sodium 2 mg/kg – 103 patients *Route of administration:* IV *Time to photoactivation:* 48 hours *Light source:* laser (type not reported)at 630nm *Light dose:* 200J/cm^2 *Treatment time:* not reported *Number of sessions / patient:* Mean: 1.26 sessions / patient Range: 1 to 2 sessions / patient <u>Esophagectomy Group</u> TTE or THE *Co-interventions:* PPI, unspecified. EMR for focally visible lesions on endoscopy	Mortality: -All cause -Cancer Progression to cancer Mortality, hazard ratio*, PDT vs. esophagectomy -Overall -Cancer free *Adverse events*	- at 1 year: 88% - at 3 years: 86% <u>Esophagectomy Group</u> Not recorded Mortality at 5 years: <u>PDT Group</u> -All cause: 11/129 patients (9%) -Cancer: 0/129 patients (0%) <u>Esophagectomy Group</u> -All cause: 6/70 patients (8.5%) -Cancer: 0/70 patients (0%) Progression to cancer: <u>PDT Group</u> - at 1 year: 6/129 patients (5%) - at 3 years: 8/129 patients (6%) <u>Esophagectomy Group</u> Not recorded Mortality, hazard ratio, at 5 years: -Overall: 1.31 (95% CI [0.4, 4.17]) -Cancer free: 2.45 (95% CI [0.85, 7.12]) *Adverse events:* <u>PDT Group</u> * Stricture: 35/131 patients (27%) Photosensitivity: 77/131 patients (59%)	

Table B 1. Studies of photodynamic therapy (PDT) for Barrett's esophagus with/without dysplasia

Study authors (year published)	Cancer / Cell Type	Study Design	Patients	Intervention	Outcome Measures	Findings	Study quality
					* Cox proportional hazards model	Post-op mortality: 0/131 patients (0%) Total post-op "morbidity": none <u>Esophagectomy Group</u> Stricture: 9/70 patients (13%) Photosensitivity: 0/70 patients (0%) Post-op mortality: 1/70 patients (1%) Total post-op "morbidity": 27/70 patients (39%) * 3 extra patients of unknown origin reported.	
Reed MF, et al. (2005)[132]	BE + HGD	Cohort study Single centre Retrospective Endoscopic Therapy vs Esophagectomy vs Observation *Countries:* not reported *Length of follow-up*: 10 yrs	*Number of patients: 115* (Endoscopic Therapy Group: 47 patients – 42 PDT, 5 EMR; Esophagectomy Group: 49 patients; Observations Group: 19 patients) *Age:* Mean 65 yrs Range 30 to 87 yrs Gender: Male: 95 Female: 20 <u>Endoscopic Group</u> <u>*PDT*</u>*: 42 patients* <u>*EMR*</u> *5 patients* *Age:* Mean 70 yrs Range 30 to 89 yrs *Gender:* Male: 38	<u>Endoscopic Group</u> Endoscopic mucosal resection (EMR) or Photodynamic therapy (PDT) No details reported <u>Esophagectomy Group:</u> Surgical resection done within 60 days of diagnosis *Type of surgery:* -TTE: 20 patients (41%) -Ivor Lewis: 18 patients (37%) -THE: 7 patients (17%) -various or mixed techniques: 4 patients(8%) <u>Observation Group:</u> No details reported	*Outcomes:* Disease specific survival Overall survival Complete response of HGD	*Outcomes:* Disease specific survival at 5 years: -Endoscopic Group: not reported -Esophagectomy Group: 94% -Observation Group: not reported Overall survival: <u>Endoscopic Group:</u> not reported <u>Esophagectomy Group</u> - at 5 yrs: 83% - at 10 yrs: 64% <u>Observation Group:</u> not reported Complete response of HGD, follow-up unknown: <u>Endoscopic Group</u> PDT: 37/42 patients (88%)	4

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Study authors (year published)	Cancer / Cell Type	Study Design	Patients	Intervention	Outcome Measures	Findings	Study quality
			Female: 9 <u>Esophagectomy Group</u> *Age:* Mean 59 yrs Range 32 to 79 yrs *Gender:* Male: 40 Female: 9 <u>Observation Group:</u> *Age:* not reported *Gender:* not reported *Prior treatments:* none reported *Length of Barretts:* not reported *Inclusion criteria*: none notable *Exclusion criteria*: none notable	*Co-interventions:* none reported	Progression to cancer *Adverse event:*	EMR 3/5 patients (60%) <u>Esophagectomy Group</u> not reported <u>Observation Group</u> 0/13 patients (0%) Progression to cancer -Endoscopic Group: 6/47 patients -Esophagectomy Group: not reported -Observation 7/13 patients *Adverse events:* <u>Esophagectomy Group</u> Post op anastomotic leak: 2/49 patients (4%) Death secondary to large cerebrovascular accident post-op: 1/49 patients (2%)	
Non-comparative studies							
Kelty CJ, et al (2004)[133]	BE	Clinical trial Single centre Prospective *Countries:* UK *Length of follow-up:* 1 month	*Number of patients:* 25 *Gender:* Male: 20 Female: 5 *Age:* Mean: 62.48 yrs Range: 31 to 81 yrs *Prior treatments:* none reported	PDT *Drug:* ALA *Dose:* 30 or 60 mg/kg *Route of administration:* oral *Light source*: diode laser @ 635 to 635nm *Light dose:* 85 J/cm^2 *Time to photoactivation:* 4 to 6 hours	*Outcomes:* Complete response of BE (assessed through endoscopy with 4 quadrant biopsy) Partial response of BE Reduction in length of	*Outcomes:* Complete response of BE) at 4 weeks: 2/25 patients (8%) Partial response of BE at 4 weeks: 23/25 patients (92%) Reduction in length of Barretts:	4

Table B 1. Studies of photodynamic therapy (PDT) for Barrett's esophagus with/without dysplasia

Study authors (year published)	Cancer / Cell Type	Study Design	Patients	Intervention	Outcome Measures	Findings	Study quality
			Length of Barretts: Median: 4 cm Range: 2 to 15 cm *Inclusion criteria:* none notable *Exclusion criteria:* none notable	*Treatment time:* not reported *Number of sessions:* 1 session / patient *Co-interventions:* Esomeprazole 40 mg/day	Barretts: *Adverse events*	Median: 60% Range: 20 to 100% *Adverse events:* Nausea and vomiting: 8/25 patients (32%) Photosensitivity: 5/25 patients (20%) Hypotension: 2/25 patients (8%) Buried glands: 6/25 patients (24%)	
Mackenzie GD, et al (2008)[134]	BE + HGD	RCT Single centre Prospective Porfimer sodium PDT vs 5-ALA PDT *Countries:* UK *Length of follow-up*: not reported	*Number of patients:* 32 (Porfimer sodium PDT Group: 16 patients; ALA PDT Group: 16 patients) *Gender*: not reported *Age:* not reported *Prior treatments:* HGD nodules removed by EMR *Length of Barretts:* not reported *Inclusion criteria:* Residual HGD after EMR *Exclusion criteria:* none notable	PDT <u>Porfimer sodium PDT Group</u> *Drug:* Porfimer sodium *Dose:* not reported *Route of administration:* not reported *Light source*: not reported *Light dose:* not reported *Time to photoactivation:* not reported *Treatment time:* not reported *Number of sessions:* not reported <u>ALA PDT Group</u> *Drug:* 5-ALA *Dose:* 60 mg/kg *Route of administration:* oral *Light source*: red laser *Light dose:* 1178J/cm *Time to photoactivation:* not reported	*Outcomes:* Complete response of HGD (assessed through endoscopy with 4 quadrant biopsies every 2 cm) *Adverse events*	*Outcomes:* Complete response of dysplasia at unknown follow-up: -Porfimer sodium PDT: 9/14 patients (64%) -5 ALA PDT: 14/14 patients (100%) ($p<0.05$) *Adverse events:* <u>Porfimer sodium PDT Group</u> Strictures 6/16 patients (38%) Photosensitivity: 7/16 patients (44%) <u>5 ALA PDT Group</u> Strictures: 1/16 patients (6%) Photosensitivity: 0/16 patients (0%) ($p<0.05$, porfimer sodium vs. ALA)	4

Table B 1. Studies of photodynamic therapy (PDT) for Barrett's esophagus with/without dysplasia

Study authors (year published)	Cancer / Cell Type	Study Design	Patients	Intervention	Outcome Measures	Findings	Study quality
				Treatment time: not reported *Number of sessions:* Mean:: 1.16 sessions Range: 1 to 2 sessions *Co-interventions:* none reported			
Mackenzie G, et al (2007)[103]* * Thought to include patients from Mackenzie et al. (2005) [102] and Mellidez et al. (2005) [114].	BE + HGD	Case series Single centre Prospective *Countries:* not reported *Length of follow-up:* 36 months	*Number of patients:* 72 *Gender:* not reported *Age:* not reported <u>Group A</u> *Number of patients:* not reported *Gender:* not reported *Age:* not reported <u>Group B</u> *Number of patients:* not reported *Gender:* not reported *Age:* not reported <u>Group C</u> *Number of patients:* not reported *Gender:* not reported *Age:* not reported *Prior treatments:* not reported *Length of Barretts:* not reported *Inclusion criteria:* none	PDT <u>Group A</u> *Drug:* ALA *Dose:* 60 mg/kg *Route of administration:* oral *Light source*: red or green light *Light dose:* 1000J/cm^2 *Time to photoactivation:* 4 hours *Treatment time:* not reported *Number of sessions:* not reported <u>Group B</u> *Drug:* ALA *Dose:* 60 mg/kg *Light source*: red light *Light dose:* 500 to 750J/cm^2 Other details as above <u>Group C</u> *Drug:* ALA *Dose:* 30 mg/kg *Light source*: red or green light	*Outcomes:* Cancer risk (assessed though endoscopy with 4 quadrant biopsy every 2 cm) at 36 months using K-M analysis -Group A (red light patients only) vs. Other groups: -Red light vs Green light (patients in groups A and C) *Adverse events*	*Outcomes:* Cancer risk (assessed though endoscopy with 4 quadrant biopsy every 2 cm) at 36 months using K-M analysis - Group A (red light patients only) vs. Other groups: 3% vs. 34% - Red light vs Green light (patients in groups A and C): 8% vs. 45% *Adverse events:* Photosensitivity or strictures: 0/72 patients (0%)	4

Table B 1. Studies of photodynamic therapy (PDT) for Barrett's esophagus with/without dysplasia

Study authors (year published)	Cancer / Cell Type	Study Design	Patients	Intervention	Outcome Measures	Findings	Study quality
			notable *Exclusion criteria:* none notable	*Light dose:* 1000J/cm^2 Other details as above *Co-interventions:* none reported			
Mackenzie G, et al (2005)[135]	BE + HGD	Case series Single centre *Countries:* UK *Length of follow-up:* Mean: 15.8 months Range: 1 to 72 months	*Number of patients:* 51* *Gender:* not reported *Age*: not reported <u>Group A</u> *Number of patients:* 21 patients *Gender:* not reported *Age:* not reported <u>Group B</u> *Number of patients:* 12 patients *Gender:* not reported *Age:* not reported <u>Group C</u> *Number of patients:* 16 patients *Gender:* not reported *Age:* not reported *Prior treatments: none reported* *Length of Barretts:* not reported *Inclusion criteria:* none notable *Exclusion criteria:* none	PDT *Drug:* ALA *Route of administration:* oral *Light source*: not reported *Time to photoactivation:* not reported *Treatment time:* not reported *Number of sessions:* Mean: 1.74 sessions / patient <u>Group A</u> *Dose:* 60 mg/kg *Light dose:* 1000J/ cm^2 Other details as above <u>Group B</u> *Dose:* 60 mg/kg *Light dose:* 500 to 750J/cm^2 Other details as above <u>Group C</u> *Dose:* 30 mg/kg *Light dose:* 1000J/ cm^2 Other details as above *Co-interventions:* none reported	*Outcomes:* Complete response of HGD: *Adverse events*	*Outcomes:* Complete response of dysplasia at 15.8 months (mean): Group A: 16/21 patients (76%) Group B: 2/12 patients (17%) Group C: 5/16 patient (31%) All patients: 23/49 patients (47%) *Adverse events:* Strictures and photosensitivity: 0/51 patients (0%) Hypotension: 3/51 patients (6%) GI bleed requiring transfusion: 1/51 patients (2%)	4

Table B 1. Studies of photodynamic therapy (PDT) for Barrett's esophagus with/without dysplasia

Study authors (year published)	Cancer / Cell Type	Study Design	Patients	Intervention	Outcome Measures	Findings	Study quality
			notable * 3 patients unaccounted for.				
Wang KK, et al (2002)[136] * * Information extracted for BE or HGD patients only	BE (10 patients) BE + LGD (34 patients) BE+ HGD (48 patients)	Case series Single centre Prospective *Countries:* US *Length of follow-up:* Mean: 45 months ± 3 months	*Number of patients:* 92 *Gender:* not reported *Age:* not reported *Prior treatments:* none reported *Length of Barretts:* Mean: 7 cm ± 4 cm *Inclusion criteria:* none notable *Exclusion criteria:* none notable	PDT *Route of administration:* IV *Light source*: not reported *Light dose:* 175 to 200J/cm^2 *Time to photoactivation:* 48 hours *Treatment time:* not reported *Number of sessions:* Median: 1 session / patient Range: 1 to 3 sessions <u>HpD Group</u> Drug: HpD Dose: 1.75 to 4.0 mg/kg Other details as above <u>Porfimer Sodium Group</u> Drug: Porfimer sodium Dose: 2 mg/kg Other details as above *Co-interventions:* Omeprazole 20 to 60 mg/day	*Outcomes:* Progression to cancer Difference in the length of BE pre- and post- PDT *Adverse events:* No BE or HGD specific information available.	*Outcomes:* Progression to cancer at 45 months (mean): 4/10 patients (40%) from BE Difference in the length of BE: -Pre-PDT: mean: 7 cm ± 0.4 cm -Post-PDT: mean: 2 cm ± 0.3 cm	4

Table B 2. Studies of argon plasma coagulation (APC) for Barrett's esophagus with/without dysplasia

Study authors (year published)	Cancer / Cell Type	Study Design	Patients	Intervention	Outcome Measures	Findings	Study quality
Comparative studies							
Dulai GS, et al. (2005)[137]	BE	RCT Prospective APC vs. MPEC *Countries:* US *Length of follow-up:* 1 to 1.5 months (after last session)	*Number of patients:* 52 (APC Group: 26 patients; MPEC Group: 26 patients) <u>APC Group</u> *Gender* Male: 21 Female: 5 *Age:* Mean: 58 yrs ± 11 yrs <u>MPEC Group</u> *Gender:* Male: 23 Female: 3 *Age:* Mean: 56 yrs ± 11 yrs *Prior treatments:* none reported *Length of Barretts:* <u>APC Group</u> Mean: 4.0 cm ± 1.5 cm <u>MPEC Group</u> Mean: 3.1cm ± 1.7 cm *Inclusion criteria:* none notable *Exclusion criteria:* Severe active comorbid disease Diagnosis of HGD or cancer Prior antireflux surgery Inability to discontinue NSAID therapy	APC vs. MPEC <u>APC Group</u> *Gas flow*: 2L/minute *Power:* 60 watts *Treatment time*: not reported *Number of sessions:* Mean: 3.8 sessions ± 1.7 sessions <u>MPEC Group</u> *Probe:* not reported *Power:* 16 watts *Treatment time:* not reported *Number of sessions:* Mean: 2.9 sessions ± 1.5 sessions *Co-interventions:* Pantoprazole, dosing unspecified.	*Outcomes:* Complete response of BE (assessed through endoscopy with 4 quadrant biopsies every 2 cm) *Adverse events:*	*Outcomes:* Complete response of BE at 1 to 1.5 months: -APC Group: 21/26 patients (81%) -MPEC Group: 23/26 patients (88%) (p=0.68) *Adverse events:* <u>APC Group</u> Chest pain, severe: 1/26 patients (4%) <u>MPEC Group</u> none	1

Table B 2. Studies of argon plasma coagulation (APC) for Barrett's esophagus with/without dysplasia

Study authors (year published)	Cancer / Cell Type	Study Design	Patients	Intervention	Outcome Measures	Findings	Study quality
			Pregnancy, lactation or non-use of birth control measures Allergy to PPI Uncontrolled coagulopathy				
Hage M, et al. (2004)[107]	BE BE+LGD	RCT Prospective APC vs PDT *Countries:* Netherlands *Length of follow-up:* 24 months	Number of patients: 40 (APC Group: 14 patients; PDT100 Group: 13 patients; PDT20+100 Group: 13 patients) <u>APC Group:</u> *Gender:* Male: 11 Female: 3 *Age:* Median: 60 yrs Range: 41 to 69 yrs <u>PDT100 Group:</u> *Gender:* Male: 10 Female: 3 *Age:* Median: 57 yrs Range: 52 to 72 yrs <u>PDT20+100 Group:</u> *Gender:* Male: 10 Female: 3 *Age:* Median: 61 yrs Range: 57 to 69 yrs *Prior treatments:* PPI, unspecified *Length of Barretts:* Median: 3 cm Range: 2 to 5 cm	<u>APC Group:</u> *Gas flow:* 2L/minute *Power:* 65 watts *Number of sessions:* 2 2/3 of the lesion ablated in the 1st session and the rest in the second <u>PDT100 Group:</u> *Drug:* 5-ALA *Dose:* 60 mg/kg *Route of administration:* oral *Light source*: diode laser @ 633 nm *Light dose:* 100 J/cm^2 *Time to photoactivation:* 4 hours post ALA *Treatment time:* not reported *Number of sessions:* not reported <u>PDT20+100 Group:</u> *Drug:* 5-ALA *Dose:* 60 mg/kg *Route of administration:* oral *Light source*: diode laser @ 633 nm *Light dose:* 20 J/cm^2 one hour post ALA + 100 J/cm^2 4 hours post ALA *Time to photoactivation:* 4 hours post ALA *Treatment time:* not reported *Number of sessions:* not	*Outcomes:* Complete response of BE (assessed *endoscopically*) Complete response of BE (assessed *histologically* through 4 quadrant biopsies every 2 cm) *Adverse events*	*Outcomes:* Complete response of BE by endoscopy at 6 weeks: -APC Group: 7/14 patients (50%) (PDT100 vs. PDT20+100: p<0.005) (PDT20+100 vs. APC: not significant) -PDT100 Group: 1/13 patients (8%) -PDT20+100 Group: 5/13 patients (38%) (PDT100 vs. APC: = p<0.05) Complete response of BE – histological at 6 weeks: -PDT100 Group: 1/13 patients (8%) -PDT20+100 Group: 4/13 patients (31%) -APC Group: 5/14 patients (36%) (no significant differences) *Adverse events:* <u>APC Group</u> Pain during treatments: 5/14 patients (36%) Odynophagia: 12/14 patients (86%) Fever: 2/14 patients (14%) Nausea/vomiting: 0/14 patients (0%) Sudden death (presumably from cardiac arrhythmia): 0/14 patients (0%) Strictures: 1/14 patients (7%) Elevated liver enzymes: 0/14 patients (0%) Buried glands: 7/14 patients (50%)	1

Table B 2. Studies of argon plasma coagulation (APC) for Barrett's esophagus with/without dysplasia

Study authors (year published)	Cancer / Cell Type	Study Design	Patients	Intervention	Outcome Measures	Findings	Study quality
			Inclusion criteria: none notable *Exclusion criteria:* Acute porphyria; pregnancy; intolerance to endoscopy; inter-current diseases with an adverse impact on survival	reported *Co-interventions:* Omeprazole 40mg/day		PDT Groups Pain during treatments: 23/26 patients (89%) Odynophagia: 24/26 patients (92%) Fever: 8/26 patients (31%) Nausea/vomiting: 7/26 patients (27%) Sudden death (presumably from cardiac arrhythmia): 1/26 patients (4%) Strictures: 0/26 patients (0%) Elevated liver enzymes: 20/26 patients (77%) Buried glands: 1/26 patients (4%)	
Kelty CJ, et al. (2004)[45]	BE	RCT Single centre Prospective APC vs. PDT *Countries:* UK *Length of follow-up*: 24 months	*Number of patients:* 72 (APC Group: 37 patients; PDT Group:35 patients) APC Group *Gender:* Male: 30 Female: 7 *Age:* Median: 59 yrs Range: 28 to 79 yrs PDT Group *Gender:* Male: 28 Female: 7 *Age:* Median: 61 yrs Range: 33 to 83 yrs *Prior treatments:* none reported *Length of Barretts:*	APC vs PDT APC Group *Gas flow:* 2L/minute *Power:* 65 watts *Number of sessions:* Median: 3 sessions Range: 1 to 5 sessions Max allowed: 5 sessions PDT Group *Drug:* 5-ALA *Dose:* 30 mg/kg *Route of administration:* oral *Light source*: diode laser @ 633 nm *Light dose:* 85 J/cm^2 *Time to photoactivation:* 4 to 6 hours post ALA *Treatment time:* not reported *Number of sessions:* Median: 5 sessions Range: 1 to 5 sessions Max allowed: 5 sessions	*Outcomes:* Complete response of BE (assessed through endoscopy and 4 quadrant biopsy every 2 cm) Partial response of BE Number of treatments to achieve complete response of BE *Adverse events*	*Outcomes:* Complete response of BE at 4 weeks: -APC Group: 33/34 patients (97%) -PDT Group: 17/34 patients (50%) Partial response of BE: -APC Group: 1/34 patients (3%) -PDT Group: 17/34 patients (50%) Number of treatments to achieve complete response of BE: APC Group Median: 3 treatments Range: 1 to 5 treatments PDT Group Median: 2 treatments Range: 1 to 4 treatments *Adverse events:* APC Group Nausea / vomiting; photosensitivity; hypotension; chest pain; elevated	1

Table B 2. Studies of argon plasma coagulation (APC) for Barrett's esophagus with/without dysplasia

Study authors (year published)	Cancer / Cell Type	Study Design	Patients	Intervention	Outcome Measures	Findings	Study quality
			APC Group Median: 4 cm Range: 2 to 8 cm PDT Group Median: 4 cm Range: 2 to 15 cm *Inclustion criteria:* none notable *Exclusion criteria:* none notable	*Co-interventions:* none reported		liver enzymes, mild: 0/34 patients (0%) Odynophagia: 32/34 patients (94%) Dysphagia secondary to strictures: 1/34 patients (3%) Buried glands (4 week follow-up): 7/33 patients (21%)PDT Group Nausea / vomiting: 11/34 patients (32%) Photosensitivity: 5/34 patients (15 %) Hypotension: 2/34 patients (6%) Chest pain: 1/34 patients (3%) Odynophagia: 1/34 patients (3%) Dysphagia secondary to strictures: 0/34 patients (0%) Elevated liver enzymes, mild: 4/34 patients (12%) Buried glands (4 week follow-up): 4/17 patients (24%)	
Ragunath K, et al. (2005)[60]	BE + HGD BE + LGD	RCT Single centre Prospective APC vs. PDT *Countries*: UK *Length of follow-up:* 12 months	Number of patients: 26 (APC Group: 13 patients; PDT Group: 13 patients) APC Group *Gender:* Male: 10 Female: 3 *Age:* Mean: 64.9 yrs Range: 41 to 86 yrs PDT Group *Gender:* Male: 13 Female: 0 *Age:* Mean: 58.1 yrs Range 35 to 79 yrs	APC vs. PDT APC Group *Gas flow:* 1.8L/minute *Power:* 65 watts *Treatment time:* not recorded *Number of sessions:* 1 session / patient PDT Group *Drug:* porfimer sodium *Dose*: 2 mg.kg *Route of administration:* IV *Time to photoactivation:* 48 hours *Light source:* argon pump dye laser @630 nm *Light dose:* 200 J/cm^2 *Treatment time:* not recorded	*Outcomes:* Complete response of BE (assessed through endoscopy with 4 quadrant biopsy every 1 cm) Complete response of HGD (assessed through endoscopy with 4 quadrant biopsy every 1 cm) Complete response of LGD	*Outcomes:* Complete response of BE: APC Group - at 4 months: 2/13 patients (15%) - at 12 months: 0/9 patients (0%) PDT Group - at 4 months: 2/13 patients (15%) - at 12 months: 2/13 patients (15%) Complete response of HGD: APC Group - at 4 months: 1/1 patient (100%) - at 12 months: 0/0 patients (0%) PDT Group - at 4 months: 2/2 patients (100%) - at 12 months: 2/2 patients (100%) Complete response of LGD:	1

Table B 2. Studies of argon plasma coagulation (APC) for Barrett's esophagus with/without dysplasia

Study authors (year published)	Cancer / Cell Type	Study Design	Patients	Intervention	Outcome Measures	Findings	Study quality
			Prior treatments: not reported *Length of Barretts:* <u>APC Group</u> Mean: 5.5 cm Range: 3 to 9 cm <u>PDT Group</u> Mean: 5.7 cm Range: 3 to 9 cm *Inclusion criteria:* none notable *Exclusion criteria:* Previous or current esophageal malignancy; previous esophagectomy; history of EMR or mucosal ablation treatment; predominantly "tongues" as opposed to circumferential BE; history of porphyria; pregnancy or lack of contraception	*Number of sessions:* 1 session / patient *Co-interventions:* Lansoprazole 60 mg/day during treatment then 30 mg/day	(assessed through endoscopy with 4 quadrant biopsy every 1 cm) Complete response of dysplasia Reduction in length of BE Progression to cancer *Adverse events*	<u>APC Group</u> - at 4 months: 7/12 patients (58%) - at 12 months: 6/9 patients (67%) <u>PDT Group</u> - at 4 months: 8/11 patients (73%) - at 12 months: 8/11 patients (73%) Complete response of dysplasia: <u>APC Group</u> - at 4 months: 8/13 patients (62%) - at 12 months: 6/9 patients (67%) <u>PDT Group</u> - at 4 months: 10/13 patients (77%) - at 12 months: 10/13 patients (77%) (p=0.03) Reduction in length of BE: <u>APC Group</u> - at 4 months: 65% reduction - at 12 months: 56% reduction <u>PDT Group</u> - at 4 months: 57% reduction - at 12 months: 61% reduction Progression to cancer: <u>APC</u> - at 4 months: 0/13 patients (0%) - at 12 months: 0/13 patients (0%) <u>PDT Group</u> - at 4 months: 0/13 patients (0%) - at 12 months: 1/13 patients (8%) *Adverse events:* <u>APC Group</u> Strictures: 3/13 patients (23%) Chest pain, odynophagia and fever: 1/13 patients (8%) Photosensitivity: 0/13 patients (0%)	

Table B 2. Studies of argon plasma coagulation (APC) for Barrett's esophagus with/without dysplasia

Study authors (year published)	Cancer / Cell Type	Study Design	Patients	Intervention	Outcome Measures	Findings	Study quality
						Buried glands: 0/13 patients (0%) <u>PDT Group</u> Strictures: 2/13 patients (15%) Chest pain, odynophagia and fever: 0/13 patients (0%) Photosensitivity: 2/13 patients (15%) Buried glands: 1/13 patients (8%)	
Sharma P, et al. (2006)[138]	BE BE + LGD	RCT Multi-centre Prospective APC vs. MPEC *Countries:* US *Length of follow-up:* 2 yrs	*Number of patients*: 35 (MPEC Group: 16 patients; APC Group: 19 patients) *Gender:* Male: 34 Female: 1 <u>APC Group</u> *Age* Mean: 65 yrs Range: 32 to 84 yrs <u>MPEC Group</u> *Age* Mean: 60 yrs Range: 42 to 68 yrs *Prior treatments:* none reported *Length of Barretts:* <u>APC Group</u> Mean: 4 cm Range: 2 to 6 cm <u>MPEC Group</u> Mean: 3 cm Range: 2 to 6 cm *Inclusion criteria:* none notable	APC vs. MPEC <u>APC Group</u> *Gas flow:* 1.4 to 1.8 L/minute *Power:* 60 watts *Number of sessions:* Mean: 3.4 sessions/patient <u>MPEC Group</u> *Probe*: 10F gold *Power:* 20 watts *Number of sessions:* not reported *Co-interventions:* Rabeprazole 40mg/day (median)	*Outcomes:* Complete response of BE (assessed through endoscopy with 4 quadrant biopsies every 2 cm) Number of sessions to achieve complete response of BE Progression to cancer Progression to HGD *Adverse events*	*Outcomes:* Complete response of BE at 2 years: -APC Group: 12/19 patients (63%) -MPEC Group: 12/16 patients (75%) Number of sessions to achieve complete response of BE: -APC Group: Mean: 3.4 sessions / patient -MPEC Group: Mean: 3.8 sessions / patient (p=0.48) Progression to cancer at 2 years: -APC Group: 0/19 patients (0%) -MPEC Group: 0/16 patients (0%) Progression to HGD at 2 years: -APC Group: 0/19 patients (0%) -MPEC Group: 0/16 patients (0%) *Adverse events:* <u>APC Group</u> : Sore throat: 9/19 patients (47%) Dysphagia: 2/19 patients (11%) Chest pain: 4/19 patients (21%) Epigastric pain: 2/19 patients (11%) Fever, low grade: 1/19 patients (5%)	1

Table B 2. Studies of argon plasma coagulation (APC) for Barrett's esophagus with/without dysplasia

Study authors (year published)	Cancer / Cell Type	Study Design	Patients	Intervention	Outcome Measures	Findings	Study quality
			Exclusion criteria: History of esophageal surgery; HGD with EAC; strictures or varices; allergy to PPI; coagulopathy; significant uncontrolled co-morbidities			Stricture: 1/19 patients (5%) Perforation: 0/19 patients (0%) Bleeding: 0/19 patients (0%)<u>MPEC Group</u> Sore throat: 9/16 patients (56%) Dysphagia: 5/16 patients (31%) Chest pain: 6/16 patients (38%) Epigastric pain: 0 /16 patients (0%) Fever, low grade: 0 /16 patients (0%) Stricture: 0 /16 patients (0%) Perforation: 0 /16 patients (0%) Bleeding: 0 /16 patients (0%)	
Thomas T, et al. (2005)[139] * * Information extracted for BE or HGD patients only	BE + HGD	Cohort study Multi-centre Retrospective APC vs Esophagectomy vs Non-Intervention vs Surveillance *Countries:* UK *Length of follow-up:* <u>APC and Non-Intervention Groups</u> Not reported <u>Surveillance Group</u> Mean: 15 months Range: 4 to 39 months <u>Esophagectomy Group</u> Mean: 21 months Range: 6 to 36 months	*Number of patients:* 27 (APC: 5 patients; Esophagectomy Group: 8 patients; Non-Intervention Group: 7 patients; Surveillance Group: 7 patients) <u>APC Group</u> *Gender:* Male: 5 *Age:* Mean: 70 yrs Range: 54 to 76 yrs <u>Esophagectomy Group</u> *Gender:* Male: 7 Female: 1 *Age:* Mean: 58 yrs Range: 46 to 76 yrs <u>Non-Intervention Group</u> *Gender:* not reported *Age:* Mean: 80 yrs Range: 74 to 95 yrs	Surveillance vs Esophagectomy vs APC vs Non-Intervention <u>APC Group</u> *Gas flow:* not reported *Power:* not reported *Treatment time:* not recorded *Number of sessions:* Mean: 4 sessions / patient Range: 1 to 14 sessions / patient <u>Esophagectomy Group</u> No details reported <u>Surveillance Group</u> *Time between endoscopies:* Mean: 4.6 months *Number of treatments:* Mean 2.9 treatments / patient Range: 1 to 5 treatments / patient 4 quadrant biopsy every 2 cm in 45% of biopsies	*Outcomes:* Overall survival Disease specific survival Complete response of HGDa	*Outcomes:* Overall survival: -APC Group: not reported -Esophagectomy Group at 21 months (mean): 5/8 patients (62.5%) -Non-Intervention Group, at unknown follow-up: 2/7 patients (28.6%) -Surveillance Group: not reported Disease-specific survival -APC Group: not reported -Esophagectomy Group at 21 months (mean): 7/8 patients (88%)* -Non-Intervention Group, at unknown follow-up: 5/7 patients (71%)** -Surveillance Group: not reported Complete response of dysplasia: -APC Group at unknown follow-up: 2/5 patients (40%) -Esophagectomy Group: not reported -Non-intervention Group: not reported	4

Table B 2. Studies of argon plasma coagulation (APC) for Barrett's esophagus with/without dysplasia

Study authors (year published)	Cancer / Cell Type	Study Design	Patients	Intervention	Outcome Measures	Findings	Study quality
			Surveillance Group *Gender:* Male: 6 Female: 1 *Age:* Mean: 65.4 yrs Range: 55 to 86 yrs *Prior treatments:* PPI, unspecified *Length of Barretts:* Mean: 6 cm Range: 3 to 14 cm APC Group Mean: 6 cm Range: 3 to 9 cm Surveillance Group Mean: 5 cm Range: 2 to 10 cm *Inclusion criteria:* none notable *Exclusion criteria:* none notable	*Co-interventions:* Omeprazole 20-40 mg daily: 17 patients Lansoprazole 30 mg daily: 14 patients Pantoprazole 40 mg daily: 1 patient Rabeprazole 40 mg daily: 2 patients Ranitidine 150 mg twice daily: 3 patients	Progression to cancer *Adverse events:* No BE or HGD specific information available	-Surveillance Group at 15 months (mean): 4/7 patients (57%) Progression to cancer: -APC Group at unknown follow-up: 2/5 patients (40%) -Esophagectomy Group at 21 months (mean): 2/8 patients (25%) -Non-Intervention Group at unknown follow-up: 2/4 patients (50%) -Surveillance Group at 15 months: 2/6 patients (33%)	
Zoepf T, et al. (2003)[108]	BE + HGD BE + LGD	RCT Single centre Prospective APC vs. PDT *Countries:* Germany *Length of follow-up*: APC Median: 24 months Range: 4 to 46 months PDT Median: 27 months	*Number of patients:* 20 (APC Group: 10 patients; PDT Group: 10 patients) *Gender:* not reported *Age:* Mean: 68 yrs Range 44 to 77 yrs *Prior treatments:* none reported *Length of Barretts:* PDT Mean: 3.5 cm	APC vs. PDT APC *Power:* 70 watts *Gas flow:* not reported *Treatment time:* not reported *Number of sessions / patient:* Mean: 4 sessions / patient Range: 2 to 9 sessions / patient PDT *Drug:* 5-ALA *Dose:* 60 mg/kg *Route of administration:* oral *Time to photoactivation:* not	*Outcomes:* Reduction in length of BE *Adverse events*	*Outcomes:* Reduction in length of BE "after treatment": APC Mean 90% Range: 50 to 100% PDT Mean: 90% Range: 0 to 100% *Adverse events:* APC Nausea / vomiting: 0/10 patients (0%)	1

Table B 2. Studies of argon plasma coagulation (APC) for Barrett's esophagus with/without dysplasia

Study authors (year published)	Cancer / Cell Type	Study Design	Patients	Intervention	Outcome Measures	Findings	Study quality
		Range: 12 to 42 months	Range: 3 to 12 cm APC Mean: 4.0 cm Range: 3 to 7 cm *Inclusion criteria:* none notable *Exclusion criteria:* none notable	reported *Light source:* diode laser @ non-reported wavelength *Light dose:* 150J/cm^2 *Treatment time:* not reported *Number of sessions / patient:* Mean: 2 sessions / patient Range: 1 to 5 sessions / patient *Co-interventions:* none reported		Dysphagia, transient: 3/10 patients (30%) Photosensitivity: 0/10 patients (0%) Mediastinal emphysema: 1/10 patients (10%)PDT Nausea / vomiting: 10/10 patients (100%) Dysphagia, transient 4/10 patients (40%) Photosensitivity: 0/10 patients (0%) Mediastinal emphysema: 0/10 patients (0%)	
Non-comparative studies							
Attwood SEA, et al. (2003)[140]	BE+HGD	Case series Single centre Prospective *Countries:* UK *Length of follow-up:* Mean: 37 months Range: 7 to 78 months	*Number of patients: 29* *Gender:* Male: 22 Female: 7 *Age:* Median: 65 yrs Range: 43 to 85 yrs *Prior treatments:* none reported *Length of Barretts:* Mean: 6 cm Range: 1 to 12 cm *Inclusion criteria:* Unfit for resection (25 patients) *Exclusion criteria:* none notable	APC under sedation *Power:* 70 watts *Gas flow:* 2L/minute *Treatment time:* not reported *Number of sessions:* Median: 2 sessions / patient Range: 1 to 13 treatments *Co-interventions:* PPI, unspecified.	*Outcomes:* Complete response of BE (assessed through endoscopy with 4 quadrant biopsies) Progression to cancer Rate of progression to cancer *Adverse events*	*Outcomes:* Complete response of BE at 4 to 8 weeks: 22/29 patients (76%) Progression to cancer at 37 months (mean): 4/29 patients (14%) Rate of progression to cancer: 3.7 cases/ 1000 patient months *Adverse events:* Esophageal perforation 1/29 patients (3%)	4
Basu, KK, et al. (2006)[141]	BE	Case series Single centre Prospective *Countries:* UK	*Number of patients:* 33 *Gender:* Male: 28 Female: 5 *Age:*	APC *Power:* 30 watts *Gas flow*: not reported *Treatment time:* not reported *Number of sessions:*	*Outcomes:* Complete response of BE Number of sessions to	*Outcomes:* Complete response of BE at 4 weeks: 28/33 patients (85%) Number of sessions to achieve	4

