Endoscopic treatments for Barrett’s esophagus: a systematic review of safety and effectiveness compared to esophagectomy

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Abstract

Background: Recently, several new endoscopic treatments have been used to treat patients with Barrett’s esophagus with high grade dysplasia. This systematic review aimed to determine the safety and effectiveness of these treatments compared with esophagectomy.

Methods: A comprehensive literature search was undertaken to identify studies of endoscopic treatments for Barrett’s esophagus or early stage esophageal cancer. Information from the selected studies was extracted by two independent reviewers. Study quality was assessed and information was tabulated to identify trends or patterns. Results were pooled across studies for each outcome. Safety (occurrence of adverse events) and effectiveness (complete eradication of dysplasia) were compared across different treatments.

Results: The 101 studies that met the selection criteria included 8 endoscopic techniques and esophagectomy; only 12 were comparative studies. The quality of evidence was generally low. Methods and outcomes were inconsistently reported. Protocols, outcomes measured, follow-up times and numbers of treatment sessions varied, making it difficult to calculate pooled estimates.

The surgical mortality rate was 1.2%, compared to 0.04% in 2831 patients treated endoscopically (1 death). Adverse events were more severe and frequent with esophagectomy, and included anastomotic leaks (9.4%), wound infections (4.1%) and pulmonary complications (4.1%). Four patients (0.1%) treated endoscopically experienced bleeding requiring transfusions. The stricture rate with esophagectomy (5.3%) was lower than with porfimer sodium photodynamic therapy (18.5%), but higher than aminolevulinic acid (ALA) 60 mg/kg PDT (1.4%). Dysphagia and odynophagia varied in frequency across modalities, with the highest rates reported for multipolar electrocoagulation (MPEC). Photosensitivity, an adverse event that occurs only with photodynamic therapy, was experienced by 26.4% of patients who received porfimer sodium.

Some radiofrequency ablation (RFA) or argon plasma coagulation (APC) studies (used in multiple sessions) reported rates of almost 100% for complete eradication of dysplasia. But the study methods and findings were not adequately described. The other studies of endoscopic treatments reported similarly high rates of complete eradication.

Conclusions: Endoscopic treatments offer safe and effective alternatives to esophagectomy for patients with Barrett’s esophagus and high grade dysplasia. Unfortunately, shortcomings in the published studies make it impossible to determine the comparative effectiveness of each of the endoscopic treatments.
Background

Barrett’s esophagus (BE) is a benign condition where abnormal cells (intestinal metaplasia), replace the normal lining of the esophagus. It is typically caused by long-term gastroesophageal reflux disease. Between 2% to 6% of Canadians may have Barrett’s esophagus [1]. Similar prevalence rates have been reported in studies from Sweden (1.6%) and the United States (5.9%) [2,3]. Although Barrett’s esophagus itself is not harmful, in some individuals, precancerous dysplasia develops in the Barrett’s tissue. The presence of dysplasia carries a higher risk of developing esophageal adenocarcinoma - a type of esophageal cancer. In addition to the cancer risk, Barrett’s esophagus decreases patients’ quality of life and increases health care costs [4-7].

The rising incidence of esophageal adenocarcinoma has focused attention on preventing cancer by removing the dysplasia and allowing normal, squamous esophageal mucosa to regenerate. Endoscopic techniques have been developed as a result. They can be applied sequentially to increase diagnostic yield and improve treatment outcomes. There are two categories: endoscopic mucosal resection (EMR) and endoscopic ablation. EMR with cautery snare excision technique can remove visible raised or flat lesions for diagnostic and therapeutic roles. Diagnostically, it allows for complete histopathological assessment of the target mucosa. Those with superficial lesions can go on to further ablative techniques. Lesions that are found to invade submucosa may need referral for surgical resection. Therapeutically, EMR can be used for curative intent if the target lesion is small. However, in most cases of Barrett’s esophagus, it is used to remove dysplastic nodules leaving the larger surface area for endoscopic ablation.

Photodynamic therapy (PDT) is one of the new endoscopic treatments used to remove dysplasia. Other endoscopic treatments include: argon plasma coagulation (APC), cryoablation, laser ablation, multipolar electrocoagulation (MPEC), radiofrequency ablation (RFA), and thermocoagulation. Depending on the extent of dysplasia, several endoscopic treatment sessions or a combination of treatments may be used.

Patients also receive long-term drug therapy to control gastroesophageal reflux and prevent further damage to the esophagus [8]. Endoscopic therapies are less invasive alternatives to esophagectomy (surgical removal of the esophagus), which is associated with high rates of morbidity and mortality, and with decreased quality of life [9-11].

Clinicians now have a variety of technologies to choose from when treating Barrett’s esophagus with dysplasia. This systematic review of published clinical studies compares the evidence on the safety and effectiveness of the endoscopic treatments and of esophagectomy and may provide some guidance for clinical practice.

Methods

Data collection

Literature search

An extensive search for published and unpublished studies of endoscopic and non-endoscopic procedures for Barrett’s esophagus was performed. Search terms included keywords and controlled vocabulary terms used to describe Barrett’s, photodynamic therapy and other endoscopic techniques, and esophagectomy. Searches for the alternative treatments (i.e., other than PDT) were limited to studies from 2003 to January 2009. The bibliographic databases searched included: PubMed (MEDLINE), The Cochrane Library, the UK Centre for Reviews and Dissemination (DARE, Health Technology Assessment, and NHS Economic Evaluation) databases, EMBASE, CINAHL, Web of Science and EconLit. Monthly update searches in PubMed were run throughout the project to identify new studies. Meeting abstracts from the American Society of Clinical Oncology and Digestive Disease Week, as well as practice guidelines and clinical trials web sites were also searched, as were the reference lists from relevant papers and earlier health technology assessments.

Study selection

Results from the literature searches were imported into a Reference Manager database to remove duplicates and manage bibliographic citations. Titles and abstracts (where available), were independently screened by two researchers. The full papers of potentially relevant studies were retrieved and assessed against pre-defined inclusion criteria (Table 1). Non-English language studies were excluded, unless an English language abstract provided sufficient detail on patients and outcomes.

