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Rees JRE, Lao-Sirieix P, Wong A, Fitzgerald RC

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[Intervention Review]

Treatment for Barrett's oesophagus

Jonathan RE Rees¹, Pierre Lao-Sirieix¹, Angela Wong¹, Rebecca C Fitzgerald¹

¹MRC Cancer Cell Unit, Hutchison/MRC Research Centre, Cambridge, UK

Contact address: Rebecca C Fitzgerald, MRC Cancer Cell Unit, Hutchison/MRC Research Centre, Hills Road, Cambridge, CB22 2XZ, UK.
rcf@hutchison-mrc.cam.ac.uk.

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ABSTRACT

Background

Treatments for Barrett's oesophagus, the precursor lesion of adenocarcinoma, are available but whether these therapies effectively prevent the development of adenocarcinoma, and in some cases eradicate the Barrett's oesophagus segment, remains unclear.

Objectives

To summarise, quantify and compare the efficacy of pharmacological, surgical and endoscopic treatments for the eradication of dysplastic and non-dysplastic Barrett's oesophagus and prevention of these states from progression to adenocarcinoma.

Search methods

We searched CENTRAL (*The Cochrane Library* 2004, issue 4), MEDLINE (1966 to June 2008) and EMBASE (1980 to June 2008).

Selection criteria

Randomised controlled trials (RCTs) comparing medical, endoscopic or non-resectional surgical treatments for Barrett's oesophagus. The primary outcome measures were complete eradication of Barrett's and dysplasia at 12 months, and reduction in the number of patients progressing to cancer at five years or latest time point.

Data collection and analysis

Three authors independently extracted data and assessed the quality of the trials included in the analysis.

Main results

Sixteen studies, including 1074 patients, were included. The mean number of participants in the studies was small ($n = 49$; range 8 to 208). Most studies did not report on the primary outcomes. Medical and surgical interventions to reduce symptoms and sequelae of gastro-oesophageal reflux disease (GORD) did not induce significant eradication of Barrett's oesophagus or dysplasia. Endoscopic therapies (photodynamic therapy (PDT with aminolevulinic acid or porfimer sodium), argon plasma coagulation (APC) and radiofrequency ablation (RFA)) all induced regression of Barrett's oesophagus and dysplasia. The data for photodynamic therapy were heterogeneous with a mean eradication rate of 51% for Barrett's oesophagus and between 56% and 100% for dysplasia, depending on the treatment regimens. The variation in photodynamic therapy eradication rates for dysplasia was dependent on the drug, source and dose of light. Radiofrequency ablation resulted in eradication rates of 77% and 86% for Barrett's oesophagus and dysplasia, while those rates were 2% and 21% in the sham treatment group respectively. Endoscopic treatments were generally well tolerated, however all were associated with some buried glands, particularly following argon plasma coagulation and photodynamic therapy, as well as photosensitivity and strictures induced by porfimer sodium based photodynamic therapy in particular.

Authors' conclusions

Despite their failure to eradicate Barrett's oesophagus, the role of medical and surgical interventions to reduce the troubling symptoms and sequelae of GORD is not questioned. Whether therapies for GORD reduce the cancer risk is not yet known. Ablative therapies have an increasing role in the management of dysplasia within Barrett's and current data would favour the use of radiofrequency ablation compared with photodynamic therapy. Radiofrequency ablation has been shown to yield significantly fewer complications than photodynamic therapy and is very efficacious at eradicating both dysplasia and Barrett's itself. However, long-term follow-up data are still needed before radiofrequency ablation can be used in routine clinical care without the need for very careful post-treatment surveillance. More clinical trial data and in particular randomised controlled trials are required to assess whether or not the cancer risk is reduced in routine clinical practice.

PLAIN LANGUAGE SUMMARY

Treatment of Barrett's oesophagus

One of the two main types of oesophageal (gullet) cancer, oesophageal adenocarcinoma, is rapidly increasing in incidence in the western world. The prognosis for patients treated for oesophageal adenocarcinoma is appalling with fewer than 15% of individuals surviving beyond five years. Barrett's oesophagus has been identified as the pre-cancerous stage of adenocarcinoma. It is recognised that Barrett's oesophagus develops as a complication of acid and bile reflux which commonly, but not inevitably, leads to heartburn symptoms. In response to these injurious agents, the normal squamous lining of the oesophagus is replaced by a columnar lining resembling the lining of the intestine. This intestinal subtype has the highest risk of malignancy and the term Barrett's oesophagus is used only for this subtype in many areas of the world, and in most research publications. Barrett's oesophagus can gradually progress to adenocarcinoma through a series of stages called dysplasia which can be identified in biopsies examined under the microscope.

As outcomes after treatment of adenocarcinoma are so poor, there has been increasing interest in treatments for Barrett's oesophagus. The aim of these treatments is to eradicate the Barrett's oesophagus lining or associated dysplasia with the aim of reducing the risk of cancer developing. This systematic review has shown that acid suppression therapies (surgery or drugs) have little or no significant effect on reversing Barrett's oesophagus but anti-reflux surgery appears to reduce dysplasia and protects against the development of dysplasia. A number of endoscopic therapies have also been developed over recent years. Argon plasma coagulation, which burns away the Barrett's oesophagus segment, and photodynamic therapy, which uses light to activate an injected drug, have both been shown to be successful at eradicating Barrett's and dysplasia. However, small areas of Barrett's oesophagus buried under the newly formed squamous oesophagus remain a concern. A relatively new technique using radiofrequency waves, called radio frequency ablation appears successful at eradicating Barrett's with fewer side effects. There are currently very few randomised controlled trials to help clinicians and patients decide on the best treatment options in the long as well as the short-term. Overall, radiofrequency ablation appears to be the most successful therapy to date for patients with early cancer or severe (high-grade) dysplasia in Barrett's oesophagus. Significantly more work is needed in this area to guide routine clinical practice for this common condition.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Summary of outcome measures per treatment category

	Primary Outcome				Significant secondary outcomes
	Studies	Eradication of Barrett's oesophagus at 12 months	Eradication of dysplasia at 12 months	Reduction of cancer at 5 years or latest time point	
PPI vs H ₂ RA	Caldwell 1996 Peters 1999 Weinstein 1996	Not reported	Not reported	Not reported	Both induced some degree of reduction of area of Barrett's oesophagus
COX-2 inhibitor vs placebo	Heath 2007	Not reported	Not reported	No reduction at 1 year	No differences in progression to dysplasia from IM
Nissen fundoplication + PPI and H ₂ RA vs PPI and H ₂ RA	Parrilla 2003	No complete eradication	No differences at 5 years	No differences	Reduction of dysplasia in surgery group (P = 0.03)
Nd-YAG + omeprazole vs omeprazole	Luman 1996	No eradication at 5 years	Not reported	Not reported	No differences identified in any of the reported outcomes
APC vs surveillance	Bright 2007	APC induced eradication of Barrett's oesophagus (P = 0.003) but very wide confidence interval	Only 2 dysplastic patients	Not reported	No differences identified in any of the reported outcomes
APC + PPI vs MPEC	Dulai 2005 Sharma 2006	No differences in eradication (63% to 88% vs 63% to 75%)	Not reported	Not reported	No differences identified in any of the reported outcomes
APC + PPI vs PDT	Hage 2004 Kelty 2004 Ragunath 2005	Degree of eradication and most successful arm dependent on the PDT regimen	No differences identified	Not reported	Photosensitivity in PDT patients Fever, nausea and vomiting more common in PDT patients

PDT (ALA or Porfimer sodium) + PPI vs PPI alone	Ackroyd 2000 Overholt 2005	PDT induced more eradication at 2 years ($P < 0.00001$, OR 14.18; 95% CI 5.38 to 37.37)	PDT induced eradication at 2 years ($P < 0.0001$, OR 9.13; 95% CI 4.42 to 18.86)	Reduction in progression to cancer ($P = 0.007$, OR 0.38; 95% CI 0.18 to 0.77)	Reduction in the length, area and reduction of progression to dysplasia in the PDT group Increase in photosensitivity, fever and stricture rates in the PDT group
ALA PDT vs porfimer sodium PDT	Mackenzie 2008	Not reported	HGD eradicated in 14/14 ALA vs 9/14 porfimer sodium	Not reported	No differences identified in any of the reported outcomes
RFA vs sham	Shaheen 2008	RFA induced eradication ($P < 0.00001$, OR 143.64; 95% CI 18.53 to 1113.87)	Induced eradication at 2 years ($P < 0.0001$, OR 22.67; 95% CI 8.72 to 58.94)	No reduction identified	Reduction in the number of patients with worsening dysplasia at 12 months ($P = 0.02$, OR 0.19; 95% CI 0.02 to 0.78)

APC = argon plasma coagulation
H₂RA = H₂-receptor antagonist
IM = intestinal metaplasia
MPEC = multipolar electrocautery
PDT = photodynamic therapy
PPI = proton pump inhibitor
RFA = radiofrequency ablation
vs = versus

BACKGROUND

Description of the condition

The incidence of oesophageal adenocarcinoma is rapidly increasing in the Western world. Its precursor lesion, Barrett's oesophagus, occurs as a consequence of chronic gastro-oesophageal reflux, with prevalence rates of 6% to 12% (Sarr 1985; Winters 1987; Cameron 1990; Blot 1991; Cameron 1992; Bonelli 1993; Pera 1993; Robinson 1998). Data from Sweden indicate an overall population prevalence of 1.6% (Ronkainen 2005).

Barrett's oesophagus is defined as an endoscopically visible segment of columnar lined epithelium in the lower oesophagus with biopsies demonstrating (in the UK) any type of metaplasia and (in the US) intestinal metaplasia (BSG 2005; Wang 2008). Intestinal metaplasia is the most common subtype with the greatest malignant potential and for this reason many investigators restrict the definition of Barrett's to this subtype (Sampliner 2002). The risk of progression from Barrett's oesophagus to high-grade dysplasia and invasive adenocarcinoma is low, at approximately 0.4% and 0.77% per year respectively (Yousef 2008).

The identification of a 'stepwise' progression through a metaplasia-dysplasia-adenocarcinoma sequence akin to that described in colon carcinogenesis provides the rationale for endoscopic surveillance, which aims to detect high-grade dysplasia or cancer at an early, asymptomatic and potentially curable stage. Early cancer detection is important because despite advances in multimodal treatment, the survival rates of symptomatic oesophageal cancers remain dismal. The overall survival of patients treated radically with chemotherapy and surgery is 43% at two years (MRC working party 2002) and 14% at five years if all patients are considered (Enzinger 2003; CRUK 2006). Evidence from non-randomised retrospective studies demonstrates an improved five-year actuarial survival in patients with surveillance-detected oesophageal carcinomas of up to 80% at five years (Streitz 1993; Bani-Hani 2000; Fountoulakis 2004) indicating a potential benefit for early detection, although lead time bias needs to be accounted for.

Description of the intervention

There has been considerable interest in treatments to reduce the risk of cancer progression through eradication of Barrett's oesophagus. Oesophagectomy is currently the only routine clinical treatment for high-grade dysplasia. However, novel research therapies may permit not to use such an invasive approach. Whether suppression of reflux, via surgical or pharmacological therapy, is sufficient to achieve this goal is uncertain. Furthermore, treatment efficacy is difficult to measure given the size of the cohort required and the duration of follow up necessary. As an alternative endpoint, investigators have measured regression or reversal of Barrett's oesophagus.

The primary aim of pharmacological acid-suppression and surgical anti-reflux treatments is to relieve symptoms. The medical treatments available (proton pump inhibitors and H₂ antagonists) reduce acid secretion. Anti-reflux surgery, typically a Nissen fundoplication, may be offered to carefully selected patients with proven reflux disease who are refractory to medical treatment or to those reluctant to take life-long medication. Surgery has the advantage of reducing both acid and bile reflux, which may act

synergistically in the aetiopathogenesis of Barrett's oesophagus (Theisen 2003; Jolly 2004) and also provides both effective symptom relief and healing of oesophagitis.

Interest in the potential role of proton pump inhibitors in the prevention of adenocarcinoma in Barrett's oesophagus has been based on laboratory data showing that recurrent pulsatile episodes of gastro-oesophageal reflux components may have detrimental effects on the cell phenotype (reviewed in Fitzgerald 2005). Specifically, an *ex vivo* explant model and cell line models have demonstrated increased proliferation and proliferation-related signalling pathways (Fitzgerald 1996; Souza 2002), as well as inducing DNA double strand breaks (Clemons 2007) upon exposure to pulsatile acid. Furthermore, effective acid suppression has been associated with increased cell differentiation, decreased proliferation and decreased COX-2 expression in Barrett's oesophagus metaplasia tissue biopsies (Ouatu-Lascar 1999; Shirvani 2000; Adballa 2004; Lao-Sirieix 2007). Cox-2 levels were also demonstrated to be normalized following anti-reflux surgery (Vallböhmer 2006). Outside of the laboratory in *in vivo* and *ex vivo* studies, the effect of proton pump inhibitors on Barrett's oesophagus and oesophageal adenocarcinoma is as yet unclear and animal models of reflux treated with proton pump inhibitor have not revealed a reduction in adenocarcinoma risk (Triadafilopoulos 2000; Moore 2001).

On the other hand, concerns have also arisen because of the effects of proton pump inhibitors on gastrin secretion. Most of the evidence is based on *in vitro* or *ex vivo* work and data need to be interpreted with caution. Proton pump inhibitors increase gastrin secretion and work in Barrett's oesophagus biopsies and using the Barrett's oesophagus adenocarcinoma cell line, OE33 with over expression of the CCK2 receptor, suggested that the Barrett's oesophagus epithelium is sensitive to the proliferative effects of gastrin (Haigh 2003; Adballa 2004). This gastrin-induced hyperproliferation *in vitro* could be inhibited by a selective COX-2 inhibitor (Adballa 2004). Whether the risk of hypergastrinaemia is real or not, the benefits of proton pump inhibitors outweigh the side effects (reviewed in Tytgat 2001). Furthermore, a large general practice database study of 18,000 patients treated with omeprazole did not identify an excess mortality, secondary to omeprazole treatment, when pre-existing conditions were taken into account (Bateman 2003).

Aside from acid suppression there has been interest in other drugs which might prevent progression to cancer (chemoprevention). The most studied are aspirin and non-steroidal anti-inflammatory drugs (NSAIDs), which have been associated with a reduced occurrence of oesophageal cancers, including adenocarcinoma, in retrospective epidemiological studies (Sadeghi 2008). Data from the ASPECT trial (phase III, randomised, study of aspirin and esomeprazole chemoprevention in Barrett's metaplasia), which aims to assess the impact of high or low-dose aspirin combined with esomeprazole, are eagerly awaited (ASPECT). Similarly, COX-2 inhibitors have been shown to suppress cell proliferation and induce apoptosis *in vitro* in a wide range of cell lines although the associated cardiotoxicity has limited their use in human chemoprevention strategies (reviewed in Thun 2002). Other potential chemopreventive agents include retinoids, however the most recent evidence in small-cell lung cancer (Freemantle 2006) and also a phase III placebo controlled trial in squamous cell carcinoma of the head and neck (Khuri 2006) suggest that traditional retinoids do not confer benefit. Citral, a retinoid

antagonist, has been demonstrated *ex vivo* to induce reversion of the Barrett's phenotype (Chang 2007). Whether these agents could be beneficial in preventing progression of preinvasive oesophageal disease is therefore of interest.

The last two decades have seen the introduction of endoscopic techniques, usually in combination with acid suppression therapy or anti-reflux surgery, that remove all or part of the Barrett's epithelium. These techniques include thermal methods such as argon plasma photocoagulation (APC), multipolar electrocautery (MPEC), laser therapy, cryotherapy and radiofrequency ablation (RFA); chemical methods including photodynamic therapy (PDT); mechanical methods such as endoscopic mucosal resection (EMR) and more recently ultrasonic surgical aspiration (Yeh 2005). The rationale for these is that replacement of the Barrett's epithelium with a neo-squamous epithelium removes the malignant potential. These methods must balance adequate depth of ablation and elimination of columnar mucosa with the risks of complications such as perforations and strictures. One of the concerns of ablative therapies is the presence of so-called buried Barrett's oesophagus glands, below the neosquamous epithelium, that may still harbour malignant potential.

How the intervention might work

The goals of therapy in Barrett's oesophagus patients are wide ranging; they include relief of reflux symptoms, healing of erosive oesophagitis, prevention of inflammatory complications, ablation of the columnar-lined segment and ultimately reduction in the risk of malignant complications. The management strategies for individuals with Barrett's oesophagus and associated high-grade dysplasia include continued surveillance with an aggressive biopsy protocol, endoscopic therapies which may include endoscopic mucosal resection or an oesophagectomy for those who are deemed fit.

Why it is important to do this review

A number of interventions for the treatment of Barrett's oesophagus have been investigated to date and new ones continue to emerge. It is important to assess the current state of the evidence before attempting novel therapies and before recommending these modalities in routine clinical practice.

OBJECTIVES

To summarise, quantify and compare the efficacy of treatments to induce reversal of Barrett's oesophagus or dysplasia or to halt the progression to cancer. Three main groups of therapeutic interventions were considered.