Table B 2. Studies of argon plasma coagulation (APC) for Barrett's esophagus with/without dysplasia

Study authors (year published)	Cancer / Cell Type	Study Design	Patients	Intervention	Outcome Measures	Findings	Study quality
			Mean: 63.4 yrs Range: 39 to 79 yrs *Prior treatments:* none reported *Length of Barretts:* Mean: 6.5 cm Range: 4 to 19 cm *Inclusion criteria:* none notable *Exclusion criteria:* none notable.	Mean: 4 sessions Range: 1 to 8 sessions One third circumference of the esophagus treated / session *Co-interventions:* PPI: -Omeprazole 20 mg twice daily (22 patients) -Lansoprazole 30 mg daily (9 patients) -Pantoprozole 40 mg daily (2 patients)	achieve complete response of BE *Adverse events:* none	complete response of BE: Mean: 4 sessions Range: 1 to 8 sessions	
Brand B, et al. (2000)[142]	BE	Case series *Countries:* Germany *Length of follow-up:* Median 12 months Range: 3 to 25 months	*Number of patients:* 12 *Gender:* Male: 8 Female: 4 *Age:* Mean:57 yrs Range: 42 to 69 yrs *Prior treatments:* none reported *Length of Barretts:* Mean: 4 cm Range: 2 to 11 cm *Inclusion criteria:* none notable *Exclusion criteria:* none notable	APC *Power:* not reported *Gas flow:* not reported *Treatment time:* not reported *Number of treatment sessions:* Mean: 5 sessions Range: 4 to 11 sessions Repeated at intervals of 2 to 3 weeks *Co-interventions:* none reported	*Outcomes:* Complete response of BE (assessed through 4 quadrant biopsies every 2 cm) Number of sessions to achieve complete response of BE Recurrence of BE *Adverse events*	*Outcomes:* Complete response of BE at one month: 11/12 patients (92%) Number of sessions to achieve complete response of BE: Mean: 5 sessions Range: 4 to 11 sessions Recurrence of BE at 12 months (median): 2/12 patients (16.7%) *Adverse events:* Chest pain and odynophagia: 11/12 patients (92%)	4
Bright T, et al (2007) [143]and Ackroyd R, et al (2004) [144]	BE BE + LGD	RCT Single centre Prospective APC vs Surveillance	*Number of patients:*40 (APC Group: 20 patients; Surveillance Group: 20 patients) <u>APC Group</u> *Gender:*	APC vs. Surveillance <u>APC Group</u> *Gas flow:* 2L/minute *Power*: 60 watts *Treatment time:* not reported *Number of sessions:*	*Outcomes:* Complete response of BE (assessed through 4 quadrant biopsy)	*Outcomes:* Complete response of BE: <u>APC Group</u> -at 4 weeks: 12/20 patients (60%) -at 1 year: 11/19 patients (58%) -at 5 years: 8/19 patients (40%)	4

Table B 2. Studies of argon plasma coagulation (APC) for Barrett's esophagus with/without dysplasia

Study authors (year published)	Cancer / Cell Type	Study Design	Patients	Intervention	Outcome Measures	Findings	Study quality
		Countries: Australia *Length of follow-up:* 1 year	Male: 15 Female: 5 *Age:* Median: 47 yrs Range: 36 to 69 yrs <u>Surveillance Group</u> *Gender:* Male: 17 Female: 3 *Age:* Mean:51 yrs Range: 31 to 73 yrs *Prior treatments:* Laparoscopic fundoplication for GERD *Length of Barretts:* Median: 4 cm Range 2 to 19 cm *Inclusion criteria:* not reported *Exclusion criteria:* HGD or ulcerative esophagitis	Median: 3 sessions Range: 2 to 6 sessions Ablation done in linear lengthwise strips APC repeated up to 6 times as needed and again one year later <u>Surveillance Group</u> Endoscopy one year later *Co-interventions:* none reported	Complete response of LGD (assessed through 4 quadrant biopsy)* Partial response of BE at 1 year Recurrence of BE given previous response at 1 year Survival at 1 year *Adverse events:* *follow-up time: 1 year	<u>Surveillance Group</u> -at 4 weeks: 3/20 patients (15%) -at 1 year: 2/20 patients (10%) -at 5 years: 4/20 patients (20%) Complete response of LGD*: -APC Group: 19/19 patients (100%) -Surveillance Group: 20/20 patients (100%) Partial response of BE at 1 year: -APC Group: not reported -Surveillance Group: 11/20 patients (55%) Recurrence of BE given previous response at 1 year: -APC Group: 1/12 patients (8.3%) Survival at 1 year: -APC Group: 19/20 patients (95%) -Surveillance Group: 20/20 patients (100%) *Adverse events:* <u>APC Group</u>: Chest pain and odynophagia observed among "some" patients Strictures, late after treatment (18 months and 5 years): 2/20 (10%) Buried glands: 2/20 (10%) <u>Surveillance Group:</u> none *follow-up time: 1 year	
Dumoulin FL, et al. (1997)[145]	BE	Case report Single centre	*Number of patients*: 2 *Gender:* Male: 2	APC *Power:* 50 watts *Gas flow:* 2L/minute	*Outcomes:* Complete response of BE	*Outcomes:* Complete response of BE post-APC: 0/2	4

Table B 2. Studies of argon plasma coagulation (APC) for Barrett's esophagus with/without dysplasia

Study authors (year published)	Cancer / Cell Type	Study Design	Patients	Intervention	Outcome Measures	Findings	Study quality
		Countries: Germany *Length of follow-up:* not reported	*Age:* 29 and 34 yrs *Prior treatments:* Omeprazole 20 mg twice daily Fundoplication *Length of Barretts:* 8cm and 10 cm *Inclusion criteria:* none notable *Exclusion criteria:* none notable	*Treatment time:* not reported *Number of sessions:* not reported *Co-interventions:* Omeprazole 20 mg twice daily Cisapride 10 mg 3 times daily	Reduction in size of BE *Adverse events*	Reduction in the size of BE: 8 cm to 5 cm 10 cm to 4 cm *Adverse events:* Chest pain, mild, transient; and dysphagia for one day: 2/2 patients (100%)	
Familiari L, et al. (2003)[146]	BE (13 patients) BE + LGD (19 patients)	Case series Single centre Prospective *Countries:* not reported *Length of follow-up:* Median: 49.5 months Range: 24 to 60 months	*Number of patients:* 32 *Gender:* Male: 26 Female: 6 *Age:* Median: 58.3 yrs Range: 29 to 78 yrs *Prior treatments:* none reported *Length of Barretts:* BE<3cm: (18 patients) BE≥3cm: (14 patients) *Inclusion criteria:* none notable *Exclusion criteria:* none notable	APC *Power:* 60 watts *Gas Flow:* 2L / minute *Treatment time:* not reported *Number of sessions:* Mean: 2.0 sessions / patient Range: 1 to 3 sessions / patient *Co-interventions:* Omeprazole 40 mg/day during treatment then 20 mg/ day for 6 months	*Outcomes:* Complete response of BE (assessed through endoscopy with 4 quadrant biopsy every 2 cm) Number of sessions to achieve complete response of BE *Adverse events*	*Outcomes:* Complete response of BE: -post APC: 32/32 patients (100%) -6 months: 31/32 patients (97%) -1 year: 30/32 patients (94%) -2 years: 29/32 patients (91%) Number of sessions to achieve complete response of BE: Mean: 2.0 sessions Range: 1 to 3 sessions *Adverse events:* Chest pain, mild: 7/32 patients (22%)	4
Ferraris R, et al. (2007)[147]	BE	Cohort Study Multi-centre (5) Retrospective *Countries:* Italy *Length of follow-up:*	*Number of patients:* 96 *Gender:* Male: 70 Female: 26 *Age:* Mean: 57.1 yrs Range: 21 to 79 yrs	APC *Power*: 40 watts *Gas flow:* not reported *Treatment time:* 10 to 20 minutes *Number of sessions:* Mean: 3.2 sessions	*Outcomes:* Complete response of BE (assessed though 4 quadrant biopsy every 2 cm): All patients APC + OM vs. APC + ARS	*Outcomes:* Complete response of BE: All patients: 94/96 patients (97.9%) APC + OM Group vs. APC + ARS: -1 yr: 97.9% vs. 100% -2 yr: 94.9% vs. 95.1% -3 yr: 80.3% vs. 95.1%	4

Table B 2. Studies of argon plasma coagulation (APC) for Barrett's esophagus with/without dysplasia

Study authors (year published)	Cancer / Cell Type	Study Design	Patients	Intervention	Outcome Measures	Findings	Study quality
		Mean: 36 months Range: 18 to 98 months	<u>APC + OM Group</u> *Number of patients:* 50 patients *Gender:* not reported *Age:* not reported <u>APC + ARS Group</u> *Number of patients:* 46 patients *Gender:* not reported *Age:* not reported *Prior treatments:* none reported *Length of Barretts:* Median: 4 cm Range: 2.5 to 11 cm *Inclusion criteria:* none notable *Exclusion criteria:* Serious disease present	Range: 1 to 8 sessions <u>APC + OM Group</u> APC as above Omeprazole 40mg/day <u>APC + ARS Group</u> APC as above Laparoscopic fundoplication *Co-interventions:* As above	Number of sessions to achieve complete response of BE *Adverse events:* none	-4 yr: 70.5% vs. 87.3% -5 yr: 43.8% vs. 76.4% ($p<0.05$) Number of sessions to achieve complete response of BE: Mean: 3.2 sessions Range: 1 to 8 sessions	
Formentini A, et al. (2007)[148]	BE	Case series Retrospective *Countries:* Germany *Length of follow-up:* Mean: 17.5 months post ARS Range: 1 to 54 months	*Number of patients:* 21 *Gender:* Male: 15 Female: 6 *Age:* Mean: 45 yrs Range: 32 to 66 yrs *Prior treatments:* none reported *Length of Barretts:* <3cm *Inclusion criteria:* none notable *Exclusion criteria:* none notable	<u>APC</u> *Power:* 75 watts *Gas Flow:* 2L / minute *Treatment time:* not reported *Number of sessions:* Mean: 3.6 sessions / patient Range: 1 to 12 sessions / patient *Co-interventions:* - ARS 360^{o} Nissen fundoplication Laparoscopic in 17/21 patients or open in 4/21 patients *Length of stay:* Mean: 7.9 days	*Outcomes:* Complete response of BE *Adverse events*	*Outcomes:* Complete response of BE: - 1 to 1.5 months post APC: 17/17 patients (100%) - 17.5 months (mean) post ARS: 11/17 patients (65%) *Adverse events:* Strictures requiring dilation: 1/21 patients (5%) Chest pain, transient: 2/21 patients (10%) Dysphagia and nausea: 1/21 patients (5%)	4

Table B 2. Studies of argon plasma coagulation (APC) for Barrett's esophagus with/without dysplasia

Study authors (year published)	Cancer / Cell Type	Study Design	Patients	Intervention	Outcome Measures	Findings	Study quality
				Range: 6 to 13 days - PPI, unspecified			
Grade AJ, et al. (1999)[149]	BE	Clinical trial Single centre Prospective *Countries:* US *Length of follow-up:* 4 to 6 weeks	*Number of patients:* 9 *Gender:* Male: 9 Female: 0 *Age:* Mean: 51.1 yrs Range: 41 to 61 yrs *Prior treatments:* none reported *Length of Barretts:* Mean: 3.6 cm Range: 2 to 5 cm *Inclusion criteria:* None notable *Exclusion criteria:* Cardiac disease; lung disease requiring supplemental oxygen; contraindications for endoscopy and extensive biopsy	APC *Power:* 60 watts *Gas flow:* 1.6L/minute *APC application time:* Mean: 8.0 minutes Range: 2 to 18 minutes *Number of sessions:* Mean: 1.7 sessions / patient Range: 1 to 3 sessions / patient Half the circumference of esophagus treated per session *Co-interventions:* Lansoprazole 70 mg ± 5 mg/day for the week prior to treatment	*Outcomes:* Complete response of BE (assessed though biopsy every 1 cm) Partial response of BE *Adverse events*	*Outcomes:* Complete response of BE at 4 to 6 weeks: 7/9 patients (78%) Partial response of BE: 2/9 patients (22%) *Adverse events:* Chest pain, transient, mild: 4/9 patients (44%) Odynophagia, transient: 1/9 patients (11%)	4
Madisch A, et al. (2005)[150]	BE	Clinical trial Prospective *Countries:* Germany *Length of follow-up:* Median: 51 months Range: 9 to 85 months	*Number of patients:* 73 *Gender:* Male: 45 Female: 28 *Age:* Mean: 55 yrs Range: 28 to 77 yrs *Prior treatments:* none reported *Length of Barretts:*	APC *Power:* not reported *Gas flow:* not reported *Treatment time:* not reported *Number of sessions:* Median: 2 sessions / patient Range: 1 to 6 sessions / patient *Co-interventions:* Omeprazole 120mg daily	*Outcomes:* Complete response of BE Relapse to BE (assessed *histologically* through 4 quadrant biopsies every 2 cm) Relapse to BE (assessed *endoscopically*)	*Outcomes:* Complete response of BE at 3 weeks: 69/70 patients (98.6%) Relapse to BE at 51 months (median): 8/66 patients (12.1%) Annual relapse rate: approximately 3% Relapse to BE (endoscopy): 13/66 patients (19.7%)	4

Table B 2. Studies of argon plasma coagulation (APC) for Barrett's esophagus with/without dysplasia

Study authors (year published)	Cancer / Cell Type	Study Design	Patients	Intervention	Outcome Measures	Findings	Study quality
			Mean: 4 cm Range: 1 to 12 cm >2cm: 56/73 patients (76.7%) *Inclusion criteria:* none notable. *Exclusion criteria:* Serious gatrointestinal or extraintestinal disease		Number of sessions to achieve complete response of BE *Adverse events*	Number of sessions to achieve complete response of BE: Median 2 sessions Range 1 to 6 sessions Adverse events: Bleeding: 0/73 Perforation: 0/73 Strictures: 3/73	
Manner H, et al. (2007)[151]* * Information extracted for BE or HGD patients only	BE	Case series Single centre Prospective *Countries:* Germany *Length of follow-up:* not reported	*Number of patients:*104 *Gender:* not reported *Age:* not reported *Prior treatments:* Previous dysplasia or EAC removed by ER *Length of Barretts:* not reported *Inclusion criteria:* Ineligible for or refused surgery *Exclusion criteria:* none notable	APC *Power:* 60 watts *Gas Flow:* 1L / minute *Treatment time:* not reported *Number of sessions:* Mean: 1.1 sessions / patient Range: 1 to 5 sessions / patient *Co-interventions:* PPI, unspecified	*Outcomes:* Number of sessions required to achieve complete response of BE *Adverse events*	*Outcomes:* Number of sessions required to achieve complete response of BE: Mean: 1.1 sessions / patient Range: 1 to 5 sessions / patient *Adverse events:* Pain; cough; dysphagia; arrhythmia; emphysema; gas accumulation in the GI wall; neuromuscular irritation: 10/104 patients (10%) Strictures: 1/104 patients (1%)	4
Manner H, et al. (2006)[152] * * Information extracted for BE or HGD patients only	BE	Case series Single centre Retrospective *Countries:* Germany *Length of follow-up:* not reported	*Number of patients:* 41 *Gender:* not reported *Age:* not reported *Prior treatments:* Dysplasia or early EAC treated successfully by EMR *Length of Barretts:* not reported *Inclusion criteria:* Patients previously received	APC *Power:* Mean: 59 watts Range: 50 to 60 watts *Gas Flow:* 2L / minute *Treatment time:* not reported *Number of sessions:* Mean: 1.1 sessions / patient Range: 1 to 2 sessions / patient APC done as additive adjunct to ER or ARS *Co-interventions:* none reported	*Outcomes:* Number of sessions to achieve complete response of BE *Adverse events*	*Outcomes:* Number of sessions to achieve complete response of BE: Mean: 1.1 sessions/ patient ± 0.4 sessions Range: 1 to 2 sessions / patient *Adverse events:* Chest pain: 4/41 patients (10%) Fever: 4/41 patients (10%) Strictures: 1/41 patients (2%) Perforation or bleeding, major: 0/41 patients (0%)	4

Table B 2. Studies of argon plasma coagulation (APC) for Barrett's esophagus with/without dysplasia

Study authors (year published)	Cancer / Cell Type	Study Design	Patients	Intervention	Outcome Measures	Findings	Study quality
			EMR. *Exclusion criteria:* none notable				
Manner H, et al. (2006)[153]	BE	Case series Multi-centre Prospective *Countries:* Germany *Length of follow-up:* Mean: 14 months Range: 12 to 32 months	*Number of patients:*51 *Gender:* Male: 41 Female: 10 *Age:* Mean: 57 yrs Range: 27 to 77 yrs *Prior treatments:* none reported *Length of Barretts:* Mean: 3.6 cm Range: 1 to 8 cm *Inclusion criteria:* none notable. *Exclusion criteria:* Coagulation disturbances: Quick's value <50% or platelet count <50/nL Previous esophageal surgery or endoscopic treatment Varicies	APC *Power:* 90 watts *Gas Flow:* 2L / minute *Treatment time:* not reported *Number of sessions:* Mean: 2.7 sessions / patient Range: 1 to 8 sessions / patient *Co-interventions:* Esomeprazole: 40 mg twice daily during and for 2 weeks post APC, then 40 mg/day until 3 weeks post APC, then 20 mg/day as needed	*Outcomes:* Complete response of BE (assessed through endoscopy with 4 quadrant biopsy every 2 cm) Partial response of BE (defined as a reduction in BE >50% but <100%) Number of sessions to achieve complete response of BE *Adverse events*	*Outcomes:* Complete response of BE at 14 months (mean): 37/48 patients (77%) Partial response of BE: 11/48 patients (23%) Number of sessions to achieve complete response of BE: Mean 2.6 sessions Range: 1 to 5 sessions *Adverse events:* Chest pain: 8/51 patients (16%) Odynophagia: 2/51 patients (4%) Fever: 1/51 patients (2%) Esophageal bleeding requiring transfusion: 2/51 patients (4%) Strictures: 2/51 patients (4%) Esophageal perforation: 1/51 patients (2%) Buried glands: 4/48 (8%)	4
Pedrazzani C, et al. (2005)[154]	BE+LGD	Clinical trial Single centre *Countries*: Italy *Length of follow-up:* Mean: 26.3 months Range: 9 to 45 months	*Number of patients:* 25 *Gender:* Male: 18 Female: 7 *Age:* Mean: 61.7 yrs Range: 34 to 74 yrs *Prior treatments:* none reported	APC *Power:*90 watts *Gas flow*: 2L/minute *Treatment time:* not reported *Number of sessions:* Mean: 1.6 sessions Range: 1 to 4 sessions *Co-interventions:* Pantoprazole or esomeprazole	*Outcomes:* Complete response of BE (assessed through 4 quadrant biopsy) Number of APC sessions to complete response of BE	*Outcomes:* Complete response of BE -at 1 month: 24/25 patients (96%) -at 26.3 months (mean): 23/25 patients (92%) Number of APC sessions to complete response of BE: 1 treatment: 15/25 patients (60%) 2 treatments: 6/25 patients (24%)	4

Table B 2. Studies of argon plasma coagulation (APC) for Barrett's esophagus with/without dysplasia

Study authors (year published)	Cancer / Cell Type	Study Design	Patients	Intervention	Outcome Measures	Findings	Study quality
			Length of Barretts: Mean: 3.4 cm Range: 1 to 13 cm *Inclusion criteria:* none notable *Exclusion criteria:* Previous malignancies or intercurrent diseases affecting prognosis	40 mg twice daily one week before and throughout treatment	*Adverse events*	≥3 treatments: 4/25 patients (16%) *Adverse events:* Chest pain: 11/40 sessions (23%) Fever: 7/40 sessions (18%) Dysphagia: 2/40 sessions (5%) Ulcer formation: 2/40 sessions (5%) Bleeding, severe: 1/40 sessions (5%)	
Pereira-Lima, JC, et al. (2000)[155]	BE (18 patient) BE + LGD (14 patients) BE + HGD (1 patient)	Case series Single centre *Countries:* Brazil *Length of follow-up:* Mean: 10.6 months Range: 6 to 18 months	*Number of patients:* 33 *Gender:* Male: 21 Female: 12 *Age:* Mean: 55.2 yrs Range: 21 to 84 yrs *Prior treatments:* ARS (9 patients) PPI, unspecified (24 patients) *Length of Barretts:* Mean: 4.05 cm Range: 0.5 to 7 cm *Inclusion criteria:* none notable *Exclusion criteria:* none notable	APC *Power:* 65 to 70 watts *Gas Flow:* 2L / minute *Treatment time:* not reported *Number of sessions:* Mean: 1.96 sessions / patient Range: 1 to 4 sessions / patient Maximum of 4 cm length circumferentially ablated / session *Co-interventions:* Omeprazole 60 mg/day until BE ablation; then omeprazole 30 mg/day or ARS recommended	*Outcomes:* Complete response of BE (assessed through endoscopy with 6 biopsies every 1 cm) Recurrence of BE at a mean of 10.6 months *Adverse events*	*Outcomes:* Complete response of BE at 1 to 2 months: 32/33 patients (97%) Recurrence of BE at 10.6 months (mean): 1/33 patients (3%) *Adverse events:* Chest pain, moderate to severe; and odynophagia: 18/33 patients (55%) Pleural effusion and high fever (39°C): 5/33 patients (15%) Strictures: 3/33 patients (9%) Chest pain; pneumomediastinum; subcutaneous emphysema 1 hour post APC: 1/33 patients (3%) Buried glands: 0/33 patients (0%)	4
Pinotti AC, et al. (2004)[156]	BE	Case series Single centre Prospective *Countries:* Brazil *Length of follow-up:*	*Number of patients:* 19 *Gender:* Male: 11 Female: 8 *Age:* Mean: 52.5 yrs Range: 32 to 72 yrs	APC +ARS *Power:* 50 watts *Gas Flow:* 2L / minute *Treatment time:* *Number of sessions:* Mean: 2 sessions / patient Range: 1 to 6 sessions / patient	*Outcomes:* Complete response of BE Recurrence of BE	*Outcomes:* Complete response of BE at 2 months: 18/19 patients (95%) Recurrence of BE at 17 months (mean): 1/19 patients (5%)	4

Table B 2. Studies of argon plasma coagulation (APC) for Barrett's esophagus with/without dysplasia

Study authors (year published)	Cancer / Cell Type	Study Design	Patients	Intervention	Outcome Measures	Findings	Study quality
		Mean: 17 months Range: 6 to 27 months	*Prior treatments:* none reported *Length of Barretts:* Mean: 3.55 cm Range: 1 to 9 cm *Inclusion criteria:* none notable *Exclusion criteria:* none notable	Half circumference treated in patients with long BE segments *Co-interventions:* ARS (Laparoscopic Nissen fundoplication) preceded APC in all patients	*Adverse events*	*Adverse events:* Strictures or perforation: 0/19 patients (0%) Dysphagia, transient; and odynophagia: 4/19 patients (21%) Chest pain, transient: 17/19 patients (89%) - duration 3 days: 11/19 patients (58%) - duration 7 days: 4/19 patients (21%) - duration >7 days: 2/19 patients (11%)	
Tigges H, et al. (2001)[157]	BE	Case series Single centre *Countries:* Germany *Length of follow-up:* 1 yr	*Number of patients:* 30 *Gender:* Male: 23 Female: 7 *Age:* Mean: 53.5 yrs Range: 31 to 77 yrs *Prior treatments:* PPI, unspecified, >6 months *Length of Barretts:* Median: 3 cm Range: 1 to 10 cm *Inclusion criteria:* none notable *Exclusion criteria:* Severe co-morbidity Life expectancy <5 yrs History of upper GI surgery including ARS	APC + ARS *Power:* up to 150 watts *Gas Flow:* 0.1 to 0.9L / minute *Treatment time:* Median: 35 minutes Range: 15 to 50 minutes *Number of sessions:* not reported Half circumference treated at first session Precedent to ARS *Co-interventions:* Omeprazole 40 / day ARS: laparoscopic Nissen fundiplication or 240^{o} Toupet fundiplication (26/30 patients)	*Outcomes:* Complete response of BE (assessed through endoscopy with 4 quadrant biopsy every 1 cm) Progression to cancer *Adverse events*	*Outcomes:* Complete response of BE: - 1.5 to 2 months (post-APC): 22/22 patients (100%) - 1 yr (post-ARS): 20/22 patients (91%) Progression to cancer at 1 year: 0/22 patients (0%) *Adverse events:* <u>Post APC</u> Dysphasia, transient or odynophagia: 2/30 patients (7%) Strictures: 1/30 patients (3%) Persistent dysphagia, perforation or bleeding: 0/30 patients (0%) <u>Post-ARS</u> Pneumothroax: 2/22 patients (9%) Skin emphysema secondary to pneumoperitoneum: 1/22 patients (4.5%)	4
Van Laethem JL, et al. (2001)[158] *	BE + HGD	Case series Single centre Prospective	*Number of patients:* 7 *Gender:* Male: 5	APC *Power:* 90 watts *Gas Flow:* not reported	*Outcomes:* Survival	*Outcomes:* Survival at 25.5 months (mean): 6/7 patients (86%)	4

Table B 2. Studies of argon plasma coagulation (APC) for Barrett's esophagus with/without dysplasia

Study authors (year published)	Cancer / Cell Type	Study Design	Patients	Intervention	Outcome Measures	Findings	Study quality
* Information extracted for BE or HGD patients only		*Countries:* Belgium *Length of follow-up:* Mean: 25.5 months Range: 12 to 36 months	Female: 2 *Age:* Mean: 72.6 yrs Range: 64 to 85 yrs *Prior treatments:* none reported *Length of Barretts:* Mean: 4.6 cm Range: 3 to 7 cm *Inclusion criteria:* Ineligible for or refused surgery *Exclusion criteria:* none notable	*Treatment time:* not reported *Number of sessions:* Mean: 2.83 sessions / patient Range: 1 to 6 sessions / patient *Co-interventions:* Omeprazole 40 mg/day	Complete response of BE (assessed through endoscopy with 4 quadrant biopsy every 1 to 2 cm) Complete response of HGD Non-response of dysplasia Progression to cancer *Adverse events:* No BE or HGD specific information available.	Complete response of BE -at 1 month: 4/7 patients (57 %) -at a mean of 25.5 months: 4/7 patients (57 %) Complete response of HGD -at 1 month: 6/7 patients (85.7%) -at 25.5 months (mean): 5/7 patients (74%) Non-response of BE/dysplasia -at 1 month: 1/7 patients (14%) -at 25.5 months (mean): 1/7 patients (14%) Progression to cancer at 25.5 months (mean): 1/7 patients (14%) *Adverse events:*	
Van Laethem JL, et al. (1998)[159]	BE BE + LGD	Case series Single centre *Countries:* Belgium *Length of follow-up:* 12 months	*Number of patients:* 31 *Gender:* Male: 25 Female: 6 *Age:* Mean: 64 yrs Range: 46 to 76 yrs *Prior treatments:* Omeprazole 20mg/day *Length of Barretts:* Mean: 4.5 cm Range: 3 to 11 cm *Inclusion criteria:* none notable	APC *Power:* not reported *Gas Flow:* not reported *Treatment time:* not reported *Number of sessions:* Mean: 2.4 sessions / patient Range: 1 to 4 sessions / patient *Co-interventions:* Omeprazole 40 mg/day or 10mg/day (randomly assigned) for < 3 months	*Outcomes:* Complete response of BE (assessed through endoscopy with 4 quadrant biopsy every 2 cm) *Adverse events*	*Outcomes:* Complete response of BE: -1 month: 19/31 patients (61%) -3 months: 15/31 patients (48%) -12 months: 9/17 patients (53%) *Adverse events:* Buried glands: 6/31 patients (19%) Odynophagia, transient or dysphagia, transient: most patients Chest pain, persistent, odynophagia persistent, dysphagia, persistent: 2/31 patients (6%) Strictures: 2/31 patients (6%) Esophageal bleeding requiring transfusion: 1/31 patients (3%)	4

Table B 2. Studies of argon plasma coagulation (APC) for Barrett's esophagus with/without dysplasia

Study authors (year published)	Cancer / Cell Type	Study Design	Patients	Intervention	Outcome Measures	Findings	Study quality
			Exclusion criteria: Intolerant to upper GI endoscopy; life expectancy <5yrs; inter-current disease affecting prognosis; previous history of gastro-esophageal surgery; use of NSAIDs			Reflux esophagitis (at 3 months): 8/31 patients (25%)	

Table B 3. Studies of cryoablation, combined EMR and PDT, and thermocoagulation for Barrett's esophagus with/without dysplasia

Study authors (year published)	Cancer / Cell Type	Study Design	Patients	Intervention	Outcome Measures	Findings	Study quality
Cryoablation							
Comparative studies							
None							
Non-comparative studies							
Dumot JA, et al. (2008) [79]* * Information extracted for BE or HGD patients only	BE+HGD (20 patients)	Clinical trial Single centre *Countries:* US *Length of follow-up:* Not reported	*Number of patients*: 20 *Gender*: Not reported *Age*: Not reported *Prior treatments:* none reported *Length of Barretts:* not reported *Inclusion criteria:* none notable *Exclusion criteria:* none notable	Cryoablation *Device:* not reported *Drug:* liquid nitrogen spray *Method:* low pressure spray *Treatment time:* not reported *Number of sessions:* Mean: 4 sessions IQR: 2 to 6 sessions *Co-interventions:* none reported	*Outcomes:* Complete response of HGD *Adverse events:* No BE or HGD specific information available.	*Outcomes:* Complete response of HGD at unreported follow-up: 16/18 patients (89%)	4
Johnston MH, et al. (2005)[37]	BE (3 patients) BE + LGD (5 patients) BE + HGD (1 patient) BE + indefinite for dysplasia (2 patients)	Clinical trial Single centre Prospective *Countries:* US *Length of follow-up:* Mean: 12 months Range: 6 to 20 months	*Number of patients*: 11 *Gender*: Male:11 *Age*: Mean: 59 yrs Range: 50 to 74 yrs *Prior treatments:* PPI, unspecified. *Length of Barretts:* Mean: 4.6cm Range: 1 to 8 cm *Inclusion criteria:* Patients with BE in an established registry Multiple previous endoscopies	Cryoablation *Device:* 9F cryogenic catheter *Drug:* liquid nitrogen spray *Method:* low pressure spray hemi-circumferentially to 4 cm long segments/ session *Treatment time:* Not reported *Number of sessions:* Mean: 4.8 sessions Range: 1 to 8 sessions Tissue frozen for 20 seconds, permitted to thaw, then re-frozen for 20 seconds *Co-interventions:* Rabeprazole 40 mg 3 times a day during treatment period	*Outcomes:* Complete response of BE (assessed through endoscopy with 4 quadrant biopsies every 2 cm) Complete response of HGD Number of sessions to achieve complete response of BE *Adverse events*	*Outcomes*: Complete response of BE - at 1 month: 9/11 patients (81.8%) - at a mean of 12 months: 7/11 patients (64%) Complete response of HGD at 1 month: 1/1 patients (100%) Number of sessions to achieve complete response of BE: Mean 3.6 sessions Adverse events: Chest pain: 2/11 (22.2%) Dysphagia: 1/11 (11.1%) Bleeding: 0/11 (0%) Perforation: 0/11(0%)	4

Table B 3. Studies of cryoablation, combined EMR and PDT, and thermocoagulation for Barrett's esophagus with/without dysplasia

Study authors (year published)	Cancer / Cell Type	Study Design	Patients	Intervention	Outcome Measures	Findings	Study quality
			Use of PPI *Exclusion criteria:* none notable				
Combined EMR+PDT							
Comparative studies							
Behrens A, et al. (2005)[106]	BE + HGD	Cohort study Single centre Prospective PDT + EMR vs. PDT vs. EMR *Countries:* Germany *Length of follow-up:* Mean: 38 months Range: 7 to 61 months	*Number of patients:* 44 (PDT+EMR: 3 patients; PDT Group: 27 patients; EMR Group: 14 patients) *Gender:* Male: 38 Female: 6 *Age:* Mean:61 yrs Range: 33 to 79 yrs <u>PDT + EMR Group</u> *Number of patients:* 3 patients *Gender:* not reported *Age:* not reported <u>EMR Group</u> *Number of patients:* 14 patients *Gender:* not reported *Age:* not reported <u>PDT Group</u> *Number of patients:* 27 patients *Gender:* not reported *Age:* not reported *Prior treatments:* none reported *Length of Barretts:* not reported *Inclusion criteria:* none notable	PDT + EMR vs. EMR vs. PDT <u>PDT Group</u> Patients with microscopic / histologic HGD *Drug:* 5-ALA *Dose:* 60 mg/kg *Route of administration:* oral *Light source*: dye laser @ 630 to 635nm *Light dose:* not reported *Time to photoactivation:* 4 to 6 hours *Treatment time:* not reported *Number of sessions:* Mean: 1 session/patient Range: 1 to 4 sessions / patient <u>EMR</u> *Technique:* EMR with ligation, or cap and snare *Injection:* none *Number of treatments:* not reported <u>PDT + EMR Group</u> Details as above. *Co-interventions:* Omeprazole 40 mg IV twice daily or Pantoprazole 40 mg IV twice daily	*Outcomes:* Complete response of dysplasia Recurrence of HGD Progression to cancer *Adverse events:*	*Outcomes:* Complete response of dysplasia … … at 1 month (after 1 treatment session): -All patients: 39/43 patients (91%) -PDT + EMR Group: 2/3 patients (67%) -EMR Group: 13/14 patients (93%) -PDT Group: 26/27 patients (96%) … at 38 months (mean) (after 1 to 4 sessions) -All patients: 29/35 patients (83%) Recurrence of HGD at 38 months (mean): 4/35 patients (11%) Progression to cancer at 38 months (mean): 2/35 patients (6%) *Adverse events:* <u>PDT Group</u> Vomiting, severe: 1/27 patients (4%) Nausea: 14/27 patients (52%) <u>EMR Group</u> Bleeding, minor: 4/17 patients (24%)	4

Table B 3. Studies of cryoablation, combined EMR and PDT, and thermocoagulation for Barrett's esophagus with/without dysplasia

Study authors (year published)	Cancer / Cell Type	Study Design	Patients	Intervention	Outcome Measures	Findings	Study quality
			Exclusion criteria: none notable				
Non-comparative studies							
Wolfsen HC, et al. (2004)[160]	BE + HGD	Case series Single centre *Countries:* US *Length of follow-up:* Median: 13 months Range: 6 to 46 months	*Number of patients:*3 *Gender:* Male: 3 *Age:* Mean: 68.67 yrs Range: 68 to 69 yrs *Prior treatments:* none reported *Length of Barretts:* Mean: 3.67 cm Range: 3 to 4 cm *Inclusion criteria:* Ineligible for or refused surgery *Exclusion criteria:* none notable	PDT + EMR <u>PDT</u> *Drug:* porfimer sodium *Dose:* 2 mg/kg *Route of administration:* IV *Light source*: diode laser @ 630nm *Light dose:* 175 to 250 J/cm^2 *Time to photoactivation:* 48 hours *Treatment time:* not reported *Number of sessions:* 1 session / patient (assumed) Provided 4 to 6 weeks post EMR <u>EMR</u> *Technique:* inject and cut *Devices:* not reported *Circumferential vs. focal:* focal *Injection:* yes *Solution:* saline ± epinephrine (1:10,000) *Number of treatments:* not reported Provided for focal lesions / mucosal irregularities before PDT *Co-interventions*: PPI, unspecified	*Outcomes:* Survival Complete response of BE Complete response of dysplasia *Adverse event*	*Outcomes:* Survival at 13 months (median): 3/3 patients (100%) Complete response of BE at 13 months (median): 3/3 patients (100%) Complete response of dysplasia at 13 months (median): 3/3 patients (100%) *Adverse events:* Strictures: 0/3 patients (0%) Chest pain, mild: common	4

Table B 4. Studies of endoscopic mucosal resection (EMR) for Barrett's esophagus with/without dysplasia