Critical appraisal and synthesis

Information from the studies was extracted by two reviewers using a pre-tested data abstraction form and a set of decision rules. The form contained elements for examining the purpose and methods of each study (Table 2). Missing data were sought from study authors. Consensus between reviewers on the information collected was assessed using the Kappa statistic.

The quality of each study was also assessed by two reviewers using the Oxford Centre for Evidence-based Medicine Levels of Evidence [12]. Discrepancies were resolved through consensus and Kappa scores were calculated.

Data analysis

Qualitative

Information was summarized in tabular form to more easily identify trends or patterns in findings reported across studies.

Quantitative

Results from individual studies were pooled using weighted mean values to generate summary estimates.
for each of the outcomes of interest. All quantitative analyses were conducted in accordance with intention-to-treat principles (i.e., patients were analyzed in the groups to which they were originally allocated, regardless of whether or not they received the assigned treatment).

**Results**

**Description of studies**

Over 400 potentially relevant papers were selected from the literature search results and reviewed for inclusion (Figure 1). Of these, 99 papers, reporting on 101 separate studies and 3042 patients, met the inclusion criteria. Descriptions of each study are presented in Additional files 1, 2, 3, 4, 5, 6, 7, and 8. A breakdown of studies by the type of intervention and study design is presented in Table 3.

**Quality of studies**

The quality of the evidence reviewed was generally low. Only 12 studies were comparative (Table 3), and of these, 5 were cohort studies with uncontrolled allocation of patients to each treatment group. Details of the study methods used were sparse, with missing information or inconsistent reporting of outcomes across patient groups.

Seven randomized controlled trials (RCTs) were identified, but these compared only APC with PDT (4 trials [13-16]), or APC with MPEC (2 trials [17,18]), or RFA with sham procedure (1 trial [19]). Sample sizes were small and follow-up times were short. Because the types of patients and the treatment protocols (e.g., number of treatment sessions) varied a meta-analysis was not used.

In the non-comparative studies of endoscopic techniques (single arm clinical trials or case series), the treatment protocols (e.g., number of treatment sessions), outcomes measured, and follow-up times also differed. There were few studies that reported long-term follow up results, and so pooling of study outcome and adverse event results is limited. As well, the number of treatment sessions provided before outcomes were measured was not often reported, although in many cases, it was after a single ablation. Patients often received interventions in addition to the study treatment. For example, in most studies EMR was performed during endoscopy to confirm the diagnosis of dysplasia. In addition, if one treatment failed to eradicate the dysplasia another treatment would typically be administered. The analyses of outcomes did not usually account for the effects of these additional interventions.

**Safety**

Adverse events reported for individual studies of esophagectomy and endoscopic alternatives are summarized in Table 4 and Additional file 9. The pooled estimates for esophagectomy and endoscopic treatments are
Notes: *10 new studies were added since the first literature review. Of these studies, 6 were included, and 4 were excluded.
shown in Tables 5 and 6. There were 2 deaths [20,21] attributed to esophagectomy among the 170 patients who underwent the procedure (a mortality rate of 1.2%). (The surgical studies employed various approaches; in some studies, the actual approach was not specified, and in the others, a number of approaches were used (i.e., the patients did not all have the same surgical approach). Therefore, data could not be analysed according to individual surgical approaches). In contrast, 1 death [13] was reported in the 2831 patients who received endoscopic treatment (0.04%). This death was due to cardiac arrhythmia in a patient who received PDT with aminolevulinic acid (ALA) at a dose of 60 mg/kg of body weight [13].

In the studies that reported bleeding complications following endoscopic treatments, 4 of 2218 patients (0.2%) experienced bleeding requiring transfusions: 1 after PDT [22], 2 after APC [23] and 1 after laser ablation [24]. Strictures were most frequently reported with porfimer sodium PDT (18.5%), followed by laser ablation (4.4%) and APC (2.9%) (Table 6). Although there were no perforations reported in the PDT studies that used a single photosensitizer (reported in Table 6), there was a perforation reported in the Prasad et al study [21], which compared esophagectomy with PDT using two different photosensitizers. Since it was impossible to separate the patients according to the photosensitizer type, this study was not included in Table 6. Patients experiencing dysphagia and odynophagia varied across the treatment modalities, but were highest with MPEC (Table 6). Photosensitivity following PDT was more common with porfimer sodium (26.4%) than with ALA (ranging from 0% to 13.6%). However, in a small series of 5 patients who received hematoporphyrin derivative (HpD), 40% experienced photosensitivity reactions (Table 6).

The most commonly reported adverse events associated with esophagectomy were anastomotic leaks (9.4%), strictures (5.3%), wound infections (4.1%) and pulmonary complications (4.1%) (Table 5). None of the studies discussed the relationship between adverse events and clinician experience.

### Efficacy or effectiveness

Values reported for the complete eradication of BE or high grade dysplasia (HGD) with endoscopic treatments are presented in Additional files 10 and 11. Pooled values for complete eradication of BE and HGD with endoscopic treatments are presented in Table 7. For the purposes of this analysis, only the complete eradication rates reported in the individual studies within the first 3 months after ablation were included. Few studies provided enough data on longer follow up periods to make pooling of the data meaningful. The studies did not all report the number of ablations that were provided before the outcome was measured, and in many cases, the authors reported a range of number of treatments.

Results of 2 of the 3 RCTs of PDT (with ALA) versus APC in patients with BE demonstrated a significant difference in complete eradication, favouring APC over PDT [13,14]. Specifically, the complete eradication rates in the APC group were almost double that of the PDT group (Additional file 10). In the third RCT, complete eradication rates were not reported for both groups of patients [16].