1. Pharmacological treatments: H₂-receptor antagonists, proton pump inhibitors, prokinetics and antacids, as well as chemopreventive agents such as NSAIDs, aspirin and COX-2 inhibitors.
2. Anti-reflux procedures. The surgical treatments have been compared with each other or with pharmacological treatment if these data are available.
3. Endoscopic ablative methods: thermal (argon plasma coagulation, multipolar electrocautery, laser therapy, cryotherapy and radiofrequency ablation), chemical (photodynamic therapy) and mechanical methods (endoscopic mucosal resection and ultrasonic surgical aspiration).

We reviewed these treatments either alone versus placebo or in combination versus placebo (or sham), or by direct comparison of two treatments. It was anticipated that there would be few randomised controlled trials (RCTs) such that comparison of treatments would be limited. The evidence from open non-randomised trials has necessarily formed a large part of the Discussion.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials in which one of the intervention types was compared with placebo or another intervention type. We considered studies in both abstract and peer reviewed format.

Types of participants

Adults (age > 18 years) of either gender in whom the diagnosis of Barrett's oesophagus has been established both endoscopically (any length of columnar appearing epithelium above the gastro-oesophageal junction) and confirmed histologically (usually intestinal metaplasia), regardless of the status of dysplasia.

Types of interventions

1. Pharmacological therapy, either alone or in combination: any proton pump inhibitor, any H₂RA, any prokinetic, any antacid, NSAIDs, selective or specific COX-2 inhibitor and any novel chemopreventive agents including retinoids and difluoromethylornithine (DFMO).
2. Anti-reflux surgery, in particular Nissen fundoplication.
3. Endoscopic therapies, either alone or in combination with (1) or (2):
 - a. thermal methods: argon plasma photocoagulation, multipolar electrocautery, laser therapy, radiofrequency ablation and cryotherapy;
 - b. chemical methods: photodynamic therapy;
 - c. mechanical methods: endoscopic mucosal resection and ultrasonic surgical aspiration.

Types of outcome measures

Primary outcomes

1. Complete eradication of Barrett's oesophagus at 12 months.
2. Complete eradication of dysplasia at 12 months.
3. Reduction in the number of patients progressing to cancer at five years or latest time point.

Secondary outcomes

1. Reduction of (a) length or (b) area of Barrett's oesophagus at 12 months (where data at 12 months were not available then the nearest point in time was reported). The maximum Barrett's length was reported in most series discussing this outcome.
2. Reduction in the number of patients progressing from intestinal metaplasia to dysplasia.
3. Presence of buried sub-squamous Barrett's glands.

4. Adverse reactions.
 - a. Mortality.
 - b. Serious adverse drug reaction, where serious represents a reaction requiring medical intervention.
 - c. Any complications.
5. Control of acid reflux (only for acid suppression therapies and surgical anti-reflux therapies).

Search methods for identification of studies

Electronic searches

We conducted searches to identify all published and unpublished randomised controlled trials. We included articles published in any language.

We identified trials by searching the following electronic databases:

- the Cochrane Central register of Controlled Trials (CENTRAL) (which includes the Cochrane Upper Gastrointestinal and Pancreatic Diseases Group Trials Register) in *The Cochrane Library* (Issue 4, 2004);
- MEDLINE (1966 to October 2003); and
- EMBASE (1980 to October 2003).

The search was updated in October 2004, October 2005, August 2006 and June 2008.

The search strategy for this review was constructed by using a combination of MESH subject headings and text words relating to the use of pharmacological and endoscopic therapies and anti-reflux surgery used for the treatment of Barrett's oesophagus. To identify RCTs we combined the following search with the Cochrane highly sensitive search strategy phases, one, two and three as contained in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2008). Details of the MEDLINE search strategy are provided in [Appendix 1](#).

We handsearched reference lists from trials selected by electronic searching to identify further relevant trials.

Searching other resources

We contacted members of the Cochrane UGPD Group, authors of papers and experts in the field and asked them to provide details of outstanding clinical trials and any relevant unpublished materials.

Abstracts

We handsearched published abstracts from conference proceedings from the United European Gastroenterology Week (published in *Gut*), British Society of Gastroenterology Meeting (published in *Gut*) and Digestive Disease Week (published in *Gastroenterology*) for the period 1996 to 2008.

Correspondence

We contacted the following experts in the field in relation to published and ongoing studies:

- Dean Brenner, University of Michigan Medical Center, Ann Arbor, Michigan, USA;
- Arlene Forastiere, Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, Maryland, USA;

- Clive Kelty, Academic Surgical Oncology Unit, University of Sheffield, Sheffield, UK;
- Marrku Luostarinen, Department of Surgery, Päijät-Häme Central Hospital, Lahti, Finland;
- Frans Peters, University Hospital Groningen, Groningen, The Netherlands;
- Stephen Sontag, VA Hines Hospital, Hines, Illinois, USA;
- Stuart Jon Spechler, Division of Gastroenterology, VA Medical Centre, Dallas, TX, USA;
- Nicholas Shaheen, Center for Esophageal Diseases and Swallowing, University of North Carolina School of Medicine, NC, USA; and
- Jacques Bergman, Department of Gastroenterology and Hepatology Academic Medical Centre Amsterdam, Academic Medical Center, Amsterdam.

Data collection and analysis

Selection of studies

We reviewed titles and abstracts of studies identified through searches of electronic databases to determine whether they met the inclusion criteria. Two authors independently identified, read and reviewed titles and abstracts. We resolved uncertainties concerning the appropriateness of studies for inclusion in the review through consultation with a third author.

Assessment of risk of bias in included studies

The three authors independently assigned each selected study to one of four quality of randomisation categories, as guided by the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2008). The four quality of randomisation categories were:

1. Indicates adequate concealment of the allocation (for example, by telephone randomisation, or use of consecutively numbered, sealed, opaque envelopes);
2. Indicates uncertainty about whether the allocation was adequately concealed (for example, where the method of concealment is not known);
3. Indicates that the allocation was definitely not adequately concealed (for example, open random number lists or quasi-randomisation such as alternate days, odd/even date of birth, or hospital number).
4. Indicates randomisation was not used.

The authors also paid attention to the extent to which both participants and outcome assessors were blind to the allocation status of participants. This was done by rating as 'met' (low risk of bias), 'unmet' (high risk of bias), or 'unclear' (unclear risk of bias) these criteria as described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Clarke 2001).

Measures of treatment effect

We entered all trials included in the systematic review into Review Manager 5.0 (RevMan 2008). The impact of interventions for dichotomous data was expressed as odds ratios (OR) together with 95% confidence intervals (CI). For continuous data, we used the mean difference (MD), again with a 95% CI. We only attempted meta-analysis if there were sufficient trials of similar comparisons reporting the same outcomes. We assessed outcomes using a

fixed-effect model, however where significant heterogeneity was detected then we also performed a random-effects assessment.

Dealing with missing data

We have reported the number of participants included in the final analysis as a proportion of all participants in each study where necessary. Reasons for missing data, if available, are provided in the narrative summary and the extent to which the results of the review could be altered by the missing data is commented upon where appropriate. For missing continuous data, a qualitative summary is provided. The standard deviations of the outcome measures are reported for each group in each trial. If these are not given, where possible the data were derived from other statistics given in the paper, for example from the CI. If this was not possible, we performed a secondary analysis if adequate data were available, with comment on the extent that the result was affected by different imputed values.

RESULTS

Description of studies

Results of the search

We identified 2225 studies using the search strategy. We identified 157 of these as being directly relevant to the review and 20 were prospective randomised studies that had adequate randomisation and Barrett's oesophagus was defined as columnar lined oesophagus with intestinal metaplasia. Of these 20 studies, two abstracts (Luman 1995; Ortiz 1996) were excluded as they contained data that were also reported in more recent publications (Luman 1996; Parrilla 2003, respectively). Two studies (Bright 2007; Overholt 2007) were updates of previously published data (Ackroyd 2004; Overholt 2005) and therefore these were used to complement the original article since longer follow-up data were available.

Included studies

Pharmacological therapies

a. Anti-secretory proton pump inhibitor therapy versus H₂RA

Weinstein 1996 performed a study on 106 individuals who were randomised to omeprazole 40 mg twice daily for one year followed by omeprazole 40 mg one daily for a year (n = 53) or ranitidine 150 mg for two years (n = 44) (97 completed six months and 76 the whole two-year study). pH monitoring was not performed and compliance to the drug regimen was not mentioned. The data were not published in full form and so care must be exercised when interpreting these data as no external peer review process has been undertaken.

The study by Peters 1999 also compared omeprazole 40 mg twice daily to ranitidine 150 mg twice daily. Sixty-one were randomised to omeprazole (n = 31) and ranitidine (n = 30). All patients were pH monitored and study medications were collected to assess compliance to the drug regimen. Fifty-three individuals completed the study at two years: 26/33 from the omeprazole group and 27/35 of the ranitidine group. Seven individuals withdrew from the omeprazole arm and eight from the ranitidine arm.

A smaller study by Caldwell 1996, published in abstract form, randomised 28 individuals to omeprazole 20 mg one daily (n = 14) or Cimetidine 400 mg three times per day (n = 14). The participants were followed for two years and underwent three-

monthly review. All patients were pH monitored and compliance to the drug regimen was not mentioned. Eight individuals were lost to follow up and therefore twenty completed the study; ten patients in each of the treatment arms.

b. Selective COX-2 inhibitor versus placebo

The study design and outcome measures were published first (Heath 2003) followed by the results four years later (Heath 2007). Barrett's oesophagus patients with either low- or high-grade dysplasia were recruited from eight clinical centres in the USA. One hundred patients were randomised to either 200 mg celecoxib (n = 49) or placebo (n = 51) twice daily for a minimum of one year and a maximum of two years. Data were recorded to assess compliance to the drug regimen. The interval between follow-up endoscopies depended on the grade of dysplasia: every three months for high-grade dysplasia and six months for low-grade dysplasia.

Surgical therapies

Nissen fundoplication combined with anti-secretory antacid therapy versus anti-secretory antacid therapy (proton pump inhibitor and H₂RAs) alone

The study by Parrilla 2003 included individuals already described by Ortiz 1996 and more patients were recruited between 1996 and 2000. One hundred and one patients were randomised to proton pump inhibitor plus H₂RA (n = 43) and Nissen fundoplication plus proton pump inhibitor and H₂RA (n = 58). All patients were pH monitored and compliance to the drug regimen was not mentioned. Patients in the proton pump inhibitor and H₂RA group were initially treated with ranitidine 150 mg twice daily, which in 1992 was converted to omeprazole 20 mg twice daily. This may be a confounding factor as acid suppression is significantly more effective with omeprazole than ranitidine. Prior to 1997 only individuals with a segment more than 3 cm were included. It was unclear whether intestinal metaplasia was an inclusion criteria. After 1997, patients with Barrett's oesophagus < 3 cm with intestinal metaplasia were also included, thus generating a varied patient group that may further confound the results. Fifty-six individuals in the surgical group had an open short Nissen fundoplication whilst the remaining two individuals had a Collis-Nissen procedure because they had a short oesophagus. Nine out of the 56 (16%) surgical patients with recurrent reflux as measured by pH monitoring were excluded since their surgery was unsuccessful.

Endoscopic therapy

a. Nd-YAG laser and omeprazole versus omeprazole

The study by Luman 1995 was published in abstract form and then published in full a year later (Luman 1996). Eight individuals with histologically proven Barrett's oesophagus containing intestinal metaplasia were recruited in a University Hospital setting in Scotland, UK. pH monitoring was not performed and compliance to the drug regimen was not mentioned. The data used were derived from the full publication. Patients were randomised to receive either omeprazole 40 mg one daily (n = 4) or omeprazole 40 mg one daily with Nd-YAG laser therapy at 25 W power in one second pulses up to a maximum dose of 1000 J for a maximum of three treatments (n = 4). Histological and endoscopic assessments were undertaken at four to six-weekly intervals for six months. No individuals were lost to follow up. This study is so small that it is difficult to interpret the findings of this work as there is a significant risk that these data

are so limited that they may not adequately represent the efficacy of the intervention tested.

b. Argon plasma coagulation (APC) versus surveillance

[Bright 2007](#) presents the data for the five-year follow-up data of the individuals presented in [Ackroyd 2004](#) and was therefore used for the analysis. The 40 patients who entered the study were randomised to receive either argon plasma coagulation at 60 W (n = 20) for a maximum of six sessions at four-weekly intervals or standard surveillance consisting of a repeat upper GI endoscopy at one year (n = 20). All of the study patients were asymptomatic and six had undergone pH monitoring which showed a median acid exposure of 0.4% of the 24-hour study period. One individual was lost to follow up at one year in the ablation group.

c. Argon plasma coagulation (APC) versus multipolar electrocoagulation (MPEC)

[Dulai 2005](#) randomised 52 individuals to either argon plasma coagulation at 60 W continuous pulse using a 10F probe (n = 26) or multipolar electrocautery continuous pulse using a 10F probe and generator (n = 26). Four individuals were lost to follow up, two from each group.

[Sharma 2006](#) randomised 35 patients according to their Barrett's oesophagus length (stratified randomisation) to receive either argon plasma coagulation (60 W, n = 19) or multipolar electrocautery (20 W, n = 16). Patients were all on ranitidine (20 mg twice daily) for the purpose of the study and underwent 24-hour pH monitoring at least seven days after starting the course of proton pump inhibitor.

d. Argon plasma coagulation (APC) with proton pump inhibitor (PPI) versus photodynamic therapy (PDT) with PPI

[Hage 2004](#) randomised 40 patients with Barrett's oesophagus with intestinal metaplasia to one of three regimens:

- 60 mg/kg aminolevulinic acid (ALA) followed by photodynamic therapy 100 J/cm² with red light at four hours post 5-ALA administration (PDT100)(n = 13)
- 60 mg/kg ALA followed by photodynamic therapy 20 J/cm² and 100 J/cm² with red light at one and four hours post 5-ALA administration (PDT20+100)(n = 13)

The energy output for both photodynamic therapy regimes was 100 mW/cm²

- Argon plasma coagulation at 65 W, in two sessions ablating two-thirds of the Barrett's oesophagus at the first application and the remaining Barrett's oesophagus at the second application(n = 14).

One person died during the study from a presumed cardiac arrhythmia which was thought to be treatment-related since atrial fibrillation (AF) has been recognised as a possible complication of ALA administration ([Overholt 1997](#)). Significant numbers of patients were lost to follow up as the time since treatment increased. By two years no individuals in the PDT100 group were being followed up. Only two out of 13 of the PDT20+100 group were followed up and none of the argon plasma coagulation group were followed up.

[Kelty 2004](#) recruited 72 patients from a University Teaching Hospital in the United Kingdom. Sixty-eight patients with Barrett's oesophagus with intestinal metaplasia were included in the study. Individuals with low-grade dysplasia or high-grade dysplasia were excluded. Patients were randomised into two groups:

- 30 mg/kg ALA PDT followed by PDT 85 J/cm² with red light at four to six hours post ALA administration. Total energy output = 68 mW/cm²(n = 34).
- Argon plasma coagulation at 65 W, ablating half of the Barrett's oesophagus segment at the first application and the remaining Barrett's oesophagus at subsequent treatments until complete ablation was achieved. A maximum of five treatments were undertaken(n = 34).

[Ragunath 2005](#) recruited 32 patients with dysplastic Barrett's oesophagus. No formal statistical comparison of the homogeneity of the two groups was shown. Individuals were randomised to receive treatment using one of the following two protocols:

- Photodynamic therapy (n = 13): 2 mg/kg porfimer sodium was administered intravenously and after 48 hours photodynamic therapy was performed using 630 nm red laser light, with a power output of 840 mW delivering 200 J/cm, through an endoscopically inserted photodynamic therapy balloon at a single, one-off treatment sitting.
- Argon plasma coagulation (n = 13) was undertaken at a power setting of 65 W with an argon gas flow of 1.8 l/min. Treatments were applied from the proximal gastric folds upwards with up to six treatment sessions. Follow up occurred at four and twelve months and quadrant biopsies were taken at 1 cm intervals in the whole of the lower third of the oesophagus, including the Barrett's oesophagus segment at each follow-up time.

At 12 months four individuals had been lost from the argon plasma coagulation group, whereas no one from the photodynamic therapy group was lost to follow up.

e. Photodynamic therapy using 5-ALA or porfimer sodium with proton pump inhibitor (PPI) versus PPI alone

[Ackroyd 2000](#) randomised 36 individuals with Barrett's oesophagus and low-grade dysplasia to receive either 5-ALA photodynamic therapy at 30 mg/kg using a 514 nm green laser (n = 16) or placebo (n = 16). Both groups received omeprazole. pH monitoring was not performed. Those who received photodynamic therapy were treated at a power density of 120 mW/cm², for 500 seconds per 3 cm up to a maximum dosing time of 1000 seconds, i.e. treating a maximum of 6 cm at each visit.