Study authors (year published)	Cancer / Cell Type	Study Design	Patients	Intervention	Outcome Measures	Findings	Study quality
Comparative studies							
Behrens A, et al. (2005)[106]	BE + HGD	Cohort study Single centre Prospective EMR vs. PDT vs. PDT + EMR *Countries:* Germany *Length of follow-up:* Mean: 38 months Range: 7 to 61 months	*Number of patients:* 44 (EMR Group: 14 patients; PDT Group: 27 patients; PDT+EMR: 3 patients) *Gender:* Male: 38 Female: 6 *Age:* Mean:61 yrs Range: 33 to 79 yrs <u>EMR Group</u> *Number of patients:* 14 patients *Gender:* not reported *Age:* not reported <u>PDT Group</u> *Number of patients:* 27 patients *Gender:* not reported *Age:* not reported <u>PDT + EMR Group</u> *Number of patients:* 3 patients *Gender:* not reported *Age:* not reported *Prior treatments:* none reported *Length of Barretts:* not reported *Inclusion criteria:* none notable *Exclusion criteria:* none notable	PDT vs. EMR vs. PDT + EMR <u>EMR</u> *Technique:* EMR with ligation, or cap and snare *Injection:* none *Number of treatments:* not reported <u>PDT Group</u> Patients with microscopic / histologic HGD *Drug:* 5-ALA *Dose:* 60 mg/kg *Route of administration:* oral *Light source*: dye laser @ 630 to 635nm *Light dose:* not reported *Time to photoactivation:* 4 to 6 hours *Treatment time:* not reported *Number of sessions:* Mean: 1 session/patient Range: 1 to 4 sessions / patient <u>PDT + EMR Group</u> Details as above. *Co-interventions:* Omeprazole 40 mg IV twice daily or Pantoprazole 40 mg IV twice daily	*Outcomes:* Complete response of HGD Recurrence of HGD Progression to cancer *Adverse events:*	*Outcomes:* Complete response of dysplasia … … at 1 month (after 1 treatment session): -All patients: 39/43 patients (91%) -EMR Group: 13/14 patients (93%) -PDT Group: 26/27 patients (96%) -PDT + EMR Group: 2/3 patients (67%) … at 38 months (mean) (after 1 to 4 sessions) -All patients: 29/35 patients (83%) Recurrence of HGD at 38 months (mean): 4/35 patients (11%) Progression to cancer at 38 months (mean): 2/35 patients (6%) *Adverse events:* <u>PDT Group</u> Vomiting, severe: 1/27 patients (4%) Nausea: 14/27 patients (52%) <u>EMR Group</u> None reported	4
Reed MF, et al.	BE + HGD	Cohort study	*Number of patients: 115*	<u>Endoscopic Group</u>	*Outcomes:*	*Outcomes:*	4

Table B 4. Studies of endoscopic mucosal resection (EMR) for Barrett's esophagus with/without dysplasia

Study authors (year published)	Cancer / Cell Type	Study Design	Patients	Intervention	Outcome Measures	Findings	Study quality
(2005)[132]		Single centre Retrospective Esophagectomy vs Endoscopic Therapy vs Observation *Countries:* not reported *Length of follow-up*: 10 yrs	(Endoscopic Therapy Group: 47 patients – 5 EMR, 42 PDT; Esophagectomy Group: 49 patients; Observations Group: 19 patients) *Age:* Mean 65 yrs Range 30 to 87 yrs Gender: Male: 95 Female: 20 Endoscopic Group *PDT: 42 patients* *EMR 5 patients* *Age:* Mean 70 yrs Range 30 to 89 yrs *Gender:* Male: 38 Female: 9 Esophagectomy Group *Age:* Mean 59 yrs Range 32 to 79 yrs *Gender:* Male: 40 Female: 9 Observation Group: *Age:* not reported *Gender:* not reported *Prior treatments:* none reported *Length of Barretts:* not reported	Endoscopic mucosal resection (EMR) or Photodynamic therapy (PDT) No details reported Esophagectomy Group: Surgical resection done within 60 days of diagnosis *Type of surgery:* -TTE: 20 patients (41%) -Ivor Lewis: 18 patients (37%) -THE: 7 patients (17%) -various or mixed techniques: 4 patients(8%) Observation Group: No details reported *Co-interventions:* none reported	Disease specific survival Overall survival Complete response of HGD Progression to cancer *Adverse event:*	Disease specific survival at 5 years: -Endoscopic Group: not reported -Esophagectomy Group: 94% -Observation Group: not reported Overall survival: Endoscopic Group: not reported Esophagectomy Group - at 5 yrs: 83% - at 10 yrs: 64% Observation Group: not reported Complete response of HGD, follow-up unknown: Endoscopic Group PDT: 37/42 patients (88%) EMR 3/5 patients (60%) Esophagectomy Group not reported Observation Group 0/13 patients (0%) Progression to cancer -Endoscopic Group: 6/47 patients -Esophagectomy Group: not reported -Observation 7/13 patients *Adverse events:* Esophagectomy Group Post op anastomotic leak: 2/49 patients (4%) Death secondary to large cerebrovascular accident post-op: 1/49 patients (2%)	

Table B 4. Studies of endoscopic mucosal resection (EMR) for Barrett's esophagus with/without dysplasia

Study authors (year published)	Cancer / Cell Type	Study Design	Patients	Intervention	Outcome Measures	Findings	Study quality
			Inclusion criteria: none notable *Exclusion criteria*: none notable				
Non-comparative studies							
Giovannini M, et al. (2004) [161]	BE + HGD	Case series Single centre *Countries:* France *Length of follow-up* Mean: 18 months Range: 6 to 34 months	*Number of patients: 12* *Gender:* Male: 5 Female: 7 *Age:* *M*ean: 61 yrs Range 42 to 71 yrs *Prior treatments:* none reported *Length of Barretts:* not reported *Inclusion criteria:* none notable *Exclusion criteria:* none notable	EMR *Technique:* inject and cut *Injection:* yes (not reported) *Number of treatments:* Median: 2 sessions/patient Hemicircumferential excision every session *Co-interventions*: PPI (details not reported)	*Outcomes:* Complete response of HGD Recurrence of HGD *Adverse events:*	*Outcomes:* Complete response of HGD - at 1 month: 12/12 patients (100%) - at 12 months: 10/12 patients (83%) - at 18 months: 10/12 patients (83%) Recurrence of HGD at 12 months: 2/12 (18%) *Adverse events:* Bleeding, managed endoscopically: 3/12 patients (25%) Perforation: 0/12 patients (0%) Stricture: 0/12 patients (0%)	4
Mino-Kenudson M, et al. (2005)[162] * * Information extracted for BE or HGD patients only	BE + HGD	Case series Single centre *Countries:* US *Length of follow-up* Mean: 23.3 months Range: 7 to 41 months	*Number of patients:*3 *Gender:* not reported *Age:* not reported *Prior treatments:* none reported *Length of Barretts:* Mean: 6.7 cm Range: 2 to 15 cm *Inclusion criteria:* Ineligible for or refused surgery *Exclusion criteria:* none notable	EMR *Technique:* inject and cut *Injection:* yes (epinephrine in saline 1:100,000) *Number of treatments:* not reported Circumferential *Co-interventions*: PPI (details not reported) (1 patient)	*Outcomes:* Complete response of BE *Adverse events:* none	*Outcomes:* Complete response of BE at 23.3 months (mean): 2/3 patients: (67%)	4
Seewald S, et al. (2003)[163]	BE + HGD	Case series Single centre	*Number of patients: 3* *Gender:* Male: 2	EMR *Technique:* simple snare resection	*Outcomes:* Complete response of BE (assessed through endoscopy	*Outcomes:* Complete response of BE at 14 months (mean): 0/3 patients (0%)	4

Table B 4. Studies of endoscopic mucosal resection (EMR) for Barrett's esophagus with/without dysplasia

Study authors (year published)	Cancer / Cell Type	Study Design	Patients	Intervention	Outcome Measures	Findings	Study quality
* Information extracted for BE or HGD patients only		*Countries:* Germany *Length of follow-up:* Mean: 14 months Range: 5 to 24 months	Female: 1 *Age:* *M*ean: 53.3 yrs Range 43 to 59 yrs *Prior treatments:* none reported *Length of Barretts:* Mean: 2 cm Range: 2 to 2 cm *Inclusion criteria:* none notable *Exclusion criteria:* none notable	*Injection:* none *Number of treatments:* Mean: 1.66 sessions/patient Range:1 to 3 cm Circumferential *Co-interventions:* PPI, unspecified	with biopsy) Complete response of HGD Progression to cancer *Adverse events:* No BE or HGD specific information available.	Complete response of HGD at 14 months (mean): 1/3 patients (33%) Progression to cancer at 14 months (mean): 0/3 patients (0%)	
Tang, SJ, et al. (2008)[164]	BE + LGD + HGD	Case report Single centre *Countries:* US *Length of follow-up:* 3 months	*Number of patients:* 1 *Gender:* Male *Age:* 58 *Prior treatments:* PPI, unspecified *Length of Barretts:* 14 cm *Inclusion criteria*: Refused surgery *Exclusion criteria*: none notable	EMR *Technique:* EMR with ligation *Injection:* none *Number of treatments:* 2 sessions Circumferential *Co-interventions:* PPI (drug and dose not reported)	*Outcomes:* Complete response of BE (assessed through endoscopy and biopsy) Complete response of HGD *Adverse events*:	*Outcomes:* Complete response of BE at 3 months: 1/1 patients (100%) Complete response of dysplasia at 3 months: 1/1 patients (100%) *Adverse events*: Pneumonia: 1/1 patient (100%) DVT secondary to IV line: 1/1 patient (100%) Chest and epigastric pain, mild, duration ≤ 7days: 1/1 patient (100%)	4

Table B 5. Studies of laser ablation for Barrett's esophagus with/without dysplasia

Study authors (year published)	Cancer / Cell Type	Study Design	Patients	Intervention	Outcome Measures	Findings	Study quality
Comparative studies							
None							
Non-comparative studies							
Barham CP, et al (1997)[165]	BE	Case series Single centre Countries: UK Laser ablation vs. omeprazole *Length of follow-up:* 6 weeks	*Number of patients:* 16 *Gender:* Male: 12 Female: 4 *Age:* Mean: 58.7 yrs Range: 36 to 76 yrs *Prior treatments:* Omeprazole, unspecified *Length of Barretts:* not reported *Inclusion criteria:* none notable *Exclusion criteria:* none notable	Laser ablation *Type:* KTP @512 nm *Power*: 20 watts *Dose:* not reported *Treatment time:* not reported *Number of sessions:* Mean: 3.4 sessions / patient Range: 1 to 6 sessions Approximately 30% circumference ablated / session *Co-interventions:* Omeprazole 40 mg / day	*Outcomes:* Complete response of BE Number of sessions to achieve complete response of BE *Adverse events*	*Outcomes:* Complete response of BE at 6 weeks: 13/16 patients (81%) Number of sessions to achieve complete response of BE: Mean: 3 sessions Range: 1 to 6 sessions *Adverse events:* Chest pain, mild, duration <48 hours: common Buried glands: 11/16 patients (69%)	4
Bonarvina L, et al (1999)[166]	BE	Case series Single centre Prospective *Countries:* Italy *Length of follow-up:* Mean: 14 months Range: 4 to 32 months	*Number of patients:* 18 *Gender:* Male: 14 Female: 4 *Age:* Mean: 55 yrs Range: 32 to 70 yrs *Prior treatments:* none reported *Length of Barretts:* Mean: 4.3 cm *Inclusion criteria:* none notable *Exclusion criteria:*	Laser ablation *Type:* Nd:YAG @ 1064nm *Power:*60 watts *Dose:* Mean: 2800 J Range: 600 to 4800 J *Treatment time:* not reported *Number of sessions:* Mean: 3 sessions / patient Range: 1 to 5 sessions Half circumference treated / session *Co-interventions:* Omeprazole 40 mg daily Anti-reflux surgery (12	*Outcomes:* Complete response of BE (assessed through endoscopy and biopsy) Partial response of BE No response to BE Progression to cancer *Adverse events*	*Outcomes:* Complete response of BE - at 4 weeks: 11/18 patients (61%) - at 14 months (mean): 9/18 patients (50%) Partial response of BE at 4 weeks: 5/18 patients (28%) No response to BE at 4 weeks: 2/18 patients (11%) Progression to cancer at 14 months (mean): 1/18 patients (5.6%) *Adverse events:*	4

Table B 5. Studies of laser ablation for Barrett's esophagus with/without dysplasia

Study authors (year published)	Cancer / Cell Type	Study Design	Patients	Intervention	Outcome Measures	Findings	Study quality
			>70 yrs	patients)		Strictures: 2/16 patients (12.5%)	
Bowers SP, et al. (2002) [167]	BE	Cohort study Single centre *Countries:* US *Length of follow-up:* approx. 5 years	*Number of patients:* 30 (Laser Ablation: 9 patients; Surveillance: 21 patients) <u>Laser ablation</u> *Number of patients:* 9 *Gender:* Male: 7 Female: 2 *Age:* Median: 49 yrs Range: 33 to 62 yrs *Number of patients with BE <3cm:* 3/9 (33.3%) <u>Surveillance</u> *Number of patients:* 21 *Gender:* Male: 13 Female: 8 *Age:* Median: 49 years Range: 31 to 73 years *Number of patients with BE <3cm:* 8/21 (38.1%) *Prior treatments:* None reported *Inclusion criteria:* none notable *Exclusion criteria:* none notable	Laser ablation *Type:* KTP laser @ 532nm *Pulse time:* not reported *Power:* 5W *Dose:* not reported *Treatment time:* not reported *Number of sessions:* Median: 2 sessions / patient Range: 1 to 5 sessions *Co-interventions:* Anti-reflux surgery	*Outcomes:* Complete response of BE (defined as no endoscopic or histological signs of BE, assessed through endoscopy with 4 quadrant biopsies) Complete response of BE (defined as no histological signs of BE, despite columnar-appearing epithelium) *Adverse events:* none	*Outcomes* Complete response of BE: <u>Laser ablation</u> -at 3 months: 2/9 patients (22.2%) -at 61.2 months (mean): 1/9 patients (11.1%) <u>Surveillance</u> Not reported Complete response of BE: <u>Laser ablation</u> -at 3 months: 5/9 patients (55.5%) -at 61.2 months (mean): 8/9 patients (88.8%) <u>Surveillance</u> - at 67.2 months: 7/21 patients (33.3%)	4
Ertan A, et al (1995)[168]	BE + HGD	Case report Single centre *Countries:* US	*Number of patients:* 1 *Gender:* Male: 1 *Age:* 80 yrs	Laser ablation *Type:* Nd: YAG *Power:* not reported *Dose:*	*Outcomes:* Progression to cancer	*Outcomes:* Progression to cancer at 2 months: 1/1 patient (100%)	4

Table B 5. Studies of laser ablation for Barrett's esophagus with/without dysplasia

Study authors (year published)	Cancer / Cell Type	Study Design	Patients	Intervention	Outcome Measures	Findings	Study quality
		Length of follow-up: 2 months	*Prior treatments:* H_2 blockers, unspecified *Length of Barretts:* 14 cm *Inclusion criteria:* none notable *Exclusion criteria:* none notable	Mean: 5063.75 J/session Range: 2761 to 5558 J / session *Treatment time:* not reported *Number of sessions:* 8 sessions Circumferential treatment, for focal HGD only *Co-interventions:* Omeprazole 40 mg/day	*Adverse events:* none		
Fisher RS, et al (2003)[169]	BE (6 patients) BE + HGD (3 patients) BE + LGD (12 patients) * * 10 additional patients unavailable for analysis	Patient cohort Single centre Prospective *Countries:* US *Length of follow-up:* Mean: 19.1 months ± 5.4 months	*Number of patients:* 21 *Gender:* Male: 21 Female: 10 *Age:* Mean: 53.6 yrs Range: 35 to 70 yrs *Prior treatments:* none reported *Length of Barretts:* Mean: 4.6 cm ± 0.7 cm *Inclusion criteria:* none notable *Exclusion criteria:* none notable	Laser ablation *Type:* Nd:YAG *Power:* Mean: 28.7 ± 3.6 watts *Dose:* Mean: 1105 ± 110 J *Treatment time:* not reported *Number of sessions:* Mean: 6.5 sessions / patient ± 1.2 sessions *Co-interventions:* PPI, unspecified	*Outcomes:* Complete response of BE (assessed through 4 quadrant biopsies) Recurrence of BE *Adverse events*	*Outcomes:* Complete response of BE - at <1 month: 21/21 patients (100%) - at 19.1 months (mean): 13/21 patients (62%) Recurrence of BE at 19.1 months (mean): 8/21 patients (38%) *Adverse events:* Bleeding, requiring transfusions: 1/21 patients (5%) Perforation, managed conservatively: 1/21 patients (5%) Strictures, requiring dilation: 1/21 patients (5%)	4
Norberto L, et al (2004)[170]	BE (11 patients) BE + LGD (2 patients) BE + HGD (2 patients	Patient cohort Single centre *Countries:* Italy *Length of follow-up:* Mean: 28 months Range: 7 to 61 months	*Number of patients:* 15 *Gender:* Male: 13 Female: 2 *Age:* Mean: 56 yrs Range: 32 to 73 yrs *Prior treatments:* ARS Nissen fundoplication (6 patients)	Laser ablation *Type:* Nd: YAG @ 940nm *Pulse time:* not reported *Power:* not reported *Dose:* Mean: 1705 J/session Range: 270 to 6135 J/session *Treatment time:* not reported *Number of sessions:* Mean: 6.5 sessions / patient Range: 2 to 19 sessions	*Outcomes:* Complete response of BE (assessed through endoscopy with jumbo biopsy) Complete response of HGD Complete response of LGD	*Outcomes:* Complete response of BE at 28 months (mean): 6/15 patients (40%) Complete response of HGD at 28 months (mean): 2/2 patients (100%) Complete response of LGD at 28	4

Table B 5. Studies of laser ablation for Barrett's esophagus with/without dysplasia

Study authors (year published)	Cancer / Cell Type	Study Design	Patients	Intervention	Outcome Measures	Findings	Study quality
			Gastric resection (1 patient) Gastric-esophageal resection for previous EAC (1 patient) *Length of Barretts:* Mean: 4 cm Range: 1 to 12 cm *Inclusion criteria:* none notable *Exclusion criteria:* none notable	*Cost*: ~$723 USD/session or ~$4692 / person Half circumference treated / session *Co-interventions:* Omeprazole 40 mg/day	Mean % of BE area reduction *Adverse events*	months (mean): 2/2 patients (100%) Mean % of BE area reduction: 77% *Adverse events:* Strictures: 0/15 patients (0%) Chest pain, mild: some	
Salo, JA, et al (1998)[171]	BE	Cohort study Single centre Prospective Laser ablation + anti-reflux surgery (ARS) vs. ARS alone *Countries:* US *Length of follow-up:* <u>Laser ablation + ARS Group</u> Mean: 26 months Range: 6 to 52 months <u>ARS Group</u> Mean: 21 months Range: 12.5 to 38 months	*Number of patients:* 17 (Laser Ablation + ARS: 11patients; ARS Only: 6 patients) *Age:* Mean: 56.6 yrs Range: 41 to 74 yrs <u>Laser Ablation + ARS</u> *Gender:* Male: 10 Female: 1 *Age:* not reported *Length of Barretts:* Mean: 4 cm <u>ARS Only</u> *Gender*: Male: 5 Female: 1 *Age:* not reported *Length of Barretts:* Mean: 8 cm *Prior treatments:*	<u>Laser ablation + ARS</u> *Type:* Nd:YAG *Power:*30 watts *Dose:* Range: 300 to 4000 J / session *Treatment time:* maximum 40 minutes *Number of sessions:* Mean: 4 sessions / patient Range: 1 to 8 sessions Preceded by ARS (fundoplication) <u>ARS</u> Fundoplication, various techniques *Co-interventions:* none reported	*Outcomes:* Complete response of BE (assessed through endoscopy with 4 quadrant biopsies every 1 cm) Number of laser sessions to achieve complete response of BE *Adverse events:* none	*Outcomes:* Complete response of BE: <u>Laser ablation + ARS Group</u> - at 3 months: 11/11 patients (100%) - at 26 months (mean): 11/11 patients (100%) <u>ARS Group</u> - at 3 months: 0/6 patients (0%) - at 21 months (mean): 0/6 patients (0%) Number of laser sessions to achieve complete response of BE: Mean: 4 sessions Range: 1 to 8 sessions	4

Table B 5. Studies of laser ablation for Barrett's esophagus with/without dysplasia

Study authors (year published)	Cancer / Cell Type	Study Design	Patients	Intervention	Outcome Measures	Findings	Study quality
			PPI Fundoplication (16 patients) Roux-en-Y duodenal diversion with partial gastrectomy and gastric vagotomy (1 patient) *Length of Barretts:* Range: 1 to 11 cm *Inclusion criteria:* none notable *Exclusion criteria:* none notable				

Table B 6. Studies of multipolar electrocoagulation (MPEC) for Barrett's esophagus with/without dysplasia

Study authors (year published)	Cancer / Cell Type	Study Design	Patients	Intervention	Outcome Measures	Findings	Study quality
Comparative studies							
Dulai GS, et al. (2005)[137]	BE	RCT Prospective MPEC vs. APC *Countries:* US *Length of follow-up:* 1 to 1.5 months (after last session)	*Number of patients:* 52 (APC Group: 26 patients; MPEC Group: 26 patients) <u>MPEC Group</u> *Gender:* Male: 23 Female: 3 *Age:* Mean: 56 yrs ± 11 yrs <u>APC Group</u> *Gender* Male: 21 Female: 5 *Age:* Mean: 58 yrs ± 11 yrs *Prior treatments:* none reported *Length of Barretts:* <u>MPEC Group</u> Mean: 3.1cm ± 1.7 cm <u>APC Group</u> Mean: 4.0 cm ± 1.5 cm *Inclusion criteria:* none notable *Exclusion criteria:* Severe active comorbid disease Diagnosis of HGD or cancer Prior antireflux surgery Inability to discontinue NSAID therapy Pregnancy, lactation or non-use	MPEC vs. APC <u>MPEC Group</u> *Probe:* not reported *Power:* 16 watts *Treatment time:* not reported *Number of sessions:* Mean: 2.9 sessions ± 1.5 sessions <u>APC Group</u> *Gas flow*: 2L/minute *Power:* 60 watts *Treatment time*: not reported *Number of sessions:* Mean: 3.8 sessions ± 1.7 sessions *Co-interventions:* Pantoprazole, dosing unspecified.	*Outcomes:* Complete response of BE (assessed through endoscopy with 4 quadrant biopsies every 2 cm) *Adverse events:*	*Outcomes:* Complete response of BE at 1 to 1.5 months: -MPEC Group: 23/26 patients (88%) -APC Group: 21/26 patients (81%) (p=0.68) *Adverse events:* <u>APC Group</u> Chest pain, severe: 1/26 patients (4%) <u>MPEC Group</u> none	1

Table B 6. Studies of multipolar electrocoagulation (MPEC) for Barrett's esophagus with/without dysplasia

Study authors (year published)	Cancer / Cell Type	Study Design	Patients	Intervention	Outcome Measures	Findings	Study quality
			of birth control measures Allergy to PPI Uncontrolled coagulopathy				
Sharma P, et al. (2006)[138]	BE BE + LGD	RCT Multi-centre Prospective MPEC vs APC *Countries:* US *Length of follow-up:* 2 yrs	*Number of patients*: 35 (MPEC Group: 16 patients; APC Group: 19 patients) *Gender:* Male: 34 Female: 1 <u>MPEC Group</u> *Age* Mean: 60 yrs Range: 42 to 68 yrs <u>APC Group</u> *Age* Mean: 65 yrs Range: 32 to 84 yrs *Prior treatments:* none reported *Length of Barretts:* <u>MPEC Group</u> Mean: 3 cm Range: 2 to 6 cm <u>APC Group</u> Mean: 4 cm Range: 2 to 6 cm *Inclusion criteria:* none notable *Exclusion criteria:* History of esophageal surgery; HGD with EAC; strictures or varices; allergy to PPI; coagulopathy; significant uncontrolled co-morbidities	MPEC vs. APC <u>MPEC Group</u> *Probe*: 10F gold *Power:* 20 watts *Number of sessions:* 3.8 sessions / patient <u>APC Group</u> *Gas flow:* 1.4 to 1.8 L/minute *Power:* 60 watts *Number of sessions:* Mean: 3.4 sessions/patient *Co-interventions:* Rabeprazole 40mg/day (median)	*Outcomes:* Complete response of BE (assessed through endoscopy with 4 quadrant biopsies every 2 cm) Number of sessions to achieve complete response of BE Progression to cancer Progression to HGD *Adverse events*	*Outcomes:* Complete response of BE at 2 years: -MPEC Group: 12/16 patients (75%) -APC Group: 12/19 patients (63%) Number of sessions to achieve complete response of BE: -MPEC Group: Mean: 3.8 sessions / patient -APC Group: Mean: 3.4 sessions / patient (p=0.48) Progression to cancer at 2 years: -MPEC Group: 0/16 patients (0%) -APC Group: 0/19 patients (0%) Progression to HGD at 2 years: -MPEC Group: 0/16 patients (0%) -APC Group: 0/19 patients (0%) *Adverse events:* <u>MPEC Group</u> Sore throat: 9/16 patients (56%) Dysphagia: 5/16 patients (31%) Chest pain: 6/16 patients (38%) Epigastric pain: 0 /16 patients (0%) Fever, low grade: 0 /16 patients (0%) Stricture: 0 /16 patients (0%) Perforation: 0 /16 patients (0%) Bleeding: 0 /16 patients (0%) <u>APC Group</u> : Sore throat: 9/19 patients (47%) Dysphagia: 2/19 patients (11%)	1

Table B 6. Studies of multipolar electrocoagulation (MPEC) for Barrett's esophagus with/without dysplasia

Study authors (year published)	Cancer / Cell Type	Study Design	Patients	Intervention	Outcome Measures	Findings	Study quality
						Chest pain: 4/19 patients (21%) Epigastric pain: 2/19 patients (11%) Fever, low grade: 1/19 patients (5%) Stricture: 1/19 patients (5%) Perforation: 0/19 patients (0%) Bleeding: 0/19 patients (0%)	
Non-comparative studies							
Faigel DO, et al (2002)[172]	BE	Clinical trial* Prospective Multicentre *Countries:* US *Length of follow-up*: 6 months *trial featured half-esophagus controls but patients went off split esophagus protocol at 9 weeks and split esophagus outcomes are not clear	*Number of patients: 25* (29 patients enrolled; 4 dropouts not extracted) *Gender:* Male: 24 Female: 1 *Age:* Mean: 58.5 yrs ± 13.5 yrs *Prior treatmetns:* none reported Length of Barretts: Mean: 3.1 cm ± 1.8 cm Range: 2-6 cm *Inclusion criteria:* none notable *Exclusion criteria:* Erosive or ulcerative esophagitis	MPEC *Probe*: 10F catheter probe *Power:* 20 to 25 Watts *Treatment time:* not reported *Number of treatments*: Mean: 3 sessions Range: 2 to 6 sessions *Co-interventions:* Omeprazole 40 mg twice daily for 1 week prior and throughout study	*Outcomes:* Complete response of BE (assessed through 4 quadrant biopsy every 1-2 cm) *Adverse events:* none	*Outcomes:* Complete response of BE at 6 months: 23/25 patients (92%)	4
Kovacs BJ, (1999)[173]	BE	Clinical trial Prospective Multicentre *Countries:* US *Length of follow-up:* 18 weeks	*Number of patients:* 27 *Gender:* Male: 21 Female: 6 *Age:* *Range:* 33-81 yrs *Prior treatments:* Nissen fundoplication (1 patient)	MPEC *Probe:* 7F Gold probe *Power:* 12-15 Watts *Treatment time:* not reported *Number of sessions:* Mean: 2.5 sessions / patient Half circumference treated with MPEC, 2-3 cm length/ session *Co-interventions:*	*Outcomes:* Complete response of BE (assessed through endoscopy with biopsies every 2 cm) Complete response of BE (assessed *histologically* through biopsy only) *Adverse events*	*Outcomes:* Complete response of BE at 18 weeks: 15/27 patients (56%) Complete response of BE at 18 weeks: 22/27 patients (81%) *Adverse events:* Dysphagia, transient, odynophagia,	4

Table B 6. Studies of multipolar electrocoagulation (MPEC) for Barrett's esophagus with/without dysplasia

Study authors (year published)	Cancer / Cell Type	Study Design	Patients	Intervention	Outcome Measures	Findings	Study quality
			Length of Barretts: Mean: 3.4 cm Range: 2-10 cm *Inclusion criteria:* none notable *Exclusion criteria:* Esophageal varices; esophageal strictures requiring dilation; esophageal ulceration >9mm diameter	Lansoprazole 30 mg twice a day 24 hours prior and throughout the study		chest pain, heart burn: 11/27 patients (41%) Strictures 1/27 patients (4%)	
Montes CG, et al (1999)[174]	BE	Case series Single centre *Countries:* Brazil *Length of follow-up:* Mean: 21.6 months Range: 18 to 30 months	*Number of patients:*14 *Gender:* Male: 11 Female: 3 *Age:* Mean: 45.7 yrs Range: 13 to 65 yrs *Prior treatments:* ARS (Laparoscopic gastric fundoplication) Ranitidine 300mg/day Cisapride 0.2mg/kg before meals *Length of Barretts:* Mean: 4.8 cm +/- 1.39 Range: 3 to 8 cm *Inclusion criteria:* none notable *Exclusion criteria:* none notable	MPEC *Probe:* 7F bipolar *Power:* 20 Watts *Treatment time:* not reported *Number of treatments:* Mean: 3.7 sessions / patient ± 1.1 sessions Range: 3 to7 sessions Half circumference of esophagus treated with MPEC, 2-3 cm length/ session *Co-interventions:* none reported	*Outcomes:* Complete response of BE (assessed through endoscopy with 4 quadrant biopsies every 2 cm) Number of sessions to achieve complete response of BE *Adverse events*	*Outcomes:* Complete response of BE at 21.6 months (mean): 14/14 patients (100%) Number of sessions to achieve complete response of BE: Mean: 3.7 sessions / patient ± 1.1 sessions Range: 3 to 7 sessions / patient *Adverse events:* Odynophagia, transient: 2/14 patients (14%) Dysphagia, transient: 1/14 patients (7%)	4
Sampliner RE (1999)[175]	BE (7 patients) BE + LGD (4 patients)	Case series Single centre *Countries:* USA	*Number of patients:* 11 *Gender*: not reported *Age:* not reported *Prior treatments:* none reported	MPEC *Probe:* not reported *Power:* not reported *Treatment time:* not reported *Number of sessions:* not	*Outcomes* Complete response of BE (assessed through endoscopy with 4 quadrant jumbo biopsy)	*Outcomes:* Complete response of BE at 36 months (mean): 8/11 patients (73%)	4

Table B 6. Studies of multipolar electrocoagulation (MPEC) for Barrett's esophagus with/without dysplasia

Study authors (year published)	Cancer / Cell Type	Study Design	Patients	Intervention	Outcome Measures	Findings	Study quality
		Length of follow-up: Mean: 36 months	*Length of Barretts:* not reported *Inclusion criteria:* none notable *Exclusion criteria:* none notable	reported *Co-interventions:* none reported	*Adverse events*	*Adverse events* Heartburn, transient, dysphagia, chest pain, mild: 7/11 patients (64%) Strictures or perforations: 0/11 patients (0%)	
Sampliner RE, et al (1996)[176]	BE	Clinical trial* Single centre *Countries:* US Omeprazole (OM) vs. MPEC + OM *Length of follow-up:* Mean: 12 months Range: 10 to 18 months *trial featured half esophagus controls but control region outcomes are not clear	*Number of patients:* 10 *Gender:* Male: 8 Female: 2 *Age:* Mean: 61 years Range: 45 to 76 yrs *Prior treatments:* None reported *Length of Barretts*: Mean: 4.7 cm Range: 2-9 cm *Inclusion criteria:* none notable *Exclusion criteria:* none notable	MPEC *Probe:* 10F gold *Power:* 50 Watts @ setting 3 *Treatment time:* not reported *Number of sessions:* Mean: 2.5 sessions / patient Range: 2 to 4 sessions Half circumference treated with MPEC, 2-3 cm length/ session *Co-interventions:* 20 mg OM twice daily 1 week prior to treatment Mean: 56 mg/day OM Range: 40 to 80 mg OM /day	*Outcomes:* Complete response of BE (assessed through endoscopy with 4 quadrant biopsy every 2 cm) Number of sessions to achieve complete response of BE *Adverse events*	*Outcomes:* Complete response of BE at 12 months: 10/10 patients (100%) Number of sessions to achieve complete response of BE: Mean: 2.5 sessions Range: 2 to 4 sessions *Adverse events* 5 events / 75 MPEC sessions (7%) Odynophagia, transient: 2/10 patients (20%) Dysphagia, transient: 1/10 patients (10%) Buried glands, transient: 2/10 patients (20%) Chest pain: 1/10 patients (10%) Upper GI bleed 2 weeks post MPEC therapy: 1/10 patients (10%)	4

Table B 7. Studies of radiofrequency ablation (RFA) for Barrett's esophagus with/without dysplasia

Study authors (year published)	Cancer / Cell Type	Study Design	Patients	Intervention	Outcome Measures	Findings	Study quality
Comparative studies							
Burgarner JM, et al. (2008)[130]	BE	Cohort study Multi-centre Retrospective RFA vs. PDT *Countries*: not stated *Length of follow-up:* not reported	*Number of patients:* (RFA Group: 103 patients; PDT Group: 122 patients) *Gender:* not reported *Age:* not reported *Prior treatments:* PPI, unspecified *Length of Barretts:* not reported *Inclusion criteria:* none notable *Exclusion criteria:* none notable	RFA vs. PDT <u>RFA</u> *Device:* not reported *Power:* 300W *Dose: n*ot reported *Treatment time:* Not reported *Number of sessions:* Not reported <u>PDT</u> *Drug:* not reported *Dose:* not reported *Route of administration:* not reported *Light source*: not reported *Light dose:* not reported *Time to photoactivation:* not reported *Treatment time:* not reported *Number of sessions:* not reported *Co-interventions:* PPI, unspecified	*Outcomes:* Complete response of dysplasia (grade unspecified), risk ratio Percentage of BE remaining after initial ablation *Adverse events: none*	*Outcomes:* Complete response of dysplasia, risk ratio RFA vs PDT, follow-up unknown: 0.69 (95% CI [0.26, 1.65]) Percentage of BE remaining after initial ablation: -RFA: 15% -PDT 30%	4
Non-comparative studies							
Eldaif SM, et al (2009)[177]	BE (25 patients) BE + LGD (2 patients)	Case series Single centre Retrospective *Countries:* US *Length of follow-up:* 8 weeks	*Number of patients:* 27 *Gender:* Male: 16 Female: 11 *Age:* Mean: 53.6 yrs ± 12.5 yrs *Prior treatments:* ARS (5 patients)	RFA *Power:* 300W *Dose:* 12 J/cm^2 *Treatment time:* not reported *Number of sessions:* 1 session / patient Circumferential ablation	*Outcomes:* Complete response of BE *Adverse events*	*Outcomes:* Complete response of BE at 8 weeks: 25/27 patients (93%) *Adverse events:* Dysphagia or strictures: 0/27 patients (0%)	4

Table B 7. Studies of radiofrequency ablation (RFA) for Barrett's esophagus with/without dysplasia

Study authors (year published)	Cancer / Cell Type	Study Design	Patients	Intervention	Outcome Measures	Findings	Study quality
			PPI, unspecified *Length of Barretts:* Mean: 4.6 cm ± 4.7 cm BE≤ 3cm (13 patients) BE 4-6 cm (9 patients) BE >6 cm (5 patients) *Inclusion criteria:* Chronic reflux symptoms *Exclusion criteria:* none notable	*Co-interventions:* Omeprazole 40 mg twice daily for 30 days then 40 mg/kg daily			
Fleischer DE, et al (2008)[178] and Sharma VK, et al (2007)[179]*	BE	Clinical trial Multi-centre Prospective *Countries:* US *Length of follow-up:* 30 months	*Number of patients:* 70 *Gender:* Male:52 Female: 18 *Age:* Mean: 55.7 yrs Range: 35 to 75 yrs *Prior treatments:* none reported *Length of Barretts:* Mean: 3.2 cm Range: 1 to 4 cm *Inclusion criteria:* none notable *Exclusion criteria:* Strictures; esophagitis; esophageal varices; previous radiation, ablation or resection of the esophagus; implantable electrical devices	RFA *Power:* 300W *Dose:* 10 J/cm^2 *Treatment time:* Mean: 27.7 minutes Range 23 to 37 minutes *Number of sessions:* -Circumferential ablations Mean: 1.51 sessions / patient Range: 1 to 2 sessions / patient -Focal ablations Mean: 1.87 sessions / patient -Any ablations Mean: 3.39 sessions / patient Circumferential ablations, followed up until 12 months, then focal ablation, followed up until 20 months *Co-interventions:* Esomeprazole 40 mg twice daily for 1 month then 40 mg/day for months 2 to 12	*Outcomes:* Complete response of BE (assessed through endoscopy with 4 quadrant biopsies every 1-2 cm) *Adverse events*	*Outcomes:* Complete response of BE - at 12 months* (after 1.5 sessions / patient): 48/69 patients (70%) - at 30 months** (after 3.4 sessions/ patient): 60/61 patients (98%) *Adverse events:* <u>After 1.5 sessions/ patient*:</u> Fever: 2/70 patients (3%) Chest / throat pain: 9/70 patients (13%) Mucosal scarring, transient: 1/70 patients (1%) Laceration, superficial: 1/70 patients (1%) Bleeding, mild: 1/70 patients (1%) Nausea, transient: 8/70 patients (11%) Sedation related hypotension: 1/70 patients (1%) Sedation related airway obstruction: 1/70 patients (1%)	4