Two RCTs reported on complete eradication of HGD [15,19]. In the RCT which compared PDT using porfimer sodium to APC, there was no statistically significant difference in complete eradication rate between treatment groups at 4 months follow-up [15]. In the RCT which compared RFA with sham procedure, there was a statistically significant difference in complete eradication...
Table 4 Studies of adverse events post-esophagectomy

| Study | No. of patients | A.leak* | CV compl.* | Del. gastric emptying* | Mortality | Pneumon.* | Pulm. compl.* | Pulm. embol.* | Small bowel perf.* | Strictures | Wound infec.* |
|-------|----------------|---------|------------|------------------------|-----------|-----------|-------------|-------------|-----------------|------------|--------------|
|       |                | (No. of patients who suffered adverse events/No. of patients who received esophagectomy) | | | | | | | | | |
| **Comparative studies** | | | | | | | | | | | |
| Prasad GA, et al. (2007)[21] | 70 | 0% (0/70) | 0% (0/70) | 1.4% (1/70) | 0% (0/70) | 0% (0/70) | 0% (0/70) | 0% (0/70) | 12.9% (9/70) | 0% (0/70) |
| Reed MF, et al. (2005)[20] | 49 | 4.1% (2/49) | 0% (0/49) | 2.0% (1/49) | 0% (0/49) | 0% (0/49) | 0% (0/49) | 0% (0/49) | 0% (0/49) | 0% (0/49) |
| Thomas T, et al. (2005)[55] | 8 | Not reported | Not reported | Not reported | Not reported | Not reported | Not reported | Not reported | Not reported | Not reported |
| **Non-comparative studies** | | | | | | | | | | | |
| Ferguson MK, et al. (1997)[107] | 15 | 73.3% (11/15) | 20.0% (3/15) | 0% (0/15) | 0% (0/15) | 26.7% (4/15) | 0% (0/15) | 0% (0/15) | 33.3% (5/15) | |
| Nguyen NT, et al. (2000)[108] | 12 | 0% (0/12) | 0% (0/12) | 25.0% (3/12) | 0% (0/12) | 16.7% (2/12) | 0% (0/12) | 8.3% (1/12) | 8.3% (1/12) | |
| Romagnoli R (2003)[109] | 33 | Not reported | Not reported | Not reported | Not reported | Not reported | Not reported | Not reported | Not reported | |
| Sujendran V, et al. (2005)[110] | 17 | 17.6% (3/17) | 0% (0/17) | 0% (0/17) | 17.6% (3/17) | 5.9% (1/17) | 0% (0/17) | 0% (0/17) | 0% (0/17) | |
| Thomson BNJ & Cade RJ (2003) [111] | 7 | 0% (0/7) | 0% (0/7) | 0% (0/7) | 0% (0/7) | 0% (0/7) | 0% (0/7) | 0% (0/7) | 0% (0/7) | 14.3% (1/7) |
| **Pooled total** | 211 | 9.4% (16/170) | 1.8% (3/170) | 1.2% (2/170) | 1.8% (3/170) | 4.1% (7/170) | 0.6% (1/170) | 0.6% (1/170) | 5.3% (9/170) | 4.1% (7/170) |

Notes: (1) *A.leak (anastomotic leak), CV compl. (cardiovascular complication), Del. gastric emptying (delayed gastric emptying), Pneumon. (pneumonia), Pulm. compl. (pulmonary complication), Pulm. embol. (pulmonary embolism), Small bowel perf. (small bowel perforation), Wound infec. (wound infection) (2) ‡Ranges of the adverse event rates post-esophagectomy for the included studies.
rate between the group treated by RFA (81.0%) and the control group (19.0%) at 12 months follow-up [19].

Discussion
Endoscopic therapies appear to be viable and effective treatment options for Barrett’s esophagus with high grade dysplasia. All of the endoscopic therapies are safer (i.e., have fewer adverse events and lower mortality rates) than esophagectomy.

Some key questions regarding these treatments cannot yet be answered and further studies are needed to address these “gaps in the evidence”. In particular, we need studies:

- to confirm the long-term safety of these endoscopic treatments, and their effectiveness in preventing esophageal cancer
- to identify the endoscopic treatments (or combinations of treatments) that produce the best outcomes
- to determine whether or not continued drug therapy (e.g., with proton pump inhibitors) or surgery (e.g., fundoplication) to treat gastroesophageal reflux is beneficial after endoscopic treatment of dysplasia
- to provide guidance on the optimal frequency of post-treatment endoscopic surveillance for patients with Barrett’s esophagus
- to measure patient preferences for, and quality of life after, the different endoscopic treatments.

Conclusions
Given the current limitations in the evidence (in terms of both quantity and quality of studies), it was not possible to conclusively determine the comparative effectiveness of the different endoscopic treatments. However, the evidence suggests that endoscopic treatments are safe and reasonably effective alternatives to esophagectomy for patients with Barrett’s esophagus with high grade dysplasia. Endoscopic treatments have the additional advantages of being outpatient procedures with shorter recovery times. They also provide treatment options for patients who would not be considered for esophagectomy due to other health conditions.

Of the endoscopic therapies, photosensitivity is only an issue with photodynamic therapy (more so with porfimer sodium than with other photosensitizing agents). Preventing adverse events due to photosensitivity requires patient and caregiver compliance and education.

There appears to be little difference between the endoscopic technologies in terms of overall efficacy. Patient and physician preferences, and the local availability of the different technologies will likely guide decision making. A combination of different endoscopic treatments may provide the best outcomes. Given that relatively few patients need these treatments each year, offering them at specialized centres will concentrate clinical expertise and be the most cost-effective approach.

Additional material

Additional file 1: Studies of photodynamic therapy (PDT) for Barrett’s esophagus with/without dysplasia. Details of study and patient characteristics, outcomes and study quality of the included studies of PDT for BE with/without dysplasia are presented in Additional file 1.

Additional file 2: Studies of argon plasma coagulation (APC) for Barrett’s esophagus with/without dysplasia. Details of study and patient characteristics, outcomes and study quality of the included studies of APC for BE with/without dysplasia are presented in Additional file 2.

Additional file 3: Studies of cryoablation, combined endoscopic mucosal resection (EMR) and photodynamic therapy (PDT), and thermocoagulation for Barrett’s esophagus with/without dysplasia. Details of study and patient characteristics, outcomes and study quality of the included studies of cryoablation, combined EMR and PDT, and thermocoagulation for BE with/without dysplasia are presented in Additional file 3.

Additional file 4: Studies of endoscopic mucosal resection (EMR) for Barrett’s esophagus with/without dysplasia. Details of study and patient characteristics, outcomes and study quality of the included studies of EMR for BE with/without dysplasia are presented in Additional file 4.