[Overholt 2005](#) randomised 208 patients in a 2:1 ratio to receive photodynamic therapy with porfimer sodium (2 mg/kg) and omeprazole 40 mg/day (n = 138) or omeprazole alone (40 mg / day) (n = 70). pH monitoring was not performed and compliance to the drug regimen was not mentioned. One hundred and thirty-two patients received at least one course of photodynamic therapy. Those who received photodynamic therapy were treated with 630 nm red laser light given at a 130 J/cm. Additionally, focal treatment of nodular areas was undertaken using a short (2.5 cm) bare fibre. Up to 7 cm of Barrett's oesophagus mucosa was treated at the first endoscopy. Patients underwent a further endoscopy at four to five days and any untreated Barrett's oesophagus mucosa was exposed to a further 50 J/cm using a 2.5 cm bare fibre. Photodynamic

therapy was undertaken up to a maximum of three times. At two years 78/132 (59%) individuals from the photodynamic therapy group remained in the study whilst 26/69 (38%) of individuals treated with omeprazole remained in the study. [Overholt 2007](#) presents the five-year follow up of these patients.

f. Photodynamic therapy using 5-ALA versus porfimer sodium

[Mackenzie 2008](#) randomised 32 patients, stratified per length of segment, to 5-ALA (n = 16) or porfimer sodium (n = 16). The authors stated that they used the standard protocol (no more details) and 60 mg/kg 5-ALA, activated by 1178 J/cm of red laser light. Patients were then followed up with quadrant biopsies every 2 cm at six weeks, four months and one year post-therapy.

g. Radiofrequency ablation (RFA) versus sham

[Shaheen 2008](#) randomised 127 patients in a 2:1 to radiofrequency ablation or sham. Patients were also stratified according to their

dysplasia status (low- or high-grade dysplasia) and the length of their Barrett's oesophagus segment. Patients underwent a maximum of four sessions of radiofrequency ablation using the HALO system. Patients in the ablation group were treated up to four times at baseline, two, four and nine months. Follow up biopsies were collected at six and 12 months for low-grade dysplasia and at three, six, nine and 12 months for high-grade dysplasia.

Risk of bias in included studies

Three authors undertook an assessment of the quality of each eligible study independently and any disagreement was resolved independently by the senior author. We assessed methods of randomisation, concealment, blinding and follow up. A summary of the risk of bias is presented in [Figure 1](#) and [Figure 2](#).

Figure 1. Methodological quality graph: review authors' judgements about each methodological quality item presented as percentages across all included studies.

Figure 2. Methodological quality summary: review authors' judgements about each methodological quality item for each included study.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding (performance bias and detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Ackroyd 2000	?	+	+	?	-	+
Bright 2007	?	+	-	+	-	+
Caldwell 1996	?	?	?	?	?	-
Dulai 2005	+	+	+	+	+	+
Hage 2004	?	?	-	?	?	?
Heath 2007	?	?	?	+	+	+
Kelty 2004	+	?	?	?	?	?
Luman 1996	?	?	?	+	+	-
Mackenzie 2008	?	?	?	?	?	-
Overholt 2005	?	?	?	?	?	?
Parrilla 2003	+	+	?	?	+	+
Peters 1999	+	?	+	?	+	?
Ragunath 2005	+	?	?	?	+	+
Shaheen 2008	+	?	+	+	+	+
Sharma 2006	?	+	?	?	+	+
Weinstein 1996	?	?	?	?	?	?

Allocation

Twelve trials stated the method of randomisation (Peters 1999; Ackroyd 2000; Parrilla 2003; Hage 2004; Kelty 2004; Dulai 2005; Overholt 2005; Ragunath 2005; Sharma 2006; Heath 2007; Bright 2007; Shaheen 2008) whilst four did not (Caldwell 1996; Luman 1996; Mackenzie 2008; Weinstein 1996).

Only Dulai 2005 and Heath 2007 indicated that the treatment performed was concealed from the investigators and the patients.

The other studies included in this review did not state whether any concealment was undertaken.

Blinding

Ten studies did not give any indication whether blinding was used with respect to the treatments undertaken (Luman 1996; Caldwell 1996; Weinstein 1996; Parrilla 2003; Hage 2004; Kelty 2004; Dulai 2005; Ragunath 2005; Sharma 2006; Bright 2007; Mackenzie 2008; Shaheen 2008). Two studies were double blinded (Peters 1999; Heath 2007). Peters 1999 used the double

dummy technique. [Ackroyd 2000](#) and [Overholt 2005](#) blinded the interpreting pathologist to the intervention undertaken.

Incomplete outcome data

Statistical power

Power calculations were performed for the studies undertaken by [Ackroyd 2000](#), [Ackroyd 2004](#), [Kelty 2004](#), [Dulai 2005](#), [Overholt 2005](#), [Ragunath 2005](#), [Heath 2007](#) and [Shaheen 2008](#).

Follow up

1. Pharmacological therapies

a. Anti-secretory proton pump inhibitor therapy versus H₂RA

[Weinstein 1996](#): No information was provided as to why some individuals left the study and which statistical method was used to take this into account.

[Peters 1999](#): During data interpretation a per protocol analysis was undertaken in this study but it is unclear whether data were actually collected from those who left the study. In addition, the actual method used to handle the missing data within the intention-to-treat analysis is not described.

[Caldwell 1996](#): No information was provided as to why some individuals left the study and which statistical method was used to take this into account.

b. Selective COX-2 inhibitor versus placebo

[Heath 2007](#): The results were presented on an intention-to-treat principle therefore all randomised patients were included in the statistical analysis.

2. Surgical therapies

Nissen fundoplication Short Collis gastroplasty combined with anti-secretory antacid therapy versus anti-secretory antacid therapy (proton pump inhibitor and H₂RAs) alone.

[Ortiz 1996](#); [Parrilla 2003](#): The numbers of individuals leaving the study and the reasons for individuals leaving the study were not given, furthermore how the individuals leaving the study were handled statistically was not described.

3. Endoscopic therapies

a. Nd-YAG laser and omeprazole versus omeprazole

[Luman 1995](#); [Luman 1996](#): No individuals were lost to follow up.

b. Argon plasma coagulation (APC) versus surveillance

[Ackroyd 2004](#): How the data from individuals lost to follow up were handled is not stated.

c. Argon plasma coagulation (APC) versus multipolar electrocoagulation (MPEC)

[Dulai 2005](#): Individuals who were lost to follow up were handled using an intention-to-treat approach and those who left the study continued to be followed up. However the actual method used to handle the missing data within the intention-to-treat analysis is not described

[Sharma 2006](#): No individuals were lost to follow up.

d. Argon plasma coagulation (APC) with proton pump inhibitor (PPI) versus photodynamic therapy (PDT) with PPI

[Hage 2004](#): Significant numbers of patients were lost in the later period of follow up (34% and 90% lost at 18 months and 24 months respectively). No information was provided on the statistical method used to take into account individuals who dropped out of the study, nor was the reason for individuals leaving the study given.

[Kelty 2004](#): No individuals were lost to follow up.

[Ragunath 2005](#): No information was provided on the statistical method used to take into account individuals who dropped out of the study nor was the reason for those individuals leaving the study given.

e. Photodynamic therapy using 5-ALA or porfimer sodium with proton pump inhibitor (PPI) versus PPI alone

[Ackroyd 2000](#): No individuals were lost to follow up.

[Overholt 2005](#); [Overholt 2007](#): An intention-to-treat analysis was undertaken and for those patients lost to follow up survival data was censored within the Kaplan Meier analysis; however the actual method used to handle the missing data within the intention-to-treat analysis is not described.

f. Photodynamic therapy using 5-ALA versus porfimer sodium

[Mackenzie 2008](#): No individuals were lost to follow up

g. Radiofrequency ablation (RFA) versus sham

[Shaheen 2008](#): Individuals who were lost to follow up were handled using an intention-to-treat approach and those who left the study continued to be followed up. However the actual method used to handle the missing data within the intention-to-treat analysis is not described.

Effects of interventions

See: [Summary of findings for the main comparison Summary of outcome measures per treatment category](#)

Sixteen RCTs were included in the review (see '[Characteristics of included studies](#)'). The studies compared:

1. Pharmacological therapies
 - a. Anti-secretory proton pump inhibitor therapy versus H₂RA ([Caldwell 1996](#); [Weinstein 1996](#); [Peters 1999](#))
 - b. Selective COX-2 inhibitor versus placebo ([Heath 2007](#))
2. Short Collis gastroplasty combined with anti-secretory antacid therapy versus anti-secretory antacid therapy (proton pump inhibitor and H₂RAs) ([Ortiz 1996](#); [Parrilla 2003](#))

3. Endoscopic therapies

- a. Nd-YAG laser and omeprazole versus omeprazole (Luman 1995; Luman 1996)
- b. Argon plasma coagulation versus surveillance (Ackroyd 2004; Bright 2007)
- c. Argon plasma coagulation versus multipolar electrocoagulation (MPEC) (Dulai 2005; Sharma 2006)
- d. Argon plasma coagulation with proton pump inhibitor (PPI) versus photodynamic therapy (PDT) with PPI (Hage 2004; Kelty 2004; Ragunath 2005)
- e. Photodynamic therapy using 5-ALA (Ackroyd 2000) or porfimer sodium (Overholt 2005; Overholt 2007) with proton pump inhibitor (PPI) versus PPI alone
- f. Photodynamic therapy using 5-ALA versus porfimer sodium (Mackenzie 2008)
- g. Radiofrequency ablation (RFA) versus sham (Shaheen 2008)

1. Pharmacological therapies

a. Anti-secretory proton pump inhibitor therapy versus H₂RA

There were three studies that compared two years treatment with proton pump inhibitor versus two years with H₂ antagonist (Caldwell 1996; Weinstein 1996; Peters 1999). These studies assessed the regression of Barrett's oesophagus (dysplasia status was not given) in terms of change in length, change in area and the development of squamous islands.

Primary outcome

- Complete eradication of Barrett's oesophagus at 12 months: none of the studies reported on this outcome.
- Complete eradication of dysplasia at 12 months: none of the studies reported on this outcome.
- Reduction in the number of patients progressing to cancer at five years or latest time point: none of the studies reported on this outcome.

Secondary outcome

- Reduction of length of Barrett's oesophagus segment at 12 months: no overall trend was detected (mean difference (MD) (fixed-effect model) -0.42 cm; 95% CI -1.65 cm to 0.82 cm; Z = 0.31, P = 0.76). Similar results were found using the random-effects model. However, significant heterogeneity was detected (Chi² statistic = 5.35, I² statistic = 62.6%) indicating that care should be exercised when interpreting these data. If a subgroup analysis is undertaken, including the two studies that used omeprazole at a higher dose only (Weinstein 1996; Peters 1999) again no trend is detected (MD (fixed-effect model) -0.81; 95% CI -2.13 to 0.50; Z = 1.21, P = 0.23) and heterogeneity still persists (Chi² statistic = 2.52, P = 0.11, I² statistic = 0.604; Analysis 1.1).
- Reduction of area of Barrett's oesophagus segment at 12 months: a reduction in the overall area of Barrett's oesophagus was detected with omeprazole (MD 4.06; 95% CI 0.08 to 8.04) with no heterogeneity detected between studies (Analysis 1.2).
- Reduction in the number of patients progressing from intestinal metaplasia to dysplasia: none of the studies reported on this outcome.
- Presence of buried sub-squamous Barrett's glands: none of the studies reported on this outcome.

- Adverse reactions.
 - * Mortality: no data available.
 - * Serious adverse drug reaction where serious represents a reaction requiring medical intervention: no data available.
 - * Any complications: no data available.
- Control of acid reflux (only for acid suppression therapies): no data available

b. Selective COX-2 inhibitor versus placebo

One study compared 48 weeks of treatment with celecoxib versus 48 weeks with placebo (Heath 2007). This study assessed the safety and efficacy of celecoxib for regression of dysplasia in Barrett's oesophagus. The data in this publication were not presented in a format allowing easy extraction of patient numbers. The statistical results given are those reported by the authors, not using the data from the Review Manager software (RevMan 2008) unless stated otherwise.

Primary outcome

- Complete eradication of Barrett's oesophagus at 12 months: no data available
- Complete eradication of dysplasia at 12 months: no statistical difference between the celecoxib and placebo groups.
- Reduction in the number of patients progressing to cancer at five years or latest time point: no statistical difference (RevMan 2008) in the numbers of patients progressing to adenocarcinoma in the celecoxib (3/49) and placebo (3/51) groups was reported at one year. All six patients who progressed to adenocarcinoma had a baseline diagnosis of high-grade dysplasia.

Secondary outcome

- Reduction of
 - * length of Barrett's oesophagus segment at 12 months: no data available;
 - * area of Barrett's oesophagus segment at 12 months: the authors did not report any statistical difference in area between baseline and one year when comparing the two groups.
- Reduction in the number of patients progressing from intestinal metaplasia to dysplasia: the authors did not report any statistical difference in progression to dysplasia between baseline and one year when comparing the two groups.
- Presence of buried sub-squamous Barrett's glands: no data available.
- Adverse reactions.
 - * Mortality: two patient deaths were reported. They were not related to the trial.
 - * Serious adverse drug reaction where serious represents a reaction requiring medical intervention: no statistical difference in the numbers of patients presenting with trial related serious drug reactions between the two groups (RevMan 2008).
 - * Any complications: no statistical difference in the numbers of patients presenting with bleeding between the two groups (RevMan 2008).
- Control of acid reflux (only for acid suppression therapies): no data available.

2. Surgical therapies: Nissen Fundoplication versus PPI

Two studies compared H₂ antagonist which was then converted to proton pump inhibitor versus Nissen fundoplication (Ortiz 1996; Parrilla 2003). These two studies compared the results of medical treatment and anti-reflux surgery in patients with Barrett's oesophagus by clinical, endoscopic, histological and functional assessment. The report of Parrilla et al includes all those individuals described by Ortiz 1996 and includes data from an additional 42 individuals. The latest data reported by Parrilla et al are therefore described.

Primary outcome

- Complete eradication of Barrett's oesophagus at 12 months: no data available at 12 months but no complete eradication was reported at five years for either treatment.
- Complete eradication of dysplasia at 12 months: no data available at 12 months but no statistical difference was seen in the eradication of dysplasia at five years: 3/43 patients on proton pump inhibitor and 5/58 patients who underwent surgery (5/49 if only patients with successful surgery were considered).
- Reduction in the number of patients progressing to cancer at five years or latest time point: there was no statistical difference in the numbers of patients progressing to cancer between the two groups: 1 in 129 patient-years of follow up for patients on proton pump inhibitor compared to 1 in 203 patient-years of follow up for patients who underwent surgery.

Secondary outcome

- Reduction of:
 - * length of Barrett's oesophagus segment at 12 months: no data at 12 months. The authors did not report any statistical differences in the length of the Barrett's oesophagus segment between the two groups at five years.
 - * area of Barrett's oesophagus segment at 12 months: no data available.
- Reduction in the number of patients progressing from intestinal metaplasia to dysplasia: no data at 12 months. There was a reduction in the number of patients developing *de novo* dysplasia in the surgery group compared to the proton pump inhibitor group (3/58 versus 8/43) (odds ratio (OR) 0.22; 95% CI 0.05 to 0.88; Z = 2.14, P = 0.03).
- Presence of buried sub-squamous Barrett's glands: no data available.
- Adverse reactions.
 - * Mortality: no death was reported in any group.
 - * Serious adverse drug reaction where serious represents a reaction requiring medical intervention: no adverse reactions to proton pump inhibitor were reported.
 - * Any complications: one patient in the surgery group underwent splenectomy.
- Control of acid reflux (only for acid suppression therapies): the authors did not report any statistical differences in the control of acid reflux as measured by 24-hour pH monitoring between the two groups at five years.

3. Endoscopic therapy

a. Nd-YAG laser and omeprazole versus omeprazole

Luman 1996 assessed whether Nd-YAG photocoagulation with proton pump inhibitor therapy was more effective than proton pump inhibitor therapy alone in the ablation of non-dysplastic Barrett's oesophagus.

Primary outcome

- Complete eradication of Barrett's oesophagus at 12 months: no data available.
- Complete eradication of dysplasia at 12 months: no data available.
- Reduction in the number of patients progressing to cancer at five years or latest time point: no data available.

Secondary outcome

- Reduction of:
 - * length of Barrett's oesophagus segment at 12 months: this study did not identify any regression in either treatment group.
 - * area of Barrett's oesophagus segment at 12 months: no data available.
- Reduction in the number of patients progressing from intestinal metaplasia to dysplasia: no data available.
- Presence of buried sub-squamous Barrett's glands: buried glands were not found in any patients.
- Adverse reactions.
 - * Mortality: No data available.
 - * Serious adverse drug reaction where serious represents a reaction requiring medical intervention: no data available.
 - * Any complications: no data available.
- Control of acid reflux (only for acid suppression therapies): no data available.

b. Argon plasma coagulation (APC) versus surveillance

Two prospective randomised controlled trials compared argon plasma coagulation ablation with endoscopic surveillance of patients with Barrett's oesophagus after anti-reflux surgery (Ackroyd 2004; data updated in Bright 2007). These studies aimed to evaluate the safety and efficacy of argon plasma coagulation ablation of Barrett's oesophagus in patients who had previously undergone surgical fundoplication.