Table B 7. Studies of radiofrequency ablation (RFA) for Barrett's esophagus with/without dysplasia

Study authors (year published)	Cancer / Cell Type	Study Design	Patients	Intervention	Outcome Measures	Findings	Study quality
* "Efficacy phase" involving 70 patients						After 1.9 additional sessions/ patient** Chest or throat pain: 1/62 patients (2%) Nausea and vomiting: 2/62 patients (3%) Sedation related hypotension: 1/62 patients (2%) Fever; laceration; bleeding; mucosal scarring; sedation related airway obstruction: 0/62 patients (0%) * circumferential ablations ** focal ablations	
Ganz RA, et al (2008)[180]	BE + HGD	Case series Multi-centre Retrospective *Countries:* US Length of follow-up: Median: 12 months	*Number of patients:* 142 *Gender:* Male: 125 Female:17 Age: Median: 67 yrs Range 59 to 75 *Prior treatments:* EMR: 24 patients *Length of Barretts:* Median 6 cm Range 3 to 8 cm *Inclusion criteria:* none notable *Exclusion criteria:* Varices; prior esophageal radiation or surgery other than fundoplication	RFA *Power:* 300W *Dose:* 24 J/cm^2 *Treatment time:* not reported *Number of treatments:* Median: 1 session / patient Inter-Quartile Range: 1 to 2 sessions / patient Circumferential ablation *Co-interventions:* PPI, unspecified	*Outcomes:* Complete response of dysplasia (assessed through endoscopy with 4 quadrant biopsy every 1 to 2 cm) *Adverse events*	*Outcomes:* Complete response of dysplasia at 3 months: 83/92 patients (90%) *Adverse events:* Strictures 1/142 patients (0.7%)	4
Hernandez JC, et al (2008)[181]	BE +/- LGD (7 patients) BE + HGD (3	Clinical trial Single centre Prospective	*Number of patients:* 10 *Gender:* Male: 8	RFA *Power:* 300W *Dose:*	*Outcomes:* Complete response of BE (assessed through endoscopy	*Outcomes:* Complete response of BE at 12 months:	4

Table B 7. Studies of radiofrequency ablation (RFA) for Barrett's esophagus with/without dysplasia

Study authors (year published)	Cancer / Cell Type	Study Design	Patients	Intervention	Outcome Measures	Findings	Study quality
	patients)	*Countries:* US *Length of follow-up:* 12 months	Female: 2 *Age:* Mean: 62 yrs Range: 19 to 73 yrs *Prior treatments*: none reported *Length of Barretts:* Mean: 4.9 cm Range: 1 to 11 cm *Inclusion criteria:* none notable *Exclusion criteria* Esphoageal strictures, active esophagitis, esophageal varices, esophageal malignancy, prior esophageal surgery, prior ablation or radiation therapy of the esophagus, comorbid condition affecting compliance	Nondysplasia patients: 20 J/cm^2 Dysplasia patients:36 J/cm^2 *Treatment time:* Not reported *Number of sessions:* Mean: 2.5 sessions / patient Range: 1 to 3 sessions Circumferential, then focal ablations to treat residual BE (<2cm) *Co-interventions:* PPI, unspecified	with 4 quadrant biopsy every 1 cm) Partial response of BE (50 to <100% of biopsies negative for BE) Number of sessions to achieve complete response of BE *Adverse events*	7/10 patients (70%) Partial response of BE at 12 months: 3/10 patients (30%) Number of sessions to achieve complete response of BE: Mean: 1.4 sessions/ patient *Adverse events:* Throat and chest pain, mild: common	
Hubbard N, & Velanovich V (2007)[182]	BE	Case series Single centre Prospective *Countries*: US *Length of follow-up:* 3 months	*Number of patients:* 7 *Gender:* Male: 5 Female: 2 *Age:* Mean: 60.57 yrs Range: 41 to 78 yrs *Prior treatments:* Fundoplication *Length of Barretts:* Mean: 4.43 cm Range: 1 to 12 cm *Inclusion criteria:* Previous fundoplication	RFA *Power:* 300W *Dose:* not reported *Treatment time:* not reported *Number of sessions:* not reported Circumferential ablation *Co-interventions:* none reported	*Outcomes:* Complete response of BE (assessed by endoscopy) *Adverse events*: none	*Outcomes:* Complete response of BE at 3 months: 6/7 patients (86%)	4

Table B 7. Studies of radiofrequency ablation (RFA) for Barrett's esophagus with/without dysplasia

Study authors (year published)	Cancer / Cell Type	Study Design	Patients	Intervention	Outcome Measures	Findings	Study quality
			Exclusion criteria: none notable				
Pouw RE, et al (2008)[183]	BE (2 patients) LGD (10 patients) HGD (32 patients)	Clinical trial Multi-centre *Countries:* Netherlands, other non-reported European countries *Length of follow-up*: Mean: 21 months Range: 10 to 27 months	*Number of patients:* 44 *Gender:* Male: 35 Female: 9 *Age:* Mean: 68 yrs Range: 57 to 75 yrs *Prior treatments:* Focal EAC or HGD by EMR (39 patients) *Length of Barretts:* Median: 7cm Range: 4 to 9 cm *Inclusion criteria:* *Exclusion criteria:* Esophageal stenosis	RFA *Source:* Balloon-based radiofrequency electrode *Power:* 40 watts *Dose:* 12 J/cm^2 *Treatment time:* not reported *Number of sessions:* Mean: 3 sessions (1 circumferential + 2 focal ablations) *Co-interventions:* Esomeprazole 40 mg twice daily Ranitidine 300 mg at bedtime Sucralfate 2 mL @ 200 mg/mL 4 times a day	*Outcomes:* Complete response of BE at 2 months post treatment (assessed though endoscopy with 4 quadrant biopsies every 1-2 cm) Progression to cancer *Adverse events:*	*Outcomes:* Complete response of BE at 2 months post treatment: 43/44 patients (98%) Progression to cancer after a mean of 21 months follow-up: 1/44 patients (2%) *Adverse events:* Laceration, superficial, at sites of previous EMR scars: 3/44 patients (7%) Dysphagia: 4/44 patients (9%) Fever: 1/44 patients (2%) Chest pain: 2/44 patients (4%)	4
Roorda AK, et al (2007)[184]	BE (6 patients) BE + HGD (3 patients) BE + LGD (4 patients)	Case series Single centre *Countries:* US *Length of follow-up:* Mean: 12 months Range: 6 to 19 months	*Number of patients:* 13 *Gender:* Male: 12 Female: 1 *Age:* Mean: 57 yrs Range: 31 to 75 yrs *Prior treatments:* Fundoplication (2 patients) PPI EMR (1 patient) *Length of Barretts:* >3cm: 10 patients	RFA *Power:* 300 watts *Dose:* -BE: 20 J/cm^2 (6 patients) -BE + dysplasia: 24 J/cm^2 (7 patients) *Treatment time:* not reported *Number of sessions:* Mean: 1.4 sessions Range: 1 to 2 sessions Circumferential ablation *Co-interventions:* PPI, unspecified	*Outcomes:* Complete response of BE (assessed through endoscopy with 4 quadrant biopsies every 1-2 cm) Complete response of dysplasia *Adverse events*	*Outcomes:* Complete response of BE at 12 months: 6/13 patients (46%) Complete response of dysplasia at 12 months: 5/7 patients (71%) *Adverse events:* Fever, low grade: 1/13 patients (8%) Dysphagia, mild; and odynophagia: 3/13 patients (23%) Strictures or buried glands: 0/13	4

Table B 7. Studies of radiofrequency ablation (RFA) for Barrett's esophagus with/without dysplasia

Study authors (year published)	Cancer / Cell Type	Study Design	Patients	Intervention	Outcome Measures	Findings	Study quality
			<3 cm: 3 patients *Inclusion criteria:* Patients with GERD *Exclusion criteria:* none notable			patients (0%)	
Sharma VK, et al (2008)[185]	BE + LGD	Clinical trial Single centre Prospective Countries: US *Length of follow-up:* 24 months	*Number of patients:* 10 *Gender:* not stated *Age:* Mean: 69.9 yrs Range 48 to 79 *Previous treatment:* PPI, unspecified *Length of Barretts*: Mean: 4.4 cm Range: 3 to 6 cm *Inclusion criteria:* none notable *Exclusion criteria:* Esophageal strictures or varices; esophagitis; previous fundoplication; previous radiation, ablation therapy or EMR	RFA *Power:* 300W *Dose:* 24 J/cm^2/session *Treatment time*: Mean: 38.36 minutes Range: 22-49 minutes *Number of sessions:* -Circumferential ablation: Mean: 1.6 sessions / patient -Focal ablation: Mean: 0.9 sessions / patient -Total (at 2 yrs follow-up): Mean: 2.5 sessions/patient; Range: 1 to 3 sessions Circumferential, then focal ablation *Co-interventions:* Lansoprazole 30 mg twice a day throughout study	*Outcomes:* Complete response of BE (assessed through endoscopy with 4 quadrant biopsy every 1 cm) Partial response of LGD to BE (50-99% of biopsy fragments negative) *Adverse events*	*Outcomes:* Complete response of BE: - at 1 year: 7/10 patients (70%) - at 2 years: 9/10 patients (90%) Partial response of LGD to BE: - at 1 year: 2/10 patients (20%) - at 2 years: 1/10 patients (10%) *Adverse events*: Hematemesis, coffee ground: 1/10 patients (10%)	4
Sharma VK, et al (2007)[179]*	BE	Clinical trial Multi-centre Prospective *Countries:* US *Length of follow-up:* 12 months	*Number of patients:* 32 *Gender:* Male: 29 Female: 3 *Age:* Mean: 56.8 yrs Range: 35 to 75 yrs *Prior treatments:* none reported	RFA *Power:* 300W *Dose:* 6, 8, 10, or 12 J/cm^2 *Treatment time:* Mean: 26.4 minutes Range 20 to 35 minutes *Number of sessions:* Mean: 1.82 sessions Range: 1 to 2 sessions	*Outcomes:* Complete response of BE (assessed through endoscopy with 4 quadrant biopsies every 1-2 cm) Partial response of BE (50 to 99% of biopsy fragments negative)	*Outcomes:* Complete response of BE: - at 3 months: 7/32 patients (22%) - at 12 months: 19/32 patients (59%) Partial response of BE: - at 3 months: 25/32 patients (78%) - at 12 months: 13/32 patients	4

Table B 7. Studies of radiofrequency ablation (RFA) for Barrett's esophagus with/without dysplasia

Study authors (year published)	Cancer / Cell Type	Study Design	Patients	Intervention	Outcome Measures	Findings	Study quality
* "Dosimetry phase" involving 32 patients			*Length of Barretts:* Mean: 2.3 cm Range: 1 to 4 cm *Inclusion criteria:* none notable *Exclusion criteria:* Strictures; esophagitis; esophageal varices; previous radiation, ablation or resection of the esophagus; implantable electrical devices	Circumferential ablation *Co-interventions:* Esomeprazole: 40 mg twice a day for 1 month post ablation; 40 mg every second day for follow-up months 2-12	*Adverse events*	(41%) *Adverse events:* Chest pain: 3/32 patients (9%) Mucosal scarring, transient: 1/32 patients (3%) Lacerations, superficial: 1/32 patients (3%)	
Smith CD, et al (2007)[186]	HGD	Clinical trial Multi-centre Prospective Countries: US Length of follow-up: immediate pathologic outcomes only	*Number of patients: 5* *Gender:* Male: 5 Female: 0 *Age:* Mean: 57 yrs Range: 45 to 71 yrs *Prior treatments* PPI, unspecified *Length of Barretts*: Mean: 7 cm Range: 4 to 10 cm *Inclusion criteria:* Consent to esophagectomy post RFA *Exclusion criteria:* Esophageal strictures Previous ablative therapy	RFA *Power:* 300W *Dose:* 20 to 56 J/cm^2 *Treatment time:* Mean: 31 minutes Range: 11 to 65 minutes *Number of sessions:* 1 session / patient Circumferential ablation *Co-interventions:* All sessions followed by esophagectomy	*Outcomes:* Complete response of BE (assessed by pathological assessment of esophagectomy specimens post-RFA) *Adverse events:* none	*Outcomes:* Complete response of BE at immediate follow-up: 9/10 ablation regions (90%)	4

Table B 8. Studies of esophagectomy for Barrett's esophagus with/without dysplasia

Study authors (year published)	Cancer / Cell Type	Study Design	Patients	Intervention	Outcome Measures	Findings	Study quality
Comparative studies							
Prasad GA, et al. (2007)[131]	BE + HGD	Cohort Study Single centre Retrospective Esophagectomy vs PDT *Countries:* United States *Length of follow-up:* 5 yrs	*Number of patients:* 199 (Esophagectomy Group: 70 patients; PDT Group: 129 patients) <u>Esophagectomy Group</u> *Gender:* Male: 61 Female: 9 *Age:* Mean: 60.5 yrs ± 10.8 yrs <u>PDT Group</u> *Gender:* Male: 121 Female: 8 *Age:* 64.5 yrs ± 10.2 yrs *Prior treatments:* none reported *Length of Barretts:* <u>PDT Group</u> Median: 5 cm Range 3 to 8.5 cm <u>Esophagectomy Group</u> Median: 5 cm Range: 5 to 10.5 cm *Inclusion criteria:* none notable *Exclusion criteria:* none notable	Esophagectomy vs. PDT <u>Esophagectomy Group</u> TTE or THE <u>PDT Group</u> *Drug and dose::* HPD 4 mg/kg – 26 patients Porfimer sodium 2 mg/kg – 103 patients *Route of administration:* IV *Time to photoactivation:* 48 hours *Light source:* laser (type not reported)at 630nm *Light dose:* 200J/cm^2 *Treatment time:* not reported *Number of sessions / patient:* Mean: 1.26 sessions / patient Range: 1 to 2 sessions / patient *Co-interventions:* PPI, unspecified. EMR for focally visible lesions on endoscopy	*Outcomes:* Complete response of dysplasia Mortality: -All cause -Cancer Progression to cancer Mortality, hazard ratio*, PDT vs. esophagectomy -Overall -Cancer free *Adverse events*	*Outcomes:* Complete response of dysplasia: <u>Esophagectomy Group</u> Not recorded <u>PDT Group</u> - at 1 year: 88% - at 3 years: 86% Mortality at 5 years: <u>Esophagectomy Group</u> -All cause: 6/70 patients (8.5%) -Cancer: 0/70 patients (0%) <u>PDT Group</u> -All cause: 11/129 patients (9%) -Cancer: 0/129 patients (0%) Progression to cancer: <u>Esophagectomy Group</u> Not recorded <u>PDT Group</u> - at 1 year: 6/129 patients (5%) - at 3 years: 8/129 patients (6%) Mortality, hazard ratio, at 5 years: -Overall: 1.31 (95% CI [0.4, 4.17]) -Cancer free: 2.45 (95% CI [0.85, 7.12]) *Adverse events:* <u>Esophagectomy Group</u> Stricture: 9/70 patients (13%) Photosensitivity: 0/70 patients (0%) Post-op mortality: 1/70 patients (1%)	2

Table B 8. Studies of esophagectomy for Barrett's esophagus with/without dysplasia

Study authors (year published)	Cancer / Cell Type	Study Design	Patients	Intervention	Outcome Measures	Findings	Study quality
					* Cox proportional hazards model	Total post-op "morbidity": 27/70 patients (39%) PDT Group * Stricture: 35/131 patients (27%) Photosensitivity: 77/131 patients (59%) Post-op mortality: 0/131 patients (0%) Total post-op "morbidity": none * 3 extra patients of unknown origin reported.	
Reed MF, et al (2005)[132]	BE + HGD	Cohort study Single centre Retrospective Esophagectomy vs Endoscopic Therapy vs Observation *Countries:* not reported *Length of follow-up*: 10 yrs	*Number of patients: 115* (Esophagectomy Group: 49 patients; Endoscopic Therapy Group: 47 patients; Observations Group: 19 patients) *Age:* Mean 65 yrs Range 30 to 87 yrs Gender: Male: 95 Female: 20 Esophagectomy Group *Age:* Mean 59 yrs Range 32 to 79 yrs *Gender:* Male: 40 Female: 9 Endoscopic Group *PDT: 42 patients* *EMR 5 patients* *Age:* Mean 70 yrs	Esophagectomy Group: Surgical resection done within 60 days of diagnosis *Type of surgery:* -TTE: 20 patients (41%) -Ivor Lewis: 18 patients (37%) -THE: 7 patients (17%) -various or mixed techniques: 4 patients(8%) Endoscopic Group Endoscopic mucosal resection (EMR) or Photodynamic therapy (PDT) No details reported Observation Group: No details reported *Co-interventions:* none reported	*Outcomes:* Disease specific survival Overall survival Complete response of HGD Progression to cancer	*Outcomes:* Disease specific survival at 5 years: -Esophagectomy Group: 94% -Endoscopic Group: not reported -Observation Group: not reported Overall survival: Esophagectomy Group - at 5 yrs: 83% - at 10 yrs: 64% Endoscopic Group: not reported Observation Group: not reported Complete response of HGD, follow-up unknown: Esophagectomy Group not reported Endoscopic Group PDT: 37/42 patients (88%) EMR 3/5 patients (60%) Observation Group 0/13 patients (0%) Progression to cancer -Esophagectomy Group: not reported	4

Table B 8. Studies of esophagectomy for Barrett's esophagus with/without dysplasia

Study authors (year published)	Cancer / Cell Type	Study Design	Patients	Intervention	Outcome Measures	Findings	Study quality
			Range 30 to 89 yrs *Gender:* Male: 38 Female: 9 <u>Observation Group:</u> *Age:* not reported *Gender:* not reported *Prior treatments:* none reported *Length of Barretts:* not reported *Inclusion criteria*: none notable *Exclusion criteria*: none notable		*Adverse event:*	-Endoscopic Group: 6/47 patients -Observation 7/13 patients *Adverse events:* <u>Esophagectomy Group</u> Post op anastomotic leak: 2/49 patients (4%) Death secondary to large cerebrovascular accident post-op: 1/49 patients (2%)	
Thomas T, et al. (2005)[139] * * Information extracted for BE or HGD patients only	BE + HGD	Cohort study Multi-centre Retrospective Esophagectomy vs APC vs Non-Intervention Surveillance vs *Countries:* UK *Length of follow-up:* <u>Esophagectomy Group</u> Mean: 21 months Range: 6 to 36 months <u>APC and Non-Intervention Groups</u> Not reported <u>Surveillance Group</u>	*Number of patients:* 27 (Esophagectomy Group: 8 patients; APC: 5 patients; Non-Intervention Group: 7 patients; Surveillance Group: 7 patients) <u>Esophagectomy Group</u> *Gender:* Male: 7 Female: 1 *Age:* Mean: 58 yrs Range: 46 to 76 yrs <u>APC Group</u> *Gender:* Male: 5 *Age:* Mean: 70 yrs Range: 54 to 76 yrs <u>Non-Intervention Group</u> *Gender:* not reported	Surveillance vs Esophagectomy vs APC vs Non-Intervention <u>Esophagectomy Group</u> No details reported <u>APC Group</u> *Gas flow:* not reported *Power:* not reported *Treatment time:* not recorded *Number of sessions:* Mean: 4 sessions / patient Range: 1 to 14 sessions / patient <u>Surveillance Group</u> *Time between endoscopies:* Mean: 4.6 months *Number of treatments:* Mean 2.9 treatments / patient Range: 1 to 5 treatments /	*Outcomes:* Overall survival Disease specific survival Complete response of	*Outcomes:* Overall survival: -Esophagectomy Group at 21 months (mean): 5/8 patients (62.5%) -APC Group: not reported -Non-Intervention Group, at unknown follow-up: 2/7 patients (28.6%) -Surveillance Group: not reported Disease-specific survival -Esophagectomy Group at 21 months (mean): 7/8 patients (88%)* -APC Group: not reported -Non-Intervention Group, at unknown follow-up: 5/7 patients (71%)** -Surveillance Group: not reported	4

Table B 8. Studies of esophagectomy for Barrett's esophagus with/without dysplasia

Study authors (year published)	Cancer / Cell Type	Study Design	Patients	Intervention	Outcome Measures	Findings	Study quality
		Mean: 15 months Range: 4 to 39 months	*Age:* Mean: 80 yrs Range: 74 to 95 yrs <u>Surveillance Group</u> *Gender:* Male: 6 Female: 1 *Age:* Mean: 65.4 yrs Range: 55 to 86 yrs *Prior treatments:* PPI, unspecified *Length of Barretts:* Mean: 6 cm Range: 3 to 14 cm <u>APC Group</u> Mean: 6 cm Range: 3 to 9 cm <u>Surveillance Group</u> Mean: 5 cm Range: 2 to 10 cm *Inclusion criteria:* none notable *Exclusion criteria:* none notable	patient 4 quadrant biopsy every 2 cm in 45% of biopsies *Co-interventions:* Omeprazole 20-40 mg daily: 17 patients Lansoprazole 30 mg daily: 14 patients Pantoprazole 40 mg daily: 1 patient Rabeprazole 40 mg daily: 2 patients Ranitidine 150 mg twice daily: 3 patients	dysplasia Progression to cancer *Adverse events:* No HGD or BE specific information availble	Complete response of dysplasia: -Esophagectomy Group: not reported -APC Group at unknown follow-up: 2/5 patients (40%) -Non-intervention Group: not reported -Surveillance Group at 15 months (mean): 4/7 patients (57%) Progression to cancer: Progression to cancer: -Esophagectomy Group at 21 months (mean): 2/8 patients (25%) -APC Group at unknown follow-up: 2/5 patients (40%) -Non-Intervention Group at unknown follow-up: 2/4 patients (50%) -Surveillance Group at 15 months: 2/6 patients (33%)	
Non-comparative studies							
Ferguson MK, et al (1997)[187]	BE + HGD	Case series Multicentre Retrospective *Countries:* US *Length of follow-up:* Mean: 41 months ± 9 months	*Number of patients:* 15 *Gender:* Male: 13 Female: 2 *Age:* Mean 63 yrs Range: 35 to 76 yrs *Prior treatments:* none reported	Esophagectomy *Type of surgery:* THE (9 patients) TTE with chest anastomosis (3 patients) TTE with cervical anastomosis (2 patients) Modified Ivor Lewis esophagectomy (1 patient) *Operative time:* not reported	*Outcomes:* Progression to cancer Survival Length of stay (LOS)	*Outcomes:* Progression to cancer at 41 months (mean): 0/15 patients (0%) Survival at 41 months (mean): 15/15 patients (100%) LOS: Mean: 18.5 ± 3.0 days Median: 16 days	4

Table B 8. Studies of esophagectomy for Barrett's esophagus with/without dysplasia

Study authors (year published)	Cancer / Cell Type	Study Design	Patients	Intervention	Outcome Measures	Findings	Study quality
			Length of Barretts: not reported *Inclusion criteria*: none notable *Exclusion criteria:* none notable	*Co-interventions:* none reported	*Adverse events*	*Adverse events*: Anastomotic leaks 11/15 patients (73%) Pulmonary complications: 4/15 patients (27%) Cardiovascular complications: 3/15 patients (20%) Infection: 5/15 patients (33%) Other complications 5/15 patients (33%)	
Nguyen NT, et al (2000)[188]	BE + HGD	Case series Single centre Countries: US *Length of follow-up:* Mean: 12.6 months	*Number of patients:* 12 *Gender:* Male:7 Female: 5 *Age:* Mean 64 yrs Range 40-78 yrs *Prior treatments:* Abdominal surgery (5 patients) *Length of Barretts:* not reported *Inclusion criteria:* Karnofsky score >60 >50% predicted force expiratory volume in 1 second Vital capacity score >60 *Exclusion criteria:* none notable	Esophagectomy *Type of surgery:* MIE with cervical anastomosis *Operative time:* Mean: 7.8 hours ± 2.1 hours *Co-interventions:* none reported	*Outcomes:* Survival Length of stay (LOS) -in ICU -in hospital *Adverse events:*	*Outcomes:* Survival at 12.6 months (mean): 12/12 patients (100%) LOS: -in ICU: Mean: 2.6 days Range: 1 to 8 days) -in hospital: Mean: 8.3 days Range: 4 to 21 days *Adverse events:* Small bowel perforation 1/12 patient (8%) Respiratory insufficiency: 2/12 patients (17%) Delayed gastric emptying requiring pyloroplasty: 3/12 patients (25%) J-tube infection: 1/12 patients (8%)	4
Romagnoli R, et al (2003)[189]	BE + LGD (3 patients) BE + HGD (24 patients) BE + HGD + LGD (6 patients)	Case series Single centre Retrospective *Countries:* Belgium *Length of follow-up:*	*Number of patients:*33 (prompt ER: 20 patients; expectant ER: 13 patients) *Gender:* Male: 28 Female: 5 *Age:*	Esophagectomy *Type of surgery:* TTE with neck or thoracic anastomosis THE MIE (thoracoscopy) *Operative time:* not reported	*Outcomes:* Survival: -Prompt Esophagectomy Group -Expectant Esophagectomy Group	*Outcomes:* Survival at 120 months: -Prompt Esophagectomy Group: 100% -Expectant Esophagectomy Group: 52.5% (p=0.0094)	4

Table B 8. Studies of esophagectomy for Barrett's esophagus with/without dysplasia

Study authors (year published)	Cancer / Cell Type	Study Design	Patients	Intervention	Outcome Measures	Findings	Study quality
		120 months	Range: 41 to 79 years <u>Prompt Esophagectomy Group</u> Number of patients: 20 Gender: not reported Age: not reported <u>Expectant Esophagectomy Group</u> Number of patients: 13 Gender: not reported Age: not reported *Prior treatments:* ARS (3 patients) *Length of Barretts:* not reported *Inclusion criteria:* none notable *Exlusion criteria:* none notable	<u>Prompt Esophagectomy Group</u> Esophagectomy after HGD detected in 1 or 2 endoscopies <u>Expectant Esophagectomy Group</u> Esophagectomy after 3 to 5 subsequent endoscopies positive for HGD or detection of EAC *Co-interventions:* none reported	Neoplastic recurrence: -Prompt Esophagectomy Group -Expectant Esophagectomy Group *Adverse events:* none reported	Neoplastic recurrence at 120 months: -Prompt Esophagectomy Group: 1/20 patients (5%) -Expectant Esophagectomy Group: 4/13 patients (31%) p=0.094	
Sujendran V, et al (2005)[190]	BE + HGD	Case series Single centre Prospective *Countries:* US *Length of follow-up:* Median: 32 months Range: 3 to 68 months	*Number of patients:* 17 *Gender:* Male: 15 Female: 2 *Age:* Mean: 62 yrs Range: 53 to 74 yrs *Prior treatments:* none reported *Length of Barretts:* not reported *Inclusion criteria:* none notable *Exclusion criteria*: none notable	Esophagectomy *Type of surgery:* THE (16 patients) Ivor Lewis (1 patient) *Operative time:* not reported *Co-interventions:* none reported	*Outcomes:* Disease free survival Length of stay (LOS): -in ICU -in hospital *Adverse event*	*Outcomes:* Disease free survival: - at 12 months: 17 patients (100%) - at 24 months: 94% - at 36 months:82% - at 43 months:70% *LOS*: -in ICU: 1 day: 16 patients (94%) 7 days: 1 patient secondary to acute lung injury (6%) -in hospital Median: 11 days Range: 9-26 days *Adverse events:*	4

Table B 8. Studies of esophagectomy for Barrett's esophagus with/without dysplasia

Study authors (year published)	Cancer / Cell Type	Study Design	Patients	Intervention	Outcome Measures	Findings	Study quality
						Lung injury, acute, requiring 7 days in ICU: 1/17 patient (6%) Pneumonia: 3/17 patients (18%) Anastomotic leak: 3/17 patients (18%)	
Thomson BNJ, et al. (2007)[191]	BE + HGD	Cohort study Single centre Prospective Esophagectomy vs Surveillance *Countries:* Australia *Length of follow-up:* <u>Esophagectomy Group</u> Mean: 17.3 months Range 8 to 31 months <u>Surveillance Group</u> Mean: 44 months Range 7 to 74 months	*Number of patients: 12* (Esophagectomy Group: 7 patients; Surveillance Group: 5 patients) <u>Esophagectomy Group</u> *Gender:* not reported *Age:* Mean: 59 yrs Range: 50 to 74 yrs <u>Surveillance Group</u> *Gender:* not reported *Age:* Mean: 56.4 yrs Range: 46 to 72 yrs *Prior treatments:* none reported *Length of Barretts:* not reported *Inclusion criteria:* none notable *Exclusion criteria:* none notable	Esophagectomy vs. Surveillance <u>Esophagectomy Group</u> No details reported <u>Surveillance Group</u> No details reported *Co-interventions:* not reported	*Outcomes:* Survival *Adverse events*	*Outcomes:* Survival: -Esophagectomy Group, at 17.3 months (mean): 7/7 patients (100%) -Surveillance Group, at 44 months (mean): 5/5 patients (100%) *Adverse events:* <u>Esophagectomy Group</u> Pulmonary embolus: 1/7 patients (14%) MRSA wound infection: 1/7 patients (14%) Respiratory complications; cardiac complications; recurrent laryngeal nerve palsy, radiological leak; DVT: 0/7 patients (0%) <u>Surveillance Group</u> None reported	4

Appendix C - Evidence tables: excluded studies

Table C 1. Excluded studies	
Study authors (year published)	**Main reason for exclusion**
Ackroyd R, et al (1998)[192]	Patients already included in study by "Ackroyd R, et al (2001)[99]"
Ackroyd R, et al (1999)[193]	Study did not include outcomes of interest
Ackroyd R, et al (2000)[194]	Patients already included in study by "Ackroyd R, et al (2001)[99]"
Ackroyd R, et al (2000)[195]	Patients already included in study by "Ackroyd R, et al (2001)[99]"
Ackroyd R, et al (2004)[144]	Patients already included in study by "Bright T, et al (2007)[143]"
Ban S, et al (2004)[196]	Patients already included in study by "Yachimski P, et al (2008)[129]"
Barr H, et al (2004)[197]	Study included patients with cancer and it was not possible to extract information for Barrett's esophagus with LGD or HGD
Beaumont H, et al (2009)[198]	Patients already included in study by "Pouw RE, et al (2008)[183]"
Beejay U, et al (2002)[199]	Study included patients with cancer and it was not possible to extract information for Barrett's esophagus with LGD or HGD
Bellinier DA, et al (2003)[200]	Study did not include outcomes of interest
Biddlestone LR, et al (1996)[201]	Patients already included in study by "Barham CP, et al (1997)[165]"
Biddlestone LR, et al (1998)[202]	Patients already included in study by "Barham CP, et al (1997)[165]"
Buttar NS, et al (2000)[203]	Patients already included in study by "Buttar NS, et al (2001)[204]"
DeVault KR, et al (2002)[205]	Study did not include outcomes of interest
Ell C, et al (2000)[206]	Study included patients with cancer and it was not possible to extract information for Barrett's esophagus with LGD or HGD
Etienne J, et al (2004)[207]	Study included patients with cancer and it was not possible to extract information for Barrett's esophagus with LGD or HGD
Fennerty MB, et al (2001)[208]	Study did not include outcomes of interest
Forcione DG, et al (2004)[209]	Study included patients with cancer and it was not possible to extract information for Barrett's esophagus with LGD or HGD
Globe J, et al (2004)[210]	Study did not include outcomes of interest
Go JT, et al (2006)[211]	Study included patients with cancer and it was not possible to extract information for Barrett's esophagus with LGD or HGD
Gondrie JJ, et al (2008)[212]	Patients already included in study by "Pouw RE, et al (2008)[183]"
Gondrie JJ, et al (2008)[213]	Patients already included in study by "Pouw RE, et al (2008)[183]"
Gossner L, et al (1998)[214]	Patients already included in study by "Behrens A, et al (2005)[106]"
Gossner L, et al (1998)[215]	Patients already included in study by "Gossner L, et al (1998)[110]"
Gossner L, et al (1999)[216]	Study included patients with cancer and it was not possible to extract information for Barrett's esophagus with LGD or HGD
Gossner L, et al (1999)[111]	Patients already included in study by "Behrens A, et al (2005)[106]"
Gossner L, et al (1999)[217]	Patients already included in study by "Gossner L, et al (1998)[110]"
Greenwald BD, et al (2008)[218]	Study included patients with cancer and it was not possible to extract information for Barrett's esophagus with LGD or HGD
Hage M, et al (2003)[219]	Patients already included in study by "Hage M, et al (2004)[107]"
Hinnen P, et al (2002)[220]	Study did not include outcomes of interest
Jamieson NF, et al (2002)[221]	Patients already included in study by "Mackenzie G, et al (2005)[135]"

Table C 1. Excluded studies	
Study authors (year published)	**Main reason for exclusion**
Jamieson N, et al (2003)[222]	Patients already included in study by "Mackenzie G, et al (2005)[135]"
Jamieson N, et al (2003)[223]	Patients already included in study by "Lovat LB, et al (2005)[119]"
Jamieson NF, et al (2003)[224]	Patients already included in study by "Mackenzie G, et al (2005)[135]"
Jamieson NF, et al (2008)[225]	Patients already included in study by "Lovat LB, et al (2005)[119]"
Jenkins JT, et al (2005)[226]	Study included patients with cancer and it was not possible to extract information for Barrett's esophagus with LGD or HGD
Kapoor N, et al (2005)[227]	Patients already included in study by "Ragunath K, et al (2005)[60]"
Kelty CJ, et al (2001)[228]	Patients already included in study by "Ackroyd R, et al (2001)[99]"
Kelty C, et al (2002)[229]	Patients already included in study by "Kelty CJ, et al (2004)[133]"
Kelty CJ, et al (2002)[230]	Patients already included in study by "Kelty CJ, et al (2004)[133]"
Kelty CJ, et al (2004)[231]	Patients already included in study by "Kelty CJ, et al (2004)[45]"
Kelty CJ, et al (2004)[232]	Patients already included in study by "Kelty CJ, et al (2004)[45]"
Kelty CJ, et al (2004)[233]	Patients already included in study by "Kelty CJ, et al (2004)[45]"
Krishnadath KK, et al (2000)[234]	Study did not include outcomes of interest
Lopes CV, et al (2007)[235]	Study included patients with cancer and it was not possible to extract information for Barrett's esophagus with LGD or HGD
Lovat LB, et al (2000)[236]	Patients already included in study by "Mackenzie G, et al (2005)[135]"
Lovat LB, et al (2000)[237]	Patients already included in study by "Mackenzie G, et al (2005)[135]"
Mackenzie GD, et al (2005)[238]	Patients already included in study by "Mackenzie G, et al (2005)[135]"
Mackenzie GD, et al (2007)[239]	Patients already included in study by "Mackenzie G, et al (2007)[103]"
May A, et al (2002)[240]	Patients already included in study by "Behrens A, et al (2005)[106]"
May A, et al (2002)[241]	Patients already included in study by "Behrens A, et al (2005)[106]"
Michopoulos S, et al (2000)[242]	Patients already included in study by "Michopoulos S, et al (1999)[243]"
Mino-Kenudson M, et al (2007)[244]	Study included patients with cancer and it was not possible to extract information for Barrett's esophagus with LGD or HGD
Montes CG, et al (1998)[245]	Patients already included in study by "Montes CG, et al (1999)[174]"
Morino M, et al (2003)[246]	Patients already included in study by "Ferraris R, et al (2007)[147]"
Nishioka NS, et al (2006)[247]	Patients already included in study by "Yachimski P, et al (2008)[129]"
Oelschlager BK, et al (2003)[248]	Study did not include outcomes of interest
O'Riodan JM, et al (2004)[249]	Study included patients with cancer and it was not possible to extract information for Barrett's esophagus with LGD or HGD
Overholt B, et al (1993)[250]	Study included patients with cancer and it was not possible to extract information for Barrett's esophagus with LGD or HGD
Overholt BF, et al (1995)[251]	Patients already included in study by "Overholt BF, et al (2003)[124]"
Overholt BF, et al (1995)[252]	Patients already included in study by "Overholt BF, et al (2003)[124]"
Overholt BF, et al (1996)[253]	Patients already included in study by "Overholt BF, et al (2003)[124]"

Table C 1. Excluded studies	
Study authors (year published)	**Main reason for exclusion**
Overholt BF, et al (1996)[126]	Patients already included in study by "Overholt BF, et al (1997)[125]"
Overholt BF, et al (1996)[254]	Patients already included in study by "Overholt BF, et al (2003)[124]"
Overholt BF, et al (1997)[255]	Patients already included in study by "Overholt BF, et al (2003)[124]"
Over holt BF, et al (1997)[256]	Patients already included in study by "Overholt BF, et al (2003)[124]"
Overholt BF, et al (1997)[257]	Patients already included in study by "Overholt BF, et al (2003)[124]"
Overholt BF, et al (1999)[258]	Patients already included in study by "Overholt BF, et al (2003)[124]"
Overholt BF, et al (2001)[259]	Patients already included in study by "Overholt BF, et al (2003)[124]"
Overholt BF, et al (2002)[260]	Patients already included in study by "Overholt BF, et al (2003)[124]"
Overholt BF, et al (2003)[261]	Patients already included in study by "Overholt BF, et al (2007)[123]"
Overholt BF, et al (2005)[262]	Patients already included in study by "Overholt BF, et al (2007)[123]"
Pacifico RJ, et al (2003)[263]	Patients already included in study by "Prasad GA, et al (2007)[131]"
Panjehpour M, et al (2000)[264]	Study included patients with cancer and it was not possible to extract information for Barrett's esophagus with LGD or HGD
Panjehpour M, et al (2004)[265]	Patients already included in study by "Panjehpour M, et al (2005)[266]"
Panjehpour M, et al (2005)[266]	Study included patients with cancer and it was not possible to extract information for Barrett's esophagus with LGD or HGD
Panjehpour M, et al (2008)[267]	Study did not include outcomes of interest
Parrilla P, et al (2003)[268]	Study did not include outcomes of interest
Pech O, et al (2005)[269]	Patients already included in study by "Behrens A, et al (2005)[106]"
Pech O, et al (2006)[270]	Study included patients with cancer and it was not possible to extract information for Barrett's esophagus with LGD or HGD
Peters FP, et al (2004)[271]	Patients already included in study by "Peters FP, et al (2005)[104]"
Peters FP, et al (2005)[272]	Patients already included in study by "Peters FP, et al (2005)[104]"
Peters FP, et al (2005)[273]	Patients already included in study by "Peters FP, et al (2005)[104]"
Peters FP, et al (2006)[274]	Study included patients with cancer and it was not possible to extract information for Barrett's esophagus with lLGD or HGD
Peters FP, et al (2007)[275]	Study did not include outcomes of interest
Peters FP, et al (2007)[276]	Study included patients with cancer and it was not possible to extract information for Barrett's esophagus with LGD or HGD
Peters FP, et al (2007)[277]	Study included patients with cancer and it was not possible to extract information for Barrett's esophagus with LGD or HGD
Phan MN, et al (2004)[278]	Patients already included in study by "Panjehpour M, et al (2005)[266]"
Pouw RE, et al (2008)[279]	Study included patients with cancer and it was not possible to extract information for Barrett's esophagus with LGD or HGD
Pouw RE, et al (2008)[280]	Study included patients with cancer and it was not possible to extract information for Barrett's esophagus with LGD or HGD
Pouw RE, et al (2008)[281]	Study included patients with cancer and it was not possible to extract information for Barrett's esophagus with LGD or HGD
Pouw RE, et al (2008)[282]	Study included patients with cancer and it was not possible to extract information for Barrett's esophagus with LGD or HGD
Pouw RE, et al (2008)[283]	Study included patients with cancer and it was not possible to extract information for Barrett's esophagus with LGD or HGD
Prasad GA, et al (2007)[284]	Patients already included in study by "Prasad GA, et al (2007)[131]"

Table C 1. Excluded studies	
Study authors (year published)	**Main reason for exclusion**
Schembre D, et al (1998)[135]	Study included patients with cancer and it was not possible to extract information for Barrett's esophagus with LGD or HGD
Selvasekar CR, et al (2004)[285]	Patients already included in study by "Mackenzie G, et al (2005)[102]"
Selvasekar CR, et al (2005)[286]	Patients already included in study by "Mackenzie G, et al (2005)[102]"
Shah AK, et al (2006)[287]	Study did not include outcomes of interest
Shaheen NJ, et al (2008)[288]	Study did not include outcomes of interest
Van Veen, RLP, et al (2002)[289]	Study did not include outcomes of interest
Wang SJ, et al (2008)[290]	Study included patients with cancer and it was not possible to extract information for Barrett's esophagus with LGD or HGD
Weiss A, et al (2005)[291]	Patients already included in study by "Weiss A, et al (2006)[127]"
Westerterp M, et al (2005)[292]	Study included patients with cancer and it was not possible to extract information for Barrett's esophagus with LGD or HGD
Weston AP, et al (2005)[293]	Study did not include outcomes of interest
Wolfsen H, et al (2000)[294]	Patients already included in study by "Wolfsen H, et al (2004)[128]"
Wolfsen HC, et al (2002)[295]	Patients already included in study by "Wolfsen H, et al (2004)[128]"
Wolfsen HC, et al (2002)[81]	Patients already included in study by "Wolfsen H, et al (2004)[128]"
Wolfsen HC, et al (2002)[296]	Patients already included in study by "Wolfsen H, et al (2004)[128]"
Wolfsen HC, et al (2004)[297]	Study included patients with cancer and it was not possible to extract information for Barrett's esophagus with LGD or HGD
Wolfsen HC, et al (2004)[298]	Patients already included in study by "Wolfsen H, et al (2004)[128]"
Yachimski PS, et al (2008)[299]	Study did not include outcomes of interest

Possible reasons for exclusion:

1. Patients already included in study by "----------"
2. Study included patients with cancer, and it was not possible to extract information for Barrett's esophagus with low grade (LGD) or high grade dysplasia (HGD)
3. Study did not include outcomes of interest
4. Study presented a single case report

Please note: Review articles and other references used for background information have not been listed in the excluded study table. Health technology assessments and guidance from other agencies are discussed separately and these reports are also not listed in the table.

