Barrett's oesophagus: ablative therapy for the treatment of Barrett's oesophagus

Full guideline

Final draft, May 2010

This guideline was developed following the NICE short clinical guideline process. This document includes all the recommendations, details of how they were developed and summaries of the evidence they were based on.

Contents

Disclaimer

NICE clinical guidelines are recommendations about the treatment and care of people with specific diseases and conditions in the NHS in England and Wales.

This guidance represents the view of NICE, which was arrived at after careful consideration of the evidence available. Healthcare professionals are expected to take it fully into account when exercising their clinical judgement.

However, the guidance does not override the individual responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

Implementation of this guidance is the responsibility of local commissioners and/or providers. Commissioners and providers are reminded that it is their responsibility to implement the guidance, in their local context, in light of their duties to avoid unlawful discrimination and to have regard to promoting equality of opportunity. Nothing in this guidance should be interpreted in a way that would be inconsistent with compliance with those duties.

Introduction

Barrett's oesophagus develops as a consequence of chronic gastro-oesophageal reflux disease. It is characterised by abnormal changes in the oesophageal lining that may, in some patients, become dysplastic and lead to oesophageal cancer. Oesophagectomy (surgical removal of the oesophagus) is the standard NHS treatment for high-grade dysplastic Barrett's oesophagus or intramucosal cancer (including T1a); however, it is associated with significant mortality and morbidity. Consequently less invasive surgical techniques, such as endoscopic mucosal resection, and ablative treatments have been developed and are being used as alternatives for patients who are unsuitable for surgery or who express a preference for less invasive options. However, in the past there has been uncertainty whether ablative therapy for Barrett's oesophagus is both clinically and cost effective compared with other management options.

Radiofrequency ablation is one of the ablative therapies currently being used. This has a standard depth of ablation that is set by the manufacturer. Photodynamic therapy has a greater depth of ablation than radiofrequency ablation, irrespective of the photosensitiser used (although only one photosensitiser (porfirmer sodium) is presently licensed in the UK). However greater depth of ablation is associated with higher rate of complications but

clinicians do not control the depth and is dependent on the ablative therapy used.

Previously no evidence-based guideline has addressed the use of ablative therapies for the treatment of Barrett's oesophagus in England and Wales, which may lead to variation in practice. This clinical guideline covers the use of ablative therapies (argon plasma coagulation, laser ablation, multipolar electrocoagulation, radiofrequency ablation and photodynamic therapy) and endoscopic mucosal resection compared with oesophageal surgery, and surveillance with proton-pump inhibitors for treating Barrett's oesophagus with high-grade dysplasia or with early intramucosal cancer in adults (18 years and older) in secondary care.

Patient-centred care

This guideline offers best practice advice on the care of adults with a diagnosis of Barrett's oesophagus with high-grade dysplasia or with intramucosal cancer.

Treatment and care should take into account patients' needs and preferences. People with a diagnosis of Barrett's oesophagus with high-grade dysplasia or with intramucosal cancer should have the opportunity to make informed decisions about their care and treatment, in partnership with their healthcare professionals. If patients do not have the capacity to make decisions, healthcare professionals should follow the Department of Health's advice on consent (available from www.dh.gov.uk/consent) and the code of practice that accompanies the Mental Capacity Act (summary available from www.publicguardian.gov.uk). In Wales, healthcare professionals should follow advice on consent from the Welsh Assembly Government (available from www.wales.nhs.uk/consent).

Good communication between healthcare professionals and patients is essential. It should be supported by evidence-based written information tailored to the patient's needs. Treatment and care, and the information patients are given about it, should be culturally appropriate. It should also be

accessible to people with additional needs such as physical, sensory or learning disabilities, and to people who do not speak or read English.

If the patient agrees, families and carers should have the opportunity to be involved in decisions about treatment and care.

Families and carers should also be given the information and support they need.

1 Summary

For the purposes of this guideline, the term ‘endoscopic mucosal resection’ is used interchangeably with ‘endoscopic resection’.

1.1 List of all recommendations

Before considering endoscopic therapy as an alternative to surgery (for patients who are unsuitable for surgery or based on their preference for a less invasive option),, a confirmed diagnosis of high-grade dysplasia or intramucosal cancer in Barrett’s oesophagus should be agreed by a designated specialist multidisciplinary team for oesophago-gastric cancer.