Additional file 5: Studies of laser ablation for Barrett’s esophagus with/without dysplasia. Details of study and patient characteristics, outcomes and study quality of the included studies of laser ablation for BE with/without dysplasia are presented in Additional file 5.

Additional file 6: Studies of multipolar electrocoagulation (MPEC) for Barrett’s esophagus with/without dysplasia. Details of study and patient characteristics, outcomes and study quality of the included studies of MPEC for BE with/without dysplasia are presented in Additional file 6.
Table 6 Summary of adverse events post-endoscopic treatments

| Study                  | Dysphagia | Photosen.* | Stricture | Perfor.*  | Odynoph.* | Bleed.* |
|------------------------|-----------|------------|-----------|-----------|-----------|---------|
| **PDT**                |           |            |           |           |           |         |
| ALA 15 mg/kg           | 15.4% (2/13) | 13.6% (3/22) | 0-23.1%† | 0% (0/22) | 0% (0/22) | 0% (0/22) |
| ALA 30 mg/kg           | 0% (0/106)  | 5.7% (6/106) | 0-14.7%† | 0% (0/106) | 0% (0/106) | 0.9% (1/106) | 0-2.9%† | 0% (0/90) |
| ALA 40 mg/kg           | 0% (0/22)  | 0% (0/22)  | 0% (0/22) | 0% (0/22) | 0% (0/22) |
| ALA (1) 60 mg/kg       | 2.7% (4/148) | 4.3% (6/140) | 0-75.0%† | 1.4% (2/148) | 0-12.5%† | 0% (0/148) | 16.2% (24/148) | 0-92.3%† | 0.9% (1/115) | 0-7.7%† |
| HpcD 1.5 mg/kg         | 0% (0/59)  | 40.0% (2/5) | 0% (0/59) | 0% (0/59) | 0% (0/5) | 0% (0/59) |
| mTHPC 0.15 mg/kg       | **         | **         | **        | **        | **        | **        |
| Porfimer sodium(2 mg/kg)| 6.6% (26/394) | 26.4% (104/394) | 0-68.8%† | 18.5% (73/394) | 0-37.5%† | 0% (0/394) | 0% (0/394) | 0% (0/394) |

| Other endoscopic treatments |
|-----------------------------|
| APC                         | 3.8% (27/719) | 0-100%† | 2.9% (21/719) | 0-23.1%† | 0.3% (2/719) | 0-3.4%† | 11.8% (85/719) | 0-94.1%† | 0.4% (3/719) | 0-3.9%† |
| Cryoablation                | 9.1% (1/11)  | 0% (0/11) | 0% (0/11) | 0% (0/11) | 0% (0/11) | 0% (0/11) |
| Combined EMR & PDT          | 0% (0/6)     | 0% (0/6)  | 0% (0/6)  | 0% (0/6)  | 0% (0/6)  | 0% (0/6)  |
| Thermocoagulation           | 0% (0/13)    | 0% (0/13) | 0% (0/13) | 0% (0/13) | 0% (0/13) | 0% (0/13) |
| EMR                         | 0% (0/32)    | 0% (0/32) | 0% (0/32) | 0% (0/32) | 0% (0/32) | 0% (0/32) | 9.4% (3/32) | 0-25.0%† |
| Laser ablation              | 0% (0/68)    | 0% (0/68) | 4.4% (3/68) | 0-12.5%† | 1.5% (1/68) | 0-4.8%† | 0% (0/68) | 1.5% (1/68) | 0-4.8%† |
| MPEC                        | 19.4% (18/93) | 0-40.7%† | 1.1% (1/93) | 0-3.7%† | 0% (0/93) | 16.1% (15/93) | 0-40.7%† | 1.1% (1/93) | 0-10.0%† |
| RFA                         | 1.4% (8/574) | 0-23.1%† | 1.9% (11/574) | 0-6.1%† | 0% (0/574) | 0.5% (3/574) | 0-23.1%† | 0.5% (3/574) | 0-1.6%† |

Notes: (1) 1 patient suffered cardiac arrhythmia resulting in sudden death [13]. (2) 2 patients required blood transfusions. (3) ALA (aminolevulinic acid), APC (argon plasma coagulation), EMR (endoscopic mucosal resection), HpcD (hematoporphyrin derivative), MPEC (multipolar electrocoagulation), mTHPC (meta-tetrahydroxyphenylchlorin), PDT (photodynamic therapy), RFA (radiofrequency ablation) (4) 1 patient required blood transfusion, but it cannot be definitely attributed to the 30 mg/kg treatment or the 60 mg/kg ALA treatment. (5) 1 patient required blood transfusion. (6) * Photosen. (photosensitivity), Perfor. (perforation), Odynoph. (odynophagia), Bleed. (bleeding). ** - (pooled total not available), † Ranges of the adverse event rates post-endoscopic treatments for the included studies
Table 7 Summary of complete eradication (CE) of BE and HGD post-endoscopic treatments