Primary outcome

- Complete eradication of Barrett's oesophagus at 12 months: complete reversal of the Barrett's oesophagus segment was seen in 11/19 patients treated with argon plasma coagulation compared to 3/20 who had surveillance alone (OR 91.46; 95% CI 4.77 to 1754.50; Z = 3.00, P = 0.003). The data need to be interpreted with caution because of the wide confidence interval.
- Complete eradication of dysplasia at 12 months: only two patients had dysplasia at initial endoscopy.
- Reduction in the number of patients progressing to cancer at five years or latest time point: none of the patients progressed to adenocarcinoma.

Secondary outcome

- Reduction of:
 - length of Barrett's oesophagus segment at 12 months: the number of patients with reduction in their segment length was not reported; however the segment length was reduced from a median of 4.0 (range 3 to 8) to 0 (0 to 3) in the argon plasma coagulation group and from 4.0 (2 to 19) to 2.0 (0 to 13) in the surveillance group. The authors reported a P value of 0.0001 using a Mann-Whitney test.
 - area of Barrett's oesophagus segment at 12 months: no data available.
- Reduction in the number of patients progressing from intestinal metaplasia to dysplasia: at five years, 0/19 patients from the argon plasma coagulation group and 2/20 from the surveillance group progressed to dysplasia (not statistically significant).
- Presence of buried sub-squamous Barrett's glands: at one year there was no statistically significant difference between the two groups (OR 3.51; 95% CI 0.13 to 91.87; Z = 0.75, P = 0.45).
- Adverse reactions.
 - Mortality: no mortality reported.
 - Serious adverse drug reaction where serious represents a reaction requiring medical intervention: no data available.
 - Any complications: 2/19 patients in the argon plasma coagulation arm developed strictures between two and five years follow up.
- Control of acid reflux (only for acid suppression therapies): not applicable.

c. Argon plasma coagulation (APC) with PPI versus multipolar electrocoagulation (MPEC) with PPI

Dulai 2005 compared the efficacy of argon plasma coagulation and multipolar electrocautery in the ablation of Barrett's oesophagus or Barrett's oesophagus with low-grade dysplasia and assessment of whether argon plasma coagulation required fewer treatments than multipolar electrocautery. Sharma 2006 compared argon plasma coagulation and multipolar electrocautery in reversing Barrett's oesophagus and assessed factors influencing successful ablation.

Primary outcome

- Complete eradication of Barrett's oesophagus at 12 months: no data available at 12 months. Dulai (Dulai 2005) reported complete eradication of Barrett's oesophagus in 88% and 81% of patients treated with argon plasma coagulation and multipolar electrocautery respectively but the length of follow up was not clearly indicated. However, Sharma et al reported lower rates of 63% and 75% for argon plasma coagulation and multipolar electrocautery respectively after two years.
- Complete eradication of dysplasia at 12 months: no data available.
- Reduction in the number of patients progressing to cancer at five years or latest time point: no data available.

Secondary outcome

- Reduction of:
 - length of Barrett's oesophagus segment at 12 months: no data available;
 - area of Barrett's oesophagus segment at 12 months: no data available.

- Reduction in the number of patients progressing from intestinal metaplasia to dysplasia: no data available.
- Presence of buried sub-squamous Barrett's glands: only Dulai 2005 reported on this outcome and no patients were reported to have buried glands *per se*.
- Adverse reactions.
- Mortality: no deaths related to the treatments were reported in these studies.
 - Serious adverse drug reaction where serious represents a reaction requiring medical intervention.
 - Any complications consisting of bleeding, infection oesophageal stricture: no statistical differences between the argon plasma coagulation and multipolar electrocautery group were identified in a number of complications (pain, fever and strictures).
- Control of acid reflux (only for acid suppression therapies): not applicable.

d. Argon plasma coagulation (APC) with proton pump inhibitor (PPI) versus photodynamic therapy (PDT)

Comparison of 5-Aminolevulinic acid photodynamic therapy versus argon plasma coagulation (APC) with proton pump inhibitor in the treatment of Barrett's oesophagus (Hage 2004; Kelty 2004).

Porfimer sodium photodynamic therapy versus argon plasma coagulation (Ragunath 2005). This study aimed to compare argon plasma coagulation and porfimer sodium photodynamic therapy in their efficacy and cost-effectiveness in ablating dysplastic Barrett's oesophagus.

When reviewing the results of these studies it should be noted that Hage, Kelty and Ragunath each differed markedly in their drug dosing and light delivery regimes.

Primary outcome

- Complete eradication of Barrett's oesophagus at 12 months: complete eradication of Barrett's oesophagus at 12 months was assessed by all three studies. There was no statistical differences in the eradication of Barrett's oesophagus between argon plasma coagulation and photodynamic therapy (OR 0.31; 95% CI 0.00 to 32.6; Z = 2.61, P = 0.62). The data however are heterogeneous (Chi² statistic = 11.75, P = 0.0006, I² statistic = 91.5%). These three studies comparing photodynamic therapy with argon plasma coagulation had different intended outcome measures. When this outcome is considered Hage showed argon plasma coagulation to be more effective for the complete ablation of Barrett's oesophagus (OR 3.00; 95% CI 0.54 to 16.64), whilst in contrast Ragunath was not able to demonstrate any difference between argon plasma coagulation and photodynamic therapy and furthermore no individual within Ragunath's study had complete eradication of Barrett's oesophagus. In contrast Kelty demonstrated more individuals having complete eradication of Barrett's oesophagus at 12 months after treatment with photodynamic therapy (OR 0.03; 95% CI 0.00 to 0.25). This significant heterogeneity may have arisen from the markedly different photodynamic therapy regimes employed.
- Complete eradication of dysplasia at 12 months: this outcome was only reported by Ragunath 2005. There was no statistical difference in the eradication of dysplasia between argon plasma

coagulation treated (6/9) and photodynamic therapy treated (10/13) patients.

- Reduction in the number of patients progressing to cancer at five years or latest time point: none of the trials reported data on progression to cancer at the latest time point.

Secondary outcome

- Reduction of:
 - * length of Barrett's oesophagus segment at 12 months: reduction in length of Barrett's oesophagus at 12 months was only reported by Ragunath and no statistically significant difference was detected between the two treatment groups (MD (fixed-effect model) -0.91 cm; 95% CI -2.10 cm to 0.28 cm; $Z = 1.51$, $P = 0.13$);
 - * area of Barrett's oesophagus segment at 12 months: no data available.
- Reduction in the number of patients progressing from intestinal metaplasia to dysplasia: no data available.
- Presence of buried sub-squamous Barrett's glands: reported by two studies (Hage 2004; Kelty 2004) and no overall trend is detected using a fixed-effect model ($Z = 0.79$, $P = 0.43$). Similar results were identified using the random-effects model. Kelty and Hage demonstrated that buried glands occur. However, Kelty was not able to demonstrate a difference in their frequency between individuals treated with photodynamic therapy versus those treated with argon plasma coagulation; whilst Hage suggested that argon plasma coagulation treatment might result in more buried glands. Overall the data are again heterogeneous and no conclusion can be reached.
- Adverse reactions
 - * Mortality: no difference in mortality was detected between the two treatments ($Z = 0.32$, $P = 0.75$).
 - * Serious adverse drug reaction where serious represents a reaction requiring medical intervention: unsurprisingly only individuals receiving photodynamic therapy experienced drug reaction (OR 31.48; 95% CI 4.04 to 245.12; $Z = 3.29$, $P = 0.0001$). Disparate results were obtained for side effect symptoms.
 - * Any complications: significant heterogeneity was demonstrated in the reporting of both "pain in general" and odynophagia perhaps due to the subjective nature of the symptoms and the lack of use of a validated tool in these studies to assess pain. Fever tended to be more frequent in individuals receiving photodynamic therapy, although the OR was 1.88 (95% CI 0.47 to 7.44) with $Z = 0.90$ and $P = 0.37$. Nausea and vomiting were much more frequently identified in individuals receiving photodynamic therapy; a previously recognised complication of the photosensitising agents (OR 19.64; 95% CI 2.51 to 153.78; $Z = 2.92$, $P = 0.005$). Finally, there was no significant difference in the frequency of strictures in the two groups nor photosensitivity although data were solely available on this final outcome from Ragunath's work which included only 13 patients in each treatment group.
- Control of acid reflux (only for acid suppression therapies): no data available.

e. Photodynamic therapy using 5-ALA or porfimer sodium with proton pump inhibitor (PPI) versus PPI alone

Ackroyd 2000 conducted a prospective, double blind, randomised, placebo controlled trial of photodynamic therapy for dysplastic

Barrett's oesophagus and Overholt 2005 conducted an international, partially blinded, randomised phase III trial of photodynamic therapy with porfimer sodium for ablation of high-grade dysplasia in Barrett's oesophagus. These studies aimed to assess the potential use of photodynamic therapy in the ablation of Barrett's oesophagus (Ackroyd 2000) and to examine the impact of porfimer sodium based photodynamic therapy for ablating high-grade dysplasia and reducing the incidence of oesophageal adenocarcinoma (Overholt 2005).

Primary outcome

- Complete eradication of Barrett's oesophagus at 12 months: Overholt 2005 reported a statistically significant trend for a complete eradication of the Barrett's segment over the course of the study (two years) (OR 14.18; 95% CI 5.38 to 37.37; $Z = 5.36$, $P < 0.00001$).
- Complete eradication of dysplasia at 12 months: no data available at 12 months but both studies reported data at two years and more eradication occurred following photodynamic therapy than proton pump inhibitor (OR 9.13; 95% CI 4.42 to 18.86; $Z = 5.98$, $P < 0.0001$).
- Reduction in the number of patients progressing to cancer at five years or latest time point: data from Overholt 2005 suggest a statistically significant trend that photodynamic therapy reduced the likelihood of progression to cancer (OR 0.38; 95% CI 0.18 to 0.77; $Z = 2.68$, $P = 0.007$).

Secondary outcome

- Reduction of length and area of Barrett's oesophagus segment at 12 months: data were available from Ackroyd 2000 on reduction in length and area of Barrett's oesophagus at 12 months, which indicates a significant trend to reduction in length (cm) (MD (fixed-effect model) 1.0 cm; 95% CI 0.41 cm to 1.59 cm; $Z = 3.34$, $P = 0.0008$) and % area (MD (fixed-effect) 30.00; 95% CI 20.53 to 39.47; $Z = 6.21$, $P = 0.00001$).
- Reduction in number of patients progressing from intestinal metaplasia to dysplasia: only Ackroyd 2000 reported on the number of patients progressing from intestinal metaplasia to dysplasia and these data suggest a statistically significant trend for the reduction in progression to dysplasia after photodynamic therapy when compared to omeprazole treatment alone (OR 0.01; 95% CI 0.00 to 0.27; $Z = 2.82$, $P = 0.005$).
- Presence of buried sub-squamous Barrett's glands: no data available.
- Adverse reactions.
 - * Mortality: both studies reported data on mortality and no differences were seen between the patient groups ($Z = 0.01$, $P = 0.99$).
 - * Serious adverse drug reaction where serious represents a reaction requiring medical intervention: no data available.
 - * Any complications: unsurprisingly, both studies reported on the occurrence of photosensitivity in the photodynamic therapy group (OR 372.83; 95% CI 29.17 to 4765.01; $Z = 7.11$, $P < 0.0001$). Higher stricture rates (OR 77.98; 95% CI 4.73 to 1286.52; $Z = 3.05$, $P = 0.002$) and fever (OR 36.37; 95% CI 2.19 to 605.21; $Z = 2.5$, $P = 0.01$) were reported by Overholt 2005 (Ackroyd 2000 did not report on these outcomes).
- Control of acid reflux (only for acid suppression therapies): data not available.

Treatment for Barrett's oesophagus (Review)

f. Photodynamic therapy using 5-ALA versus porfimer sodium

Mackenzie 2008 studied photodynamic therapy for high-grade dysplasia in Barrett's oesophagus where patients were stratified per length of segment prior to randomisation to 5-ALA ($n = 16$) or porfimer sodium ($n = 16$). The study aimed at assessing the safety and efficacy of 5-ALA versus porfimer sodium photodynamic therapy. All patients had a six-month follow up and half had 12-month follow up.

Primary outcome

- Complete eradication of Barrett's oesophagus at 12 months: data not available.
- Complete eradication of dysplasia at 12 months: no data available at 12 months. The authors reported on the complete eradication of high-grade dysplasia in 14/14 patients treated with 5-ALA and 9/14 with porfimer sodium. This did not reach statistical significance.
- Reduction in the number of patients progressing to cancer at five years or latest time point: data not available.

Secondary outcome

- Reduction of
 - * length of Barrett's oesophagus segment at 12 months: data not available;
 - * area of Barrett's oesophagus segment at 12 months: data not available.
- Reduction in the number of patients progressing from intestinal metaplasia to dysplasia: data not available.
- Presence of buried sub-squamous Barrett's glands: data not available.
- Adverse reactions
 - * Mortality: data not available.
 - * Serious adverse drug reaction where serious represents a reaction requiring medical intervention: none were reported.
 - * Any complications: more strictures were seen in the porfimer sodium group (6/16) than in the 5-ALA group (1/16). This did not reach statistical significance.
- Control of acid reflux (only for acid suppression therapies): data not available.

g. Radiofrequency ablation versus sham

Shaheen 2008 compared radiofrequency ablation with sham in a randomised 2:1 controlled trial. This study aimed to compare the efficacy of radiofrequency ablation for dysplastic Barrett's oesophagus (low- or high-grade dysplasia) with a sham intervention. For all patients this was followed by an extensive surveillance protocol and high dose proton pump inhibitor. All data were presented as an intention-to-treat analysis.

Primary outcome

- Complete eradication of Barrett's oesophagus at 12 months: radiofrequency ablation induced a reversal of Barrett's oesophagus in 74% of patients ($n = 65/84$) compared with 0% of patients in the sham group (0/43) (OR 143.64; 95% CI 18.53 to 1113.87; $Z = 4.75$, $P < 0.00001$).
- Complete eradication of dysplasia at 12 months: dysplasia was successfully eradicated in 86% of patients treated with radiofrequency ablation (72/84) and 21% of sham treated

patients (9/43) (OR 22.67; 95% CI 8.72 to 58.94; $Z = 6.4$, $P < 0.00001$).

- Reduction in the number of patients progressing to cancer at five years or latest time point: during the year of follow up, 1/84 of the radiofrequency ablation treated patients and 4/43 of the sham treated patients progressed from high-grade dysplasia to adenocarcinoma, but this did not reach statistical significance ($P = 0.06$).

Secondary outcome

- Reduction of:
 - * length of Barrett's oesophagus segment at 12 months: data not available;
 - * area of Barrett's oesophagus segment at 12 months: data not available.
- Reduction in the number of patients progressing from intestinal metaplasia to dysplasia: no data available for this outcome measure but a reduction of progression to higher grades of dysplasia was reported with the radiofrequency ablation treatment (OR 0.19; 95% CI 0.05 to 0.78; $Z = 2.31$, $P = 0.02$).
- Presence of buried sub-squamous Barrett's glands: data could not be extracted.
- Adverse reactions
 - * Mortality: no deaths were reported.
 - * Serious adverse drug reaction where serious represents a reaction requiring medical intervention: none were reported.
 - * Any complications: there was one episode of upper gastrointestinal haemorrhage in a patient receiving anti-platelets therapy for heart disease. Two patients were admitted for overnight observation; one eight days after treatment for chest pain and one on the day of treatment for chest pain and nausea. The rate of complication did not reach statistical significance when compared to sham. A low rate of stricture rates (5/84 treated versus 0/43 sham) resolved after a mean of 2.6 dilatation sessions, chest pain and gastrointestinal bleed were reported and none were statistically higher in radiofrequency ablation compared to sham.
- Control of acid reflux (only for acid suppression therapies): data not available.

DISCUSSION

Despite the number of techniques available for the treatment of Barrett's oesophagus only 15 randomised controlled trials (RCTs) have been undertaken in the last 13 years. These trials compared various combinations of techniques and various doses (drugs and laser energy) of treatments and thus only limited comparisons were possible. Part of the reason for the lack of RCTs is likely to be the rapid development of new endoscopic techniques during this time, which are often costly and require specialised equipment and skills which limits their widespread availability.

1. Pharmacological therapies

a. Proton pump inhibitors

Three trials comparing H_2 receptor and proton pump inhibitor therapy have been undertaken ([Caldwell 1996](#); [Weinstein 1996](#); [Peters 1999](#)). When data from these studies were combined, accepting that there were missing data points, omeprazole was

shown to have a significant effect to the overall change in length or area of Barrett's oesophagus. The number of squamous islands could not be compared as the available data were not in a format compatible with a meta-analysis. There was a reduction in area of Barrett's oesophagus. This is contrary to a number of early non-randomised studies which suggested that aggressive acid suppression did not cause clinically significant regression of Barrett's oesophagus (Sharma 1997; Cooper 1998). However, such data must be viewed with caution because of the subjective nature of the endoscopic assessment of these parameters. It has been demonstrated, even with the same endoscopist using a fixed landmark approach to assess the length and area of Barrett's oesophagus, that only changes in length of greater than 1.6 cm can be considered as true regression or progression (Dekel 2003). However, it is possible that this variation in measurement could be avoided by using computerised analysis of digital images (Kim 1995).