Appendix D - Safety (adverse events)

Table D 1. Studies of adverse events in patients treated with PDT for BE/LGD or HGD

Study	No. of patients	Reported adverse events (% of study sample)											
		Atrial fibrillation	Bleed	Buried glands	Chest pain	Dysphagia	Fever	Hypotension	Nausea and vomiting	Odynophagia	Photo-sensitivity	Stricture	Other
ALA 15mg/kg administered via topical spray													
Comparative studies – none													
Non-comparative studies													
Ortner MA, et al. (2001) [97]	13	0 (0.0%)	0 (0.0%)	Not reported	2 (15.4%)	2 (15.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (23.1%)	0 (0.0%)	None
Ortner MA, et al. (1997) [98]	9	0 (0.0%)	0 (0.0%)	Not reported	"Occa-sionally"	"Occa-sionally"	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	None
Pooled total	**22**	0 (0.0%)	0 (0.0%)	-	2 (15.4%)	2 (15.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (13.7%)	0 (0.0%)	
Cumulative pooled total	**22**	0.0%	0.0%	-	15.4%	15.4%	0.0%	0.0%	0.0%	0.0%	13.7%	0.0%	
ALA 30mg/kg administered orally													
Comparative studies													
Kelty CJ, et al. (2004) [45]	34	0 (0.0%)	0 (0.0%)	4/17 (23.6%)	1 (2.9%)	0 (0.0%)	0 (0.0%)	2 (5.9%)	11 (32.4%)	1 (2.9%)	5 (14.7%)	0 (0.0%)	Elevated liver enzyme in 4 (11.8%)
PDT vs APC	34	0 (0.0%)	0 (0.0%)	7 (21%)	0 (0.0%)	1 (3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	32 (94%)	0 (0.0%)	0 (0.0%)	
Pooled total	34	0 (0.0%)	0 (0.0%)	4 23.6%	1 (2.9%)	0 (0.0%)	0 (0.0%)	2 (5.9%)	11 (32.4%)	1 (2.9%)	5 (14.7%)	0 (0.0%)	
Non-comparative studies													
Ackroyd R, et al. (2007) [99]	40	0 (0.0%)	0 (0.0%)	1 (2.5%)	"Most" patients	0 (0.0%)	0 (0.0%)	0 (0.0%)	"Most" patients	0 (0.0%)	1 (2.5%)	0 (0.0%)	None
Ackroyd R, et al. (1999) [101]	5	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	None
Ackroyd R, et al. (1999) [100]	7	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	None
Pooled total	**52**	0 (0.0%)	0 (0.0%)	1 (2.5%)	-	0 (0.0%)	0 (0.0%)	0 (0.0%)	-	0.0%	1 (2.5%)	0.0%	
Cumulative pooled total	**86**	0.0%	0.0%	12.2%	2.9%	0.0%	0.0%	2.7%	32.4%	1.3%	8.1%	0.0%	
ALA 40mg/kg administered orally													
Comparative studies - none													
Non-comparative studies													

Table D 1. Studies of adverse events in patients treated with PDT for BE/LGD or HGD

Study	No. of patients	Reported adverse events (% of study sample)											
		Atrial fibrillation	Bleed	Buried glands	Chest pain	Dysphagia	Fever	Hypotension	Nausea and vomiting	Odynophagia	Photo-sensitivity	Stricture	Other
Peters F, et al. (2005) [104]	20	1 (5.0%)	0 (0.0%)	8/15 (53.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (10.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	Hematemesis: 1 (5%)
van Hillegerberg R, et al. (2003) [105]	2	0 (0.0%)	0 (0.0%)	Not reported	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (50.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	None
Pooled total	**22**	1 (4.5%)	0 (0.0%)	8 (53.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (9.1%)	1 (5.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Cumulative pooled total	**22**	4.5%	0.0%	53.3%	0.0%	0.0%	0.0%	9.1%	5.0%	0.0%	0.0%	0.0%	
ALA 60mg/kg administered orally													
Comparative studies													
Behrens A, et al. (2005) [106]	27	0 (0.0%)	0 (0.0%)	Not reported	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	15/30 (50.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	None
PDT	14	0 (0.0%)	4/17 (23.5%)	Not reported	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	None
vs EMR													
vs PDT+EMR	3	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	None
Hage M, et al. (2004) [107]	26	0 (0.0%)	0 (0.0%)	1 (3.8%)	0 (0.0%)	0 (0.0%)	8 (30.8%)	0 (0.0%)	7 (26.9%)	24 (92.3%)	0 (0.0%)	0 (0.0%)	Sudden death due to arrhythmia in 1 (3.8%), elevated liver enzymes in 20 (76.9%)
PDT													Pain during treatments: 5 (35.7%)
vs APC	14	0 (0.0%)	0 (0.0%)	7 (50.0%)	0 (0.0%)	0 (0.0%)	2 (14.3%)	0 (0.0%)	0 (0.0%)	12 (85.7%)	0 (0.0%)	1 (7.1%)	Sudden death from cardiac arrhythmia: 0 (0%) Elevated liver enzymes: 0 (0%)
Zoepf T, et al. (2003) [108]	10	0 (0.0%)	0 (0.0%)	Not reported	0 (0.0%)	4 (40.0%)	0 (0.0%)	0 (0.0%)	10 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	None
PDT	10	0 (0.0%)	0 (0.0%)	Not reported	0 (0.0%)	3 (30.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	Mediastinal emphysema:
vs APC													

Table D 1. Studies of adverse events in patients treated with PDT for BE/LGD or HGD

Study	No. of patients	Reported adverse events (% of study sample)											
		Atrial fibrillation	Bleed	Buried glands	Chest pain	Dysphagia	Fever	Hypotension	Nausea and vomiting	Odynophagia	Photo-sensitivity	Stricture	Other
													1 (10.0%)
Pooled total	**63**	0 (0.0%)	0 (0.0%)	1 (3.8%)	0 (0.0%)	4 (6.3%)	8 (12.1%)	0 (0.0%)	18 (48.4%)	24 (38.1%)	0 (0.0%)	0 (0.0%)	
Non-comparative studies													
Barr H, et al. (1996) [109]	5	Not reported	Not reported	2 (40.0%)	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	None
Gossner L, et al. (1999) [110]	10	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	None
Gossner L, et al. (1999) [111]	2	0 (0.0%)	0 (0.0%)	Not reported	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	None
Kashtan H, et al. (2002) [112]	8	0 (0.0%)	0 (0.0%)	Not reported	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	4 (50.0%)	0 (0.0%)	6 (75.0%)	0 (0.0%)	None
Mackenzie G, et al. (2008) [134]	16	0 (0.0%)	0 (0.0%)	Not reported	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (6.3%)	None
Macrae FA, et al. (2004) [113]	8	0 (0.0%)	0 (0.0%)	Not reported	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	"Common"	1 (12.5%)	None
Pooled total	**49**	0 (0.0%)	0 (0.0%)	2 (40.0%)	0 (0.0%)	0 (0.0%)	0 (%)	0 (0.0%)	4 (11.8%)	0 (0.0%)	6 (23.1%)	2 (5.9%)	
Cumulative pooled total	**112**	0.0%	0.0%	9.6%	0.0%	4.1%	8.3%	0.0%	35.6%	24.7%	6.7%	2.1%	
HpD 1.5mg/kg administered intravenously													
Comparative studies - none													
Non-comparative													
Laukka MA, et al. (1995) [115]	5	0 (0.0%)	0 (0.0%)	"Observed"	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (40.0%)	0 (0.0%)	2 (40.0%)	0 (0.0%)	None
Wang KK, et al. 1999 [116]	54	0 (0.0%)	0 (0.0%)	Not reported	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	"Common"	"Common"	0 (0.0%)	None
Wang KK, et al. (1999) [117]	50	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	None
Pooled total	**109**	0 (0.0%)	0 (0.0%)	-	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (3.4%)	0 (0.0%)	2 (40.0%)	0 (0.0%)	
Cumulative pooled total	**109**	0 (0.0%)	0 (0.0%)	-	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3.4%	0.0%	40.0%	0.0%	
mTHPC 1.5mg/kg administered intravenously													
Comparative studies - none													
Non-comparative studies													
Javaid B, et al.	6	Not reported	Not	Not	Not	Not	Not	Not reported	Not	Not reported	Not	Not	None

Table D 1. Studies of adverse events in patients treated with PDT for BE/LGD or HGD

Study	No. of patients	Reported adverse events (% of study sample)											
		Atrial fibrillation	**Bleed**	**Buried glands**	**Chest pain**	**Dysphagia**	**Fever**	**Hypotension**	**Nausea and vomiting**	**Odynophagia**	**Photo-sensitivity**	**Stricture**	**Other**
(2002) [118]			reported	reported	reported	reported	reported		reported		reported	reported	
Lovat LL, et al. (2005) [119]	7	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	None
Pooled total	**13**	-	-	-	-	-	-	-	-	-	-	-	
Cumulative pooled total	**13**	-	-	-	-	-	-	-	-	-	-	-	
Porfimer sodium 2mg/kg administered intravenously													
Comparative studies													
Ragunath K, et al. (2005) [60]	13	0 (0.0%)	0 (0.0%)	1 (7.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (15.4%)	2 (15.4%)	None
PDT vs APC	13	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (7.7%)	0 (0.0%)	1 (7.7%)	0 (0.0%)	0 (0.0%)	1 (7.7%)	0 (0.0%)	3 (23.1%)	None
Pooled total	**13**	0 (0.0%)	0 (0.0%)	1 (7.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (15.4%)	2 (15.4%)	
Non-comparative studies													
Attila T, et al. (2005) [121]	19	0 (0.0%)	0 (0.0%)	Not reported	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	7 (36.8%)	None
Bronner M, et al. (2006) [121]	138	Not reported	Not reported	- 31.0%	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	None
Keeley SB, et al. (2007) [122]	13	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	None
Mackenzie G, et al. (2008) [134]	16	0 (0.0%)	0 (0.0%)	Not reported	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	7 (43.8%)	6 (37.5%)	None
Overholt BF, et al. (2007) [123]	138	0 (0.0%)	0 (0.0%)	Not reported	30 (21.7%)	26 (18.8%)	31 (21.7%)	0 (0.0%)	44 (31.9%)	0 (0.0%)	95 (68.8%)	50 (36.2%)	Hiccups: 14 (10.1%); dehydration: 17 (12.3%); constipation: 18 (13.0%).
Overholt BF, et al. (2003) [124]	94	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	None
Overholt BF, et al. (1997) [126]	11	0 (0.0%)	0 (0.0%)	Not reported	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	Pleural effusions in 10/14 (71.4%)
Weiss AA, et al. (2006) [127]	13	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	None
Wolfsen HC,	69	Not reported	Not	Not	Not	Not	Not	Not reported	Not	Not reported	Not	Not	None

Table D 1. Studies of adverse events in patients treated with PDT for BE/LGD or HGD

Study	No. of patients	Reported adverse events (% of study sample)											
		Atrial fibrillation	**Bleed**	**Buried glands**	**Chest pain**	**Dysphagia**	**Fever**	**Hypotension**	**Nausea and vomiting**	**Odynophagia**	**Photo-sensitivity**	**Stricture**	**Other**
et al. (2004) [128]			reported	reported	reported	reported	reported		reported		reported	reported	
Yachimski P, et al. (2008) [129]	59	0 (0.0%)	0 (0.0%)	Not reported	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	8 (13.6%)	None
Pooled total	**570**	0 (0.0%)	0 (0.0%)	- (31.0%)	30 (12.3%)	26 (10.7%)	31 (12.3)	0 (0.0%)	44 (18.1%)	0 (0.0%)	102 (42.0%)	71 (29.2%)	
Cumulative pooled total	**583**	0.0%	0.0%	29.0%	11.7%	10.1%	11.7%	0.0%	17.2%	0.0%	40.6%	28.5%	
Mixed													
Comparative studies													
Burgarner JM, et al. (2008) [130] *	122	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	None
PDT vs RFA	103	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	None
Prasad GA, et al. (2007) [131] **	131	0 (0.0%)	0 (0.0%)	Not reported	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	77 (58.8%)	35 (26.7%)	None
PDT vs Surgery	70	0 (0.0%)	0 (0.0%)	Not reported	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	9 (12.9%)	Post-operative mortality: 1 (1.4%) Post-operative morbidity: 27 (38.6%)
Reed MF, et al. (2005) [132] *	42	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	None
PDT vs EMR	5	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	None
vs esophagectomy vs observation	49	0 (0.0%)	0 (0.0%)	Not reported	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	Post-operative anastomotic leak: 2 (4%) Death

Table D 1. Studies of adverse events in patients treated with PDT for BE/LGD or HGD

Study	No. of patients	Reported adverse events (% of study sample)											
		Atrial fibrillation	Bleed	Buried glands	Chest pain	Dysphagia	Fever	Hypotension	Nausea and vomiting	Odynophagia	Photo-sensitivity	Stricture	Other
	19	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	secondary to stroke: 1 (2%) None
Pooled total	**295**	0 (0.0%)	0 (0.0%)	-	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	77 (58.8%)	35 (26.7%)	
Non-comparative studies													
Kelty CJ, et al. (2004) [133] [tt]	25	0 (0.0%)	0 (0.0%)	6 (24.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (8.0%)	8 (32.0%)	5 (20.0%)	0 (0.0%)	0 (0.0%)	None
Mackenzie G, et al. (2005) [135] ***	51	0 (0.0%)	1 (8.3%), requiring transfusion	Not reported	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (5.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	Hematemesis: 1 (2.0%)
Mackenzie G, et al. (2007) [103] [t]	72	0 (0.0%)	1/13 (7.7%)	Not reported	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	None
Wang KK, et al. (2002) [136] [ttt]	105	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	None
Pooled total	**253**	0 (0.0%)	1 (6.6%)	6 (24.0%)	-	0 (0.0%)	0 (0.0%)	5 (3.4%)	8 (5.4%)	5 (3.4%)	0 (0.0%)	0 (0.0%)	
Cumulative pooled total	**548**	0.0%	3.5%	24.0%	-	0 (0.0%)	0 (0.0%)	1.8%	2.9%	1.8%	27.6%	12.5%	

* PDT protocol unspecified

** Prasad et al. 2007 [131] provides PDT with HPD or porfimer sodium.

*** Mackenzie G, et al. 2005 [135] provides PDT with ALA at 30 or 60mg/kg. Adverse events are not reported separately for the groups.

[t] Mackenzie G, et al. 2007 [103] – PDT provided with ALA at 30 or 60mg/kg, activated with 500 to 750 or 100J/cm^2 of energy. This study is listed here instead of Mellidez JC, et al. (2005) [114] and Mackenzie G, et al. (2005) [102].

[tt] Kelty et al. 2004 [133] provided PDT with ALA at 30 or 60mg/kg.

[ttt] Wang et al. 2002 [136] provided PDT with HpD or porfimer.

Table D 2. Studies of adverse events in patients treated with APC for BE/LGD or HGD

Study	No. of patients	Reported adverse events (% of study sample)									
		Bleeding	Buried glands	Dysphagia	Chest pain	Fever	Nausea/Vomiting	Odynophagia	Perforation	Strictures	Other
Comparative studies											
Dulai GS, et al. (2005)[137]	26	0 (0.0%)	Not reported	0 (0.0%)	1 (3.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	None
APC vs MPEC	26	0 (0.0%)	Not reported	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	None
Hage M, et al. (2004)[107]	14	0 (0.0%)	7 (50.0%)	0 (0.0%)	0 (0.0%)	2 (14.3%)	0 (0%)	12 (85.7%)	0 (0.0%)	1 (7.1%)	Pain during treatments: 5 (35.7%) Sudden death from cardiac arrhythmia: 0 (0%) Elevated liver enzymes: 0 (0%)
APC vs PDT	26	0 (0.0%)	1 (3.8%)	0 (0.0%)	0 (0.0%)	8 (30.1%)	7 (26.9%)	24 (92.3%)	0 (0.0%)	1 (7.1%)	Sudden death due to arrhythmia in 1 (3.8%), elevated liver enzymes in 20 (76.9%)
Kelty CJ, et al. (2004)[45]	34	0 (0.0%)	7 (21%)	1 (3%)	0 (0%)	0 (0.0%)	0 (0%)	32 (94%)	0 (0.0%)	0 (0.0%)	Photosensitivity: 0 (0%) Hypotension: 0 (0%) Elevated liver enzymes: 0 (0%)
APC vs PDT	34	0 (0.0%)	4/17 (23.6%)	0 (0.0%)	1 (2.9%)	0 (0.0%)	11 (32.4%)	1 (2.9%)	0 (0.0%)	0 (0.0%)	Hypotension: 2 (5.9%) Photosensitivity: 5 (14.7%) Elevated liver enzymes: 4 (11.8%)
Ragunath K, et al. (2005)[60]	13	0 (0.0%)	0 (0%)	0 (0.0%)	1 (7.7%)	1 (7.7%)	0 (0.0%)	1 (7.7%)	0 (0.0%)	3 (23.1%)	Photosensitivity: 0 (0%)
APC vs PDT	13	0 (0.0%)	1 (7.7%	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (15.4%)	Photosensitivity: 2 (15.4%)
Sharma P, et al. (2006)[138]	19	0 (0%)	Not reported	2 (10.5%)	4 (21.1%)	1 (5.3%)	0 (0.0%)	0 (0.0%)	0 (0%)	1 (5.3%)	Sore throat: 9 (47.4%) Epigastric pain: 2 (10.5%)
APC	16	0 (0.0%)	Not	5 (31.3%)	6	0 (0.0%)	0	0	0 (0.0%)	0 (0.0%)	None

Table D 2. Studies of adverse events in patients treated with APC for BE/LGD or HGD

Study	No. of patients	Reported adverse events (% of study sample)									
		Bleeding	Buried glands	Dysphagia	Chest pain	Fever	Nausea/Vomiting	Odynophagia	Perforation	Strictures	Other
vs MPEC			reported		(37.5%)		(0.0%)	(0.0%)			
Thomas T, et al. (2005)[139]	14	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	None
APC	8	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	None
vs Esophagectomy	7	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	None
vs Non-Intervention	7	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	None
vs Surveillance											
Zoepf T, et al. (2003)[108]	10	0 (0.0%)	Not reported	3 (30.0%)	0 (0.0%)	0 (0.0%)	0 (0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	Photosensitivity: 0 (0%) Mediastinal emphysema: 1 (10.0%)
APC	10	0 (0.0%)	Not reported	4 (40.0%)	0 (0.0%)	0 (0.0%)	10 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	None
Vs PDT											
Pooled total	**120**	0 (0.0%)	14 (23.2%)	6 (5.2%)	6 (5.2%)	4 (1.7%%)	0 (0.0%)	45 (38.8%)	0 (0.0%)	5 (4.3%)	
Non-comparative studies											
Attwood SEA, et al (2003)[140]	29	0 (0.0%)	Not reported	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.4%)	0 (0.0%)	None
Basu, KK, et al (2006)[141]	33	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	None
Brand B, et al (2000)[142]	12	0 (0.0%)	Not reported	0 (0.0%)	11 (91.7%)	0 (0.0%)	0 (0.0%)	11 (91.7%)	0 (0.0%)	0 (0.0%)	None
Bright T, et al. (2007)[143]	20	0 (0.0%)	2 (10.0%)	0 (0.0%)	"Some"	0 (0.0%)	0 (0.0%)	"Some"	0 (0.0%)	2 (10.0%)	None
Dumoulin FL, et al (1997)[145]	2	0 (0.0%)	Not reported	2 (100%)	2 (100%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	None
Familiari L, et al (2003)[146]	32	0 (0.0%)	Not reported	0 (0.0%)	7 (21.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	None
Ferraris R, et al (2007)[147]	96	0 (0.0%)	Not reported	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	None
Formentini A, et al (2007)[148]	21	0 (0.0%)	Not reported	1 (4.8%)	2 (9.5%)	0 (0.0%)	1 (4.8%)	0 (0.0%)	0 (0.0%)	1 (4.8%)	None
Grade AJ, et al (1999)[149]	9	0 (0.0%)	Not reported	0 (0.0%)	4 (44.4%)	0 (0.0%)	0 (0.0%)	1 (11.1%)	0 (0.0%)	0 (0.0%)	None

Table D 2. Studies of adverse events in patients treated with APC for BE/LGD or HGD

Study	No. of patients	Reported adverse events (% of study sample)									
		Bleeding	Buried glands	Dysphagia	Chest pain	Fever	Nausea/Vomiting	Odynophagia	Perforation	Strictures	Other
Madisch A, et al (2005)[150]	73	0 (0.0%)	Not reported	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (4.1%)	None
Manner H, et al (2007)[151]	104	0 (0.0%)	Not reported	10 (9.6%)	10 (9.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1%)	Cough: 10 (9.6%) Arrhythmia: 10 (9.6%) Emphysema: 10 (9.6%) Gas accumulation in the GI wall: 10 (9.6%) Neuromuscular irritation: 10 (9.6%)
Manner H, et al (2006)[152]	41	0 (0%) major	Not reported	0 (0.0%)	4 (9.8%)	4 (9.8%)	0 (0.0%)	0 (0.0%)	0 (0%)	1 (2.4%)	None
Manner H, et al (2006)[153]	51	2 (3.9%) requiring transfusion	4 (8%)	0 (0.0%)	8 (15.7%)	1 (2.0%)	0 (0.0%)	2 (3.9%)	1 (2.0%)	2 (3.9%)	None
Pedrazzani C, et al (2005)[154]*	25	1/40 sessions (2.5%) (severe)	Not reported	2/40 sessions (5%)	11/40 sessions (27.5%)	7/40 sessions (17.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	Ulcer formation: 2/40 sessions (5%)
Pereira-Lima, JC, et al (2000)[155]	33	0 (0.0%)	0 (0%)	0 (0.0%)	18 (54.5%)	5 (15.2%)	0 (0.0%)	18 (54.5%)	0 (0.0%)	3 (9.1%)	Subcutaneous emphysema 1 hour post APC: 1 (3.0%) Pleural effusion: 5 (15.2%)
Pinotti AC, et al (2004)[156]	19	0 (0.0%)	Not reported	4 (21.1%)	17 (89.5%)	0 (0.0%)	0 (0.0%)	4 (21.1%)	0 (0%)	0 (0%)	None
Tigges H, et al (2001)[157]	30	0 (0%)	Not reported	2 (6.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (6.7%)	0 (0%)	1 (3.3%)	None
Van Laethem JL, e al (2001)[158]	7	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	None
Van Laethem JL, et al (1998)[159]	31	1 (3.2%)	6 (19.4%)	2 (6.5%)	2 (6.5%)	0 (0.0%)	0 (0.0%)	2 (6.5%)	0 (0.0%)	2 (6.5%)	Reflux esophagitis (at 3 months): 8 (25.8%)

Table D 2. Studies of adverse events in patients treated with APC for BE/LGD or HGD

Study	No. of patients	Reported adverse events (% of study sample)									
		Bleeding	Buried glands	Dysphagia	Chest pain	Fever	Nausea/Vomiting	Odynophagia	Perforation	Strictures	Other
Pooled total	**668**	3 (0.5%)	12 (9.0%)	21 (3.5%)	85 (14.6%)	10 (3.5%)	1 (0.2%)	39 (6.6%)	2 (0.3%)	14 (2.6%)	
Cumulative pooled total	**788**	0.4%	13.4%	3.8%	13.0%	2.0%	0.1%	11.7%	0.3%	2.8%	

* Adverse events from Pereira-Lima et al. 2005 are excluded from pooled totals because units are given as "per session".

Table D 3. Studies of adverse events in patients who underwent cryoablation, combination PDT & EMR, or thermocoagulation for BE with LGD or HGD

Study	No. of patients	Reported adverse events (% of study sample)										
		Bleeding	Buried glands	Chest pain	Dysphagia	Fever	Hypotension	Nausea and vomiting	Odynophagia	Photosensitivity	Stricture	Other
Cryoablation												
Comparative studies – none												
Non-comparative studies												
Dumot JA, et al. (2008) [79]	20	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	None
Johnston MH, et al. (2005) [37]	11	0 (0.0%)	Not reported	2 (22.2%)	1 (11.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	None
Pooled total	**11**	0 (0.0%)	0 (0.0%)	2 (22.2%)	1 (11.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Cumulative pooled total	**11**	0.0%	0.0%	22.2%	11.1%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	
Combined PDT and EMR												
Comparative studies – none												
Behrens A, et al. (2005) [106]	3	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	None
PDT+EMR	14	4/17 (23.5%)	Not reported	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	None
vs EMR												
vs PDT	27	0 (0.0%)	Not reported	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	15/30 (50.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	None
Pooled total	**3**	-	-	-	-	-	-	-	-	-	-	
Non-comparative studies												
Wolfsen HC, et al. (2004) [160]	3	0 (0.0%)	Not reported	"Common" and "mild"	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	None
Pooled total	**3**	0 (0.0%)	-	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	None
Cumulative pooled total	**6**	0.0%	-	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	
Thermocoagulation												
Comparative studies – none												
Non-comparative studies												
Michopoulos S, et al. (1999) [243]	13	0 (0.0%)	3/12 (25.0%)	1 (7.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	None
Pooled total	**13**	0 (0.0%)	3 (25.0%)	1 (7.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Cumulative pooled total	**13**	0.0%	25.0%	7.7%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	

Table D 4. Studies of adverse events in patients who underwent endoscopic mucosal resection (EMR) for BE with LGD or HGD

Study	No. of patients	Reported adverse events									
		Bleeding	**Buried glands**	**Chest pain**	**Dysphagia**	**Fever**	**Nausea and vomiting**	**Odynophagia**	**Perforation**	**Strictures**	**Other**
Comparative studies											
Behrens A, et al. (2005) [106] *EMR vs PDT vs PDT+EMR*	14	4/17 (23.5%)	Not reported	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	None
	27	0 (0.0%)	Not reported	0 (0.0%)	0 (0.0%)	0 (0.0%)	15/30 (50.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	None
	3	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	None
Reed MR, et al. (2005) [132] *EMR vs Esophagectomy vs Observation vs PDT*	5	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	None
	49	0 (0.0%)	Not reported	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	Anastomotic leak: 2 (4%) Death secondary to stroke: 1 (2%)
	19	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	None
	42	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	None
Pooled total	**19**	4 (23.5%)	-	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Non-comparative studies											
Giovannini M, et al. (2004) [161]	12	3 (25.0%)	Not reported	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	None
Mino-Kenudson M, et al (2005)[162]	3	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	None
Seewald S, et al (2003)[163] *	3	Not reported	0 (0.0%)	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	None
Tang, SJ, et al (2008)[164]	1	0 (0.0%)	Not reported	1 (100%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	Pneumonia: 1 (100%) DVT secondary to IV line: 1 (100%)
Pooled total	**19**	3 (23.1%)	0 (0.0%)	1 (7.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Cumulative pooled total	**38**	23.3%	0.0%	3.7%	0.0%	0.0%	0.0%	-	0.0%	0.0%	

* Seewald S, et al (2003) [163] report 4 episodes of minor bleeding during 31 EMR procedures, and 2 strictures among 12 patients. No BE or HGD specific results available.

Table D 5. Studies of adverse events in patients who underwent laser ablation for Barrett's esophagus or HGD									
Study	**No. of patients**	**Reported adverse events (% of study sample)**							
		Bleed	**Buried glands**	**Chest pain**	**Dysphagia**	**Odynophagia**	**Perforation**	**Stricture**	**Other**
Comparative studies - none									
Non-comparative studies									
Barham CP, et al. (1997) [165]	16	0 (0.0%)	11 (68.8%)	"Common"	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	None
Bonarvina L, et al. (1999) [166]	16	0 (0.0%)	Not reported	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (12.5%)	None
Bowers SP, et al. (2002) [167]	30	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	None
Ertan A, et al. (1995) [168]	1	0 (0.0%)	Not reported	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	None
Fisher RS, et al. (2003) [169]	21	1 (4.8%), required transfusion	Not reported	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (4.8%)	1 (4.8%)	None
Norberto L, et al. (2004) [170]	15	0 (0.0%)	Not reported	"Some"	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	None
Salo JA, et al. (1998) [171]	11	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	None
Pooled total	**110**	1 (1.5%)	11 (68.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.5%)	3 (4.4%)	

Table D 6. Studies of adverse events in patients who underwent multipolar electrocoagulation (MPEC) for BE with LGD or HGD											
Study	**No. of patients**	**Reported adverse events (% of study sample)**									
		Buried glands	**Bleeding**	**Chest pain**	**Dysphagia**	**Fever**	**Nausea / Vomiting**	**Odynophagia**	**Perforation**	**Strictures**	**Other**
Comparative studies											
Dulai GS, et al. (2005)[137] *MPEC vs APC*	26	Not reported	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	None
	26	Not reported	0 (0%)	1 (4%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	None
Sharma P, et al. (2006)[138] *MPEC vs APC*	16	Not reported	0 (0%)	6 (38%)	5 (31%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	Sore throat: 9 (56%) Epigastric pain: 0 (0%)
	19	Not reported	0 (0%)	4 (21%)	2 (11%)	1 (5%)	0 (0%)	0 (0%)	0 (0%)	1 (5%)	Sore throat: 9 (47%) Epigastric pain: 2 (11%)
Pooled total	**42**		0 (0.0%)	7 (14.5%)	5 (11.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0%)	0 (0%)	
Non-comparative studies											
Faigel DO, et al. (2002)[172]	25	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	None
Kovacs BJ, et al. (1999)[173]	27	Not reported	0 (0%)	11 (41%)	11 (41%)	0 (0%)	0 (0%)	11 (41%)	0 (0%)	1 (4%)	None
Montes CG, et al. (1999)[174]	14	Not reported	0 (0%)	0 (0%)	1 (7%)	0 (0%)	0 (0%)	2 (14%)	0 (0%)	0 (0%)	None
Sampliner RE, et al. (1996)[176]	10	2 (20%)	1 (10%)	1 (10%)	1 (10%)	0 (0%)	0 (0%)	2 (20%)	0 (0%)	0 (0%)	None
Sampliner RE, et al. (1999)[175]	11	Not reported	0 (0%)	7 (64%)	7 (64%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	Heartburn, transient: 7 (64%)
Pooled total	**87**	2 (20%)	1 (1.6%)	19 (30.8%)	20 (32.4%)	0 (0.0%)	-	15 (24.2%)	0 (0%)	1 (1.7%)	
Cumulative pooled total	**129**	20.0%	1.0%	24.2%	24.1%	0.0%	-	14.5%	0.0%	1.0%	

Table D 7. Studies of adverse events in patients who underwent radiofrequency ablation (RFA) for BE with LGD or HGD

Study	No. of patients	Reported adverse events (% of study sample)										
		Buried glands	Bleed	Chest pain	Dysphagia	Fever	Hypo-tension	Nausea and vomiting	Odyno-phagia	Photo-sensitivity	Stricture	Other
Comparative Studies												
Burgarner JC, et al. (2008) [130] *PDT*	103	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	None
vs RFA	122	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	None
Pooled total	**103**	-	-	-	-	-	-	-	-	-	-	
Non-comparative studies												
Eldaif SM, et al. (2009) [177]	27	Not reported	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	None
Fleischer DE, et al. (2008) [178]*	70	Not reported	1 (1.4%) Mild	9 (12.9%)	0 (0.0%)d	2 (2.9%)	1 (1.4%)	8 (11.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	Laceration of the esophagus: 1 (1.4%) Mucosal scarring, transient: 1 (1.4%).
Fleischer et al. (2008) [178]*	62	Not reported	0 (0.0%)	1 (1.6%)	0 (0.0%)	0 (0.0%)	1 (1.6%)	2 (3.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	None
Ganz RA, et al. (2008) [180]	142	Not reported	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.7%)	None
Hernandez JC, et al. (2008) [181]	10	Not reported	0 (0.0%)	"Common"	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	None
Hubbard N, et al. (2007) [182]	7	Not reported	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	None
Pouw RE, et al. (2008) [183]	44	Not reported	0 (0.0%)	2 (4.5%)	4 (9.1%)	1 (2.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	Laceration of the esophagus: 3 (6.8%)
Roorda AK, et al. (2007) [184]	13	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (23.1%)	1 (7.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	None
Sharma VK, et al. (2008) [185]	10	Not reported	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	Hematemesis: 1 (10.0%)

Sharma VK, et al. (2007) [179]	32	Not reported	0 (0.0%)	3 (9.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	Laceration of the esophagus: 1 (3.2%) Mucosal scarring, transient: 1 (3.2%)
Smith CD, et al. (2007) [186]	5	Not reported	0 (0.0%)	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	None
Pooled total	**360**	0 (0.0%)	1 (0.2%)	15 (3.7%)	7 (1.7%)	4 (1.0%)	2 (0.5%)	10 (2.4%)	0 (0.0%)-	0 (0.0%)	1 (0.2%)	
Cumulative pooled total	**463**	0.0%	0.2%	3.7%	1.7%	1.0%	0.5%	2.4%	0.0%	0.0%	0.2%	

* Adverse events are reported separately for 70 patients undergoing circumferential RFA (mean 1.5 sessions/patient), and for 62 of the original 70 undergoing additional focal ablation (mean 1.9 additional sessions/patient). The latter figure is not considered in the patient totals.