| Study | CE rates of BE post-treatments (No. of patients who achieved CE of BE/No. of patients who received treatments) | CE rates of HGD post-treatments (No. of patients who achieved CE of HGD/No. of patients who received treatments) |
|-------|-------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------|
|       | Up to 3 months                                                                                   | Up to 3 months                                                                                   |
|       | At 12 months                                                                                     | At 12 months                                                                                     |
|       | PDT                                                                                              | Other endoscopic treatments                                                                       |
| ALA 15 mg/kg | 30.4% (7/23) 21.4-44.4%†                                                                  | No studies of HGD                                                                              |
| ALA 30 mg/kg | 43.9% (18/41) 14.3-50.0%†                                                                  | No studies of HGD                                                                              |
| ALA 40 mg/kg | 0% (0/2)                                                                                       | 68.2% (15/22) 0-75.0%†                                                                         |
| ALA 60 mg/kg | 19.2% (5/26)                                                                                   | 96.6% (28/29) 96.3-100%†                                                                       |
| HpD 1.5 mg/kg | 0% (0/5)                                                                                      | 100% (1/1)                                                                                     |
| mTHPC 0.15 mg/kg | 16.7% (1/6)                                                                                   | 66.7% (4/6)                                                                                     |
| Porfimer sodium (2 mg/kg) | 51.6% (94/182) 26.3-56.4%†                                                                   | 77.5% (62/80) 100% (2/2)                                                                      |
| APC                                                                                           |                                                                                                 |
| 85.5% (372/435) 0-100%†                                                                  | 64.9% (50/77) 0-93.8%†                                                                         | 85.7% (6/7) 0% (0/0)                                                                          |
| Cyroablation                                                                                   |                                                                                                 |
| 81.8% (9/11)                                                                                   | 63.6% (7/11)                                                                                   | 100% (1/1)                                                                                     |
| Combined EMR & PDT                                                                              |                                                                                                 |
| .**                                                                                           | .**                                                                                             | 66.7 (2/3)                                                                                     |
| Thermocoagulation                                                                              |                                                                                                 |
| 100% (13/13)                                                                                  | .**                                                                                             | No studies of HGD                                                                              |
| EMR                                                                                           |                                                                                                 |
| 100% (1/1)                                                                                    | No studies of HGD                                                                              |
| Laser ablation                                                                                 |                                                                                                 |
| 77.3% (58/75) 22.2-100%†                                                                       | 96.3% (26/27) 92.9-100%‡                                                                       |
| MPEC                                                                                           |                                                                                                 |
| 88.5% (23/26)                                                                                 | 100% (10/10)                                                                                   |
| RFA                                                                                           |                                                                                                 |
| 69.0% (118/171) 21.9-97.7%†                                                                   | 72.3% (170/235) 46.2%-92.6%‡                                                                  |
| Notes: (1) ALA (aminolevulinic acid), APC (argon plasma coagulation), EMR (endoscopic mucosal resection), HpD (hematoporphyrin derivative), MPEC (multipolar electrocoagulation), mTHPC (meta-tetrahydroxyphenylchlorin), PDT (photodynamic therapy), RFA (radiofrequency ablation) (2) † (pooled total not available), ‡ Ranges of the complete eradication rates post-endoscopic treatments for the included studies.  

Additional file 7: Studies of radiofrequency ablation (RFA) for Barrett’s esophagus with/without dysplasia. Details of study and patient characteristics, outcomes and study quality of the included studies of RFA for BE with/without dysplasia are presented in Additional file 7.

Additional file 8: Studies of esophagectomy for Barrett’s esophagus with/without dysplasia. Details of study and patient characteristics, outcomes and study quality of the included studies of esophagectomy for BE with/without dysplasia are presented in Additional file 8.

Additional file 9: Studies of adverse events (endoscopic treatments). Adverse events reported for individual studies of endoscopic alternatives are presented in Additional file 9.

Additional file 10: Studies of complete eradication of Barrett’s esophagus (endoscopic treatments). Values reported for the complete eradication of BE with endoscopic treatments are presented in Additional file 10.

Additional file 11: Studies of complete eradication of high grade dysplasia (endoscopic treatments). Values reported for the complete eradication of HGD with endoscopic treatments are presented in Additional file 11.

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Authors’ contributions

DM and CW made substantial contributions to the conception and design of the study, to interpretation of the data, and have reviewed and revised the manuscript for important intellectual and clinical content. TS made a substantial contribution to the conception and design of the study, interpretation of the data, and was involved in writing and critically reviewing drafts of the manuscript. HW was involved in the acquisition, analysis and interpretation of the data and making major revisions to draft manuscripts. DL was involved in the conception and design of the study, acquisition and analysis of data and drafting the manuscript. All authors have given approval for submission of this version.

Competing interests

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References

1. Tougas G, Chen Y, Hwang P, Liu MM, Eggleston A: Prevalence and impact of upper gastrointestinal symptoms in the Canadian population: findings from the DIGEST study. Domestic/International Gastroenterology Surveillance Study. Am J Gastroenterol 1999, 94:2845-2854.

2. Ronkainen J, Aro P, Storskrubb T, Johansson SE, Lind T, Bolling-Stermeyva E, Vieth M, Stolte M, Talley NJ, Agreus L: Prevalence of Barrett’s esophagus in the general population: an endoscopic study. Gastroenterology 2005, 129:1825-1831.
acid for high grade dysplasia in Barrett’s esophagus: Longterm follow up of 51 patients [abstract]. Gastroenterology 2005, 128:A238.

24. Fisher RS, Bromer MQ, Thomas RM, Cohen S, Krevisky B, Horwitz B, Glazer KD, Das K, Das RA: Predictors of recurrent specialized intestinal metaplasia after complete laser ablation. Am J Gastroenterology 2003, 98:1945-1951.

25. Behrens A, May A, Gassner L, Gunter E, Peck O, Veth M, Stolte M, Seitz G, Ell C: Curative treatment for high-grade intraepithelial neoplasia in Barrett’s esophagus. Endoscopy 2005, 37:999-1005.

26. Orttner MA, Zumbusch K, Liebfreund J, Ebert B, Feigen B, Dietel M, Holmes C: Is topical delta-aminolevulinic acid adequate for photodynamic therapy in Barrett’s esophagus? A pilot study. Endoscopy 2002, 34:611-616.

27. Orttner M, Zumbusch K, Liebfreund J, Ernst H, Weber J, Werth J, Wedel S, Loch H: Photodynamic therapy of Barrett’s esophagus after local administration of 5-aminolaevulinic acid [abstract]. Gastroenterology 1997, 112:A633.

28. Ackroyd R, Kelty CJ, Brown NJ, Stephenson TJ, Stoddard CJ, Reed MW: Eradication of dysplastic Barrett’s oesophagus using photodynamic therapy: long-term follow-up. Endoscopy 2003, 35:496-501.

29. Ackroyd R, Davis MF, Brown NJ, Stephenson TJ, Stoddard CJ, Reed MW: Photodynamic therapy (PDT): a new treatment for Barrett’s oesophagus [abstract]. Lasers Med Sci 1997, 12:292.

30. Ackroyd R, Brown NJ, Davis MF, Stephenson TJ, Stodddard CJ, Reed MW: Aminolaevulinic acid-induced photodynamic therapy in the treatment of dysplastic Barrett’s oesophagus and adenocarcinoma. Lasers Med Sci 1999, 14:278-285.