Unfortunately none the RCTs included in this review, nor other RCTs of proton pump inhibitor therapy whose primary outcome was the assessment of gastro-oesophageal reflux disease (GORD), give us any information on the effect of proton pump inhibitors on the risk of developing dysplasia or adenocarcinoma. Two recent longitudinal cohort studies with larger numbers of individuals with Barrett's oesophagus ($n = 236$ to 350) and longer follow up (~5 years) have suggested that proton pump inhibitor therapy may be associated with a decreased risk of dysplasia within the Barrett's epithelial segment (El-Serag 2004; Hillman 2004). The AspECT trial may help us understand the role of proton pump inhibitors in the prevention of adenocarcinoma in Barrett's oesophagus. The National Institute of Health and Clinical Excellence (NICE), an independent Governmental body giving recommendations on the efficacy and cost-effectiveness of treatments in the UK, recommends that patients with reflux oesophagitis or Barrett's oesophagus should receive proton pump inhibitor at a dose required to control symptoms (NICE 2005). Although proton pump inhibitors are usually successful in relieving patient's symptoms and preventing GORD complications, such as oesophagitis and stricture formation (Havelund 1988), they are associated with hypergastrinaemia. There has been concern that hypergastrinaemia may increase the risk of Barrett's oesophagus progression or adenocarcinoma development (Harris 2004) and some parties have suggested that surgical anti-reflux procedures may be a better alternative.

b. NSAIDs and COX-2 inhibitors

A meta-analysis of observational human studies demonstrated a 33% reduction in the odds ratio of developing oesophageal adenocarcinoma for patients using aspirin and/or NSAIDs (OR 0.67). There was also evidence for a dose effect with greater reduction of the odds ratio of progression with increasing doses of NSAIDs and aspirin; however the data were presented in a combined form for any squamous carcinoma and adenocarcinomas (Corley 2003). Data from a prospective study demonstrated a lower five-year cumulative cancer incidence of 6.6% for current NSAID users, 9.7% for previous users and 14.3% for non-users. The frequency and duration of usage did not impact on the risk of oesophageal cancer development (Vaughan 2005). Some experimental evidence also exists for the protective effect of aspirin in oesophageal adenocarcinoma (Sturmer 1998; Baron 2003; Sandler 2003).

The role of COX-2 inhibitors in patients with Barrett's oesophagus is less clear. A rat model of Barrett's using oesophago-jejunostomy demonstrated that sulindac (NSAID) and MF-tricyclic (selective COX-2 inhibitor) reduced the incidence of adenocarcinoma by 79% ($P < 0.008$) and 55% ($P < 0.001$) respectively when compared to control animals. The prevalence of Barrett's oesophagus was, however, not altered by treatment, suggesting a chemopreventative effect for the development of adenocarcinoma but not Barrett's oesophagus (Buttar 2002). However, Miwa 2005 reported a decrease in the incidence of Barrett's oesophagus and adenocarcinoma. A recent RCT reported in this review has failed to show any benefit of celecoxib above that of placebo for the reversal of dysplasia in the context of Barrett's oesophagus (Heath 2007). Caution is necessary when using COX-2 inhibitors since Rofecoxib use has been associated with a $> 50\%$ increase in the risk of cardiovascular events (Bresalier 2005). There were no increased cardiovascular complications in patients in the celecoxib group compared to the placebo group (Heath 2007); this is in keeping with data from a meta-analysis which suggests the cardiovascular effects may be rofecoxib specific (Simon 2005). However, studies of other COX-2 inhibitors (valdecoxib) suggest that the deleterious cardiovascular effects may affect the COX-2 inhibitor drug class as a whole (Andersohn 2006). Thus increasing caution is being applied in the use of COX-2 inhibitors. Overall, aspirin may be beneficial but RCT data are required to substantiate this.

c. Novel oral agents

The role of the ornithine decarboxylase inhibitor difluoromethylornithine (DFMO) is not clear. In a rat model for the development of oesophageal adenocarcinoma there was a reduction in cancer risk only when DFMO was combined with a NSAID (Chen 2002). A pilot clinical trial showed suppression of Barrett's oesophagus tissue polyamine levels in individuals treated with DFMO, which further suggested a potential therapeutic role for the drug (Gerner 1994). A clinical trial of NSAIDs combined with DFMO was recently completed at the University of Michigan Medical Centre, but has yet to report and preliminary data are not yet available from the authors (Personal Communication Dr D Brenner). *In vitro* and early *in vivo* studies of retinoids suggested that they may impair epithelial cancer formation (Freemantle 2003). Despite disappointing phase III clinical trials in small cell lung cancer and head and neck cancers (Freemantle 2006; Khuri 2006), further work continues in non-small cell lung carcinoma using novel synthetic retinoids targeting the non-classical nuclear retinoid X receptor in combination with epidermal growth factor receptor inhibitors (Dragnev 2005), since a multimodality approach using retinoids in combination with other agents may be necessary to achieve clinical benefits.

2. Surgical therapies

A single randomised surgical trial comparing antacid therapy with an open Collis Nissen gastropasty has been undertaken which was reported initially in 1996 (Ortiz 1996) and then in 2003 with longer-term results, including additional patients (Parrilla 2003). No benefit was shown for the histological regression of Barrett's oesophagus. Individuals who had successful surgery, as defined by normal pH studies, were statistically significantly less likely to develop *de novo* high-grade dysplasia. However, this study was performed in a single centre and treatment protocols, acid suppression methods and surgical interventions were variable for both groups in the study. The reduction in the incidence

of oesophagitis and strictures suggested a benefit for surgical intervention when GORD complications are considered and these data are consistent with previous findings (Spechler 1992; Spechler 2001). It should also be remembered that both the medication used and the surgical approaches followed have now changed.

The role of surgery in the management of GORD symptoms in patients with Barrett's oesophagus was controversial. Although early surgical anti-reflux operations were associated with high morbidity and were considered to have high failure rates in patients with Barrett's oesophagus, it has now become clear that laparoscopic anti-reflux surgery (LARS) (most commonly laparoscopic Nissen fundoplication) is safe (Hinder 1997; Viljakka 1997; Pessaux 2002) and has been shown to have a better symptomatic improvement compared to proton pump inhibitor (Mehta 2006). Furthermore, there are data to suggest that it is more effective in GORD symptom control in the short and medium-term than proton pump inhibitor therapy (Spechler 1992) and failure is uncommon at approximately 2.8% (Smith 2005). Procedural failure tends to occur early because of fundoplication wrap herniation (Gopal 2006). There is however concern that individuals with Barrett's oesophagus are at a higher risk of LARS failure due to the presence of a large hiatus hernia. It is therefore recommended that these individuals should have a thorough dissection and mobilisation of the oesophagus, appropriate reduction of any hiatus hernia and reduction in the hiatal defect size by suturing the crura or the application of a crural patch. Furthermore, some groups suggest that "liberal use" of a Collis gastroplasty to lengthen the oesophagus should be employed to reduce fundoplication wrap herniation (Jackson 2005). A recent non-randomised study suggests that the Collis Nissen approach may be superior to Nissen fundoplication in individuals with Barrett's oesophagus (Chen 2005) but this too remains controversial. Non-randomised controlled trial evidence however suggested that surgical therapy was associated with significant regression of the Barrett's segment in 14% to 35% of patients and complete regression of low-grade dysplasia in 44% to 93% of patients (Hofstetter 2001; O'Riordan 2004; Rossi 2006). Caution must be applied when interpreting these data since diagnosis of low-grade dysplasia is notoriously difficult and even the most stringent biopsy protocol can still miss foci.

The long-term efficacy of surgical anti-reflux procedures must also be borne in mind. Long-term follow up of individuals treated with open Nissen fundoplication as part of a larger RCT assessing reflux therapy as an outcome (Spechler 2001), showed that after ten years follow up without acid suppression therapy standardised treatment scores (Gastro-oesophageal Reflux Disease Activity Index (GRACI) scores) in the surgical group were significantly better than in the medically treated group ($P = 0.03$). However, there were no significant differences between the groups in terms of grade of oesophagitis, frequency of oesophageal stricture and subsequent anti-reflux operations. There were also similar effects of both treatments in terms of SF-36 standardised physical and mental component scale scores, and overall satisfaction with anti-reflux therapy.

Overall, laparoscopic anti-reflux surgery is a valuable approach for the control of reflux symptoms. However, at present no randomised trial has been published comparing the laparoscopic Nissen fundoplication, which is the currently favoured anti-reflux approach, with proton pump inhibitor therapy for the regression of Barrett's oesophagus and prevention of adenocarcinoma. Such a

study would be difficult to perform because the low incidence of adenocarcinoma in individuals with Barrett's oesophagus means that a very large, probably multinational study, would be required to achieve adequate statistical power.

3. Endoscopic therapies

The biggest body of data exists for the endoscopic therapies, although as mentioned previously this rapidly evolving field has led to a paucity of appropriately powered RCTs.

In a pilot study of only eight patients, differences could be detected between Nd-YAG laser treatment and proton pump inhibitor alone in altering Barrett's oesophagus length or inducing squamous islands at six months (Luman 1995; Luman 1996). However, the pilot nature of this study limits the conclusions that can be drawn. Nd-YAG laser therapy has also been studied in non-randomised descriptive studies where complete regression rates of 40% have been reported (Norberto 2004). On the basis of these studies, the true efficacy of Nd-Yag therapy in the eradication of Barrett's oesophagus is unclear.

Three randomised trials have compared various ablative techniques, both as the primary treatment and after anti-reflux surgery. Argon plasma coagulation was more effective than proton pump inhibitor alone in achieving ablation and maintenance of ablation of Barrett's oesophagus (Ackroyd 2004) but glands buried underneath squamous epithelium remain a concern (Basu 2002b; Hage 2004). The eradication of Barrett's oesophagus by argon plasma coagulation is relatively stable since 40% of patients were reported to be eradicated at one and five years of follow up (Ackroyd 2000; Bright 2007). Argon plasma coagulation and multipolar electrocautery were shown to be of equal efficacy for the decrease in length and area of Barrett's oesophagus (Dulai 2005) as well as for complete eradication of Barrett's oesophagus (Dulai 2005; Sharma 2006). Multipolar electrocoagulation has high complete ablation rates after six treatment sessions achieving 85% macroscopic resolution and 78% histological regression of Barrett's oesophagus (Sampliner 2001).

Drawing conclusions on the efficacy of photodynamic therapy compared to argon plasma coagulation is difficult since the efficacy of photodynamic therapy to eradicate Barrett's oesophagus is dictated by the choice of drug and regimens of treatment used. Photodynamic therapy can be either more, less or equally effective as argon plasma coagulation depending on the study or the photodynamic therapy regimens used within a single study (Hage 2004; Kelty 2004; Ragunath 2005). This is also true for the presence of buried glands after treatment. Overall argon plasma coagulation has equal and perhaps greater efficacy than photodynamic therapy depending on the dosing regimens and the dysplasia status of Barrett's oesophagus being treated; however, because of the conflicting reports of the incidence of buried glands the relative merits of argon plasma coagulation over photodynamic therapy may be blunted.

Two trials compared proton pump inhibitor therapy with photodynamic therapy (Ackroyd 2000; Overholt 2005) and Overholt's data were updated in Overholt 2007. Although these groups used different photosensitisers and different light dosing regimens, both showed that photodynamic therapy was significantly more efficacious at ablating Barrett's oesophagus when compared with proton pump inhibitor alone. It should be noted, however,

that Ackroyd's study was not designed to show any change in dysplastic Barrett's oesophagus using 5-ALA. Overholt reported that photodynamic therapy with porfimer sodium, using both diffuse and focal light application to discrete lesions resulted in a statistically significant decrease in high-grade dysplasia and adenocarcinoma risk when compared with proton pump inhibitor alone ($P < 0.004$). This is the first randomised study to demonstrate a reduction in adenocarcinoma risk in Barrett's oesophagus patients with any therapeutic intervention. The follow-up data from this trial confirm that porfimer sodium photodynamic therapy with omeprazole remains more effective than omeprazole alone in eliminating high-grade dysplasia ($P < 0.0001$) and in preventing progression to cancer after five years (Overholt 2007). However, the low conversion rate (28%) of high-grade dysplasia patients on omeprazole should also be noted. Longer-term follow up would be necessary to correctly assess the protective effect of photodynamic therapy for the development of adenocarcinoma. The RCT by Mackenzie 2008 highlighted the difference in efficacy and safety between 5-ALA and porfimer sodium photodynamic therapy despite not reaching statistical significance. Overall, 5-ALA seems to be better tolerated and has fewer complications (such as strictures) than porfimer sodium and may also be more efficacious in the reversal of dysplasia (reviewed in Dunn 2008).

The timing at which intervention should occur in patients with high-grade dysplasia, however, remains unclear. Descriptive studies of individuals offered surgical treatment for high-grade dysplasia in Barrett's oesophagus suggest that early intervention is safer (Romagnoli 2003). This report described two groups of individuals with dysplasia in Barrett's oesophagus: individuals with high-grade dysplasia were offered oesophagectomy either soon after diagnosis or after a period of follow up (range seven to 70 months) as part of routine clinical management; no randomisation took place. This revealed a higher overall stage of invasive disease, an increased lymph node burden and poorer cancer related survival in the follow-up group when compared to the early intervention group (early intervention group survival at 168 months = 100% versus 52% survival in the follow-up group, $P = 0.0094$).

Radiofrequency ablation has first been shown in porcine and phase two clinical trials to be efficacious in treating the oesophageal mucosa without injuring the sub-mucosa (Ganz 2004). Radiofrequency ablation has been demonstrated to successfully eradicate Barrett's oesophagus and dysplasia without significant side effects (Shaheen 2008). Until this year, most publications were in abstract form or pilot studies. The two largest studies of 70 (Fleischer 2008) and 44 (Pouw 2008) patients treated with radiofrequency ablation reported 98% complete eradication of intestinal metaplasia at 25 and 21 months respectively. The study by Pouw included only patients with high-grade dysplasia and dysplasia was cleared in 98% of patients at 21 months. These two studies had 16% to 22% minor complications (Fleischer 2008; Pouw 2008); mild bleeds and nausea were the most common. There was one incidence of perforation. None of these studies reported any strictures and buried glands were only found in 0.01% of neo-squamous biopsies. Longer-term follow-up data are required to confirm the lasting efficacy of this treatment.

A number of other endoscopic modalities have been studied but these have not undergone RCT assessment in the context of Barrett's oesophagus treatment. These include cryotherapy which was first described in a porcine model (Johnston 1999) and has

been shown in a pilot prospective study ($n = 11$) to partially ablate Barrett's oesophagus in 100% patients and to completely ablate Barrett's oesophagus, both macroscopically and histologically, in 78% of those treated. The treatment was undertaken using a low pressure spray cryoablation technique and no complications were described. There was no recurrence of Barrett's oesophagus seen in those completely ablated at six months follow up (Johnston 2005).

Endomucosal resection (EMR) of Barrett's oesophagus lesions has also been employed. It has predominantly been used in individuals with discrete visible lesions, and has been shown to produce a complete remission in 97% of individuals with smaller, lower risk lesions (< 20 mm in size, high-grade dysplasia or well/moderately differentiated adenocarcinoma on histology with a polypoid or flat macroscopic morphology) and 59% in those with large higher risk lesions (> 20 mm in size, poorly differentiated adenocarcinoma on histology and ulcerated macroscopically; Eli 2000). It has also been recognised to be a useful diagnostic adjunct as the larger and more complete nature of specimens obtained may make histological examination easier. This is particularly evident if a cut and lift rather than a suction cap approach is used, since this reduces both the cautery (Nijhawan 2000) and crushing artefact. RCTs comparing this technique with other therapeutic interventions have not yet been undertaken in Barrett's oesophagus. Although, EMR is used increasingly in combination with endoscopic therapy aiming to ablate a larger segment (Pouw 2008), none of the RCTs included in this review used this in conjunction with other treatment modalities.

AUTHORS' CONCLUSIONS

Implications for practice

Randomised controlled trial evidence shows that surgical and pharmacological anti-reflux therapies do not appear to eradicate Barrett's and existing dysplasia; at best they induce a regression of the segment but eradication of low-grade dysplasia was apparent in prospective surgical series. Furthermore, there may be a reduction in the development of *de novo* dysplasia, although this has not been confirmed by a meta-analysis of non-randomised, surgical anti-reflux trials. Anti-reflux therapies are valuable for providing symptomatic control of gastro-oesophageal reflux disease (GORD) and prevention of inflammatory complications and may allow for a reduction of dysplasia. With regards to endoscopic therapies, a comparison of porfimer sodium photodynamic therapy compared with proton pump inhibitor therapy is the first RCT evidence to demonstrate superiority of an endoscopic intervention in reducing progression to adenocarcinoma. Both argon plasma coagulation and photodynamic therapy have similar success rates in the eradication of Barrett's oesophagus and dysplasia. The presence of buried glands following argon plasma coagulation would suggest not using argon plasma coagulation for full segment eradication. Compared with porfimer sodium, data published since the 2004 guidelines (NICE 2004) suggest that 5-ALA has lower side effects is effective at treating Barrett's oesophagus and dysplasia compared with porfimer sodium (as reviewed by Dunn 2008). The data available so far suggest that radiofrequency ablation is promising for the treatment of Barrett's oesophagus with and without dysplasia. Provided that the NICE guidelines endorse radiofrequency ablation in Barrett's oesophagus, it would be the treatment of choice. However, until longer-term RCT data are published, radiofrequency ablation should only be used in expert centres with careful follow up.