Table D 8. Studies of adverse events in patients who underwent esophagectomy for BE with LGD or HGD

Study	No. of patients	Reported adverse events (% of study sample)										
		Anasto-motic leak	Cardio-vascular com-plications	Delayed gastric emptying	Mortality	Pneumonia	Pulmonary compli-cations	Pulmonary embolsim	Small bowel perfora-tion	Strictures	Wound infection	Other
Comparative studies												
Prasad GA, et al. (2007) [131] *Esophagectomy vs PDT*	70	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	9 (12.9%)	0 (0.0%)	Photo-sensitivity: 0 (0.0%) "Total post-op morbidity": 27 (38.6%)
	129	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	35 (27.1%)	0 (0.0%)	Photo-sensitivity: 77 (58.8%) "Total post-op morbidity": 0 (0.0%)
Reed MF, et al. (2005) [132] *Esophagectomy vs EMR or PDT vs Observation*	49	2 (4.1%)	0 (0.0%)	0 (0.0%)	1 (2.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	None
	47	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	None
	19	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	None
Thomas T, et al. (2005) [139] *Esophagectomy vs APC vs Non-Intervention vs Surveillance*	8*	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	None
	5	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	None
	7	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	None
	7	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	None
Pooled total	**127**	2 (1.7%)	0 (0.0%)	0 (0.0%)	2 (1.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	9 (7.6%)	0 (0.0%)	
Non-comparative studies												
Ferguson MK, et al. (1997) [187]	15	11 (73.3%)	3 (20.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	4 (26.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	5 (33.3%)	None
Nguyen NT, et al. (2000) [188]	12	0 (0.0%)	0 (0.0%)	3 (25.0%)	0 (0.0%)	0 (0.0%)	2 (16.7%)	0 (0.0%)	1 (8.3%)	0 (0.0%)	1 (8.3%)	None
Romagnoli R, et al.	33	Not	Not reported	Not	Not	Not reported	Not reported	Not reported	Not	Not	Not	None

Table D 8. Studies of adverse events in patients who underwent esophagectomy for BE with LGD or HGD

Study	No. of patients	Reported adverse events (% of study sample)										
		Anasto-motic leak	Cardio-vascular com-plications	Delayed gastric emptying	Mortality	Pneumonia	Pulmonary compli-cations	Pulmonary embolsim	Small bowel perfora-tion	Strictures	Wound infection	Other
(2003) [189]		reported		reported	reported				reported	reported	reported	
Sujendran V, et al. (2005) [190]	17	3 (17.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (17.6%)	1 (5.9%)**	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	None
Thomson BNJ, et al. (2007) [191]	7	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (14.3%)	0 (0.0%)	0 (0.0%)	1 (14.3%)	None
Pooled total	**84**	14 (27.4%)	3 (5.9%)	3 (5.9%)	0 (0.0%)	3 (5.9%)	7 (13.7%)	1 (2.0%)	1 (2.0%)	0 (0.0%)	7 (13.7%)	
Cumulative pooled total	**211**	9.4%	1.8%	1.8%	1.2%	1.8%	4.1%	0.6%	0.6%	5.3%	4.1%	

* No BE/LGD or HGD specific adverse events. Adverse events among these patients and 6 additional adenocarcinoma patients were: 1/14 deaths due to acute respiratory distress syndrome (ARDS); pneumonia, ARDS, and pneumothorax in 4/14 patients; and strictures in 2/14 patients.

** Acute lung injury requiring ICU.

Appendix E - Efficacy / effectiveness tables

Table E 1. Complete response of Barrett's esophagus in patients receiving PDT

Study	Treatment groups (No. of treatments)	No. of patients	F/U U/K**	Response of lesion (% of study sample) 0-2 months*	~3 months	~6 months	~12 months	~18 months	~24 months	~60 months	Recurrence	Favors PDT	Favors Comparator
ALA 15mg/kg													
Comparative studies													
None													
Non-comparative studies													
Ortner MA, et al. (2001) [98]	(1)	9	CR** PR NR	Not reported	44.4% 33.3% 22.2%	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	n/a	
Ortner MA, et al. (1997) [97]	(mean: 1.4)	14	CR PR NR	Not reported	21.4% 78.6% 0.0%	28.6% 71.4% 0.0%	Not reported	Not reported	Not reported	Not reported	0.0% 6 months	n/a	
Pooled total		**23**	CR PR NR	-	30.4% 60.9% 8.7%	28.6% 71.4% 0.0%	-	-	-	-	0.0% 6 months		
Cumulative pooled total		**23**	CR PR NR	-	30.4% 60.9% 8.7%	28.6% 71.4% 0.0%	-	-	-	-	0.0% 6 months		
ALA 30mg/kg													
Comparative studies													
Kelty CJ, et al. (2004) [45]	PDT (median:1)	35	CR PR NR	50.0% 50.0% 0.0% P<0.001	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported		
	APC (median: 3)	37	CR PR NR	97.1% 2.9% 0.0%	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported		
Pooled total		**35**	CR PR NR	50.0% 50.0% 0.0%-	-	-	-	-	-	-	-		
Non-comparative studies													
Ackroyd R, et al. (2007) [99]	(1)	40	CR PR NR	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	n/a	
Ackroyd R,	(1)	7	CR	14.3%	Not	Not	Not	Not	14.3%	Not	0.0%	n/a	

Table E 1. Complete response of Barrett's esophagus in patients receiving PDT

Study	Treatment groups (No. of treatments)	No. of patients		F/U U/K**	Response of lesion (% of study sample) 0-2 months*	~3 months	~6 months	~12 months	~18 months	~24 months	~60 months	Recurrence	Favors PDT	Favors Comparator
et al. (1999) [100]			PR NR		- -	reported	reported	reported	reported	- -	reported	24 months		
Ackroyd R, et al. (1999) [101]	(1)	5	CR PR NR		Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported		n/a
Mackenzie G, et al. (2005) [135]	(mean: 1.74)	16	CR PR NR		Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported		n/a
Pooled total		**68**	CR		14.3%	-	-	-	-	14.3%	-	0.0% 24 months		
Cumulative pooled total		**103**	CR PR NR		44.1% 50.0% 0.0%	-	-	-	-	14.3% - -	-	0.0% 24months		
ALA 40mg/kg														
Comparative studies														
None														
Non-comparative studies														
Peters F, et al. (2005) [104]	(1)	16	CR PR NR		Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported		n/a
Van Hillegerberg R, et al. (2003) [105]	(mean: 2)	2	CR PR NR		Not reported	0.0% - -	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported		n/a
Pooled total		**18**	CR		-	0.0%	-	-	-	-	-	-		
Cumulative pooled total		**18**	CR		-	0.0%	-	-	-	-	-	-		
ALA 60mg/kg														
Comparative studies														
Behrens A, et al. (2005) [106]	PDT (1)	27	CR PR NR		Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported		
	EMR (not reported)	14	CR PR		Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported		

Table E 1. Complete response of Barrett's esophagus in patients receiving PDT

Study	Treatment groups (No. of treatments)	No. of patients	F/U U/K**	Response of lesion (% of study sample) 0-2 months*	~3 months	~6 months	~12 months	~18 months	~24 months	~60 months	Recurrence	Favors PDT	Favors Comparator
	PDT+EMR (1)	3	NR CR PR NR	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported		
Hage M, et al. (2004) [107]	PDT *** (20+100J/cm^2) (not reported)	13	CR PR NR	38.0% - - P=0.55	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Neither	
	APC (2)	14	CR PR NR	35.7% - -	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported		
Zoepf T, et al. (2003) [108]	PDT (mean: 2)	10	CR PR NR	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported		
	APC (mean:4)	10	CR PR NR	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported		
Pooled total		**50**	CR	38.2%	-	-	-	-	-	-	-		
Non-comparative studies													
Barr H, et al. (1996) [109]	(1)	5	CR PR NR	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	n/a	
Gossner L, et al. (1999) [110]	(mean: 2.2)	10	CR PR NR	Not reported	Not reported	0.0% 100.0% 0.0%	Not reported	Not reported	Not reported	Not reported	Not reported	n/a	
Gossner L, et al. (1999) [111]	(not reported)	2	CR PR NR	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	n/a	
Kashtan H, et al. (2002) [112]	(1)	8	CR PR NR	Not reported	Not reported	Not reported	Not reported	Not reported	37.5% - -	Not reported	Not reported	n/a	
Mackenzie G, et al. (2005) [135]	(mean: 1.74)	33	CR PR NR	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	n/a	

Table E 1. Complete response of Barrett's esophagus in patients receiving PDT

Study	Treatment groups (No. of treatments)	No. of patients		F/U U/K**	Response of lesion (% of study sample) 0-2 months*	~3 months	~6 months	~12 months	~18 months	~24 months	~60 months	Recurrence	Favors PDT	Favors Comparator
Mackenzie G, et al. (2008) [134]	(not reported)	16	CR PR NR		Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported		n/a
Macrae FA, et al. (2004) [113]	(1)	8	CR PR NR		Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported		n/a
Pooled total		**82**	CR PR NR		-	-	0.0% 100.0% 0.0%	-	-	37.5% - -	-	-		
Cumulative pooled total		**132**	CR PR NR		30.8% - -	-	0.0% 100.0% 0.0%	-	-	37.5% - -	-	-		
HpD 1.5mg/kg														
Comparative studies														
None														
Non-comparative studies														
Laukka MA, et al. (1995) [115]	(1)	5	CR PR NR		Not reported	0.0% - -	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported		n/a
Wang KK, et al. 1999 [116]	(mean: 1)	55	CR PR NR	13%	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported		n/a
Wang KK, et al. (1999) [117]	(1)	50	CR PR NR		Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported		n/a
Pooled total		**110**	CR		-	0.0%	-	-	-	-	-	-		
Cumulative pooled total		**110**	CR		-	0.0%	-	-	-	-	-	-		
mTHPC 0.15mg/kg														
Comparative studies														
None														
Non-comparative studies														
Javaid B, et al. (2002) [118]	(mean: 1.5)	6	CR PR		16.7% 50.0%	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported		n/a

Table E 1. Complete response of Barrett's esophagus in patients receiving PDT

Study	Treatment groups (No. of treatments)	No. of patients		F/U U/K**	Response of lesion (% of study sample) 0-2 months*	~3 months	~6 months	~12 months	~18 months	~24 months	~60 months	Recurrence	Favors PDT	Favors Comparator
Lovat LL, et al. (2005) [119]	(1)	7	NR CR PR NR		33.3% Not reported	Not reported	Not reported	Not reported	0.0% - -	Not reported	Not reported	Not reported		n/a
Pooled total		**13**	CR PR NR		16.7% 50.0% 33.3%	-	-	-	0.0% - -	-	-	-		
Cumulative pooled total		**13**	CR PR NR		16.7% 50.0% 33.3%	-	-	-	0.0% - -	-	-	-		
Porfimer sodium 2mg/kg														
Comparative studies														
Ragunath K, et al. (2005) [60]	PDT (1)	13	CR PR NR		Not Reported	15.4% - -	Not reported	15.4% - - P=0.23	Not reported	Not reported	Not reported	Not reported		Neither
	APC (1)	13	CR PR NR		Not reported	15.4% - -	Not reported	0.0% - -	Not reported	Not reported	Not reported	Not reported		
Pooled total		**13**	CR		-	15.4%		15.4%	-	-	-	-		
Non-comparative studies														
Attila T, et al. (2005) [121]	(not reported)	19	CR PR NR		Not reported	26.3% 47.4% 26.3%	Not reported	Not reported	Not reported	Not reported	63.2% [t] - -	Not reported		n/a
Bronner M, et al. (2006) [121]	(mean not reported)	138	CR PR NR		Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported		n/a
Keeley SB, et al. (2007) [122]	(not reported)	13	CR PR NR		Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported		n/a
Mackenzie G, et al. (2008) [134]	(not reported)	16	CR PR NR		Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported		n/a
Overholt BF,	(mean: 2)	138	CR		Not	Not	Not	Not	Not	Not	Not	Not		n/a

Table E 1. Complete response of Barrett's esophagus in patients receiving PDT

Study	Treatment groups (No. of treatments)	No. of patients		F/U U/K**	Response of lesion (% of study sample) 0-2 months*	~3 months	~6 months	~12 months	~18 months	~24 months	~60 months	Recurrence	Favors PDT	Favors Comparator
et al. (2007) [123]			PR NR		reported	reported	reported	reported	reported	reported	reported	reported		
Overholt BF, et al. (2003) [124]	(median: 1.4)	94	CR PR NR		Not reported	56.4% - -	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported		n/a
Overholt BF, et al. (1997) [126]	(not reported)	11	CR PR NR		Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported		n/a
Weiss AA, et al. (2006) [127]	(not reported)	13	CR PR NR		Not reported	Not reported	Not reported	Not reported	Not reported	30.8% 61.5% 6.4%	Not reported	Not reported		n/a
Wolfsen HC, et al. (2004) [128]	(not reported)	69	CR PR NR		52.5% - -	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported		n/a
Yachimski P, et al. (2008) [129]	(not reported)	59	CR PR NR		Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported		n/a
Pooled total		**570**	CR PR NR		52.5% - -	51.3% 47.4% 26.3%	-	-	-	30.8% 61.5% 6.4%	63.2% - -	-		
Cumulative pooled total		**583**	CR PR NR		52.5% - -	47.6% 47.4% 26.3%	-	15.4% - -	-	30.8% 61.5% 6.4%	63.2% - -	-		
Mixed														
Comparative studies														
Burgarner JM, et al. (2008) [130]	PDT[tt] (not reported)	122	CR PR NR		Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported		
	RFA (not reported)	103	CR PR NR		Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported		
Prasad GA, et al. (2007)[131]	PDT [ttt] (mean: 1.26)	129	CR PR NR		Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported		

Table E 1. Complete response of Barrett's esophagus in patients receiving PDT

Study	Treatment groups (No. of treatments)	No. of patients		F/U U/K**	Response of lesion (% of study sample) 0-2 months*	~3 months	~6 months	~12 months	~18 months	~24 months	~60 months	Recurrence	Favors PDT	Favors Comparator
	Esophagectomy (n/a)	70	CR PR NR		Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported		
Reed MF, et al. (2005) [132]	PDT[tt] (not reported)	42	CR PR NR		Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported		
	EMR (not reported)	5	CR PR NR		Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported		
	Esophagectomy (n/a)	49	CR PR NR		Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported		
	Observation (n/a)	19	CR PR NR		Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported		
Pooled total		**293**	CR		-	-	-	-	-	-	-	-		
Non-comparative studies														
Kelty CJ, et al. (2004) [133o]	(1)	25	CR PR NR		8.0% 92.0% 0.0%	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported		n/a
Mackenzie G, et al. (2007) [103 oo]	(not reported)	72	CR PR NR		Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported		n/a
Wang KK, et al. (2002) [136ooo]	(median: 1)	92	CR PR NR		Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported		n/a
Pooled total		**189**	CR PR NR		8.0% 92.0% 0.0%	-	-	-	-	-	-	-		
Cumulative pooled total		**482**	CR PR NR		8.0% 92.0% 0.0%	-	-	-	-	-	-	-		

* Approximate follow-up time intervals are as follows: Immediate, from 0 to 2 months; ~3m, from 2 to 5 months; ~6m, from 5 to 9 months; ~12m, from 9 to 15 months; ~18m, from 15 to 21 months; ~24m, from 21 to 27 months; and ~60m, above 27 months.

** F/U U/K (follow-up time unknown), CR (complete response), PR (partial response), NR (no response)

*** Hage et al. 2004 also treat 13 patients with PDT ALA 60mg/kg illuminated with 100J/cm2 only. CR of Barrett's esophagus was 7.7% in this group, significantly lower than the APC rate.
[t] Complete response improved following additional PDT or APC sessions.
[tt] PDT protocol unspecified.
[ttt] Prasad et al. 2007 [131] – Patients provided HpD (26) or porfimer sodium (103).
[o] Kelty et al. 2004 [133] – Patients provided with ALA at either 30 or 60mg/kg. Distribution of patients among treatment protocols is unknown.
[oo] Mackenzie et al. 2007 [103] – Patients provided ALA at various doses and energy amounts – distribution of patients among protocols unknown. This study is listed in this table instead of Mackenzie et al. (2005) [102] and Mellidez et al. (2005) [114].
[ooo] Wang et al. 2002 [136] – Patients provided HpD or porfimer sodium PDT. Distribution of patients among treatment protocols is unknown.

Table E 2. Complete response of HGD in patients receiving PDT

Study	Treatment groups (No. of treatments)	No. of patients	F/U U/K**	Response of lesion (% of study sample) 0-2 months *	~3 months	~6 months	~12 months	~18 months	~24 months	~60 months	Recurrence	Favors PDT	Favors Comparator
ALA 30mg/kg													
Comparative studies													
None													
Non-comparative studies													
Ackroyd R, et al. (1999) [101]	(1)	4	CR ** 100% PR NR	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	n/a	
Ackroyd R, et al. (1999) [100]	(1)	4	CR PR NR	100.0% - -	Not reported	Not reported	Not reported	Not reported	100.0% - -	Not reported	Not reported	n/a	
Mackenzie G, et al. (2005) [135]	(mean: 1.74)	16	CR PR NR	Not reported	Not reported	Not reported	Not reported	31.8%	Not reported	Not reported	Not reported	n/a	
Mackenzie G, et al. (2005) [102ttt]	(mean: 2.15)	16	CR PR NR	23.5%*** - -	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	n/a	
Pooled total		**40**	CR	38.8%	-	-	-	31.8%	100.0%	-	-		
Cumulative pooled total		**40**	CR	38.8%	-	-	-	31.8%	100.0%	-	-		
ALA 40mg/kg													
Comparative studies													
None													
Non-comparative studies													
Peters F, et al. (2005) [104]	(1)	16	CR PR NR	Not reported	77.8% - -	Not reported	Not reported	Not reported	Not reported	55.6% - -	28.5% 30 months	n/a	
Van Hillegerberg R, et al. (2003) [105]	(mean: 2)	2	CR PR NR	Not reported	0.0% - -	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	n/a	
Pooled total		**18**	CR	-	69.2%	-	-	-	-	55.6%	28.5% 30 months		
Cumulative pooled total		**18**	CR	-	69.2%	-	-	-	-	55.6%	28.5% 30 months		
ALA 60mg/kg													
Comparative studies													

Table E 2. Complete response of HGD in patients receiving PDT

Study	Treatment groups (No. of treatments)	No. of patients	F/U U/K**	Response of lesion (% of study sample) 0-2 months *	~3 months	~6 months	~12 months	~18 months	~24 months	~60 months	Recurrence	Favors PDT	Favors Comparator
Behrens A, et al. (2005) [106]	PDT (1)	27	CR PR NR	96.3% - - NS[t]	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Neither	
	EMR (not reported)	14	CR PR NR	92.9% - - NS	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported		
	PDT+EMR (1)	3	CR PR NR	66.7% - - NS	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported		
Zoepf T, et al. (2003) [108]	PDT (mean: 2)	10[tt]	CR PR NR	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported		
	APC (mean: 4)	10[tt]	CR PR NR	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported		
Pooled total		**37**	CR	96.3%	-	-	-	-	-	-	-		
Non-comparative studies													
Barr H, et al. (1996) [109]	(1)	5	CR PR NR	0.0% 100.0% 0.0%	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	n/a	
Gossner L, et al. (1999) [110ttt]	(mean: 2.2)	10	CR PR NR	Not reported	Not reported	100.0% - -	Not reported	Not reported	Not reported	Not reported	Not reported	n/a	
Gossner L, et al. (1999) [111]	(not reported)	2	CR PR NR	100.0% - -	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	n/a	
Kashtan H, et al. (2002) [112]	(1)	1	CR PR NR	Not reported	Not reported	Not reported	Not reported	Not reported	0.0% - -	Not reported	Not reported	n/a	
Mackenzie G, et al. (2005) [135] – 1000J/cm^2	(mean: 1.74)	21	CR PR NR	Not reported	Not reported	Not reported	Not reported	76.2% - -	Not reported	Not reported	Not reported	n/a	
Mackenzie G, et al. (2005) [135] – 500 to 750J/cm^2	(mean: 1.74)	12	CR PR NR	Not reported	Not reported	Not reported	Not reported	16.7% - -	Not reported	Not reported	Not reported	n/a	

Table E 2. Complete response of HGD in patients receiving PDT

Study	Treatment groups (No. of treatments)	No. of patients		F/U U/K**	Response of lesion (% of study sample) 0-2 months *	~3 months	~6 months	~12 months	~18 months	~24 months	~60 months	Recurrence	Favors PDT	Favors Comparator
Mackenzie G, et al. (2008) [134]	(not reported)	16	CR PR NR		Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported		n/a
Macrae FA, et al. (2004) [113]	(1)	8	CR PR NR		Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	37.5% - -	Not reported		n/a
Mellidez JC, et al. (2005) [114 ttt]	(not reported)	13	CR PR NR	88%	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported		n/a
Pooled total		**88**	CR PR NR		28.6% 100.0% 0.0%	-	100.0% - -	-	54.6% - -	0.0% - -	37.5% - -	-		
Cumulative pooled total		**125**	CR PR NR		82.4% - -	-	100.0% - -	-	54.6% - -	0.0% - -	37.5% - -	-		
HpD 1.5mg/kg														
Comparative studies														
None														
Non-comparative studies														
Laukka MA, et al. (1995) [115]	(1)	1	CR PR NR		Not reported	Not reported	100.0% - -	Not reported	Not reported	Not reported	Not reported	Not reported		n/a
Wang KK, et al. 1999 [116]	(mean: 1)	55[tt]	CR PR NR		Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported		n/a
Wang KK, et al. (1999) [117]	(1)	11	CR PR NR		Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported		n/a
Pooled total		**67**	CR		-	-	100.0%	-	-	-	-	-		
Cumulative pooled total		**67**	CR		-	-	100.0%	-	-	-	-	-		
mTHPC 0.15mg/kg														
Comparative studies														
None														
Non-comparative studies														
Javaid B, et al. (2002) [118]	(mean: 1.5)	6	CR PR NR		66.7% 33.3% 33.3%	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported		n/a

Table E 2. Complete response of HGD in patients receiving PDT

Study	Treatment groups (No. of treatments)	No. of patients		F/U U/K**	Response of lesion (% of study sample) 0-2 months *	~3 months	~6 months	~12 months	~18 months	~24 months	~60 months	Recurrence	Favors PDT	Favors Comparator
Lovat L, et al. (2005) [119] – Red light	(1)	4	CR PR NR		Not reported	Not reported	Not reported	Not reported	75.0% - -	Not reported	Not reported	Not reported		n/a
Lovat L, et al. (2005) [119] – Green light	(1)	3	CR PR NR		Not reported	Not reported	Not reported	Not reported	0.0% - -	Not reported	Not reported	Not reported		n/a
Pooled total		**13**	CR PR NR		66.7% 33.3% 33.3%	-	-	-	42.9% - -	-	-	-		
Cumulative pooled total		**13**	CR PR NR		66.7% 33.3% 33.3%	-	-	-	42.9% - -	-	-	-		
Porfimer sodium 2mg/kg														
Comparative studies														
Ragunath K, et al. (2005) [60]	PDT (1)	2	CR PR NR		Not reported	100.0% - NS	Not reported	100.0% NS	Not reported	Not reported	Not reported	Not reported		Neither
	APC (1)	1	CR PR NR		Not reported	100.0% - -	Not reported	0.0% - -	Not reported	Not reported	Not reported	Not reported		
Pooled total		**2**	CR		-	100.0%	-	100.0%	-	-	-	-		
Non-comparative studies														
Attila T, et al. (2005) [121]	(not reported)	19	CR PR NR		Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported		n/a
Bronner M, et al. (2006) [121]	(mean not reported)	138	CR PR NR		Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported		n/a
Keeley SB, et al. (2007) [122]	(not reported)	13	CR PR NR		Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	38.5%	Not reported		n/a
Mackenzie G, et al. (2008) [134]	(not reportede)	16	CR PR NR	64% - -	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported		n/a
Overholt BF, et al. (2007) [123]	(mean: 2)	138	CR PR NR		Not reported	Not reported	40.3% - -	34.5% - -	40.7% - -	41.5% - -	Not reported	52.0% 60 months [o]		n/a
Overholt BF,	(median: 1.4)	80	CR		Not	77.5%	Not	Not	Not	Not	58.1%	25.0%		n/a

Table E 2. Complete response of HGD in patients receiving PDT

Study	Treatment groups (No. of treatments)	No. of patients	F/U U/K**	Response of lesion (% of study sample) 0-2 months *	~3 months	~6 months	~12 months	~18 months	~24 months	~60 months	Recurrence	Favors PDT	Favors Comparator
et al. (2003) [124]			PR NR	reported	- -	reported	reported	reported	reported	- -	50.7 months		
Overholt BF, et al. (1997) [126]	(not reported)	11	CR PR NR	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported		n/a
Weiss AA, et al. (2006) [127]	(not reported)	13	CR PR NR	Not reported	Not reported	Not reported	Not reported	Not reported	30.8% - -	Not reported	Not reported		n/a
Wolfsen HC, et al. (2004) [128]	(not reported)	69	CR PR NR	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported		n/a
Yachimski P, et al. (2008)	(not reported)	59	CR PR NR	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported		n/a
Pooled total		**556**	CR	-	77.5%	40.3%	34.5%	40.7%	41.5%	-	42.1% 51 to 60 months		
Cumulative pooled total		**558**	CR	-	78.0%	40.2%	35.4%	40.7%	41.5%	-	42.1% 51 to 60 months		
Mixed													
Comparative studies													
Prasad GA, et al. (2007) [131]	PDT [oo] (mean: 1.26)	129	CR PR NR	Not reported	Not reported	Not reported	88.0% - -	Not reported	Not reported	86.0% - -	Not reported		
	Esophagectomy (n/a)	70	CR PR NR	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported		
Reed MF, et al. (2005) [132]	PDT [ooo] (not reported)	42	CR PR NR	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported		
	EMR (not reported)	5	CR PR NR	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported		
	Esophagectomy (n/a)	49	CR PR NR	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported		
	Observation (n/a)	19	CR PR NR	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported		

Table E 2. Complete response of HGD in patients receiving PDT

Study	Treatment groups (No. of treatments)	No. of patients	F/U U/K**	Response of lesion (% of study sample) 0-2 months *	~3 months	~6 months	~12 months	~18 months	~24 months	~60 months	Recurrence	Favors PDT	Favors Comparator
Pooled total		**171**	CR	-	-	-	88.0%	-	-	86.0%	-		
Non-comparative studies													
Wang KK, et al. (2002) [136 a]	(median: 1)	48	CR PR NR	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	n/a	
Pooled total		**48**	CR	-	-	-	-	-	-	-	-		
Cumulative pooled total		**219**	CR	-	-	-	88.0%	-	-	86.0%	-		

* Approximate follow-up time intervals are as follows: Immediate, from 0 to 2 months; ~3m, from 2 to 5 months; ~6m, from 5 to 9 months; ~12m, from 9 to 15 months; ~18m, from 15 to 21 months; ~24m, from 21 to 27 months; and ~60m, above 27 months.

** F/U U/K ((follow-up time unknown), CR (complete response), PR (partial response), NR (no response).

*** Outcomes reported for green light and red light PDT arms as 1/19 (5.3%) and 4/17 (23.5%) of PDT *sessions*, respectively. The latter proportion is reported here.

[t] PDT vs EMR, p=0.63; PDT vs PDT+EMR, p=0.05; EMR vs PDT+EMR, p=0.20.

[tt] Mixed patient population – Number of patients with HGD unknown.

[ttt] Mackenzie et al. 2005 [102] and Mellidez et al. 2005 [114] are included in this table instead of Mackenzie et al. 2007 [103].

[o] Recurrence rates were 24.0%, 39.0%, 46.0%, and 46.0% at 6, 12, 18, and 24 months, respectively.

[oo] Prasad et al. 2007 [131] – Patients provided HpD or porfimer sodium.

[ooo] PDT protocol unspecified.

[a] Wang et al. 2002 [136] – Patients provided HpD or porfimer sodium PDT. Distribution of patients among treatment protocols is unknown.

Table E 3. Complete response of Barrett's esophagus in patients receiving argon plasma coagulation (APC)

Study	Treatment groups (No. of treatments)	No. of patients		Response of lesion (% of study sample) 0-2 months	~3 months	~6 months	~12 months	~18 months	~24 months	~60 months	Recurrence	Favors APC	Favors comparator
Comparative studies													
Dulai GS, et al. (2005) [137]	APC (mean: 3.8))	26	CR** PR NR	81% ** - - (p=0.68)	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported		Neither
	MPEC (mean: 2.9)	26	CR PR NR	88%	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported		
Hage M, et al. (2004) [107]	APC (2)	14	CR PR NR	36% - - Not sig. dif.	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported		Neither
	PDT 100 J ALA 60mg/kg (not reported)	13	CR PR NR	8% - - Not sig. dif.	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported		
	PDT 20 + 100 J ALA 60 mg/kg (not reported)	13	CR PR NR	31% - - Not sig. dif.	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported		
Kelty CJ, et al. (2004) [45]	APC (median: 3)	37	CR PR NR	97% 3% - p<0.001	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	✓	
	PDT ALA 30mg/kg (median: 5)	35	CR PR NR	50% 50% -	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported		
Ragunath K, et al. (2005) [60]	APC (1)	13	CR PR NR	Not reported	15% - -	Not reported	0% - - p=0.22	Not reported	Not reported	Not reported	100% ~12 months		Neither
	PDT porfimer 2mg/kg (1)	13	CR PR NR	Not reported	15% - -	Not reported	15% - -	Not reported	Not reported	Not reported	Not reported		
Sharma P, et al. (2006) [138]	APC (mean: 3.4)	19	CR PR NR	Not reported	Not reported	Not reported	Not reported	Not reported	63% Not sig. dif.	Not reported	Not reported		

Table E 3. Complete response of Barrett's esophagus in patients receiving argon plasma coagulation (APC)

Study	Treatment groups (No. of treatments)	No. of patients		Response of lesion (% of study sample) 0-2 months	~3 months	~6 months	~12 months	~18 months	~24 months	~60 months	Recurrence	Favors APC	Favors comparator
	MPEC (not reported)	16	CR PR NR	Not reported	Not reported	Not reported	Not reported	Not reported	75% Not sig. dif.	Not reported	Not reported		
Thomas T, et al. (2005) [139]	APC (mean: 4)	5	CR PR NR	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported		
	Esophagectomy (n/a)	8	CR PR NR	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported		
	Non-intervention (n/a)	7	CR PR NR	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported		
	Surveillance (mean: 2.9)	7	CR PR NR	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported		
Zoepf T, et al. (2003) [108]	APC (mean: 4)	10	CR PR NR	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported		
	PDT ALA 60mg/kg (mean: 2)	10	CR PR NR	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported		
Pooled total		**124**	CR PR	80.5% 3%	15% -	-	0% -	-	-	-	100% 12 months		
Non-comparative studies													
Attwood SEA, et al. (2003)[140]	(median: 2)	29	CR PR NR	76% - -	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported		n/a
Basu, KK, et al. (2006)[141]	(mean: 4)	33	CR PR NR	85% - -	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported		n/a
Brand B, et al. (2000)[142]	(mean: 5)	12	CR PR NR	92% - -	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	16.7% 12 months		n/a
Bright T, et al. (2007) [143]	(median:3)	20	CR PR NR	60% - -	Not reported	Not reported	58% - -	Not reported	Not reported	40% - -	8.3% 12 months		n/a
Dumoulin FL, et al. (1997)[145]	(not reported)	2	CR PR NR	0% - -	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported		n/a
Familiari L, et al. (2003)[146]	(mean: 2.0)	32	CR PR	100% -	Not reported	97% -	94% -	Not reported	91% -	Not reported	6% 12 months ***		n/a

Table E 3. Complete response of Barrett's esophagus in patients receiving argon plasma coagulation (APC)

Study	Treatment groups (No. of treatments)	No. of patients		Response of lesion (% of study sample) 0-2 months	~3 months	~6 months	~12 months	~18 months	~24 months	~60 months	Recurrence	Favors APC	Favors comparator
Ferraris R, et al. (2007)[147]	(mean: 3.2)	96	NR CR PR NR	- Not reported 	 Not reported 	- Not reported 	- 97.9% - -	 Not reported 	- Not reported 	 Not reported 	Not reported		n/a
Formentini A, et al. (2007)[148]	(nean: 3.6)	21	CR PR NR	100% - -	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported		n/a
Grade AJ, et al. (1999)[149]	(mean: 1.7)	9	CR PR NR	78% 22% -	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported		n/a
Madisch A, et al. (2005)[150]	(median: 2)	73	CR PR NR	98.6% - -	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	3% 12 months[t]		n/a
Manner H, et al. (2007)[151]	(mean: 1.1)	104	CR PR NR	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported		n/a
Manner H, et al. (2006)[152]	(mean: 1.1)	41	CR PR NR	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported		n/a
Manner H, et al. (2006)[153]	(mean: 2.7)	51	CR PR NR	Not reported	Not reported	Not reported	77% 23% -	Not reported	Not reported	Not reported	Not reported		n/a
Pedrazzani C, et al. (2005)[154]	(mean: 1.6)	25	CR PR NR	96% - -	Not reported	Not reported	Not reported	Not reported	92% - -	Not reported	Not reported		n/a
Pereira-Lima, JC, et al. (2000)[155]	(mean: 1.96)	33	CR PR NR	97% - -	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	3% 10.6 months		n/a
Pinotti AC, et al. (2004)[156]	(mean: 2)	19	CR PR NR	Not reported	95% - -	Not reported	Not reported	Not reported	Not reported	Not reported	5% 17 months		n/a
Tigges H, et al. (2001)[157]	(not reported)	30	CR PR NR	100% - -	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported		n/a
Van Laethem JL, et al. (2001)[158]	(mean: 2.83)	7	CR PR NR	57% - 14%	Not reported	Not reported	Not reported	Not reported	57% - 14%	Not reported	Not reported		n/a
Van Laethem JL, et al. (1998)[159]	(mean: 2.4)	31	CR PR NR	61% - -	48% - -	Not reported	53% [tt] - -	Not reported	Not reported	Not reported	52.4% 12 months [ttt]		n/a
Pooled total		**668**	CR	88.0%	48%	97%	83.%	-	87.7%	40.0%	11.8%		

Table E 3. Complete response of Barrett's esophagus in patients receiving argon plasma coagulation (APC)

Study	Treatment groups (No. of treatments)	No. of patients		Response of lesion (% of study sample) 0-2 months	~3 months	~6 months	~12 months	~18 months	~24 months	~60 months	Recurrence	Favors APC	Favors comparator
			PR	22%	-	-	23%		-	-	10.6 to 17		
			NR	14%	-	-	-		14%	-	months		
Cummulative pooled total		**792**	CR	86.6%	48%	97%	78.8%		87.7%	40.0%	16.7%		
			PR	6.7%	-	-	23%	-	-	-	10.6 to 17		
			NR	14%	-	-	-		14%	-	months		

*Approximate follow-up time intervals are as follows: Immediate, from 0 to 2 months; ~3m, from 2 to 5 months; ~6m, from 5 to 9 months; ~12m, from 9 to 15 months; ~18m, from 15 to 21 months; ~24m, from 21 to 27 months; and ~60m, above 27 months