31. Mackenzie G, Selvasekar C, Clark BR, Novelli M, Thorpe S, Mosse C, Bown S, Lovat L: Randomised controlled trial of photodynamic therapy using low dose 5 aminolaevulinic acid activated by red or green light for high grade dysplasia in Barrett’s oesophagus [abstract]. Gastroenterology 2005, 128:A239.

32. Peters F, Kara M, Rossmolen W, Aalders M, ten KF, Krishnadath K, van LJ, Fockens P, Bergman J: Poor results of 5-aminolaevulinic acid-photodynamic therapy for residual high-grade dysplasia and early cancer in Barrett’s esophagus after endoscopic resection. Endoscopy 2005, 37:418-424.

33. van Hillegersberg R, Haringsma J, Ten Kate FJ, Tytgat GN, van Lanschot J: Invasive carcinoma after endoscopic ablative therapy for high-grade dysplasia in Barrett’s oesophagus. Dig Surg 2003, 20:440-444.

34. Barr H, Shepherd NA, Dixon A, Roberts DJ, Tan WC, Krasner N: Eradication of high-grade dysplasia in columnar-lined (Barrett’s) oesophagus by photodynamic therapy with endogenously generated protoporphyrin IX. Gut 1996, 38:584-585.

35. Gassner L, Stolte M, Sroka R, Rick K, May A, Hahn EG, Ell C: Photodynamic ablation of high-grade dysplasia and early cancer in Barrett’s esophagus by means of 5-aminolaevulinic acid. Gastroenterology 1998, 114:448-455.

36. Gassner L, May A, Sroka R, Ell C: A new long-range through-the-scope balloon applicator for photodynamic therapy in the esophagus and cardia. Endoscopy 1999, 31:370-376.

37. Kashlan H, Umanisky M, Birkenfeld S, Schenkel H, Haddad R, Greenberg R, Konikoff F: Photodynamic therapy of Barrett’s esophagus with dysplasia using systemic aminolaevulinic acid and a non-laser light source. A phase I pilot study. Gastrointestinal Oncology 2002, 4:153-157.

38. Mackenzie GD, Dunn JM, Novelli MR, Mosse S, Thorpe SM, Bown SG, Lovat LB: Preliminary results of a randomised controlled trial into the safety and efficacy of ALA versus photofrin photodynamic therapy for high grade dysplasia in Barrett’s oesophagus [abstract]. Gut 2008, 57:A14.

39. Macrae FA, Rajsekaram R, Thomas R, Bhatnal PS: Photodynamic therapy in high grade dysplasia in Barrett’s oesophagus using 5 aminolaevulinic acid sensitization [abstract]. Gastroenterology 2004, 59:P252.

40. Mehlitz JC, Mackenzie G, Selvasekar C, Novelli M, Thorpe S, Mosse C, Bown S, Lovat L: Reversal of Barrett’s oesophagus following photodynamic therapy using high dose 5 aminolaevulinic acid activated by red or green laser light [abstract]. Gastroenterology 2005, 128:A239.
41. Laakkia, MA, Wang, K.K. Initial results using low-dose photodynamic therapy in the treatment of Barrett's esophagus. Gastroenterol Endosc 1995, 42:59-63.

42. Wang, K.K., Wongkeesong, LN, Nourbakhsh, A., Laakkia, M., Gutta, K., Geller, A., Balm, P. Controlled trial of low dose photodynamic therapy for Barrett's esophagus [abstract]. Gastroenterology 1997, 112:A476.

43. Wang, K.K., Njihawun, P., Nourbakhsh, A., Lutzer, L., WongkeeSong, M., Anderson, M. Does residual Barrett's esophagus progress after photodynamic therapy? [abstract]. Gastroenterology 1999, 116:A438.

44. Javadi, B., Watt, P., Krasner, N. Photodynamic therapy (PDT) for oesophageal dysplasia and early carcinoma with mTHPC (m-tetrahydroxyphenyl chlorin): a preliminary study. Lasers Med Sci 2002, 17:51-56.

45. Lovat, L.B., Jamieson, N.F., Novelli, M.R., Mosse, C.A., Selvasekar, C., Mackenzie, G.D., Thorpe, S.M., Bown, S.G. Photodynamic therapy with m-tetrahydroxyphenyl chlorin for high-grade dysplasia and early cancer in Barrett's columnar lined esophagus. Gastroenterol Endosc 2005, 42:617-623.

46. Attia, T., Kortan, P., Kandel, G.T., Marcon, N. Photodynamic therapy (PDT) for Barrett's esophagus with high grade dysplasia (BE-HGD) [abstract]. Gastroenterol Endosc 2005, 41:A127.

47. Bronner, M., Taylor, S., Overholt, B., Wang, K., Burdick, S., Lightdale, C., Kimmey, M., Nava, H., Sivak, M., Nishioka, N., et al. Squamous overgrowth in a 5-year randomized phase III trial of photodynamic therapy using porfimer sodium in the treatment of high-grade dysplasia in Barrett's esophagus [abstract]. Gastroenterology 2006, 130:A121.

48. Keeley, S.B., Pennathur, A., Gooding, W., Landreneau, R., Christie, N.A., Luketich, J. Photodynamic therapy with curative intent for Barrett's esophagus with high grade dysplasia and superficial esophageal cancer. Ann Surg Oncol 2007, 14:2406-2410.

49. Overholt, B.F., Wang, K.K., Burdick, J.S., Lighthall, C., Kimmey, M., Nava, H., Sivak, M.V., Nishioka, N., et al. Five-year efficacy and safety of photodynamic therapy with Photofrin in Barrett's high-grade dysplasia. Gastroenterol Endosc 2007, 66:460-468.

50. Overholt, B.F., Panjehpour, M., Halberg, D.L. Photodynamic therapy for Barrett's esophagus with dysplasia and/or early stage carcinoma: long-term results. Gastroendosc Endosc 2003, 58:183-188.

51. Yachimski, P., Puricelli, W.P., Nishioka, N.S. Patient predictors of esophageal stricture development after photodynamic therapy. Clin Gastroenterol Hepatol 2008, 6:302-308.

52. Weiss, A.A., Wiesinger, H.O., Oren, D. Photodynamic therapy in Barrett's esophagus: Results of treatment of 17 patients. Can J Gastroenterol 2006, 20:261-264.