Implications for research

The only surgical study discussed here was limited by the use of different acid suppression therapies with an open Collis Nissen gastropasty, which is now outmoded. The efficacy of surgery using LARS techniques compared to proton pump inhibitor alone in the prevention of Barrett's oesophagus, the regression of Barrett's oesophagus and the prevention of adenocarcinoma requires further study. The relative efficacy of photodynamic therapy using 5-ALA and porfimer sodium is unknown and a comparison of these photosensitising drugs would allow the identification of the most efficacious agent in this setting. Furthermore, the safety profile of photodynamic therapy types with particular reference to stricture risk and photosensitivity complications that are seen with porfimer sodium need to be taken into account. However, with the advent of radiofrequency ablation, it is likely that photodynamic therapy will become an obsolete technique. Long-term, multicentre studies on the efficacy of radiofrequency ablation to eradicate Barrett's oesophagus and dysplasia, and the incidence of strictures and buried glands, are needed before radiofrequency ablation can

be used in routine clinical care without very careful surveillance post-treatment. It would also be important to assess whether or not the risk of progression to adenocarcinoma is reduced following radiofrequency ablation compared to surveillance. The results of the AsPECT trial may inform debate on the utility of chemopreventive agents for Barrett's associated adenocarcinoma. Overall, the field is in dire need of long-term RCT with a primary endpoint of cancer development. However, the relatively low conversion rate of Barrett's oesophagus may lead to difficulties obtaining funding for such long-term studies. It may therefore be appropriate to use biomarkers predictive of progression as an endpoint.

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Yousef 2008

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Ackroyd 2000

Methods	Prospective randomised controlled trial
Participants	36 individuals with Barrett's esophagus and confirmed LGD 30 M: 6 F Median age 56 (30 to 71)
Interventions	5-ALA (aminolevulinic acid) PDT and omeprazole 20 mg od and laser (green light 514 nm) per 3 cm vs Placebo (omeprazole 20 mg od)
Outcomes	Presence or absence of Barrett's and/or dysplasia (length/area) (endoscopic/histological-6 Bx) at T 1/12, 6/12, 12/12, 24/12
Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	—

Treatment for Barrett's esophagus (Review)

Ackroyd 2000 (Continued)

Allocation concealment (selection bias)	Low risk	Quote "performed 1:1 by opening 36 previously sealed envelopes"
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote "pharmacy staff and the outcome was unknown to clinical staff and patients"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not mentioned
Selective reporting (reporting bias)	High risk	Outcomes not clearly outlined
Other bias	Low risk	—

Bright 2007

Methods	Prospective randomised controlled trial
Participants	0 individuals 32 M :8 F Mean age 49
Interventions	Post-surgery Argon plasma coagulation (up to 6 treatments) or Surveillance
Outcomes	Presence or absence of Barrett's (endoscopic/histological) Regression of Barrett's by length
Notes	This study is looking at long-term follow up from the patients in Ackroyd 2004 . Data from this article will only be used to discuss long-term efficacy of PDT.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	—
Allocation concealment (selection bias)	Low risk	Quote "performed ... by opening 1 in 40 sealed opaque envelopes"
Blinding (performance bias and detection bias) All outcomes	High risk	Nature of the study made blinding impossible
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote "statistical significance claimed if $p < 0.01$ "
Selective reporting (reporting bias)	High risk	Outcomes not clearly outlined in methodology

Treatment for Barrett's oesophagus (Review)

Bright 2007 (Continued)

Other bias	Low risk	—
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Caldwell 1996

Methods	Prospective randomised controlled trial
Participants	28 individuals 20 completed study
Interventions	Omeprazole 20 mg od vs Cimetidine 300 mg tds
Outcomes	Endoscopic length of Barrett's oesophagus and presence of squamous islands
Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Published only in abstract format
Allocation concealment (selection bias)	Unclear risk	Published only in abstract format
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Published only in abstract format
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Published only in abstract format
Selective reporting (reporting bias)	Unclear risk	Published only in abstract format
Other bias	High risk	Published only in abstract format

Dulai 2005

Methods	Prospective, single blind, randomised controlled trial
Participants	52 individuals 26 APC vs 26 MPEC APC mean age 58 (21 M: 5 F) MPEC mean age 56 (18 M : 8F)
Interventions	Argon plasma coagulation + pantoprazole 40 mg bd vs multipolar coagulation + pantoprazole 40 mg bd pantoprazole inc. if symptomatic or persistent oesophagitis
Outcomes	Primary: Number of treatments with APC vs MPEC to achieve endoscopic ablation or treatment failure (6 or more Rx with no endoscopic or histological response)

Treatment for Barrett's oesophagus (Review)

Dulai 2005 (Continued)

Notes	Secondary Proportion of patients with endoscopic regression Proportion of patients with histological Barrett's oesophagus regression Proportion of patients with post-treatment symptoms
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Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote "table of random numbers"
Allocation concealment (selection bias)	Low risk	Quote "randomisation was determined by opening a sealed opaque envelope"
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote "treatment allocation was concealed from the investigators...patients, primary care provider(s), investigators....were blinded to the endoscopic treatment"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote " collected and analysed on an intention to treat basis"
Selective reporting (reporting bias)	Low risk	All outcomes were reported
Other bias	Low risk	—

Hage 2004

Methods	Prospective randomised trial
Participants	40 individuals 31 M: 9 F Mean age 59
Interventions	Argon plasma coagulation (65 w) or 5-ALA PDT 60 mg/kg (100 J/cm ²) or 5-ALA PDT 60 mg/kg (high dose 100 + 20 J/cm ² divided) administration regime)
Outcomes	Presence or absence of BE/IM (endoscopic/histological) & Regression of Barrett's 6/52, 6/12, 12/12, 18/12, 24/12
Notes	25 watts max dose 1000 J

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	—

Treatment for Barrett's oesophagus (Review)

Hage 2004 (Continued)

Allocation concealment (selection bias)	Unclear risk	—
Blinding (performance bias and detection bias) All outcomes	High risk	Nature of the study made blinding impossible
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	—
Selective reporting (reporting bias)	Unclear risk	Outcomes not clearly outlined in methodology
Other bias	Unclear risk	—

Heath 2007

Methods	Phase IIb, randomised, parallel treatment, placebo controlled, double masked, multicentre trial	
Participants	100 patients randomised to celecoxib (n = 49) or placebo (n = 51)	
Interventions	Celecoxib 200 mg twice daily or placebo twice daily for at least a year and a maximum of 2 years	
Outcomes	<p>Primary study outcomes: safety and efficacy of celecoxib for regression of dysplasia in patients with Barrett's oesophagus (including overall mortality, morbidity, adverse drug reactions)</p> <p>Secondary study outcomes: change from baseline in the highest grade of dysplasia, extent of HGD, extent of LGD and surface area of Barrett's oesophagus</p>	
Notes	—	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	—
Allocation concealment (selection bias)	Unclear risk	—
Blinding (performance bias and detection bias) All outcomes	Unclear risk	—
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote "All analyses between the two randomized groups (celecoxib vs placebo) will be based on the intention to-treat principle."
Selective reporting (reporting bias)	Low risk	—
Other bias	Low risk	—

Treatment for Barrett's oesophagus (Review)

Kelty 2004

Methods	Randomised controlled trial
Participants	72 individuals; 4 withdrew; N = 68 58 M:14 F. Median age 61
Interventions	APC (65 W) +PPI or ALA (85 J/cm ²) + PPI
Outcomes	Presence or absence of BE/IM (endoscopic/histological) at 4/52, 6/12, 12/12, 24/12 Median number of treatments to achieve complete macroscopic reversal Side effects at 24 hours
Notes	Maximal 5 treatments

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote "patients were randomised by a computer"
Allocation concealment (selection bias)	Unclear risk	—
Blinding (performance bias and detection bias) All outcomes	Unclear risk	—
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	—
Selective reporting (reporting bias)	Unclear risk	Outcomes not clearly outlined in methodology
Other bias	Unclear risk	—

Luman 1996

Methods	Randomised controlled trial
Participants	8 individuals, 6M, 2F. All completed
Interventions	Omeprazole 40 mg od vs omeprazole 40 mg od with 4 to 6-weekly Nd-Yag laser for 6 months
Outcomes	Omeprazole 40 mg od vs omeprazole 40mg od with 4 to 6-weekly Nd-Yag laser for 6 months
Notes	Full publication of abstract version

Risk of bias

Bias	Authors' judgement	Support for judgement
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Luman 1996 (Continued)

Random sequence generation (selection bias)	Unclear risk	—
Allocation concealment (selection bias)	Unclear risk	—
Blinding (performance bias and detection bias) All outcomes	Unclear risk	—
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Low risk	—
Other bias	High risk	Very small study

Mackenzie 2008

Methods	Prospective randomised trial
Participants	Planned 66, 40 recruited and 32 treated so far (16 for ALA and 16 for porfimer sodium)
Interventions	Porfimer sodium: use the standard protocol (no more details) ALA: 60 mg/kg, activated by 1178 J/cm of red laser light Follow up with quadrantic biopsies every 2 cm at 6 weeks, 4 months and 1 year post-therapy
Outcomes	Not clearly stated in the abstract
Notes	Published in abstract format

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Published only in abstract format
Allocation concealment (selection bias)	Unclear risk	Published only in abstract format
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Published only in abstract format
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Published only in abstract format
Selective reporting (reporting bias)	Unclear risk	Published only in abstract format

Mackenzie 2008 (Continued)

Other bias	High risk	Published only in abstract format
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Overholt 2005

Methods	Multicentre, randomised, partially blinded clinical trial
Participants	485 patients screened, 208 in the intention-to-treat group and 202 in the safety group Randomised 2:1
Interventions	PDT (130 J/cm ²) after 2 mg/kg porfimer sodium, using diffuser with centring balloon. Focal nodules pretreated with 50 J/cm ² PDT with bare fibre with omeprazole 20 mg bd versus omeprazole 20 mg bd alone.
Outcomes	Primary: complete ablation of HGD at any time Secondary: Occurrence of cancer, duration of complete ablation, quality and duration of a complete response, time to progression to cancer and time to treatment failure
Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Refer to Parrilla 2003
Allocation concealment (selection bias)	Unclear risk	Refer to Parrilla 2003
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Refer to Parrilla 2003
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Refer to Parrilla 2003
Selective reporting (reporting bias)	Unclear risk	Refer to Parrilla 2003
Other bias	Unclear risk	Refer to Parrilla 2003

Parrilla 2003

Methods	Prospective, randomised
Participants	113 individuals (12 declined surveillance) 101 in study 72 M: 29 F Median age medical 50, surgical 43

Parrilla 2003 (Continued)

Interventions	Acid suppression (ranitidine 1982 to 1992 omeprazole 20 mg 1992 to 2000) vs Surgery (Short Nissen 56 or Collis Nissen 2); no acid suppression
Outcomes	Clinical symptoms Presence or absence of Barrett's oesophagus (endoscopic and histological) Surgical group functional studies
Notes	Randomisation not specified Paper using same patients published 1996; concern re. the prospective nature of study Medical 51 to 43 Surgical 62 to 58 Only per protocol data given

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote "Randomisation was performed...by computer-generated numbers..."
Allocation concealment (selection bias)	Low risk	Quote "...computer-generated numbers...concealed in sequentially numbered, sealed, opaque envelopes."
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Nature of the study made blinding impossible
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	—
Selective reporting (reporting bias)	Low risk	—
Other bias	Low risk	—

Peters 1999

Methods	Prospective randomised double blind study
Participants	68 individuals entered, 61 suitable, 43M, 18F. 53 completed study
Interventions	Acid suppression with ranitidine 150 mg bd versus omeprazole 20 mg bd
Outcomes	Clinical symptoms, length and surface area of Barrett's oesophagus, % reflux, presence of oesophagitis and lower oesophageal sphincter pressure
Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
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Peters 1999 (Continued)

Random sequence generation (selection bias)	Low risk	Quote "Treatment with either...according to a computer generated randomisation list"
Allocation concealment (selection bias)	Unclear risk	—
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote "...double blind using the double dummy technique"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	—
Selective reporting (reporting bias)	Low risk	—
Other bias	Unclear risk	—

Ragunath 2005

Methods	Prospective, randomised
Participants	32 patients identified, 26 patients suitable 21 M, 5 F. 22 completed 12 months of follow up
Interventions	APC was performed at a power setting of 65 W and argon gas flow at 1.8 l/min in 1 to 6 sessions (mean 5) versus PDT was performed 48 hours after intravenous injection of porfimer sodium 2 mg/kg with a 630 nm red laser light, 200 J/cm through a PDT balloon in 1 session
Outcomes	Cost-effectiveness and eradication of dysplastic Barrett's
Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote "computer-generated randomisation was done for allocating the enrolled patients in either...."
Allocation concealment (selection bias)	Unclear risk	—
Blinding (performance bias and detection bias) All outcomes	Unclear risk	—
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	—

Treatment for Barrett's oesophagus (Review)

Ragunath 2005 (Continued)

Selective reporting (reporting bias)	Low risk	—
Other bias	Low risk	—

Shaheen 2008

Methods	Randomised, sham-controlled design
Participants	127 patients enrolled (64 LGD and 63 HGD); 117 completed the study (59 LGD and 58 HGD) RFA: 40 LGD and 38 HGD completed Sham: 19 LGD and 20 HGD completed
Interventions	Radio frequency ablation: 40 W/cm ² and 12 J/cm ² ; repeat RFA at 2, 4, 9 months if residual Barrett's oesophagus All patients had high-dose PPI for the duration of the study (40 mg bd)
Outcomes	12 months primary outcome: Complete response for dysplasia (HGD and LGD cohorts) Complete response for intestinal metaplasia Secondary outcome: Histological progression (HGD to AC, LGD to AC) Adverse event incidence Sub-squamous intestinal metaplasia
Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote "...assigned to a study group with the use of a computer generated block randomisation sequence..."
Allocation concealment (selection bias)	Unclear risk	—
Blinding (performance bias and detection bias) All outcomes	Low risk	Patients were randomised to either treatment or sham. Endoscopists were not blinded. Not clear whether pathologists were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote "the study population for the primary intention-to-treat analysis included all patients who underwent randomisation."
Selective reporting (reporting bias)	Low risk	—
Other bias	Low risk	—

Sharma 2006

Methods	Prospective, randomised controlled trial
Participants	35 patients enrolled 34 M: 1 F. 35 completed the study
Interventions	Multipolar electrocoagulation 20 W continuous power APC: 60W gas flow 1.4 to 1.8 L/min
Outcomes	Primary: endoscopic and histological reversal of Barrett's oesophagus Secondary: side effects, number of treatments, clinical factor (age, length of Barrett's oesophagus, hiatus hernia size, PPI, pH score)
Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	—
Allocation concealment (selection bias)	Low risk	Quote "...using sealed opaque envelopes..."
Blinding (performance bias and detection bias) All outcomes	Unclear risk	—
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	—
Selective reporting (reporting bias)	Low risk	—
Other bias	Low risk	—

Weinstein 1996

Methods	Controlled, randomised double blind study
Participants	106 individuals (97 completed more than 6 months follow up)
Interventions	Acid suppression with ranitidine (150 mg bd) for 2 years vs omeprazole 80 mg for 1 year, then 40 mg in second year
Outcomes	Length, area and presence of squamous islands at T0, T12/12 and T24/12 (endoscopically)
Notes	No information on randomisation, diagnostic criteria of Barrett's oesophagus

Risk of bias

Treatment for Barrett's oesophagus (Review)

Weinstein 1996 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	—
Allocation concealment (selection bias)	Unclear risk	—
Blinding (performance bias and detection bias) All outcomes	Unclear risk	—
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	—
Selective reporting (reporting bias)	Unclear risk	—
Other bias	Unclear risk	—

AC = adenocarcinoma
ALA = aminolevulinic acid
APC = argon plasma coagulation
bd = twice daily
F = female
HGD = high-grade dysplasia
IM = intestinal metaplasia
LGD = low-grade dysplasia
M = male
MPEC = multipolar electrocautery
od = once daily
PDT = photodynamic therapy
PPI = proton pump inhibitor
RFA = radiofrequency ablation
tds = three times daily
vs = versus

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Ackroyd 1996	Non-randomised
Ackroyd 1996b	Non-randomised
Ackroyd 1999	Endpoint not Barrett's oesophagus regression
Ackroyd 2004	Short-term follow up of the patients presented in Bright 2007
Aguirre 2003	Commentary
Aguirre 2003b	Commentary
Attwood 2003	Non-randomised