Key principles of care

1.1.1 All treatments for high-grade dysplasia and intramucosal cancer in Barrett’s oesophagus should be performed by specialist oesophago-gastric cancer teams with the experience and facilities to deliver the treatments recommended in this guideline.

Endoscopic therapies

1.1.2 Offer endoscopic therapy as an alternative to oesophagectomy to people with high-grade dysplasia and intramucosal cancer (T1a), taking into account patient individual preferences, fitness and general health.

Endoscopic mucosal resection

1.1.3 Consider using endoscopic mucosal resection alone to treat localised lesions.

1.1.4 Use circumferential endoscopic mucosal resection with care because of the high incidence of stricture formation.

1.1.5 If residual or recurrent disease is suspected, consider additional or repeated therapies (either endoscopic mucosal resection (also referred to as endoscopic resection) with further pathological assessment or ablative therapies [RFA, APC or PDT]) with appropriate follow-up.

Ablative therapies

1.1.6 Consider using radiofrequency ablation alone or photodynamic therapy alone for flat high-grade dysplasia, taking into account the evidence of their long-term efficacy, cost and complication rates[1].

1.1.7 Do not use argon plasma coagulation, laser ablation or multipolar electrocoagulation alone, or in combination with each other, unless as part of a clinical trial.

Endoscopic mucosal resection in combination with ablative therapies

1.1.8 If using endoscopic mucosal resection, consider following with an additional ablative therapy (radiofrequency ablation, argon plasma coagulation or photodynamic therapy) to completely remove residual flat dysplasia, taking into consideration the side-effect profiles[2].

Patient and carer support and information

1.1.9 Give patients verbal and written information about their diagnosis, available treatments, patient support groups and the uncertainty of the long-term outcomes of ablative therapies. Give patients time to consider this information when making decisions about their care.

1.1.10 Discuss the multidisciplinary team's views on the range of appropriate treatments with the patient.

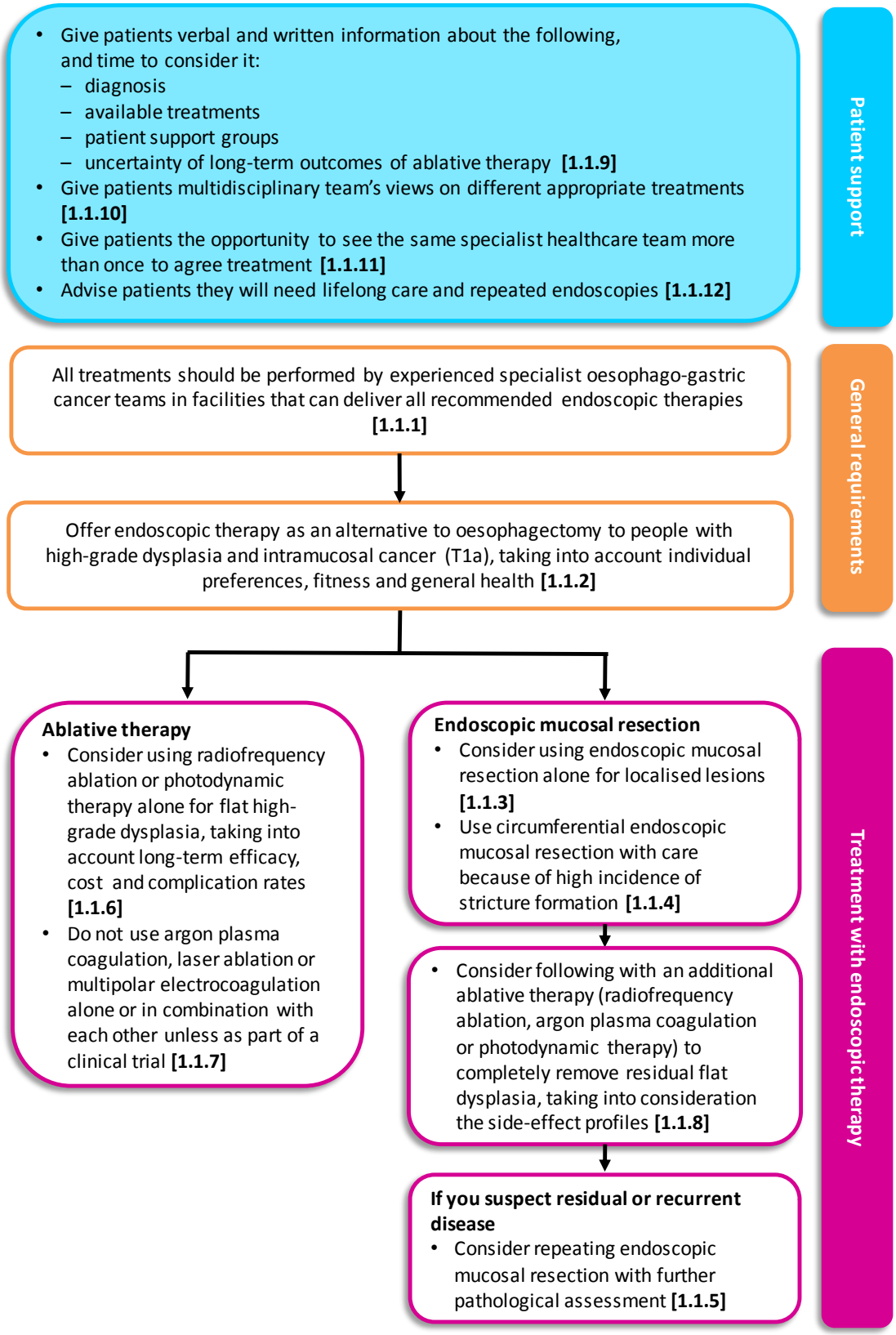
[1] Recommendation linked to IPG82 (www.nice.org.uk/guidance/IPG82) and IPG244 (www.nice.org.uk/guidance/IPG244)