** Complete response (CR); partial response (PR); non-response (NR)

*** Familiari L, et al. (2003) -- 3% recurrence rate at 6 months and 9% at 24 months

[t] Madisch A, et al. (2005) -- 12.1% recurrence rate at a median of 51 months

[tt] Van Laethem JL, et al. (1998) -- Loss of patients to follow-up

[ttt] Van Laethem JL, et al. (1998) -- 21.3% recurrence rate at 3 months

Table E 4. Complete response of HGD in patients receiving argon plasma coagulation (APC)

Study	Treatment groups (No. of treatments)	No. of patients	F/U U/K**	Response of lesion (% of study sample) 0-2 months*	~3 months	~6 months	~12 months	~18 months	~24 months	~60 months	Recurrence	Favors APC	Favors comparator
Comparative studies													
Ragunath K, et al. 2005 [60]	APC (1)	1	CR PR NR	Not reported	100% - -	Not reported	0% 100% -	Not reported	Not reported	Not reported	Not reported	Neither	
	PDT porfimer 2mg/kg (1)	2	CR PR NR	Not reported	100%- - -	Not reported	100% - -	Not reported	Not reported	Not reported	Not reported		
Thomas T, et al. 2005 [139]	APC (mean: 4)	5	CR PR NR	40% - -	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported		
	Esophagectomy (n/a)	8	CR PR NR		Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported		
	Surveillance (mean: 2.9)	7	CR PR NR	57% - -	Not reported	Not reported	Not reported	Not reported	57% - -	Not reported	Not reported	Not reported	
	Non-intervention (n/a)	7	CR PR NR		Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported		
Zoepf T, et al. (2003) [108]	APC (mean: 4)	10	CR PR NR		Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported		
	PDT ALA 60mg/kg (mean: 2)	10	CR PR NR		Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported		
Pooled total		**16**	CR		-	100%	-	0.0%	-	-	-	-	
Non-comparative studies													
Attwood SEA, et al. (2003) [140]	(median: 2)	29	CR PR NR		Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	n/a
Pereira-Lima JC, et al. (2000) [155]	(mean: 1.96)	1	CR PR NR		Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	n/a
Van Laethem JL, et al. (2001)[158]	(mean: 2.83)	7	CR PR NR		85.7% - 14%	Not reported	Not reported	Not reported	Not reported	71.4% - 14%	Not reported	16.7% 25.5 months	n/a
Pooled total		**37**	CR PR		85.7% -	-	-	-	-	71.4% -	-	16.7% 25.5 months	

Table E 4. Complete response of HGD in patients receiving argon plasma coagulation (APC)

Study	Treatment groups (No. of treatments)	No. of patients	F/U U/K**	Response of lesion (% of study sample) 0-2 months*	~3 months	~6 months	~12 months	~18 months	~24 months	~60 months	Recurrence	Favors APC	Favors comparator
			NR	14%					14%				
Cumulative pooled total		**53**	CR	85.7%	100.0%		0.0%		71.4%		16.7%		
			PR	-	-	-	-	-	-	-			
			NR	14%	-		-		14%				

* Approximate follow-up time intervals are as follows: Immediate, from 0 to 2 months; ~3m, from 2 to 5 months; ~6m, from 5 to 9 months; ~12m, from 9 to 15 months; ~18m, from 15 to 21 months; ~24m, from 21 to 27 months; and ~60m, above 27 months

** F/U U/K (follow-up time unknown), Complete response (CR); partial response (PR); non-response (NR)

*** follow-up time unknown

Table E 5. Complete response of Barrett's esophagus in patients receiving cryoablation, combined PDT+EMR, or thermocoagulation

Study	Treatment groups (No. of tretments)	No. of patients		Response of lesion (% of study sample)							Recurrence	Favors treatment	Favors Comparator
				0-2 months*	~3 months	~6 months	~12 months	~18 months	~24 months	~60 months			
Cryoablation													
Comparative studies													
None													
Non-comparative studies													
Dumot JA, et al. (2008) [79]	(mean: 4)	20	CR** PR NR	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	n/a	
Johnston MH, et al. (2005) [37]	(mean: 4.8)	11	CR PR NR	81.8% - -	Not reported	Not reported	63.7% - -	Not reported	Not reported	Not reported	Not reported	n/a	
Pooled total		**11**	CR	81.8%	-	-	63.7%	-	-	-	-		
Combined PDT+EMR													
Comparative studies													
Behrens A, et al. (2005) [106]	EMR + PDT (mean: 1)	3	CR PR NR	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported		
	EMR (not reported)	14	CR PR NR	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not Reported		
	PDT (mean: 1)	27	CR NR PR	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported		
Pooled total		**3**	CR	-	-	-	-	-	-	-	-		
Non-comparative studies													
Wolfsen HC, et al. (2004) [160]	(mean: 1)	3	CR PR NR	Not reported	Not reported	Not reported	100.0% - -	Not reported	Not reported	Not reported	Not reported	n/a	
Pooled total		**3**	CR	-	-	-	100.0%	-	-	-	-		
Cumulative pooled total		**6**	CR	-	-	-	100.0%	-	-	-	-		
Thermocoagulation													
Comparative studies													
None													
Non-comparative studies													
Michopoulos S, et al. (1999) [243]	(mean: 2.8)	13	CR PR NR	Not reported	Not reported	83.3% - -	88.9% - -	75.0% - -	Not reported	Not reported	16.7% 12 month	n/a	

Table E 5. Complete response of Barrett's esophagus in patients receiving cryoablation, combined PDT+EMR, or thermocoagulation

Study	Treatment groups (No. of tretments)	No. of patients		Response of lesion (% of study sample) 0-2 months*	~3 months	~6 months	~12 months	~18 months	~24 months	~60 months	Recurrence	Favors treatment	Favors Comparator
Pooled total		**13**	CR	-	-	83.3%	88.9%	75.0%	-	-	16.7% 12 month		

* Approximate follow-up time intervals are as follows: Immediate, from 0 to 2 months; ~3m, from 2 to 5 months; ~6m, from 5 to 9 months; ~12m, from 9 to 15 months; ~18m, from 15 to 21 months; ~24m, from 21 to 27 months; and ~60m, above 27 months.

** CR (complete response), PR (partial response), NR (no response)

Table E 6. Complete response of HGD in patients receiving cryoablation, combined EMR+PDT, or thermocoagulation

Study	Treatment groups (No. of treatments)	No. of patients		F/U U/K**	Response of lesion (% of study sample) 0-2 months*	~3 months	~6 months	~12 months	~18 months	~24 months	~60 months	Recurrence	Favors Treatment	Favors Comparator
Cryoablation														
Comparative studies														
None														
Non-comparative studies														
Dumot JA, et al. (2008) [79]	(mean: 4)	20	CR ** PR NR	89% - -	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	n/a	
Johnston MH, et al. (2005) [37]	(mean: 4.8)	1	CR PR NR		100.0% - -	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	n/a	
Pooled total		**1**	CR		100.0%	-	-	-	-	-	-	-		
Combined EMR+PDT														
Comparative studies														
Behrens A, et al. (2005) [106]	EMR+PDT (mean: 1)	3	CR NR PR		66.7% - -	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Neither	
	EMR (not reported)	14	CR NR PR		92.9% - -	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported		
	PDT (mean: 1)	27	CR NR PR		96.3% - -	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported		
Pooled total		**3**			66.7%									
Non-comparative studies														
Wolfsen HC, et al. (2004) [160]	(not reported)	3	CR PR NR		Not reported	Not reported	Not reported	100.0% - -	Not reported	Not reported	Not reported	Not reported	n/a	
Pooled total		**3**			-	-	-	100.0%	-	-	-	-		
Cumulative pooled total		**6**			66.7%	-	-	100.0%	-	-	-	-		
Thermocoagulation														
Comparative studies														
None														
Non-comparative studies														

Table E 6. Complete response of HGD in patients receiving cryoablation, combined EMR+PDT, or thermocoagulation

Study	Treatment groups (No. of treatments)	No. of patients	F/U U/K**	Response of lesion (% of study sample)							Recurrence	Favors Treatment	Favors Comparator
				0-2 months*	~3 months	~6 months	~12 months	~18 months	~24 months	~60 months			
Michopoulos S, et al. (1999) [243]	(mean: 2.8)	0	CR PR NR	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	n/a	
Pooled total		**0**	CR	-	-	-	-	-	-	-	-		

* Approximate follow-up time intervals are as follows: Immediate, from 0 to 2 months; ~3m, from 2 to 5 months; ~6m, from 5 to 9 months; ~12m, from 9 to 15 months; ~18m, from 15 to 21 months; ~24m, from 21 to 27 months; and ~60m, above 27 months.

** F/U U/K (follow-up time unknown), CR (complete response), PR (partial response), NR (no response)

Table E 7. Complete response of Barrett's esophagus in patients receiving endoscopic mucosal resection (EMR)

Study	Treatment groups (No. of treatments)	No. of patients		Response of lesion (% of study sample)							Recurrence	Favors treatment	Favors comparator
				Immediate*	~3 months	~6 months	~12 months	~18 months	~24 months	~60 months			
Comparative studies													
Behrens A, et al. 2005 [106]	EMR (not reported)	14	CR** PR NR	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported		
	PDT ALA 60 mg/kg (1)	27	CR PR NR	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported		
	PDT+EMR (1)	3	CR PR NR	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported		
Reed MF, et al (2005)[132]	EMR (not reported)	5	CR PR NR	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported		
	Esophagectomy (n/a)	49	CR PR NR	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported		
	PDT (not reported)	42	CR PR NR	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported		
	Observation (m/a)	19	CR PR NR	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported		
Pooled total		**19**		-	-	-	-	-	-	-	-		
Non-comparative studies													
Giovannini M, et al. (2004) [161]	(median: 2)	12	CR PR NR	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	n/a	
Mino-Kenudson M, et al. (2005)[162]	(not reported)	3	CR PR NR	Not reported	Not reported	Not reported	Not reported	Not reported	66.6% - -	Not reported	Not reported	n/a	
Seewald S, et al. (2003)[163]	(mean: 1.66)	3	CR PR NR	Not reported	Not reported	Not reported	0.0% - -	Not reported	Not reported	Not reported	Not reported	n/a	
Tang, SJ, et al. (2008)[164]	(2)	1	CR PR NR	Not reported	100.0% - -	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	n/a	
Pooled total		**19**	CR	-	100.0%	-	0.0%	-	66.6%	-	-		
Cumulative		**38**	CR	-	100.0%	-	0.0%	-	66.6%	-	-		

Table E 7. Complete response of Barrett's esophagus in patients receiving endoscopic mucosal resection (EMR)

Study	Treatment groups (No. of treatments)	No. of patients	Response of lesion (% of study sample)							Recurrence	Favors treatment	Favors comparator
			Immediate*	~3 months	~6 months	~12 months	~18 months	~24 months	~60 months			
pooled total												

* Approximate follow-up time intervals are as follows: Immediate, from 0 to 2 months; ~3m, from 2 to 5 months; ~6m, from 5 to 9 months; ~12m, from 9 to 15 months; ~18m, from 15 to 21 months; ~24m, from 21 to 27 months; and ~60m, above 27 months

** Complete response (CR); partial response (PR); non-response (NR)

Table E 8. Complete response of HGD in patients receiving endoscopic mucosal resection (EMR)

Study	Treatment groups (No. of treatments)	No. of patients		F/U U/K **	Response of lesion (% of study sample) 0-2 months*	~3 months	~6 months	~12 months	~18 months	~24 months	~60 months	Recurrence	Favors treatment	Favors comparator
Comparative studies														
Behrens A, et al. 2005 [106]	EMR (not reported)	14	CR**		93.0%	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported		
			PR		-									
			NR		-									
	PDT ALA 60 mg/kg (mean: 1)	27	CR		96.0%	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported		
			PR		-									
			NR		-									
	PDT+EMR (mean: 1)	3	CR		67.0%	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported		
			PR		-									
			NR		-									
Reed MF, et al (2005)[132]	EMR (not reported)	5	CR	60%	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported		
			PR	-										
			NR	-										
	Esophagectomy (n/a)	49	CR		Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported		
			PR											
			NR											
	PDT (not reported)	42	CR	88%	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported		
			PR	-										
			NR	-										
	Observation (n/a)	19	CR	0%	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported		
			PR	-										
			NR	-										
Pooled total		**19**			93.0%	-	-	-	-	-	-	-		
Non-comparative studies														
Giovannini M, et al. (2004)[161]	(median: 2)	12	CR		100.0%	91.7%	Not reported	83.3%	83.3%	Not reported	Not reported	16.7% 12 months		n/a
			PR		-	-		-	-					
			NR		-	-		-	-					
Mino-Kenudson M, et al. (2005)[162]	(not reported)	3	CR		Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported		n/a
			PR											
			NR											
Seewald S, et al. (2003)[163]	(mean: 1.66)	3	CR		Not reported	Not reported	Not reported	33.0%	Not reported	Not reported	Not reported	Not reported		n/a
			PR					-						
			NR					-						
Tang, SJ, et al. (2008)[164]	(2)	1	CR		Not reported	100.0%	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported		n/a
			PR											
			NR											
Pooled total		**19**	CR		100.0%	92.3%%	-	73.2%	83.3%	-	-	16.7% 12 months		
Cumulative		**38**	CR		96.2%	92.3%%	-	73.2%	83.3%	-	-	Not pooled		

Table E 8. Complete response of HGD in patients receiving endoscopic mucosal resection (EMR)

Study	Treatment groups (No. of treatments)	No. of patients	F/U U/K **	Response of lesion (% of study sample)							Recurrence	Favors treatment	Favors comparator
				0-2 months*	~3 months	~6 months	~12 months	~18 months	~24 months	~60 months			
pooled total													

* Approximate follow-up time intervals are as follows: Immediate, from 0 to 2 months; ~3m, from 2 to 5 months; ~6m, from 5 to 9 months; ~12m, from 9 to 15 months; ~18m, from 15 to 21 months; ~24m, from 21 to 27 months; and ~60m, above 27 months

** Unknown follow-up time (F/U U/K); Complete response (CR); partial response (PR); non-response (NR)

Table E 9. Complete response of Barrett's esophagus in patients receiving laser ablation

Study	Treatment groups (No. of treatments)	No. of patients		Response of lesion (% of study sample)							Recurrence	Favors laser	Favors comparator
				Immediate*	~3 months	~6 months	~12 months	~18 months	~24 months	~60 months			
Comparative studies													
None													
Non-comparative studies													
Barham CP, et al (1997)[165]	(mean: 3.4)	16	CR** PR NR	81% - -	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported		n/a
Bonarvina L, et al (1999)[166]	(mean: 3)	18	CR PR NR	61% 28% 11%	Not reported	Not reported	50% - -	Not reported	Not reported	Not reported	Not reported		n/a
Bowers SP, et al. (2002) [167]	(median: 2)	30	CR PR NR	Not reported	22.2% - -	Not reported	Not reported	Not reported	Not reported	11.1% - -	50.0% 61.2 months		n/a
Ertan A, et al (1995)[168]	(8)	1	CR PR NR	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported		n/a
Fisher RS, et al (2003)[169]	(mean: 6.5)	21	CR PR NR	100% - -	Not reported	Not reported	Not reported	62% - -	Not reported	Not reported	38% 19.1 months		n/a
Norberto L, et al (2004)[170]	(mean: 6.5)	15	CR PR NR	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	40% - -	Not reported		n/a
Salo, JA, et al (1998)[171]	(mean: 4)	17	CR PR NR	Not reported	100% - -	Not reported	Not reported	Not reported	100% - -	Not reported	Not reported		n/a
Pooled total		**88**	CR PR NR	82% 28% 11%	50.3% - -	-	50% - -	62% - -	100% - -	20.7% - -	Not pooled, see above		
Cumulative pooled total		**88**	CR PR NR	82% 28% 11%	50.3% - -	-	50% - -	62% - -	100% - -	20.7% - -	Not pooled, see above		

* Approximate follow-up time intervals are as follows: Immediate, from 0 to 2 months; ~3m, from 2 to 5 months; ~6m, from 5 to 9 months; ~12m, from 9 to 15 months; ~18m, from 15 to 21 months; ~24m, from 21 to 27 months; and ~60m, above 27 months

** Complete response (CR); partial response (PR); non-response (NR)

Table E 10. Complete response of HGD in patients receiving laser ablation

Study	Treatment groups (No. of treatments)	No. of patients		Response of lesion (% of study sample)							Recurrence	Favors laser	Favors comparator
				0-2 months *	~3 months	~6 months	~12 months	~18 months	~24 months	~60 months			
Comparative studies													
None													
Non-comparative studies													
Ertan A, et al (1995)[168]	(8)	1	CR** PR NR	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	n/a	
Fisher RS, et al (2003)[169]	(mean: 6.5)	3	CR PR NR	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	n/a	
Norberto L, et al (2004)[170]	(mean: 6.5)	2	CR PR NR	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	100.0%*** - -	Not reported	n/a	
Pooled total		**6**		-	-	-	-	-	-	100.0%	-		
Cumulative pooled total		**6**		-	-	-	-	-	-	100.0%	-		

* Approximate follow-up time intervals are as follows: Immediate, from 0 to 2 months; ~3m, from 2 to 5 months; ~6m, from 5 to 9 months; ~12m, from 9 to 15 months; ~18m, from 15 to 21 months; ~24m, from 21 to 27 months; and ~60m, above 27 months

** Complete response (CR); partial response (PR); non-response (NR)

*** Outcome measured at a mean of 28 months.

Table E 11. Complete response of Barrett's esophagus in patients receiving multipolar electrocoagulation (MPEC)

Study	Treatment groups (No. of treatments)	No. of patients		Response of lesion (% of study sample)							Recurrence	Favors MPEC	Favors comparator
				Immediate *	~3 months	~6 months	~12 months	~18 months	~24 months	~60 months			
Comparative studies													
Dulai GS, et al. (2005) [137]	MPEC (mean: 2.0)	26	CR **	88.5%	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Neither	
			PR	-									
			NR	-									
				p=0.68									
	APC (mean: 3.8)	26	CR	81.0%	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported		
			PR	-									
			NR	-									
Sharma P, et al. (2006) [138]	MPEC (not reported)	16	CR	Not reported	Not reported	Not reported	Not reported	Not reported	75.0%	Not reported	Not reported	Neither	
			PR						-				
			NR						-				
									p=0.78				
	APC (mean: 3.4)	19	CR	Not reported	Not reported	Not reported	Not reported	Not reported	63.0%	Not reported	Not reported		
			PR						-				
			NR						-				
Pooled total		**42**	CR	88.0%	-	-	-	-	75.0%	-	-		
Non-comparative studies													
Faigel DO, et al (2002)[172]	(mean: 3)	25	CR	Not reported	Not reported	92.0%	Not reported	Not reported	Not reported	Not reported	Not reported	n/a	
			PR			-							
			NR			-							
Kovacs BJ, (1999)[173]	(mean: 2.5)	27	CR	Not reported	56.0%	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	n/a	
			PR		-								
			NR		-								
Montes CG, et al (1999)[174]	(mean: 3.7)	14	CR	Not reported	Not reported	Not reported	Not reported	Not reported	100.0%	Not reported	Not reported	n/a	
			PR						-				
			NR						-				
Sampliner RE, et al (1996)[176]	(mean: 2.5)	10	CR	Not reported	Not reported	Not reported	100.0%	Not reported	Not reported	Not reported	Not reported	n/a	
			PR				-						
			NR				-						
Sampliner RE (1999)[175]	(not reported)	11	CR	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	73.0%	Not reported	n/a	
			PR							-			
			NR							-			
Pooled total		**87**	CR	-	56.0%	92.0%	100.0%	-	100.0%	73.0%	-		
Cumulative pooled total		**129**	CR	88.5%	56.0%	92.0%	100.0%	-	86.7%	73.0%	-		

* Approximate follow-up time intervals are as follows: Immediate, from 0 to 2 months; ~3m, from 2 to 5 months; ~6m, from 5 to 9 months; ~12m, from 9 to 15 months; ~18m, from 15 to 21 months; ~24m, from 21 to 27 months; and ~60m, above 27 months; ** Complete response (CR); partial response (PR); non-response (NR)

Table E 12. Complete response of Barrett's esophagus in patients receiving radiofrequency ablation (RFA)

Study	Treatment groups (No. of treatments)	No. of patients		Response of lesion (% of study sample)							Recurrence	Favors RFA	Favors comparator
				Immediate*	~3 months	~6 months	~12 months	~18 months	~24 months	~60 months			
Comparative studies													
Burgarner JM, et al. (2008)[130]	RFA (not reported)	103	CR** PR NR	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported		
	PDT (agent not reported) (not reported)	122	CR PR NR	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported		
Pooled total		**103**		-	-	-	-	-	-	-	-		
Non-comparative studies													
Eldaif SM, et al (2009)[177]	(1)	27	CR PR NR	Not reported	93.0% - -	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported		n/a
Fleischer DE, et al (2008) [178]	(mean: 3.39)	70	CR PR NR	Not reported	Not reported	Not reported	70.0% - -	Not reported	Not reported	98.4% - -	Not reported		n/a
Ganz RA, et al. (2008) [180]	(median: 1)	142	CR PR NR	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported		n/a
Hernandez JC, et al (2008)[181]	(mean: 2.5)	10	CR PR NR	Not reported	Not reported	Not reported	70.0% 30.0% -	Not reported	Not reported	Not reported	Not reported		n/a
Hubbard N, & Velanovich V (2007)[182]	(not reported)	7	CR PR NR	Not reported	86.0% - -	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported		n/a
Pouw RE, et al. (2008) [183]	(mean: 3)	44	CR PR NR	Not reported	98.0% - -	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported		n/a
Roorda AK, et al (2007)[184]	(mean: 1.4)	13	CR PR NR	Not reported	Not reported	Not reported	46.0%	Not reported	Not reported	Not reported	Not reported		n/a
Sharma VK, et al (2007)[179] ***	(mean: 1.82)	32	CR PR NR	Not reported	22.0% 78.0% -	Not reported	59.0% 41.0% -	Not reported	Not reported	Not reported	0.0% 12 months		n/a
Sharma VK, et al (2008)[185]	(mean: 2.5)	10	CR PR NR	Not reported	Not reported	Not reported	70% 20% -	Not reported	90% 10% -	Not reported	0.0% 24 months		n/a
Smith CD, et al. 2007 [186]	(1)	5	CR PR NR	90.0% - -	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported		n/a

Table E 12. Complete response of Barrett's esophagus in patients receiving radiofrequency ablation (RFA)

Study	Treatment groups (No. of treatments)	No. of patients		Response of lesion (% of study sample)							Recurrence	Favors RFA	Favors comparator
				Immediate*	~3 months	~6 months	~12 months	~18 months	~24 months	~60 months			
Pooled total		**360**	CR	90.0%	73.9%	-	65.1%	-	90.0%	98.0%	0.0%		
			PR	-	78.0%		34.8%		10.0%	-	12 to 24 months		
Cumulative pooled total		**463**	CR	90.0%	73.9%	-	65.1%	-	90.0%	98.0%	0.0%		
			PR	-	78.0%		34.8%		10.0%	-	12 to 24 months		

* Approximate follow-up time intervals are as follows: Immediate, from 0 to 2 months; ~3m, from 2 to 5 months; ~6m, from 5 to 9 months; ~12m, from 9 to 15 months; ~18m, from 15 to 21 months; ~24m, from 21 to 27 months; and ~60m, above 27 months

** Complete response (CR); partial response (PR); non-response (NR)

*** "Dosimetry phase" involving 32 patients

Table E 13. Complete response of HGD in patients receiving radiofrequency ablation (RFA)

Study	Treatment groups (No. of treatments)	No. of patients		Response of lesion (% of study sample)							Recurrence	Favors RFA	Favors comparator
				Immediate*	~3 months	~6 months	~12 months	~18 months	~24 months	~60 months			
Comparative studies													
Burgarner JM, et al. (2008)[130]	RFA (not reported)	103	CR** PR NR	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported		
	PDT (agent not reported) (not reported)	122	CR PR NR	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported		
Pooled total		**103**	CR	-	-	-	-	-	-	-	-		
Non-comparative studies													
Ganz RA, et al (2008)[180]	(median: 1)	142	CR PR NR	Not reported	90.0% - -	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported		n/a
Hernandez JC, et al (2008)[181]	(mean: 2.5)	3	CR PR NR	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported		n/a
Pouw RE, et al. (2008) [183]	(mean: 3)	32	CR PR NR	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported		n/a
Roorda AK, et al (2007)[184]	(mean: 1.4)	3	CR PR NR	Not reported	Not reported	Not reported	Not reported ***	Not reported	Not reported	Not reported	Not reported		n/a
Smith CD, et al. 2007 [186]	(1)	5	CR PR NR	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported		n/a
Pooled total		**189**	CR	-	90.0%	-	-	-	-	-	-		
Cumulative pooled total		**292**	CR	-	90.0%	-	-	-	-	-	-		

* Approximate follow-up time intervals are as follows: Immediate, from 0 to 2 months; ~3m, from 2 to 5 months; ~6m, from 5 to 9 months; ~12m, from 9 to 15 months; ~18m, from 15 to 21 months; ~24m, from 21 to 27 months; and ~60m, above 27 months

** Complete response (CR); partial response (PR); non-response (NR)

*** No HGD-specific outcomes available.

Appendix F - Progression to cancer evidence tables

Table F 1. Progression to esophageal cancer in patients receiving PDT for Barrett's esophagus or LGD without HGD

Study	Treatment groups	No. of patients	Progression to EAC (% of study sample) 6 months*	12 months	24 months	36 months	48 months	60 months	Favors PDT	Favors comparator
ALA 15mg/kg										
Comparative studies										
None										
Non-comparative studies										
Ortner MA, et al. (2001) [97]		14	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	n/a	
Ortner MA, et al. (1997) [98]		9	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	n/a	
Pooled total		**23**	-	-	-	-	-	-		
Cumulative pooled total		**23**	-	-	-	-	-	-		
ALA 30mg/kg										
Comparative studies										
Kelty CJ, et al. (2004) [45]	PDT	35	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported		
	APC	37	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported		
Pooled total		**35**	-	-	-	-	-	-		
Non-comparative studies										
Ackroyd R, et al. (2007) [99]		40	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	n/a	
Ackroyd R, et al. (1999) [101]		1	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	n/a	
Ackroyd R, et al. (1999) [100]		3	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	n/a	
Pooled total		**44**	-	-	-	-	-	-		
Cumulative pooled total		**79**	-	-	-	-	-	-		
ALA 60mg/kg										
Comparative studies										
Hage M, et al. (2004) [107]	PDT	26	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported		
	APC	14	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported		
Zoepf T, et al. (2003) [108]	PDT	10 **	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported		
	APC	10 **	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported		
Pooled total		**36**	-	-	-	-	-	-		

Table F 1. Progression to esophageal cancer in patients receiving PDT for Barrett's esophagus or LGD without HGD

Study	Treatment groups	No. of patients	Progression to EAC (% of study sample) 6 months*	12 months	24 months	36 months	48 months	60 months	Favors PDT	Favors comparator
Non-comparative studies										
Kashtan H, et al. (2002) [112]		7	Not reported	Not reported	0.0%	Not reported	Not reported	Not reported	n/a	
Pooled total		**7**	-	-	0.0%	-	-	-		
Cumulative pooled total		**43**	-	-	0.0%	-	-	-		
HpD 1.5mg/kg										
Comparative studies										
None										
Non-comparative studies										
Laukka MA, et al. (1995) [115]		4	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	n/a	
Wang KK, et al. (1999) [117]		39	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	n/a	
Wang KK, et al. (1999) [116]		55 **	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	n/a	
Pooled total		**98**	-	-	-	-	-	-		
Combine pooled total		**98**	-	-	-	-	-	-		
Porfimer sodium 2mg/kg										
Comparative studies										
Ragunath K, et al. (2005) [60]	PDT	13	***	Not reported	Not reported	Not reported	Not reported	Not reported		
	APC	13	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported		
Pooled total		**13**	-	-	-	-	-	-		
Non-comparative studies										
Overholt BF, et al. (2003) [124]		14	Not reported	Not reported	Not reported	Not reported	Not reported	0.0%	n/a	
Pooled total		**14**	-	-	-	-	-	0.0%		
Cumulative pooled total		**27**	-	-	-	-	-	0.0%		
Mixed										
Comparative studies										
Burgarner JM, et al. (2008) [130]	PDT[t]	122	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported		
	RFA	103	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported		
Pooled total		**122**	-	-	-	-	-	-		
Non-comparative studies										

Table F 1. Progression to esophageal cancer in patients receiving PDT for Barrett's esophagus or LGD without HGD

Study	Treatment groups	No. of patients	Progression to EAC (% of study sample)						Favors PDT	Favors comparator
			6 months*	12 months	24 months	36 months	48 months	60 months		
Kelty CJ, et al. (2004) [133] [tt]		25	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	n/a	
Wang KK, et al. (2002) [136ttt]		44	Not reported	Not reported	Not reported	Not reported	40.0%	Not reported	n/a	
Pooled total		**69**	-	-	-	-	-	-		
Cumulative pooled total		**191**	-	-	-	-	-	-		

* Progression reported for follow-up times during the first 6 months, from 6 to 12 months, from 12 to 24 months, from 24 to 36 months, from 36 to 48 months, and from 48 to 60 months.

** Mixed patient population – Number of patients with BE/LGD only unknown.

*** No BE/LGD specific progression outcomes available.

[t] PDT protocol unspecified.

[tt] Kelty et al. 2004 [133] – Patients provided ALA at 30 or 60 mg/kg. Distribution of patients among treatment protocols is unknown.

[ttt] Wang et al. 2002 [136] – Patients provided HpD or porfimer sodium PDT. Distribution of patients among treatment protocols is unknown.

Table F 2. Progression to esophageal cancer in patients receiving PDT for HGD

Study	Treatment groups	No. of patients	Progression to EAC (% of study sample) 6 months*	12 months	24 months	36 months	48 months	60 months	Favors PDT	Favors comparator
ALA 30mg/kg										
Comparative studies										
None										
Non-comparative studies										
Ackroyd R, et al. (1999) [101]		4	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported		n/a
Ackroyd R, et al. (1999) [100]		4	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported		n/a
Mackenzie G, et al. (2005) [135]		16	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported		n/a
Pooled total		**24**	-	-	-	-	-	-		
Cumulative pooled total		**24**	-	-	-	-	-	-		
ALA 40mg/kg										
Comparative studies										
None										
Non-comparative studies										
Peters F, et al. (2005) [104]		16	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported		n/a
Van Hellegerberg R, et al. (2003) [105]		2	100.0%	Not reported	Not reported	Not reported	Not reported	Not reported		n/a
Pooled total		**18**	100.0%	-	-	-	-	-		
Cumulative pooled total		**18**	100.0%	-	-	-	-	-		
ALA 60mg/kg										
Comparative studies										
Behrens A, et al. (2005) [106]	PDT	27	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported		
	EMR	14	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported		
	PDT+EMR	3	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported		
Zoepf T, et al. (2003) [108]	PDT	10 **	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported		
	APC	10 **	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported		
Pooled total		**37**	-	-	-	-	-	-		
Non-comparative studies										
Barr H, et al. (1996) [109]		5	Not	Not	Not	Not	Not	Not		n/a

Table F 2. Progression to esophageal cancer in patients receiving PDT for HGD

Study	Treatment groups	No. of patients	Progression to EAC (% of study sample)						Favors PDT	Favors comparator
			6 months*	12 months	24 months	36 months	48 months	60 months		
Gossner L, et al. (1999) [110]		10	reported Not reported	reported Not reported	reported Not reported	reported Not reported	reported Not reported	reported Not reported		n/a
Gossner L, et al. (1999) [111]		2	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported		n/a
Kashtan H, et al. (2002) [112]		1	Not reported	Not reported	0.0%	Not reported	Not reported	Not reported		n/a
Mackenzie G, et al. (2008) [134]		16	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported		n/a
Mackenzie G, et al. (2005) [135]		33	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported		n/a
Macrae FA, et al. (2004) [113]		8	Not reported	Not reported	Not reported	Not reported	Not reported	12.5%		n/a
Pooled total		**75**	-	-	0.0%	-	-	12.5%		
Cumulative pooled total		**112**	-	-	0.0%	-	-	12.5%		
HpD 1.5mg/kg										
Comparative studies										
None										
Non-comparative studies										
Laukka MA, et al. (1995) [115]		1	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported		n/a
Wang KK, et al. (1999) [117]		11	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported		n/a
Wang KK, et al. (1999) [116]		55**	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported		n/a
Pooled total		**67**	-	-	-	-	-	-		
Cumulative pooled total		**67**	-	-	-	-	-	-		
mTHPC 0.15mg/kg										
Comparative studies										
None										
Non-comparative studies										
Javaid B, et al. (2002) [118]		6	Not reported	Not reported	0.0%	Not reported	Not reported	Not reported		n/a
Lovat L, et al. (2005) [119] (Red light group)		4	Not reported	Not reported	0.0%	Not reported	Not reported	Not reported		n/a
Lovat L, et al. (2005) [119] (Green light group)		3	Not reported	Not reported	33.3%	Not reported	Not reported	Not reported		n/a

Table F 2. Progression to esophageal cancer in patients receiving PDT for HGD

Study	Treatment groups	No. of patients	Progression to EAC (% of study sample) 6 months*	12 months	24 months	36 months	48 months	60 months	Favors PDT	Favors comparator
Pooled total		**13**	-	-	7.7%	-	-	-		
Cumulative pooled total		**13**	-	-	7.7%	-	-	-		
Porfimer sodium 2mg/kg										
Comparative studies										
Ragunath K, et al. (2005) [60]	PDT	2	***	Not reported	Not reported	Not reported	Not reported	Not reported		
	APC	1	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported		
Pooled total		**2**	-	-	-	-	-	-		
Non-comparative										
Attila T, et al. (2005) [120]		19	Not reported	Not reported	Not reported	Not reported	10.5%	Not reported		n/a
Bronner M, et al. (2006) [121]		138	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported		n/a
Keeley SB, et al. (2007) [122]		13	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported		n/a
Mackenzie G, et al. (2008) [134]		16	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported		n/a
Overholt BF, et al. (2007) [123]		138	Not reported	Not reported	Not reported	Not reported	Not reported	13.0%		n/a
Overholt BF, et al. (2003) [124]		80	Not reported	Not reported	Not reported	Not reported	Not reported	2.5%		n/a
Overholt BF, et al. (1997) [126]		11	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported		n/a
Weiss AA, et al. (2006) [127]		13	Not reported	Not reported	30.8%	Not reported	Not reported	Not reported		n/a
Wolfsen HC, et al. (2004) [128]		69	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported		n/a
Yachimski P, et al. (2008) [129]		59	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported		n/a
Pooled total		**556**	-	-	30.8%	-	10.5%	9.1%		
Cumulative pooled total		**558**	-	-	30.8%	-	10.5%	9.1%		
Mixed										
Comparative studies										
Prasad GA, et al. (2007) [131 t]	PDT	129	Not reported	4.7%	Not reported	6.2%	Not reported	Not reported		
	Esophagectomy	70	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported		

Table F 2. Progression to esophageal cancer in patients receiving PDT for HGD

Study	Treatment groups	No. of patients	Progression to EAC (% of study sample) 6 months*	12 months	24 months	36 months	48 months	60 months	Favors PDT	Favors comparator
Reed MF, et al. (2005) [132]	PDT[tt]	42	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported		
	EMR	5	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported		
	Esophagectomy	49	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported		
	Observation	19	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported		
Pooled total		**171**	-	4.7%	-	6.2%	-	-		
Non-comparative studies										
Mackenzie G, et al. (2007) [103 ttt]		72	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	n/a	
Wang KK, et al. (2002) [136o]		48	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	n/a	
Pooled total		**120**	-	-	-	-	-	-		
Cumulative pooled total		**291**	-	4.7%	-	6.2%	-	-		

* Progression reported for follow-up times during the first 6 months, from 6 to 12 months, from 12 to 24 months, from 24 to 36 months, from 36 to 48 months, and from 48 to 60 months.

** Mixed patient population – Number of patients with BE/LGD only unknown.

*** No HGD specific outcome available.

[t] Prasad et al. 2007 [131] – Patients provided HpD (26) or porfimer sodium (103).

[tt] PDT protocol unspecified.

[ttt] Mackenzie et al. 2007 [103] – Patients provided ALA at various doses and energy amounts. Distribution of patients among treatment protocols is unknown. Progression rate provided for ALA 60mg/kg group. Results from this report are not included in pooled total totals. Mackenzie et al. 2005 [103] listed here instead of Mackenzie et al. 2007 [102] and Mellidez et al. 2005 [114].

[o] Wang et al. 2002 [136] – Patients provided HpD or porfimer sodium PDT. Distribution of patients among treatment protocols is unknown.