Study	Reason for exclusion
Barham 1995	Non-randomised
Barr 1996	Commentary
Basu 2002	Non-randomised
Bellnier 2003	Non-randomised
Bowers 2002	Non-randomised
Bowers 2003	Non-randomised
Braghetto 2002	Non-randomised
Cameron 2002	Non-randomised
Canto 1996	Non-randomised
Caos 2000	Detected difference not change in Barrett's oesophagus
Carlson 2002	Non-randomised
Csendes 2000	Endpoint not Barrett's oesophagus regression
Csendes 2002	Non-randomised
Dar 2003	Non-randomised
DeMeester 2002	Review
Deviere 2002	Commentary
Dietz 2003	Non-randomised
Doak 2003	Non-randomised
Egger 2003	Non-randomised
Eubanks 2000	Non-randomised
Familiari 2003	Non-randomised
Farrell 2001	Non-randomised, non-human
Felix 2002	Non-randomised
Ferguson 1997	Non-randomised
Fitzgerald 2001	Non-randomised
Fleischer 2008	Non-randomised
Foroulis 2006	Non-randomised
Fujii 2003	Non-randomised

Study	Reason for exclusion
Gastal 1999	Non-randomised
Gossner 1995	Non-randomised
Gurski 2003	Non-randomised
Hage 2005	Did not fulfil endpoints
Headrick 2002	Non-randomised
Heath 2002	Non-randomised
Hebbard 2004	Editorial
Hetzel 1988	Non-randomised
Hill 1997	Non-randomised
Hillman 2003	Non-randomised
Hinnen 2002	Endpoint not Barrett's oesophagus regression
Hofstetter 2001	Non-randomised
Hornick 2008	Non-randomised
Hur 2003	Non-randomised
Incarbone 2002	Non-randomised
Ito 2002	Non-randomised gastric study
Javaid 2002	Non-randomised
Johnston 2005	Non-randomised
Jung 2003	Review
Kamolz 2003	Non-randomised
Kashtan 2002	Non-randomised
Kaur 2002	Non-randomised
Keeley 2007	Non-randomised
Krska 2002	Non-randomised
Lanas 2007	Only 6-month follow up and regression of Barrett's oesophagus not measured
Luostarinen 1993	Non-randomised
Malhi-Chowla 2001	Non-randomised
Manner 2006	Non-randomised

Study	Reason for exclusion
Marcus 1996	Review
May 2002	Non-randomised
Menke-Pluymers 1992	Non-randomised
Messmann 1998	Non-randomised
Mino-Kenudson 2007	Non-randomised
Miros 1991	Non-randomised
Montgomery 2002	Non-randomised
Morino 2003	Non-randomised
Mork 2003	Non-randomised
Morris 2001	Non-randomised
Niemantsverdriet 199	Non-randomised
O'Riordan 2004	Non-randomised
Oberg 2001	Non-randomised
Ochando-Cerdan 2002	Non-randomised
Oelschlager 2003	Non-randomised
Ofman 2000	Endpoint not Barrett's oesophagus regression
Oleynikov 2003	Review
Olliver 2003	Non-randomised
Ormsby 2002	Non-randomised
Ortiz 1996b	Data included in later study Parrilla 2003
Ortner 2003	Non-randomised
Pacifico 2003	Non-randomised
Pagani 2003	Non-randomised
Panjehpour 2000	Detected difference not change in Barrett's oesophagus
Panjehpour 2008	Non-randomised
Peters 1999b	Study endpoint not Barrett's oesophagus regression
Peters 2000	Study endpoint not Barrett's oesophagus regression
Ponce 2003	Non-randomised

Study	Reason for exclusion
Pouw 2008	Non-randomised
Pouw 2008b	Non-randomised
Prasad 2007	Non-randomised
Ragunath 2003	Study endpoint not Barrett's oesophagus regression
Reed 1995	Non-randomised
Robinson 2002	Non-randomised
Salminen 2002	Non-randomised
Salo 1998	Non-randomised
Sampliner 2002	Non-randomised
Sampliner 2004	Review
Scott Bolton 2001	Non-randomised
Sharma 2003	Non-randomised
Smith 2007	Non-randomised
Smythe 2003	Study endpoint not Barrett's oesophagus regression
Soni 2000	Non-randomised
Sontag 1997	Study endpoint not Barrett's oesophagus regression
Spechler 1992	Not Barrett's oesophagus
Spechler 2001	Study endpoint not Barrett's oesophagus regression
Stolte 2000	Non-randomised
Streitz 1991	Non-randomised
Suspiro 2003	Non-randomised
Taha 2003	Non-randomised
Theisen 2002	Non-randomised
Thomson 2003	Non-randomised
Todd 2002	Leading article comment - not clinical study
Tseng 2003	Non-randomised
Wehrmann 2001	Non-randomised
Weiss 2006	Non-randomised

Study	Reason for exclusion
Weston 2002	Non-randomised
Wetscher 2001	Non-randomised
White 2002	Non-randomised
Wickramasinghe 2002	Non-randomised
Wolfsen 2002	Non-randomised
Zopf 2001	Non-randomised

DATA AND ANALYSES

Comparison 1. Omeprazole vs histamine type 2 receptor antagonists

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Reduction in length (cm) of Barrett's oesophagus at 12 months	3	306	Mean Difference (IV, Fixed, 95% CI)	-0.60 [-1.50, 0.30]
1.1 All trials	3	163	Mean Difference (IV, Fixed, 95% CI)	-0.42 [-1.65, 0.82]
1.2 Trials using omeprazole 40 mg	2	143	Mean Difference (IV, Fixed, 95% CI)	-0.81 [-2.13, 0.50]
2 Reduction in area (%) of Barrett's oesophagus at 12 months	2	143	Mean Difference (IV, Fixed, 95% CI)	4.06 [0.08, 8.04]

Analysis 1.1. Comparison 1 Omeprazole vs histamine type 2 receptor antagonists, Outcome 1 Reduction in length (cm) of Barrett's oesophagus at 12 months.

Analysis 1.2. Comparison 1 Omeprazole vs histamine type 2 receptor antagonists, Outcome 2 Reduction in area (%) of Barrett's oesophagus at 12 months.

Comparison 2. Celecoxib vs placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
2 Any serious drug reactions	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected

Analysis 2.1. Comparison 2 Celecoxib vs placebo, Outcome 1 Mortality.

Analysis 2.2. Comparison 2 Celecoxib vs placebo, Outcome 2 Any serious drug reactions.

Study or subgroup	celecoxib n/N	placebo n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
Heath 2007	2/49	3/51		0.68[0.11,4.26]

Comparison 3. Anti-reflux surgery vs omeprazole

Outcome or subgroup title	No. of studies	No. of parti- pants	Statistical method	Effect size
1 Any reduction/reversal of Barrett's oe- sophagus/dysplasia at 12 months	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
2 Progression to cancer at latest possible time point	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
3 Any complication	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
4 Complete eradication of Barrett's oe- sophagus at 12 months	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
5 Numbers progressing to dysplasia from intestinal metaplasia	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
6 Complete eradication of dysplasia (at 5- year follow up)	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected

Analysis 3.1. Comparison 3 Anti-reflux surgery vs omeprazole, Outcome 1 Any reduction/reversal of Barrett's oesophagus/dysplasia at 12 months.

Study or subgroup	Antireflux surgery n/N	Omeprazole n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
Parrilla 2003	2/53	2/40		0.75[0.1,5.53]

Analysis 3.2. Comparison 3 Anti-reflux surgery vs omeprazole, Outcome 2 Progression to cancer at latest possible time point.

Study or subgroup	Antireflux surgery n/N	Omeprazole n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
Parrilla 2003	2/53	2/40		0.75[0.1,5.53]

Analysis 3.3. Comparison 3 Anti-reflux surgery vs omeprazole, Outcome 3 Any complication.

Study or subgroup	Antireflux surgery n/N	Omeprazole n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
Parrilla 2003	1/58	0/43		2.27[0.09,57.07]
Favours treatment 0.01 0.1 1 10 100 Favours control				

Analysis 3.4. Comparison 3 Anti-reflux surgery vs omeprazole, Outcome 4 Complete eradication of Barrett's oesophagus at 12 months.

Study or subgroup	Antireflux surgery n/N	Omeprazole n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
Parrilla 2003	0/53	0/40		Not estimable
Favours treatment 0.1 0.2 0.5 1 2 5 10 Favours control				

Analysis 3.5. Comparison 3 Anti-reflux surgery vs omeprazole, Outcome 5 Numbers progressing to dysplasia from intestinal metaplasia.

Study or subgroup	Successful Surgical n/N	Medical n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
Parrilla 2003	1/44	8/40		0.09[0.01,0.78]
Successful Surgical 0.01 0.1 1 10 100 Medical				

Analysis 3.6. Comparison 3 Anti-reflux surgery vs omeprazole, Outcome 6 Complete eradication of dysplasia (at 5-year follow up).

Study or subgroup	Surgical n/N	medical n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
Parrilla 2003	5/58	3/43		1.26[0.28,5.58]
Favours experimental 0.01 0.1 1 10 100 Favours control				

Comparison 4. Nd-YAG laser therapy vs omeprazole

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Any reduction/reversal of Barrett's oesophagus/dysplasia at 12 months	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
2 Any complication	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
2.1 Pain	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.2 Odynophagia	0		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.3 Fever	0		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.4 Nausea and vomiting	0		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.5 Stricture formation	0		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.6 Photosensitivity	0		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Analysis 4.1. Comparison 4 Nd-YAG laser therapy vs omeprazole, Outcome 1 Any reduction/reversal of Barrett's oesophagus/dysplasia at 12 months.

Study or subgroup	Nd-YAG Laser n/N	Omeprazole n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
Luman 1996	0/4	0/4		Not estimable

Analysis 4.2. Comparison 4 Nd-YAG laser therapy vs omeprazole, Outcome 2 Any complication.

Study or subgroup	Nd-YAG Laser n/N	Omeprazole n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
4.2.1 Pain				
Luman 1996	1/4	0/4		3.86[0.12,126.73]
4.2.2 Odynophagia				
4.2.3 Fever				
4.2.4 Nausea and vomiting				
4.2.5 Stricture formation				
4.2.6 Photosensitivity

Comparison 5. Argon plasma coagulation vs no treatment after anti-reflux surgery

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Any reduction/reversal of Barrett's oesophagus/dysplasia at 12 months	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2 Complete eradication of Barrett's oesophagus at 12 months	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
3 Presence of buried subsquamous Barrett's glands	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected

Analysis 5.1. Comparison 5 Argon plasma coagulation vs no treatment after anti-reflux surgery, Outcome 1 Any reduction/reversal of Barrett's oesophagus/dysplasia at 12 months.

Study or subgroup	APC n/N	None n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
Bright 2007	20/20	3/20		205[9.89,4247.47]
Favours treatment 0.001 0.1 1 10 1000 Favours control				

Analysis 5.2. Comparison 5 Argon plasma coagulation vs no treatment after anti-reflux surgery, Outcome 2 Complete eradication of Barrett's oesophagus at 12 months.

Study or subgroup	PDT n/N	APC n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
Bright 2007	14/20	0/20		91.46[4.77,1754.5]
Favours treatment 0.001 0.1 1 10 1000 Favours control				

Analysis 5.3. Comparison 5 Argon plasma coagulation vs no treatment after anti-reflux surgery, Outcome 3 Presence of buried subsquamous Barrett's glands.

Study or subgroup	APC n/N	Surveillance n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
Bright 2007	1/18	0/20		3.51[0.13,91.87]
Favours experimental 0.01 0.1 1 10 100 Favours control				

Comparison 6. Argon plasma coagulation vs multipolar electrocoagulation

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Any reduction/reversal of Barrett's oesophagus/dysplasia at 12 months	2		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
2 Any complication	2	141	Odds Ratio (M-H, Fixed, 95% CI)	0.72 [0.24, 2.14]
2.1 Pain	2	79	Odds Ratio (M-H, Fixed, 95% CI)	0.48 [0.13, 1.79]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.2 Odynophagia	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.3 Fever	1	31	Odds Ratio (M-H, Fixed, 95% CI)	2.03 [0.08, 53.87]
2.4 Nausea and vomiting	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.5 Stricture formation	1	31	Odds Ratio (M-H, Fixed, 95% CI)	2.03 [0.08, 53.87]
2.6 Photosensitivity	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3 Mortality	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
4 Control of acid reflux	1	24	Odds Ratio (M-H, Fixed, 95% CI)	2.5 [0.36, 17.32]

Analysis 6.1. Comparison 6 Argon plasma coagulation vs multipolar electrocoagulation, Outcome 1 Any reduction/reversal of Barrett's oesophagus/dysplasia at 12 months.

Study or subgroup	APC n/N	MPEC n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
Dulai 2005	24/24	24/24		Not estimable
Sharma 2006	0/19	0/16		Not estimable

Favours treatment 0.001 0.1 1 10 1000 Favours control

Analysis 6.2. Comparison 6 Argon plasma coagulation vs multipolar electrocoagulation, Outcome 2 Any complication.

Study or subgroup	Favours treatment n/N	MPEC n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
6.2.1 Pain					
Dulai 2005	1/24	0/24		6.35%	3.13[0.12,80.68]
Sharma 2006	4/19	6/12		78.49%	0.27[0.05,1.29]
Subtotal (95% CI)	43	36		84.84%	0.48[0.13,1.79]
Total events: 5 (Favours treatment), 6 (MPEC)					
Heterogeneity: Tau ² =0; Chi ² =1.81, df=1(P=0.18); I ² =44.74%					
Test for overall effect: Z=1.09(P=0.27)					
6.2.2 Odynophagia					
Subtotal (95% CI)	0	0			Not estimable
Total events: 0 (Favours treatment), 0 (MPEC)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
6.2.3 Fever					
Sharma 2006	1/19	0/12		7.58%	2.03[0.08,53.87]
Subtotal (95% CI)	19	12		7.58%	2.03[0.08,53.87]

Favours treatment 0.01 0.1 1 10 100 Favours control

Analysis 6.3. Comparison 6 Argon plasma coagulation vs multipolar electrocoagulation, Outcome 3 Mortality.

Analysis 6.4. Comparison 6 Argon plasma coagulation vs multipolar electrocoagulation, Outcome 4 Control of acid reflux.

Comparison 7. Photodynamic therapy vs argon plasma coagulation

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Any reduction/reversal of Barrett's oesophagus/dysplasia at 12 months	3		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
2 Any serious drug reactions	2	108	Odds Ratio (M-H, Fixed, 95% CI)	31.48 [4.04, 245.12]
3 Any complication	3	670	Odds Ratio (M-H, Random, 95% CI)	0.73 [0.15, 3.61]
3.1 Pain	3	134	Odds Ratio (M-H, Random, 95% CI)	0.13 [0.00, 3231.55]
3.2 Odynophagia	3	134	Odds Ratio (M-H, Random, 95% CI)	0.10 [0.00, 10.60]
3.3 Fever	3	134	Odds Ratio (M-H, Random, 95% CI)	1.88 [0.47, 7.44]
3.4 Nausea and vomiting	2	108	Odds Ratio (M-H, Random, 95% CI)	19.64 [2.51, 153.78]
3.5 Stricture formation	3	134	Odds Ratio (M-H, Random, 95% CI)	0.51 [0.11, 2.44]
3.6 Photosensitivity	1	26	Odds Ratio (M-H, Random, 95% CI)	5.87 [0.25, 135.15]
4 Mortality	3		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
5 Reduction in length (cm) of Barrett's oesophagus at 12 months	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
6 Persistence of sub-squamous glands	2	89	Odds Ratio (M-H, Random, 95% CI)	0.34 [0.02, 4.93]
7 Complete eradication of Barrett's oesophagus at 12 months	3	127	Odds Ratio (M-H, Random, 95% CI)	0.31 [0.00, 32.60]
8 Eradication of dysplasia at 12 months	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected

Analysis 7.1. Comparison 7 Photodynamic therapy vs argon plasma coagulation, Outcome 1 Any reduction/reversal of Barrett's oesophagus/dysplasia at 12 months.

Study or subgroup	PDT n/N	APC n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
Hage 2004	21/21	12/12		Not estimable
Kelty 2004	34/34	34/34		Not estimable
Ragunath 2005	13/13	11/11		Not estimable
Favours treatment 0.1 0.2 0.5 1 2 5 10 Favours control				

Analysis 7.2. Comparison 7 Photodynamic therapy vs argon plasma coagulation, Outcome 2 Any serious drug reactions.

Analysis 7.3. Comparison 7 Photodynamic therapy vs argon plasma coagulation, Outcome 3 Any complication.

Analysis 7.4. Comparison 7 Photodynamic therapy vs argon plasma coagulation, Outcome 4 Mortality.

Analysis 7.5. Comparison 7 Photodynamic therapy vs argon plasma coagulation, Outcome 5 Reduction in length (cm) of Barrett's oesophagus at 12 months.

Study or subgroup	PDT		APC		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI	Fixed, 95% CI
Ragunath 2005	13	2.3 (1.8)	13	3.2 (1.3)		-0.91[-2.1,0.28]
					Favours treatment	Favours control

Analysis 7.6. Comparison 7 Photodynamic therapy vs argon plasma coagulation, Outcome 6 Persistence of sub-squamous glands.

Study or subgroup	PDT		APC		Odds Ratio	Weight	Odds Ratio
	n/N		n/N		M-H, Random, 95% CI		M-H, Random, 95% CI
Hage 2004	1/25		5/14			44.38%	0.08[0.01,0.73]
Kelty 2004	4/17		7/33			55.62%	1.14[0.28,4.62]
Total (95% CI)	42		47			100%	0.34[0.02,4.93]
Total events: 5 (PDT), 12 (APC)							
Heterogeneity: Tau ² =2.83; Chi ² =4.04, df=1(P=0.04); I ² =75.25%							
Test for overall effect: Z=0.79(P=0.43)							
					Favours treatment	Favours control	

Analysis 7.7. Comparison 7 Photodynamic therapy vs argon plasma coagulation, Outcome 7 Complete eradication of Barrett's oesophagus at 12 months.