53. Thomas, T., Richards, A., de Caestecker, J., Robinson, R.J. High-grade dysplasia in Barrett's oesophagus: natural history and review of clinical practice. Aliment Pharmacol Ther 2005, 21:747-755.

54. Attila, T., Kortan, P., Kandel, G.T., Marcon, N. Photodynamic therapy for oesophageal dysplasia and early carcinoma with mTHPC (m-tetrahydroxyphenyl chlorin): a preliminary study. Lasers Med Sci 2002, 17:51-56.

55. Pedrazzani, C., Catalano, F., Festini, M., Zerman, G., Ruzzenente, A., Guglielmi, A., de MG. Endoscopic ablation of Barrett's esophagus using high power setting argon plasma coagulation: a prospective study. World J Gastroenterol 2005, 11:1872-1875.

56. Pereira-Lima, J.C., Buinello, J.V., Saul, C., Tonekota, E.B., Lopes, C.V., Ryndzenko, C.B., Biya, C. High power setting argon plasma coagulation for the eradication of Barrett's esophagus. Am J Gastroenterol 2000, 95:1661-1668.

57. Pinotti, A.C., Ceccanello, I., Filho, F.M., Sakai, P., Gama-Rodrigues, J.J., Pinotti, H.W. Endoscopic ablation of Barrett's esophagus using argon plasma coagulation: a prospective study after fundoplication. Dis Esophagus 2004, 17:243-246.

58. Tiggas, H., Fuchs, H., Moroske, J., Fein, M., Freys, S.M., Muller, J., Thieme A. Combination of endoscopic argon plasma coagulation and antireflux surgery for treatment of Barrett's esophagus. J Gastroint Surg 2001, 5:251-259.

59. Van Laethem, J.L., Jagodzinski, R., Peny, M.O., Cremer, M., Deviere, J. Argon plasma coagulation in the treatment of Barrett's high-grade dysplasia and in situ adenocarcinoma. Endoscopy 2001, 33:257-261.

60. Van Laethem, J.L., Cremer, M.O., Peny, M.O., Dehaeye, M., Deviere, J. Eradication of Barrett's mucosa with argon plasma coagulation and acid suppression: immediate and mid term results. Gut 1998, 43:747-751.

61. Damot, J.A., Vargo, J.J., Zuccaro, G., Falk, W.G., Frey, L., Rice, T. Results of cryosurgery ablation for esophageal high grade dysplasia (HGD) and intramucosal cancer (lmc) in high risk non-surgical patients (abstract). Digestive Disease Week 2008, M1304.

62. Johnston, M.H. Cryoablation of Barrett's esophagus: A pilot study. Gastroint Endosc 2005, 62:842-848.

63. Wolfsen, H.C., Hemminger, L.L., Raimondi, M., Woodward, T.A. Photodynamic therapy and endoscopic mucosal resection for Barrett's dysplasia and early esophageal adenocarcinoma. South Med J 2004, 97:827-830.

64. Michopoulos, S., Tsibouri, P., Bouzakis, G., Sotiropoulou, M., Kalonis, N. Complete regression of Barrett's esophagus with heat probe thermoocoagulation: mid-term results. Gastroint Endosc 1999, 50:165-172.

65. Giovannini, M., Bories, E., Pesenti, C., Moutardier, V., Morges, G., Danilo, C., Leibng, B., Delpero, J.R. Circumferential endoscopic mucosal resection in Barrett's esophagus with high-grade intraepithelial neoplasia or mucosal cancer. Preliminary results in 21 patients. Endoscopy 2004, 36:782-787.

66. Mino-Kenudson, M., Brugge, W., Puricelli, W.P., Nakatsuka, L.N., Nishioka, N.S., Zuberberg, L.R., Jia, S., Lauwers, G.Y. Management of superficial Barrett's esophagus: endoscopic neoplasms by endoscopic mucosal resection - Clinicopathologic analysis of 27 cases. Am J Surg Pathol 2005, 29:680-688.

67. Seenwald, S., Akaraviputh, T., Seitz, U., Brand, B., Groth, S., Mendoza, G., He, X.K., Thonke, F., Stolte, M., Schroeder, S., et al. Circumferential EMR and complete removal of Barrett's epithelium: a new approach to management of Barrett's esophagus containing high-grade intraepithelial neoplasia and intramucosal carcinoma. Gastroendosc Endosc 2003, 57:854-859.