[2] Recommendation linked to IPG82 (www.nice.org.uk/guidance/IPG82) and IPG244 (www.nice.org.uk/guidance/IPG244)

1.1.11 Offer patients the opportunity to see the same specialist healthcare team more than once to agree treatment.

1.1.12 Advise patients who have endoscopic therapy that they will need lifelong care and repeated endoscopies.

1.2 Care pathway



1.3 Overview

1.3.1 Endoscopic mucosal resection and ablative therapies for Barrett's oesophagus

Barrett's oesophagus is an acquired condition that develops as a consequence of chronic gastro-oesophageal reflux disease. It is found in 15-20% of people undergoing upper gastrointestinal endoscopy for symptoms of chronic gastro-oesophageal reflux. The condition is characterised by the replacement of squamous mucosa with columnar mucosa in the lower oesophagus. This change is known as metaplasia and results in the lining of the oesophagus becoming similar to that of the stomach and small intestine (Garside et al., 2006).

Barrett's oesophagus can progress from no dysplasia to low- and high-grade dysplasia, and it is considered to be a major risk factor for oesophageal adenocarcinoma. The incidence of oesophageal adenocarcinoma has increased considerably over the past two decades while the overall 5-year survival rate has remained around 9% over the past decade.

Endoscopic mucosal resection and ablation are currently used to treat Barrett's oesophagus. Endoscopic mucosal resection is an invasive procedure that involves the removal of the mucosal and submucosal layers of the oesophagus; conventional techniques involve a simple snare technique or a double channel gastroscope (strip biopsy) technique. Recent modifications involve suction onto the lesion with or without submucosal injection, using a cap and snare technique or a ligation device (Green et al., 2009).

Ablation destroys the abnormal cells without removing the entire oesophagus and is used in conjunction with acid suppression (usually proton-pump inhibitors). The ablative therapies considered in this guideline are:

- argon plasma coagulation (destroys the affected tissue using ionised argon gas)
- laser ablation (destroys the abnormal cells using thermal ablation achieved through photocoagulation)

- multipolar electrocoagulation (destroys the abnormal cells by using thermal ablation achieved by completing an electric circuit)
- radiofrequency ablation (delivers high-power short bursts of thermal energy to the affected tissue using either a balloon-based or a focal device with radiofrequency electrodes) and
- photodynamic therapy (uses a photosensitising agent that selectively accumulates in the abnormal cells and causes cell death when activated by light [Fernando et al., 2009; Green et al., 2009; Rees et al., 2010]).

This short clinical guideline aims to provide clear evidence-based recommendations on the use of ablative therapy to treat Barrett's oesophagus with high-grade dysplasia or intramucosal cancer.

1.3.2 Who this guideline is for

This document is for healthcare professionals involved in the care of adults (18 years or over) with Barrett's oesophagus with high-grade dysplasia or intramucosal cancer.