Study or subgroup	PDT		APC		Odds Ratio	Weight	Odds Ratio
	n/N		n/N		M-H, Random, 95% CI		M-H, Random, 95% CI
Hage 2004	18/21		8/12			50.85%	3[0.54,16.64]
Kelty 2004	17/34		33/34			49.15%	0.03[0,0.25]
Ragunath 2005	0/13		0/13				Not estimable
Total (95% CI)	68		59			100%	0.31[0,32.6]
Total events: 35 (PDT), 41 (APC)							
Heterogeneity: Tau ² =10.28; Chi ² =11.75, df=1(P=0); I ² =91.49%							
Test for overall effect: Z=0.49(P=0.62)							
					Favours treatment	Favours control	

Analysis 7.8. Comparison 7 Photodynamic therapy vs argon plasma coagulation, Outcome 8 Eradication of dysplasia at 12 months.

Study or subgroup	PDT		APC		Odds Ratio	Odds Ratio
	n/N		n/N		M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Ragunath 2005	10/13		6/9			1.67[0.25,11.07]
					Favours experimental	Favours control

Comparison 8. Photodynamic therapy versus omeprazole

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Any reduction/reversal of Barrett's oesophagus/dysplasia at 12 months	2	244	Odds Ratio (M-H, Fixed, 95% CI)	202.73 [38.10, 1078.74]
2 Progression to cancer at latest possible time point	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
3 Any serious drug reactions	2		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
4 Any complication	2	873	Odds Ratio (M-H, Fixed, 95% CI)	65.84 [20.80, 208.45]
4.1 Pain	2	175	Odds Ratio (M-H, Fixed, 95% CI)	23.37 [2.99, 182.42]
4.2 Odynophagia	2	38	Odds Ratio (M-H, Fixed, 95% CI)	8.35 [0.40, 174.50]
4.3 Fever	1	208	Odds Ratio (M-H, Fixed, 95% CI)	36.37 [2.19, 605.21]
4.4 Nausea and vomiting	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.5 Stricture formation	1	208	Odds Ratio (M-H, Fixed, 95% CI)	77.98 [4.73, 1286.52]
4.6 Photosensitivity	2	244	Odds Ratio (M-H, Fixed, 95% CI)	372.83 [29.17, 4765.01]
5 Mortality	2		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
6 Reduction in length (cm) of Barrett's oesophagus at 12 months	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
7 Reduction in area (%) of Barrett's oesophagus at 12 months	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
8 Numbers progressing to dysplasia from intestinal metaplasia	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
9 Complete eradication over the course of the study (5 years)	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
10 Complete eradication of dysplasia	2	244	Odds Ratio (M-H, Fixed, 95% CI)	9.13 [4.42, 18.86]

Analysis 8.1. Comparison 8 Photodynamic therapy versus omeprazole, Outcome 1 Any reduction/reversal of Barrett's oesophagus/dysplasia at 12 months.

Analysis 8.2. Comparison 8 Photodynamic therapy versus omeprazole, Outcome 2 Progression to cancer at latest possible time point.

Analysis 8.3. Comparison 8 Photodynamic therapy versus omeprazole, Outcome 3 Any serious drug reactions.

Analysis 8.4. Comparison 8 Photodynamic therapy versus omeprazole, Outcome 4 Any complication.

Analysis 8.5. Comparison 8 Photodynamic therapy versus omeprazole, Outcome 5 Mortality.

Analysis 8.6. Comparison 8 Photodynamic therapy versus omeprazole, Outcome 6 Reduction in length (cm) of Barrett's oesophagus at 12 months.

Study or subgroup	PDT		Omeprazole		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI	Fixed, 95% CI
Ackroyd 2000	18	1.1 (1.2)	18	0.1 (0.3)		1[0.41,1.59]
					Favours treatment	Favours control

Analysis 8.7. Comparison 8 Photodynamic therapy versus omeprazole, Outcome 7 Reduction in area (%) of Barrett's oesophagus at 12 months.

Study or subgroup	PDT		Omeprazole		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI	Fixed, 95% CI
Ackroyd 2000	18	31.1 (20.3)	18	1.1 (3.2)		30[20.53,39.47]
					Favours treatment	Favours control

Analysis 8.8. Comparison 8 Photodynamic therapy versus omeprazole, Outcome 8 Numbers progressing to dysplasia from intestinal metaplasia.

Study or subgroup	PDT	Omeprazole	Odds Ratio	Odds Ratio
	n/N	n/N	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Ackroyd 2000	0/18	12/18		0.01[0.027]
			Successful Surgical	Medical

Analysis 8.9. Comparison 8 Photodynamic therapy versus omeprazole, Outcome 9 Complete eradication over the course of the study (5 years).

Study or subgroup	PDT	Control	Odds Ratio	Odds Ratio
	n/N	n/N	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Overholt 2005	72/138	5/70		14.18[5.38,37.37]
			Favours experimental	Favours control

Analysis 8.10. Comparison 8 Photodynamic therapy versus omeprazole, Outcome 10 Complete eradication of dysplasia.

Study or subgroup	PDT	Control	Odds Ratio	Weight	Odds Ratio
	n/N	n/N	M-H, Fixed, 95% CI		M-H, Fixed, 95% CI
Ackroyd 2000	6/18	0/18		5.66%	19.24[0.99,373.01]
Overholt 2005	81/138	10/70		94.34%	8.53[4.03,18.06]
Total (95% CI)	156	88		100%	9.13[4.42,18.86]
Total events: 87 (PDT), 10 (Control)					
Heterogeneity: Tau ² =0; Chi ² =0.27, df=1(P=0.6); I ² =0%					
Test for overall effect: Z=5.98(P<0.0001)					
			Favours experimental		Favours control

Comparison 9. 5-ALA vs photofrin

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Eradication of high-grade dysphagia	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
2 Strictures	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected

Analysis 9.1. Comparison 9 5-ALA vs photofrin, Outcome 1 Eradication of high-grade dysphagia.

Study or subgroup	5ALA n/N	photofrin n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
Mackenzie 2008	14/14	9/14		16.79[0.83,340.08]
			Favours experimental	Favours control

Analysis 9.2. Comparison 9 5-ALA vs photofrin, Outcome 2 Strictures.

Study or subgroup	5ALA n/N	photofrin n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
Mackenzie 2008	1/16	6/16		0.11[0.01,1.07]
			Favours experimental	Favours control

Comparison 10. Radiofrequency ablation vs sham

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Any reduction/reversal of Barrett's oesophagus/dysplasia at 12 months	0		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
2 Progression to cancer at latest possible time point	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
3 Any complication	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
3.1 Pain	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.2 Stricture formation	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4 Complete eradication of Barrett's oesophagus at 12 months	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
5 Numbers progressing to dysplasia from intestinal metaplasia	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6 Complete clearance of dysplasia	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
7 Numbers progressing to dysplasia from intestinal metaplasia	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected

Analysis 10.2. Comparison 10 Radiofrequency ablation vs sham, Outcome 2 Progression to cancer at latest possible time point.

Study or subgroup	RFA n/N	Sham n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
Shaheen 2008	1/84	4/43		0.12[0.01,1.09]

Analysis 10.3. Comparison 10 Radiofrequency ablation vs sham, Outcome 3 Any complication.

Study or subgroup	RFA n/N	Sham n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
10.3.1 Pain				
Shaheen 2008	2/84	0/43		2.64[0.12,56.14]
10.3.2 Stricture formation				
Shaheen 2008	5/84	0/43		6.02[0.33,111.44]

Analysis 10.4. Comparison 10 Radiofrequency ablation vs sham, Outcome 4 Complete eradication of Barrett's oesophagus at 12 months.

Study or subgroup	RFA n/N	Sham n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
Shaheen 2008	65/84	1/43		143.68[18.53,1113.87]

Analysis 10.5. Comparison 10 Radiofrequency ablation vs sham, Outcome 5 Numbers progressing to dysplasia from intestinal metaplasia.

Study or subgroup	RFA n/N	Sham n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
Shaheen 2008	0/39	3/19		0.06[0,1.22]

Analysis 10.6. Comparison 10 Radiofrequency ablation vs sham, Outcome 6 Complete clearance of dysplasia.

Study or subgroup	RFA n/N	Sham n/N	Odds Ratio	
			M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
Shaheen 2008	72/84	9/43		22.67[8.72,58.94]
			Favours experimental	Favours control

Analysis 10.7. Comparison 10 Radiofrequency ablation vs sham, Outcome 7 Numbers progressing to dysplasia from intestinal metaplasia.

Study or subgroup	RFA n/N	Sham n/N	Odds Ratio	
			M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
Shaheen 2008	3/84	7/43		0.19[0.05,0.78]
			Favours experimental	Favours control

APPENDICES

Appendix 1. MEDLINE search strategy

1. (mucosal adj5 protecting adj5 agent\$.tw.
2. exp carbenoxolone/
3. exp misoprostol/
4. exp sucralfate/
5. exp muscarinic antagonists/
6. exp dicyclomine/
7. exp propantheline/
8. carbenoxolone.tw.
9. misoprostol.tw.
- 10.sucralfate.tw.
- 11.antimuscarinic\$.tw.
- 12.(muscarinic adj5 receptor adj5 antagonist\$.tw.
- 13.dicyclomine.tw.
- 14.propantheline.tw.
- 15.exp metoclopramide/
- 16.metoclopramide\$.tw.
- 17.exp domperidone/
- 18.domperidone\$.tw.
- 19.exp cisapride/
- 20.cisapride\$.tw.
- 21.Anti-inflammatory agents, non-steroidal/
- 22.nsaid\$.tw.
- 23.nonsteroidal anti-inflammatory.tw.
- 24.non-steroidal anti-inflammatory.tw.
- 25.exp ibuprofen/
- 26.ibuprofen\$.tw.
- 27.aceclofenac\$.tw.
- 28.acemetacin\$.tw.
- 29.dexketoprofen\$.tw.

30.exp diclofenac/
31.diclofenac\$.tw.
32.fenbufen\$.tw.
33.fenoprofen\$.tw.
34.flurbiprofen\$.tw.
35.exp indometacin/
36.indometacin\$.tw.
37.exp ketoprofen/
38.ketoprofen\$.tw.
39.exp mefenamic acid/
40.(mefenamic adj3 acid\$).tw.
41.nabumetone\$.tw.
42.exp naproxen/
43.naproxen\$.tw.
44.exp phenylbutazone/
45.phenylbutazone\$.tw.
46.exp piroxicam/
47.piroxicam\$.tw.
48.exp sulindac/
49.sulindac\$.tw.
50.tenoxicam\$.tw.
51.(tiaprofenic adj3 acid\$).tw.
52.exp cyclooxygenase inhibitor/
53.COX 2.tw.
54.celecoxib\$.tw.
55.etoricoxib\$.tw.
56.valdecoxib\$.tw.
57.rofecoxib\$.tw.
58.exp etodolac/
59.etodolac\$.tw.
60.meloxicam\$.tw.
61.exp aspirin/
62.aspirin\$.tw.
63.(acetylsalicylic adj3 acid\$).tw.
64.exp antioxidants/
65.antioxida\$.tw.
66.exp vitamins/
67.exp vitamin a/
68.retinol\$.tw.
69.exp vitamin c/
70.(ascorb\$ adj3 acid\$).tw.
71.exp vitamin d/
72.calcium\$.tw.
73.exp vitamin e/
74.exp tocopherols/
75.tocopherol\$.tw.
76.exp vitamin k/
77.vitamin\$.tw.
78.exp carotenoids/
79.caroten\$.tw.
80.lutein.tw.
81.lycopene.tw.

82.xanthophylls.tw.
83.exp selenium/
84.selenium\$.tw.
85.difluoromethylornithine\$.tw.
86.dfmo\$.tw.
87.exp lasers/
88.exp laser coagulation/
89.exp light coagulation/
90.exp catheter ablation/
91.(argon adj5 plasma adj5 coagulat\$).tw.
92.APC.tw.
93.exp sclerotherapy/
94.sclerotherap\$.tw.
95.exp electrocoagulation/
96.electrocoagulat\$.tw.
97.(multipolar adj5 coagulat\$).tw.
98.(therm\$ adj5 coagulat\$).tw.
99.(heater adj5 probe).tw.
100(argon\$ adj5 laser\$).tw.
101(YAG adj5 laser\$).tw.
102yag adj5 nd).tw.
103yag adj5 ktp).tw.
104monopolar adj5 coagulat\$).tw.
105bipolar adj5 coagulat\$).tw.
106multipolar adj5 coagulat\$).tw.
107mpc.tw.
108exp photochemotherapy/
109photodynamic adj5 therap\$).tw.
110PDT.tw.
111(ala adj5 pdt).tw.
112aminolaevulin\$ adj5 acid).tw.
113photophrin adj5 pdt).tw.
114endoscopic adj5 mucosal adj5 resect\$).tw.
115ultrasonic adj3 surgical adj3 aspirat\$).tw.
116exp fundoplication/
117fundoplicat\$.tw.
118antireflux adj5 surgery).tw.
119nissen or rossetti).tw.
120toupet or lind or watson or besley).tw.
121(partial\$ adj5 fundoplication\$).tw.
122laparoscop\$ adj5 fundoplication\$).tw.
123exp esophagectomy/
124esophagectomy.tw.
125esophagectomy.tw.
126esophag\$ adj250 neoplas\$).tw.
127oesophag\$ adj250 neoplas\$).tw.
128esophag\$ adj250 cancer\$).tw.
129oesophag\$ adj250 cancer\$).tw.
130esophag\$ adj250 carcin\$).tw.
131oesophag\$ adj250 carcin\$).tw.
132esophag\$ adj250 tumor\$).tw.
133oesophag\$ adj250 tumor\$).tw.

134esophag\$ adj250 metasta\$.tw.
135oesophag\$ adj250 metasta\$.tw.
136esophag\$ adj250 malig\$.tw.
137oesophag\$ adj250 malig\$.tw.
138adenocarcinoma\$ adj250 esophag\$.tw.
139adenocarcinoma\$ adj250 oesophag\$.tw.
140transthoracic adj10 esophag\$.tw.
141transthoracic adj10 oesophag\$.tw.
142thoracic adj10 resect\$.tw.
143ivor adj1 lewis).tw.
144tanner adj25 esophag\$.tw.
145tanner adj25 oesophag\$.tw.
146santy adj25 esophag\$.tw.
147santy adj25 oesophag\$.tw.
148transhiatal adj10 esophag\$.tw.
149transhiatal adj10 oesophag\$.tw.
150orringer adj25 esophag\$.tw.
151orringer adj25 oesophag\$.tw.
152exp cryotherapy/
153cryothera\$ adj5 endoscop\$.tw.
154r/39-234
1558 and 235
15636 and 29

Appendix 2. Criteria for assessment of quality of randomisation of studies

1. Indicates adequate concealment of the allocation (for example, by telephone randomisation, or use of consecutively numbered, sealed, opaque envelopes);
2. Indicates uncertainty about whether the allocation was adequately concealed (for example, where the method of concealment is not known);
3. Indicates that the allocation was definitely not adequately concealed (for example, open random number lists or quasi-randomisation such as alternate days, odd/even date of birth, or hospital number).
4. Indicates randomisation was not used.

WHAT'S NEW

Date	Event	Description
15 May 2013	Amended	Correction to the graph labels in analysis 1.2.

HISTORY

Protocol first published: Issue 1, 2003

Review first published: Issue 1, 2010

Date	Event	Description
7 June 2011	Amended	Correction to abstract and updating risk of bias terminology but no change to overall assessments.
30 October 2008	Amended	Protocol converted to new review format.

CONTRIBUTIONS OF AUTHORS

Jonathan Rees and Pierre Lao-Sirieix contributed equally to this review.

Jonathan Rees and Angela Wong reviewed all manuscripts identified by the search strategy, selected those meeting the inclusion criteria, abstracted data from the included studies and entered these data into RevMan.

Jonathan Rees prepared the manuscript, updated the searches, identified the most recent studies included and abstracted data from these.

Pierre Lao-Sirieix edited the manuscript following editors' comments, updated the searches, identified the studies published since 2006 and abstracted data from these.

Rebecca Fitzgerald reviewed the included studies and reviewed the prepared manuscript.

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Jonathan Rees has also received research funding awards from the Royal College of Surgeons of Edinburgh and Cancer Research UK.

Rebecca Fitzgerald has occasionally acted as a consultant to Astra Zeneca and has research collaboration with Merck and GlaxoSmithKline.

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INDEX TERMS

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Adenocarcinoma [prevention & control]; Barrett Esophagus [*therapy]; Catheter Ablation [methods]; Esophageal Neoplasms [prevention & control]; Gastroesophageal Reflux [therapy]; Laser Coagulation [methods]; Photochemotherapy [methods]; Precancerous Conditions [prevention & control]; Randomized Controlled Trials as Topic

MeSH check words

Humans