Table F 3. Progression to esophageal cancer in patients receiving argon plasma coagulation (APC) for Barrett's esophagus with LGD without HGD

Study	Treatment groups	No. of patients	Progression to EAC (% of study sample) 6 months*	12 months	24 months	36 months	48 months	60 months	Favors APC	Favors comparator
Comparative studies										
Dulai GS, et al. (2005)[137]	APC	26	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported		
	MPEC	26	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported		
Hage M, et al. (2004)[107]	APC	14	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported		
	PDT ALA 60mg/kg	26	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported		
Kelty CJ, et al. (2004)[45]	APC	37	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported		
	PDT ALA 30mg/kg	35	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported		
Ragunath K, et al. (2005)[60]	APC	13 ***	**	Not reported	Not reported	Not reported	Not reported	Not reported		
	PDT porfimer 2mg/kg	13 ***	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported		
Sharma P, et al. (2006)[138]	APC	19	Not reported	Not reported	0.0%	Not reported	Not reported	Not reported	Neither	
	MPEC	16	Not reported	Not reported	0.0%	Not reported	Not reported	Not reported		
Zoepf T, et al. (2003)[108]	APC	10 ***	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported		
	PDT ALA 60mg/kg	10 ***	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported		
Pooled total		**119**	-	-	0.0%	-	-	-		
Non-comparative studies										
Basu, KK, et al. (2006)[141]		33	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	n/a	
Brand B, et al. (2000)[142]		12	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	n/a	
Bright T, et al. (2007) [143]		20	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	n/a	
Dumoulin FL, et al. (1997)[145]		2	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	n/a	
Familiari L, et al. (2003)[146]		32	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	n/a	
Ferraris R, et al. (2007)[147]		96	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	n/a	
Formentini A, et al.		21	Not	Not	Not	Not	Not	Not	n/a	

Table F 3. Progression to esophageal cancer in patients receiving argon plasma coagulation (APC) for Barrett's esophagus with LGD without HGD

Study	Treatment groups	No. of patients	Progression to EAC (% of study sample) 6 months*	12 months	24 months	36 months	48 months	60 months	Favors APC	Favors comparator
(2007)[148]			reported	reported	reported	reported	reported	reported		
Grade AJ, et al. (1999)[149]		9	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported		n/a
Madisch A, et al. (2005)[150]		73	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported		n/a
Manner H, et al. (2007)[151]		104	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported		n/a
Manner H, et al. (2006)[152]		41	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported		n/a
Manner H, et al. (2006)[153]		51	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported		n/a
Pedrazzani C, et al. (2005)[154]		25	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported		n/a
Pereira-Lima, JC, et al. (2000)[155]		32	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported		n/a
Pinotti AC, et al. (2004)[156]		19	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported		n/a
Tigges H, et al. (2001)[157]		30	Not reported	0.0%	Not reported	Not reported	Not reported	Not reported		n/a
Van Laethem JL, et al. (1998)[159]		31	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported		n/a
Pooled total		**631**	-	0.0%	-	-	-	-		
Cumulative pooled total		**750**	-	0.0%	0.0%	-	-	-		

* Progression reported for follow-up times during the first 6 months, from 6 to 12 months, from 12 to 24 months, from 24 to 36 months, from 36 to 48 months, and from 48 to 60 months.

** No BE/LGD specific progression outcomes available.

*** Mixed patient population – Number of patients with BE/LGD only unknown.

Table F 4. Progression to esophageal cancer in patients receiving argon plasma coagulation (APC) for HGD

Study	Treatment groups	No. of patients	F/U U/K*	Progression to EAC (% of study sample) 6 months*	12 months	24 months	36 months	48 months	60 months	Favors APC	Favors comparator
Comparative studies											
Ragunath K, et al. (2005)[60]	APC	1		**	Not reported	Not reported	Not reported	Not reported	Not reported		
	PDT porfimer 2mg/kg	2		Not reported	Not reported	Not reported	Not reported	Not reported	Not reported		
Thomas T, et al. (2005)[139]	APC	5	40%	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported		
	Esophagectomy	8		Not reported	Not reported	25.0%	Not reported	Not reported	Not reported		
	Non-intervention	7	50%	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported		
	Surveillance	7		Not reported	Not reported	33.3%	Not reported	Not reported	Not reported		
Zoepf T, et al. (2003)[108]	APC	10 ***		Not reported	Not reported	Not reported	Not reported	Not reported	Not reported		
	PDT ALA 60mg/kg	10 ***		Not reported	Not reported	Not reported	Not reported	Not reported	Not reported		
Pooled total		**16**		-	-	-	-	-	-		
Non-comparative studies											
Attwood SEA, et al. (2003)[140]		29		Not reported	Not reported	Not reported	Not reported	14.0%	Not reported		n/a
Pereira-Lima, JC, et al. (2000)[155]		1		Not reported	Not reported	Not reported	Not reported	Not reported	Not reported		n/a
Van Laethem JL, et al. (2001)[158]		7		Not reported	Not reported	14.3%	Not reported	Not reported	Not reported		n/a
Pooled total		**37**		-	-	14.3%	-	14.0%	-		
Cumulative pooled total		**53**		-	-	14.3%	-	14.0%	-		

* Progression reported for follow-up times during the first 6 months, from 6 to 12 months, from 12 to 24 months, from 24 to 36 months, from 36 to 48 months, and from 48 to 60 months; follow-up time unknown (F/U U/K).
** No HGD specific progression outcomes available.
*** Mixed patient population – Number of patients with BE/LGD only unknown.

Table F 5. Progression to esophageal cancer in patients receiving endoscopic mucosal ressection for HGDs.

Study	Treatment groups	No. of patients	Progression to EAC (% of study sample)						Favors treatment	Favors comparator
			6 months*	12 months	24 months	36 months	48 months	60 months		
Comparative										
Behrens A, et al. (2005) [106]	- EMR	14	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported		
	- PDT	27	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported		
	- PDT+EMR	3	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported		
Reed MF, et al. (2004) [132]	- EMR	5	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported		
	- PDT	42	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported		
	- Esophagectomy	49	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported		
	- Observation	19	Not reported	53.8%	Not reported	Not reported	Not reported	Not reported		
Pooled total		**19**	-	-	-	-	-	-		
Non-comparative										
Giovannini M, et al. (2004) [161]		12	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	n/a	
Mino-Kenudson M, et al. (2005)[162]		3	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	n/a	
Seewald S, et al. (2003)[163]		3	Not reported	0.0%	Not reported	Not reported	Not reported	Not reported	n/a	
Tang, SJ, et al. (2008)[164]		1	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	n/a	
Pooled total		**19**	-	0.0%	-	-	-	-		
Cumulative pooled total		**38**	-	0.0%	-	-	-	-		

* Progression reported for follow-up times during the first 6 months, from 6 to 12 months, from 12 to 24 months, from 24 to 36 months, from 36 to 48 months, and from 48 to 60 months.

Table F 6. Progression to esophageal cancer in patients receiving laser ablation for Barrett's esophagus or LGD without HGD

Study	Treatment groups	No. of patients	Progression to EAC (% of study sample)						Favors laser	Favors comparator
			6 months*	12 months	24 months	36 months	48 months	60 months		
Comparative studies										
None										
Non-comparative studies										
Barham CP, et al (1997)[165]		16	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	n/a	
Bonarvina L, et al (1999)[166]		18	Not reported	Not reported	5.6%	Not reported	Not reported	Not reported	n/a	
Bowers SP, et al. (2002)[167]		30	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	n/a	
Fisher RS, et al (2003)[169]		18	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	n/a	
Salo, JA, et al (1998)[171]		17	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	n/a	
Norberto L, et al (2004)[170]		13	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	n/a	
Pooled total		**112**	-	-	5.6%	-	-	-		
Cumulative pooled total		**112**	-	-	5.6%	-	-	-		

* Progression reported for follow-up times during the first 6 months, from 6 to 12 months, from 12 to 24 months, from 24 to 36 months, from 36 to 48 months, and from 48 to 60 months.

Table F 7. Progression to esophageal cancer in patients receiving laser ablation for Barrett's esophagus with HGD

Study	Treatment groups	No. of patients	Progression to EAC (% of study sample)						Favors laser	Favors comparator
			6 months*	12 months	24 months	36 months	48 months	60 months		
Comparative studies										
None										
Non-comparative studies										
Ertan A, et al (1995)[168]		1	100.0%	Not reported	Not reported	Not reported	Not reported	Not reported	n/a	
Fisher RS, et al (2003)[169]		3	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	n/a	
Norberto L, et al (2004)[170]		2	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	n/a	
Pooled total		**6**	100.0%	-	-	-	-	-		
Cumulative pooled total		**6**	-	-	-	-	-	-		

* Progression reported for follow-up times during the first 6 months, from 6 to 12 months, from 12 to 24 months, from 24 to 36 months, from 36 to 48 months, and from 48 to 60 months.

Table F 8. Progression to esophageal cancer in patients receiving esophagectomy for HGD

Study	Treatment groups	No. of patients	Follow-up time unknown	Progression to EAC (% of study sample)						Favors surgery	Favors comparator
				6 months*	12 months	24 months	36 months	48 months	60 months		
Comparative studies											
Prasad GA, et al. (2007)[131]	Esophagectomy	70		Not reported	Not reported	Not reported	Not reported	Not reported	Not reported		
	PDT with HpD or porfimer sodium	129		Not reported	Not reported	Not reported	Not reported	Not reported	Not reported		
Reed MF, et al. (2005)[132]	Esophagectomy	49		Not reported	Not reported	Not reported	Not reported	Not reported	Not reported		
	EMR	5		Not reported	Not reported	Not reported	Not reported	Not reported	Not reported		
	Observation	19		Not reported	53.8%	Not reported	Not reported	Not reported	Not reported		
	PDT	42		Not reported	Not reported	Not reported	Not reported	Not reported	Not reported		
Thomas T, et al. (2005)[139]	Esophagectomy	8	25%	Not reported	Not reported	25.0% P=0.73 **	Not reported	Not reported	Not reported	Neither **	
	APC	5	40%	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported		
	Non-intervention	7	50%	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported		
	Surveillance	7	33%	Not reported	Not reported	33.3%	Not reported	Not reported	Not reported		
Pooled total		**127**		-	-	25.0%	-	-	-		
Non-comparative studies											
Ferguson MK, et al (1997)[187]		15		Not reported	Not reported	Not reported	Not reported	0.0%	Not reported	n/a	
Thomson BNJ, et al. (2007)[191]		7		Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	n/a	
Nguyen NT, et al (2000)[188]		12		Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	n/a	
Romagnoli R, et al (2003)[189] ***		20		Not reported	Not reported	Not reported	Not reported	Not reported	5.0% [t]	n/a	
Sujendran V, et al (2005)[190]		17		Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	n/a	
Pooled total		**71**		-	-	-	-	0.0%	5.0%		
Cumulative pooled total		**198**		-	-	25.0%	-	0.0%	5.0%		

* Progression reported for follow-up times during the first 6 months, from 6 to 12 months, from 12 to 24 months, from 24 to 36 months, from 36 to 48 months, and from 48 to 60 months; ** Esophagectomy versus surveillance only; *** An additional 13 patients were treated with "expectant" esophagectomy. Progression to cancer ("neoplastic recurrence") among these patients was 30.8% at 120 months; [t] At 120 months follow-up.

Table F 9. Progression to esophageal cancer in patients receiving radiofrequency ablation (RFA) for HGD

Study	Treatment groups	No. of patients	Progression to EAC (% of study sample)						Favors surgery	Favors comparator
			6 months*	12 months	24 months	36 months	48 months	60 months		
Comparative studies										
None										
Non-comparative studies										
Pouw RE, et al (2008)[183]		42	Not reported	Not reported	2.0%	Not reported	Not reported	Not reported	n/a	
Pooled total		**42**	-	-	2.0%	-	-	-		
Cumulative pooled total		**42**	-	-	2.0%	-	-	-		

* Progression reported for follow-up times during the first 6 months, from 6 to 12 months, from 12 to 24 months, from 24 to 36 months, from 36 to 48 months, and from 48 to 60 months.

Appendix G - Evidence tables: survival

Table G 1. Survival in patients receiving PDT for Barrett's esophagus or LGD without HGD

Study	Treatment groups	No. of patients	Survival (*i.e.* Freedom from EAC-related death) (% of study sample) 6 months*	12 months	24 months	36 months	60 months	Favors PDT	Favors comparator
ALA 15mg/kg									
Comparative studies									
None									
Non-comparative studies									
Ortner MA, et al. (2001) [97]		14	Not reported	Not reported	Not reported	Not reported	Not reported		n/a
Ortner MA, et al. (1997) [98]		9	Not reported	Not reported	Not reported	Not reported	Not reported		n/a
Pooled total		**23**	-	-	-	-	-		
Cumulative pooled total		**23**	-	-	-	-	-		
ALA 30mg/kg									
Comparative studies									
Kelty CJ, et al. (2004) [45]	- PDT	35	Not reported	Not reported	Not reported	Not reported	Not reported		
	- APC	37	Not reported	Not reported	Not reported	Not reported	Not reported		
Pooled total		**35**	-	-	-	-	-		
Non-comparative studies									
Ackroyd R, et al. (2007) [99]		40	Not reported	Not reported	Not reported	Not reported	Not reported		n/a
Ackroyd R, et al. (1999) [100]		3	100.0%	Not reported	100.0%	Not reported	Not reported		n/a
Ackroyd R, et al. (1999) [101]		1	Not reported	Not reported	Not reported	Not reported	Not reported		n/a
Pooled total		**44**	100.0%	-	100.0%	-	-		
Cumulative pooled total		**79**	100.0%	-	100.0%	-	-		
ALA 60mg/kg									
Comparative studies									
Hage M, et al. (2004) [107]	- PDT	26	Not reported	Not reported	Not reported	Not reported	Not reported		
	- APC	14	Not reported	Not reported	Not reported	Not reported	Not reported		
Zoepf T, et al. (2003) [108]	- PDT	10 **	Not reported	Not reported	Not reported	Not reported	Not reported		
	- APC	10 **	Not reported	Not reported	Not reported	Not reported	Not reported		

Table G 1. Survival in patients receiving PDT for Barrett's esophagus or LGD without HGD

Study	Treatment groups	No. of patients	Survival (*i.e.* Freedom from EAC-related death) (% of study sample) 6 months*	12 months	24 months	36 months	60 months	Favors PDT	Favors comparator
Pooled total		**36**	-	-	-	-	-		
Non-comparative studies									
Kashtan H, et al. (2002)		7	Not reported	Not reported	Not reported	Not reported	Not reported		n/a
Pooled total		**7**	-	-	-	-	-		
Cumulative pooled total		**43**	-	-	-	-	-		
HpD 1.5mg/kg									
Comparative studies									
None									
Non-comparative studies									
Laukka MA, et al. (1995) [115]		4	Not reported	Not reported	Not reported	Not reported	Not reported		n/a
Wang KK, et al. 1999 [116]		55 **	Not reported	Not reported	Not reported	Not reported	Not reported		n/a
Wang KK, et al. (1999) [117]		39	Not reported	Not reported	Not reported	Not reported	Not reported		n/a
Pooled total		**98**	-	-	-	-	-		
Cumulative pooled total		**151**	-	-	-	-	-		
Porfimer sodium 2mg/kg									
Comparative studies									
Ragunath K, et al. (2005) [60]	- PDT	13**	Not reported	Not reported	Not reported	Not reported	Not reported		
	- APC	13**	Not reported	Not reported	Not reported	Not reported	Not reported		
Pooled total		**13**	-	-	-	-	-		
Non-comparative studies									
Overholt BF, et al. (2003) [124]		14	Not reported	Not reported	Not reported	Not reported	92.9%		n/a
Pooled total		**14**	-	-	-	-	92.9%		
Cumulative pooled total		**27**	-	-	-	-	92.9%		
Mixed									
Comparative studies									
Burgarner JM, et al. (2008) [130] ****	- PDT	122	Not reported	Not reported	Not reported	Not reported	Not reported		
	- RFA	103	Not reported	Not	Not	Not	Not		

Table G 1. Survival in patients receiving PDT for Barrett's esophagus or LGD without HGD

Study	Treatment groups	No. of patients	Survival (*i.e.* Freedom from EAC-related death) (% of study sample)					Favors PDT	Favors comparator
			6 months*	12 months	24 months	36 months	60 months		
				reported	reported	reported	reported		
Pooled total		**122**	-	-	-	-	-		
Non-comparative studies									
Kelty CJ, et al. (2004) [133] [t]		25	Not reported	Not reported	Not reported	Not reported	Not reported		n/a
Wang KK, et al. (2002) [136] [tt]		44	Not reported	Not reported	Not reported	Not reported	Not reported		n/a
Pooled total		**69**	-	-	-	-	-		
Cumulative pooled total		**191**	-	-	-	-	-		

* Survival reported for follow-up times during the first 6 months, from 6 to 12 months, from 12 to 24 months, from 24 to 36 months, and from 36 to 60 months.
** Mixed patient population – Number of patients with BE/LGD only unknown.
*** PDT protocol unspecified.
[t] Kelty et al. 2004 [133] – Patients provided with ALA at either 30 or 60mg/kg. Distribution of patients among treatment protocols is unknown.)
[tt] Wang et al. 2002 [136] – Patients provided HpD or porfimer sodium PDT. Distribution of patients among treatment protocols is unknown.)

Table G 2. Survival in patients receiving PDT for Barrett's esophagus with HGD

Study	Treatment groups	No. of patients	Survival (*i.e.* Freedom from EAC-related death) (% of study sample) 6 months *	12 months	24 months	36 months	60 months	Favors PDT	Favors comparator
ALA 30mg/kg									
Comparative studies									
None									
Non-comparative studies									
Ackroyd R, et al. (1999) [101]		4	100.0%	Not reported	100.0%	Not reported	Not reported	n/a	
Ackroyd R, et al. (1999) [100]		4	Not reported	Not reported	Not reported	Not reported	Not reported	n/a	
Mackenzie G, et al. (2005) [135]		16	Not reported	Not reported	Not reported	Not reported	Not reported	n/a	
Pooled total		**24**	100.0%	-	100.0%	-	-		
Cumulative pooled total		**24**	100.0%	-	100.0%	-	-		
ALA 40mg/kg									
Comparative studies									
None									
Non-comparative studies									
Peters F, et al. (2005) [104]		16	Not reported	Not reported	Not reported	Not reported	Not reported	n/a	
Van Hillegerberg R, et al. (2003) [105]		2	Not reported	Not reported	Not reported	Not reported	Not reported	n/a	
Pooled total		**18**	-	-	-	-	-		
Cumulative pooled total		**18**	-	-	-	-	-		
ALA 60mg/kg									
Comparative studies									
Behrens A, et al. (2005) [106]	PDT	27	Not reported	Not reported	Not reported	Not reported	Not reported		
	EMR	14	Not reported	Not reported	Not reported	Not reported	Not reported		
	PDT+EMR	3	Not reported	Not reported	Not reported	Not reported	Not reported		
Zoepf T, et al. (2003) [108]	PDT	10 **	Not reported	Not reported	Not reported	Not reported	Not reported		
	APC	10 **	Not reported	Not reported	Not reported	Not reported	Not reported		
Pooled total		**37**	-	-	-	-	-		
Non-comparative studies									

Table G 2. Survival in patients receiving PDT for Barrett's esophagus with HGD

Study	Treatment groups	No. of patients	Survival (*i.e.* Freedom from EAC-related death) (% of study sample) 6 months *	12 months	24 months	36 months	60 months	Favors PDT	Favors comparator
Barr H, et al. (1996) [109]		5	Not reported	Not reported	Not reported	Not reported	Not reported		n/a
Gossner L, et al. (1999) [110]		10	Not reported	Not reported	Not reported	Not reported	Not reported		n/a
Gossner L, et al. (1999) [111]		2	Not reported	100.0%	Not reported	Not reported	Not reported		n/a
Kashtan H, et al. (2002) [112]		1	Not reported	Not reported	Not reported	Not reported	Not reported		n/a
Mackenzie G, et al. (2008) [134]		16	Not reported	Not reported	Not reported	Not reported	Not reported		n/a
Mackenzie G. et al. (2005) [135]		33	Not reported	Not reported	Not reported	Not reported	Not reported		n/a
Macrae FA, et al. (2004) [113]		8	Not reported	Not reported	Not reported	Not reported	100.0%		n/a
Pooled total		**75**	-	100.0%	-	-	100.0%		
Cumulative pooled total		**112**	-	100.0%	-	-	100.0%		
HpD 1.5mg/kg									
Comparative studies									
None									
Non-comparative studies									
Laukka MA, et al. (1995) [115]		1	Not reported	Not reported	Not reported	Not reported	Not reported		n/a
Wang KK, et al. 1999 [116]		55**	Not reported	Not reported	Not reported	Not reported	Not reported		n/a
Wang KK, et al. (1999) [117]		11	Not reported	Not reported	Not reported	Not reported	Not reported		n/a
Pooled total		**67**	-	-	-	-	-		
Cumulative pooled total		**67**	-	-	-	-	-		
mTHPC 0.15mg/kg									
Comparative studies									
None									
Non-comparative studies									
Javaid B, et al. (2002) [118]		6	Not reported	Not reported	Not reported	Not reported	Not reported		n/a
Lovat L, et al. (2005) [119]		7	Not reported	Not reported	100.0%	Not reported	Not reported		n/a
Pooled total		**13**	-	-	100.0%	-	-		
Cumulative pooled total		**13**	-	-	100.0%	-	-		

Table G 2. Survival in patients receiving PDT for Barrett's esophagus with HGD

Study	Treatment groups	No. of patients	Survival (*i.e.* Freedom from EAC-related death) (% of study sample) 6 months *	12 months	24 months	36 months	60 months	Favors PDT	Favors comparator
Porfimer sodium 2mg/kg									
Comparative studies									
Ragunath K, et al. (2005) [60]	- PDT	2	Not reported	Not reported	Not reported	Not reported	Not reported		
	- APC	1	Not reported	Not reported	Not reported	Not reported	Not reported		
Pooled total		2	-	-	-	-	-		
Non-comparative studies									
Attila T, et al. (2005) [121]		19	Not reported	Not reported	Not reported	Not reported	Not reported	n/a	
Bronner M, et al. (2006) [121]		138	Not reported	Not reported	Not reported	Not reported	Not reported	n/a	
Keeley SB, et al. (2007) [122]		13	Not reported	Not reported	Not reported	100.0%	Not reported	n/a	
Mackenzie G, et al. (2008) [134]		16	Not reported	Not reported	Not reported	Not reported	Not reported	n/a	
Overholt BF, et al. (2007) [123]		138	Not reported	Not reported	Not reported	Not reported	Not reported	n/a	
Overholt BF, et al. (2003) [124]		80	Not reported	Not reported	Not reported	Not reported	91.3%	n/a	
Overholt BF, et al. (1997) [126]		11	Not reported	Not reported	Not reported	Not reported	Not reported	n/a	
Weiss AA, et al. (2006) [127]		13	Not reported	Not reported	Not reported	Not reported	Not reported	n/a	
Wolfsen HC, et al. (2004) [128]		69	Not reported	Not reported	Not reported	Not reported	Not reported	n/a	
Yachimski P, et al. (2008)		59	Not reported	Not reported	Not reported	Not reported	Not reported	n/a	
Pooled total		**556**	-	-	-	100.0%	91.3%		
Cumulative pooled total		**558**	-	-	-	100.0%	91/3%		
Mixed									
Comparative studies									
Prasad GA, et al. (2007) [131]***	PDT	129	Not reported	Not reported	Not reported	Not reported	100.0% P=1.0 [t]	Neither	
	Esophagectomy	70	Not reported	Not reported	Not reported	Not reported	100.0%		
Reed MF, et al. (2005) [132]	PDT	42	Not reported	Not reported	Not reported	Not reported	Not reported		
	EMR	5	Not reported	Not reported	Not reported	Not reported	Not reported		

Table G 2. Survival in patients receiving PDT for Barrett's esophagus with HGD

Study	Treatment groups	No. of patients	Survival (*i.e.* Freedom from EAC-related death) (% of study sample)					Favors PDT	Favors comparator
			6 months *	12 months	24 months	36 months	60 months		
	Esophagectomy	49	Not reported	Not reported	Not reported	Not reported	94.0%		
	Observation	19	Not reported	Not reported	Not reported	Not reported	Not reported		
Pooled total		**171**	-	-	-	-	100.0%		
Non-comparative studies									
Mackenzie G, et al. (2007) [103] [tt]		72	Not reported	Not reported	Not reported	Not reported	Not reported	n/a	
Wang KK, et al. (2002) [136] [ttt]		48	Not reported	Not reported	Not reported	Not reported	Not reported	n/a	
Pooled total		**120**	-	-	-	-	-		
Cumulative pooled total		**291**	-	-	-	-	-		

* Survival reported for follow-up times during the first 6 months, from 6 to 12 months, from 12 to 24 months, from 24 to 36 months, and from 36 to 60 months.

** Mixed patient population – Number of patients with HGD unknown.

*** Prasad et al. 2007 [131] – Patients provided HpD or porfimer sodium.

[t] Overall survival was 91.5%, compared to 91.4% for esophagectomy.

[tt] Mackenzie et al. (2007) [103] – Patients provided ALA at various doses and energy amounts – distribution of patients among protocols unknown. This study is listed instead of Mellidez et al 2005 [114] and Mackenzie et al. 2005 [102].

[ttt] Wang et al. 2002 [136] – Patients provided HpD or porfimer sodium PDT. Distribution of patients among treatment protocols is unknown.

Table G 3. Survival in patients receiving argon plasma coagulation for Barrett's esophagus with LGD without HGD

Study	Treatment groups	No. of patients	Survival (*i.e.* Freedom from EAC-related death) (% of study sample) 6 months*	12 months	24 months	36 months	60 months	Favors APC	Favors comparator
Comparative studies									
Dulai GS, et al. (2005)[137]	APC	26	Not reported	Not reported	Not reported	Not reported	Not reported		
	MPEC	26	Not reported	Not reported	Not reported	Not reported	Not reported		
Hage M, et al. (2004)[107]	APC	14	Not reported	Not reported	Not reported	Not reported	Not reported		
	PDT ALA 60mg/kg	26	Not reported	Not reported	Not reported	Not reported	Not reported		
Kelty CJ, et al. (2004)[45]	APC	37	Not reported	Not reported	Not reported	Not reported	Not reported		
	PDT ALA 30mg/kg	35	Not reported	Not reported	Not reported	Not reported	Not reported		
Ragunath K, et al. (2005)[60]	APC	12	Not reported	Not reported	Not reported	Not reported	Not reported		
	PDT porfimer 2mg/kg	11	Not reported	Not reported	Not reported	Not reported	Not reported		
Sharma P, et al. (2006)[138]	APC	19	Not reported	Not reported	Not reported	Not reported	Not reported		
	MPEC	16	Not reported	Not reported	Not reported	Not reported	Not reported		
Zoepf T, et al. (2003)[108]	APC	10 **	Not reported	Not reported	Not reported	Not reported	Not reported		
	PDT ALA 60mg/kg	10 **	Not reported	Not reported	Not reported	Not reported	Not reported		
Pooled total		**118**	-	-	-	-	-		
Non-comparative studies									
Basu, KK, et al. (2006)[141]		33	Not reported	Not reported	Not reported	Not reported	Not reported		n/a
Brand B, et al. (2000)[142]		12	Not reported	Not reported	Not reported	Not reported	Not reported		n/a
Bright T, et al. (2007) [143]		20	Not reported	95.0%	Not reported	Not reported	Not reported		n/a
Dumoulin FL, et al. (1997)[145]		2	Not reported	Not reported	Not reported	Not reported	Not reported		n/a
Familiari L, et al. (2003)[146]		32	Not reported	Not reported	Not reported	Not reported	Not reported		n/a
Ferraris R, et al. (2007)[147]		96	Not reported	Not reported	Not reported	Not reported	Not reported		n/a

Table G 3. Survival in patients receiving argon plasma coagulation for Barrett's esophagus with LGD without HGD

Study	Treatment groups	No. of patients	Survival (*i.e.* Freedom from EAC-related death) (% of study sample)					Favors APC	Favors comparator
			6 months*	12 months	24 months	36 months	60 months		
Formentini A, et al. (2007)[148]		21	Not reported	Not reported	Not reported	Not reported	Not reported		n/a
Grade AJ, et al. (1999)[149]		9	Not reported	Not reported	Not reported	Not reported	Not reported		n/a
Madisch A, et al. (2005)[150]		73	Not reported	Not reported	Not reported	Not reported	Not reported		n/a
Manner H, et al. (2007)[151]		104	Not reported	Not reported	Not reported	Not reported	Not reported		n/a
Manner H, et al. (2006)[152]		41	Not reported	Not reported	Not reported	Not reported	Not reported		n/a
Manner H, et al. (2006)[153]		51	Not reported	Not reported	Not reported	Not reported	Not reported		n/a
Pedrazzani C, et al. (2005)[154]		25	Not reported	Not reported	Not reported	Not reported	Not reported		n/a
Pereira-Lima, JC, et al. (2000)[155]		32	Not reported	Not reported	Not reported	Not reported	Not reported		n/a
Pinotti AC, et al. (2004)[156]		19	Not reported	Not reported	Not reported	Not reported	Not reported		n/a
Tigges H, et al. (2001)[157]		30	Not reported	Not reported	Not reported	Not reported	Not reported		n/a
Van Laethem JL, et al. (1998)[159]		31	Not reported	Not reported	Not reported	Not reported	Not reported		n/a
Pooled total		**631**	-	95.0%	-	-	-		
Cumulative pooled total		**749**	-	95.0%	-	-	-		

* Survival reported for follow-up times during the first 6 months, from 6 to 12 months, from 12 to 24 months, from 24 to 36 months, and from 36 to 60 months.
** Mixed patient population – Number of patients with BE/LGD only unknown.

Table G 4. Survival in patients receiving argon plasma coagulation (APC) for Barrett's esophagus with HGD

Study	Treatment groups	No. of patients	Survival (*i.e.* Freedom from EAC-related death) (% of study sample) 6 months *	12 months	24 months	36 months	60 months	Favors APC	Favors comparator
Comparative studies									
Ragunath K, et al. (2005) [60]	APC	1	Not reported	Not reported	Not reported	Not reported	Not reported		
	PDT porfimer 2mg/kg	2	Not reported	Not reported	Not reported	Not reported	Not reported		
Thomas T, et al. (2005) [139]	APC	5	Not reported	Not reported	Not reported	Not reported	Not reported		
	Esophagectomy	8	Not reported	Not reported	87.5%	Not reported	Not reported		
	Non-intervention	7	Not reported	Not reported	Not reported	Not reported	Not reported		
	Surveillance	7	Not reported	Not reported	Not reported	Not reported	Not reported		
Zoepf T, et al. (2003) [108]	APC	10 **	Not reported	Not reported	Not reported	Not reported	Not reported		
	PDT ALA 60mg/kg	10 **	Not reported	Not reported	Not reported	Not reported	Not reported		
Pooled total		**16**	-	-	-	-	-		
Non-comparative studies									
Attwood SEA, et al. (2003)[140]		29	Not reported	Not reported	Not reported	Not reported	Not reported		n/a
Pereira-Lima, JC, et al. (2000)[155]		1	Not reported	Not reported	Not reported	Not reported	Not reported		n/a
Van Laethem JL, et al. (2001)[158]		7	Not reported	Not reported	85.7%	Not reported	Not reported		n/a
Pooled total		**37**	-	-	85.7%	-	-		
Cumulative pooled total		**53**	-	-	85.7%	-	-		

* Survival reported for follow-up times during the first 6 months, from 6 to 12 months, from 12 to 24 months, from 24 to 36 months, and from 36 to 60 months.
** Mixed patient population – Number of patients with BE/LGD only unknown.

Table G 5. Survival in patients receiving cryoablation, combined PDT+EMR, or thermocoagulation for Barrett's esophagus with HGD

Study	Treatment groups	No. of patients	Survival (*i.e.* Freedom from EAC-related death) (% of study sample)					Favors treatment	Favors comparator
			6 months*	12 months	24 months	36 months	60 months		
Cryoablation									
Comparative studies									
None									
Non-comparative studies									
Dumot JA, et al. (2008) [79]		20	Not reported	Not reported	Not reported	Not reported	Not reported	n/a	
Johnston MH, et al. (2005) [37]		1	Not reported	Not reported	Not reported	Not reported	Not reported	n/a	
Pooled total		**1**	-	-	-	-	-		
Combined PDT+EMR									
Comparative studies									
Behrens A, et al. (2005) [106]	EMR+PDT	3	Not reported	Not reported	Not reported	Not reported	Not reported		
	EMR	14	Not reported	Not reported	Not reported	Not reported	Not reported		
	PDT	27	Not reported	Not reported	Not reported	Not reported	Not reported		
Pooled total		**3**	-	-	-	-	-		
Non-comparative studies									
Wolfsen HC, et al. (2004) [160]		3	Not reported	Not reported	100.0%	Not reported	Not reported	n/a	
Pooled total		**3**	-	-	100.0%	-	-		
Cumulative pooled total		**6**	-	-	100.0%	-	-		
Thermocoagulation									
Comparative studies – none									
Non-comparative studies – none									
Pooled total		**0**	-	-	-	-	-		

* Survival reported for follow-up times during the first 6 months, from 6 to 12 months, from 12 to 24 months, from 24 to 36 months, and from 36 to 60 months.

Table G 6. Survival in patients receiving esophagectomy for Barrett's esophagus with HGD

Study	Treatment groups	No. of patients	Survival (*i.e.* Freedom from EAC-related death) (% of study sample)						Favors surgery	Favors comparator
			6 months*	12 months	24 months	36 months	48 months	60 months		
Comparative studies										
Prasad GA, et al. (2007)[131]	Esophagectomy	70	Not reported	Not reported	Not reported	Not reported	Not reported	100.0% ** P=1.0	Neither	
	PDT with HpD or porfimer sodium	129	Not reported	Not reported	Not reported	Not reported	Not reported	100.0% **		
Reed MF, et al. (2005)[132]	Esophagectomy	49	Not reported	Not reported	Not reported	Not reported	Not reported	94.0% ***		
	EMR	5	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported		
	Observation	19	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported		
	PDT	42	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported		
Thomas T, et al. (2005)[139]	Esophagectomy	8	Not reported	Not reported	87.5% [t]	Not reported	Not reported	Not reported		
	APC	5	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported		
	Non-intervention	7	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported		
	Surveillance	7	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported		
Pooled total		**127**	-	-	87.5%	-	-	97.5%		
Non-comparative studies										
Ferguson MK, et al (1997)[187]		15	Not reported	Not reported	Not reported	Not reported	100.0%	Not reported	n/a	
Nguyen NT, et al (2000)[188]		12	Not reported	Not reported	100.0%	Not reported	Not reported	Not reported	n/a	
Romagnoli R, et al (2003)[189] [tt]		20	Not reported	Not reported	Not reported	Not reported	Not reported	100.0% [ttt]	n/a	
Sujendran V, et al (2005)[190]		17	Not reported	100.0%°	94.0%°	82.0%°	70.0%°	Not reported	n/a	
Thomson BNJ, et al. (2007)[191]		7	Not reported	Not reported	100.0%	Not reported	Not reported	Not reported	n/a	
Pooled total		**71**	-	100.0%	97.2%	82.0%	84.1%	100.0%		
Cumulative pooled total		**198**	-	100.0%	95.4%	82.0%	84.1%	97.9%		

* Survival reported for follow-up times during the first 6 months, from 6 to 12 months, from 12 to 24 months, from 24 to 36 months, and from 36 to 60 months.
** Overall survival was 91.4%, compared to 91.5% in the comparator arm (PDT with HpD or porfimer sodium), p=0.99.

*** Overall survival was 83.0% and 64.0% at 5 and 10 years, respectively.
[t] Overall survival at 21 months was 62.5%.
[tt] An additional 13 patients were treated with “expectant” esophagectomy. Overall survival at 120 months in this group was 52.5%.
[ttt] Survival at 120 months; ° Disease-free survival.

Appendix H - Levels of Evidence & Grades of Recommendation

Levels of Evidence

Level	Study design
1a	Systematic review with homogeneity of RCTs
1b	Individual RCT with narrow confidence interval
1c	All or none studies (where all patients died before the treatment became available)
2a	Systematic review with homogeneity of cohort studies
2b	Individual cohort study or low quality RCT (e.g., <80% follow-up)
2c	"Outcomes" research; ecological studies
3a	Systematic review with homogeneity of case-control studies
3b	Individual case-control study
4	Case-series or poor quality cohort or case-control studies
5	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"

Grades of Recommendation

Grade	Levels of evidence
A (excellent)	Consistent level 1 studies
B (good)	Consistent level 2 or 3 studies *or* extrapolations from level 1 studies
C (fair)	Level 4 studies or extrapolations from level 2 or 3 studies
D (poor)	Level 5 evidence or troublingly inconsistent or inconclusive studies of any level

Adapted from the *Oxford Centre for Evidence-based Medicine levels of evidence and grades of recommendation for studies of therapy*. Oxford: Centre for Evidence-based Medicine; 2009. Available: http://www.cebm.net/index.aspx?o=1047

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