2 How this guideline was developed

2.1 Introduction

'Barrett's oesophagus: ablative therapy for the treatment of Barrett's oesophagus' (NICE clinical guideline [XX]) is a NICE short clinical guideline. The primary outcomes and adverse outcomes that were considered in this guideline are listed in table 1. All results from the included studies (relative risk or risk ratio [RR], absolute risk reduction [ARR], number needed to treat [NNT] and number needed to harm [NNH]) are presented in grading of recommendations assessment, development and evaluation (GRADE) profiles and subsequent evidence statements. The GRADE profiles were modified to allow for evidence assessment from case series and registry data to be included appropriately alongside randomised controlled trial and observational studies for the same outcomes. For the imprecision category of GRADE, the minimum requirement of 300 events for outcomes to be of 'high' quality was not considered for this guideline as agreed by the Guideline Development

Group. All the included studies are represented in an evidence map in figure 1.

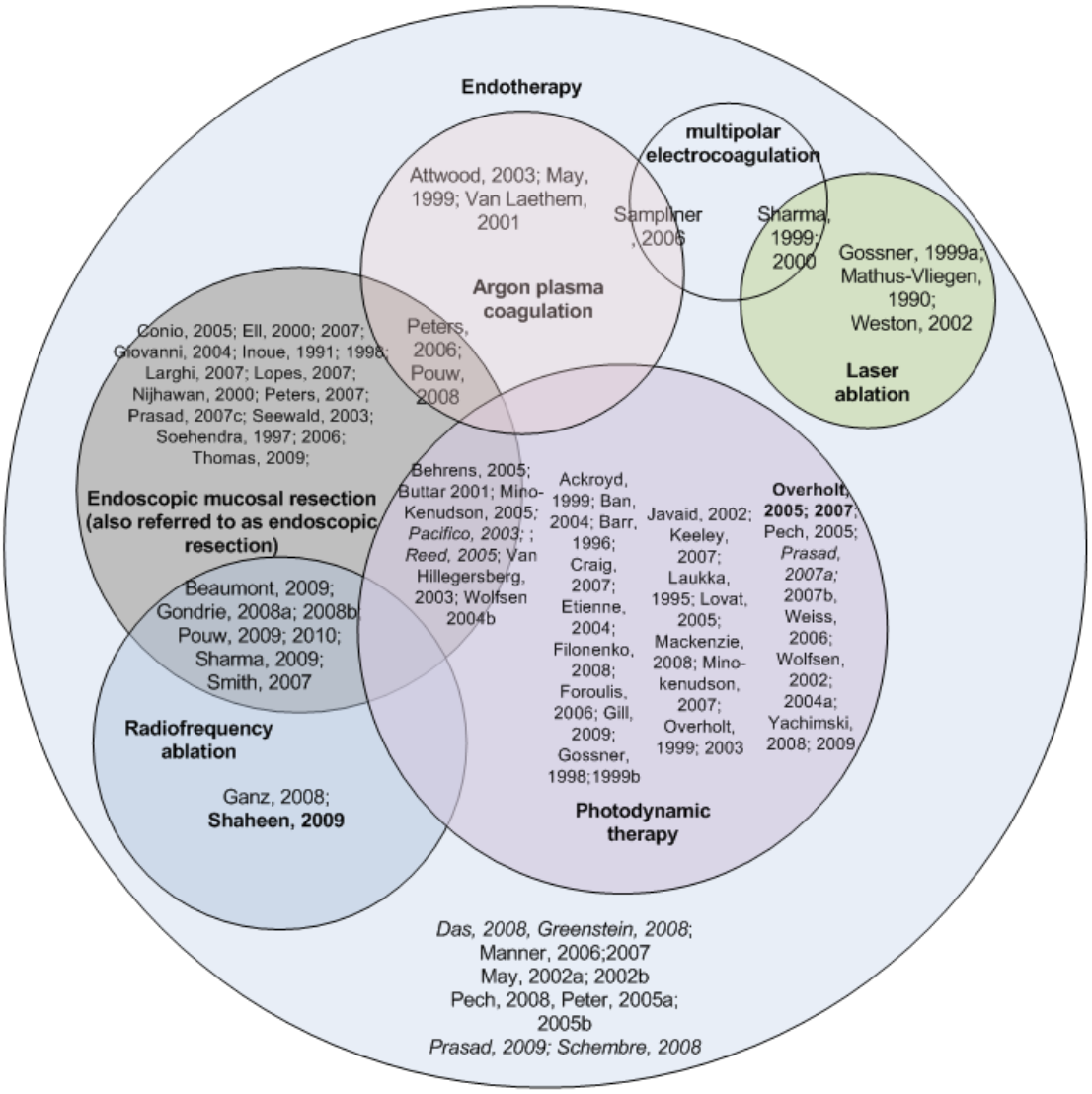
For a full explanation of how this type of guideline is developed, see 'The guidelines manual' (2009) at www.nice.org.uk/GuidelinesManual.