68. Tang, C.L., Jang, N., Jazrawi, S.F. Circumferential endoscopic mucosal resection of a 14-cm Barrett's dysplasia with the Duette mucosectomy device (with videos). Gastroint Endosc 2008, 68:789-789.
histological evidence of squamous re-epithelialisation. Gut 1997, 41:281-284.
83. Bonavina L, Ceriani C, Canazzone A, Segalin A, Ferro S, Peracchia A: Endoscopic laser ablation of nondysplastic Barrett’s oesophagus: is it worthwhile? J Gastrointest Surg 1999, 3:194-198.
84. Bowers SP, Mattar SG, Waring PJ, Galloway K, Nair A, Pascal R, Hunter JG: KTP laser ablation of Barrett’s oesophagus after anti-reflux surgery results in long-term loss of intestinal metaplasia. Potassium-titanyl-phosphate. Surg Endosc 2003, 17:49-54.
85. Ertan A, Zimmerman M, Younes M: Esophageal adenocarcinoma associated with Barrett’s oesophagus - long-term management with laser-ablation. Am J Gastroenterol 1999, 90:2201-203.
86. Norberto L, Polese L, Angriam I, Erroi F, Cecchetto A, D’Amico DF: High-energy laser therapy of Barrett’s oesophagus: Preliminary results. World J Surg 2004, 28:350-354.
87. Sala JA, Salminen JT, Kiviluoto TA, Nemlander AT, Ramo OJ, Farkkila MA, Kiviluoto AL, Mattila SP: Treatment of Barrett’s oesophagus by endoscopic laser ablation and antireflux surgery, Ann Surg 1996, 227:40-44.
88. Faigel DO, Lieberman DA, Weinstein WM, Fanning S, Fennerty MB, Dunkin BJ, Smith CD, Bejarano PA, Melvin WS, Patti MG, Muthusamy R, Menon: Outcomes of dysplasia arising in Barrett’s oesophagus. J Gastrointest Surg 2008, 12:55-563.
89. Kovacs BJ, Chen YK, Lewis TD, DeGuzman LJ, Thompson KS: Successful reversal of Barrett’s oesophagus with endoscopic electrocautery even in the presence of high-grade dysplasia despite inadequate acid suppression. Gastrointest Endosc 1999, 49:547-553.
90. Montes CG, Brandalise NA, Deliza R, de Magalhaes AFN, Fernaz JGF: Antireflux surgery followed by bipolar electrocautery in the treatment of Barrett’s oesophagus. Gastrointest Endosc 2000, 51:175-177.
91. Sampuliner RE, Fennerty B, Garewal HS: Reversal of Barrett’s oesophagus with acid suppression and multipolar electrocoagulation: Preliminary results. Gastrointest Endosc 1996, 44:523-533.
92. Bumgamer JM, Panehypour M, Long D, Domen ES, Overholt BF, Shaheen NJ: Comparison of catheter-based radiofrequency ablation and photodynamic therapy for Barrett’s oesophagus [abstract]. Gastroenterology 2008, 134:A436.
93. Eldad SA, Lin E, Singh KA, Force SD, Miller DL: Radiofrequency ablation of Barrett’s oesophagus: short-term results. Ann Thorac Surg 2009, 87:405-410.
94. Fleischer DE, Overholt BF, Sharma VK, Reymunde A, Kimmey MB, Chuttani R, Chang KJ, Lightdale CJ, Santiago N, Pleskow DK, et al: Endoscopic ablation of Barrett’s oesophagus: a multicenter study with 2.5-year follow-up. Gastrointest Endosc 2008, 68:867-876.
95. Ganz RA, Overholt BF, Sharma VK, Fleischer DE, Shaheen NJ, Lightdale CJ, Freeman SR, Prutt RE, Unayama SM, Gress F, et al: Circumferential ablation of Barrett’s oesophagus that contains high-grade dysplasia: a U.S. Multicenter Registry. Gastrointest Endosc 2008, 68:35-40.
96. Hernandez JC, Reicher S, Chung D, Pham BV, Tsai F, Disibio G, French S, Eyselien VE: Pilot series of radiofrequency ablation of Barrett’s esophagus with or without neoplasia. Endoscopy 2008, 40:388-392.
97. Hubbard N, Velanovich V: Endoscopic endoluminal radiofrequency ablation of Barrett’s esophagus in patients with fundoplications. Surg Endosc 2007, 21:625-628.
98. Pouw RE, Gondrie JJ, Sondermeijer CM, Ten Kate FJ, van Gulik TM, Krishnadath KK, Fockens P, Weinerten BL, Bergman JJ: Eradication of Barrett esophagus with early neoplasia by radiofrequency ablation, with or without endoscopic resection. J Gastrointest Surg 2008, 12:1627-1636.
99. Roorda AK, Marcus SN, Tripadilopoulos G: Early experience with radiofrequency energy ablation therapy for Barrett’s esophagus with and without dysplasia. Dis Esophagus 2007, 20:516-522.
100. Sharma VK, Wang KK, Overholt BF, Lightdale CJ, Fennerty MB, Dean PJ, Pleskow DK, Chuttani R, Reymunde A, Santiago N, et al: Balloon-based, circumferential, endoscopic radiofrequency ablation of Barrett’s esophagus: 1-year follow-up of 100 patients. Gastrointest Endosc 2007, 65:185-195.
101. Smith CD, Bejarano PA, Melvin WS, Patti MG, Muthusamy R, Dunkin BJ: Endoscopic ablation of intestinal metaplasia containing high-grade dysplasia in esophagectomy patients using a balloon-based ablation system. Surg Endosc 2007, 21:560-569.
102. Sharma VK, Jaek KH, Das A, Wells CD, Nguyen CC, Fleischer DE: Circumferential and focal ablation of Barrett’s esophagus containing dysplasia. Am J Gastroenterol 2009, 104:310-317.
103. Vassiliou MC, von RD, Wiener DC, Gordon SR, Rothstein R: Treatment of ultralong-segment Barrett’s using focal and balloon-based radiofrequency ablation. Surg Endosc 2009, 23:2175-2180.
104. Velanovich V: Endoscopic endoluminal radiofrequency ablation of Barrett’s esophagus: initial results and lessons learned. Surg Endosc 2009, 23:2175-2180.
105. Gondrie JJ, Pouw RE, Sondermeijer CM, Peters FP, Curvers WL, Rosmolen WD, Krishnadath KK, Ten Kate F, Fockens P, Bergman JJ: Stepwise circumferential and focal ablation of Barrett’s esophagus with high-grade dysplasia: results of the first prospective series of 11 patients. Endoscopy 2008, 40:359-369.
106. Gondrie JJ, Pouw RE, Sondermeijer CM, Peters FP, Curvers WL, Rosmolen WD, ten KF, Fockens P, Bergman JJ: Effective treatment of early Barrett’s neoplasia with stepwise circumferential and focal ablation using the HALO system. Endoscopy 2008, 40:370-379.
107. Ferguson MK, Naurheim KS: Resection for Barrett’s mucosa with high-grade dysplasia: implications for prophylactic photodynamic therapy. J Thorac Cardiovasc Surg 1997, 114:829-829.
108. Nguyen NT, Schauer P, Luekett JD: Minimally invasive esophagectomy for Barrett’s esophagus with high-grade dysplasia. Surgery 2000, 127:284-290.
109. Romagnoli R: Outcomes of dysplasia arising in Barrett’s esophagus: A dynamic view. J Am Coll Surg 2003, 197:365-371.
110. Sujendran V, Sica G, Warren R, Maynard N: Oesophagectomy remains the gold standard for treatment of high-grade dysplasia in Barrett’s oesophagus. Eur J Cardiothorac Surg 2005, 28:763-766.
111. Thomson BN, Cade RJ: Oesophagectomy for early adenocarcinoma and dysplasia arising in Barrett’s oesophagus. ANZ J Surg 2003, 73:121-124.

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