Table 1 Primary and adverse outcomes studied in the guideline

Primary outcomes in GRADE profiles		**Adverse outcomes in GRADE profiles**	
1	Complete eradication of dysplasia or cancer	7	Major adverse events
2	Complete eradication of intestinal metaplasia/Barrett's oesophagus	8	Minor adverse events
3	Complete eradication of high-grade dysplasia or cancer	9	Stricture or stenosis requiring treatment
4	Reduction in length of Barrett's oesophagus[3]	10	Photosensitivity
5	Progression of disease to cancer	11	Cardiac complications
6	Overall survival	12	Perforations
		13	Chest pain and/or retrosternal pain
		14	Bleeding

[3] The length of the Barrett's oesophagus segment refers to the section of the oesophagus where the squamous mucosa is replaced with columnar mucosa

Figure 1 Evidence map



Randomised controlled trials – Overholt 2005, 2007; Shaheen, 2009
Controlled observational studies – Das, 2008; Greenstein, 2008; Pacifico, 2003; Prasad, 2007a; Prasad, 2009; Reed, 2005; Schembre, 2008

2.2 Endoscopic therapies

2.2.1 Evidence review

Through systematic searching, 1888 articles were identified; 364 of these met the inclusion criteria at the abstract and title stage and were ordered as full articles[4]. Of these, nine studies investigating the clinical effectiveness of different endoscopic therapies (endoscopic mucosal resection combined with different ablative therapies) for the treatment of high-grade dysplastic Barrett's oesophagus or early adenocarcinoma were eligible for inclusion[5]. The quality of evidence was predominantly very low. The evidence from these studies is summarised in GRADE profiles 1 and 2.

[4] See appendix 4 for the inclusion and exclusion criteria, study selection flowcharts and list of excluded studies

[5] See appendix 2 for the full review protocol, appendix 3 for the full search strategies and appendix 4 for the inclusion and exclusion criteria, study selection flowcharts and list of excluded studies

GRADE profile 1 Endoscopic therapies – studies with follow-up not stated

Study	Design	Treatment	Placebo	Risk	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Quality
Primary outcome 2.Complete eradication of Barrett's oesophagus or intestinal metaplasia										
Manner et al. (2007)	Uncontrolled	104/131 (79.39%)			Single-centre study, mainly looking at safety n = 215; relevant population n = 131					+ (Very low)
Adverse outcome 8. Minor adverse events										
Manner et al. (2006, 2007)[a]	Uncontrolled	10.69–11.71%[b]			Two studies from the same centre n = 111, n = 131					+ (Very low)
Adverse outcome 9. Stricture or stenosis needing dilation										
Manner et al. (2006, 2007)[a]	Uncontrolled	0.76–0.96%			Two studies from the same centre n = 111, n = 131					+ (Very low)

[a] Studies used argon plasma coagulation after treatment with endoscopic mucosal resection or endoscopic mucosal resection with photodynamic therapy.

[b] Manner et al. (2006); n = 215; 13 cases of minor adverse events occurred: chest pain (7) and fever (6) in the relevant population (n = 111). Manner et al. (2007); n = 216; 14 cases of minor adverse events occurred: pain, dysphagia, cough after argon plasma coagulation, cardiac arrhythmia, gas accumulation in the gastrointestinal wall, neuromuscular irritation.

GRADE profile 2 Endoscopic therapies – studies with follow-up of 12 months or longer

Study	Design	Treatment	Placebo	Relative risk (RR, 95% confidence interval [CI]); absolute risk reduction (ARR); number needed to treat (NNT) or to harm (NNH, 95%CI)	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Quality
Primary outcome 1. Complete eradication of dysplasia or cancer										
Schembre et al. (2008)[a]	Cohort	54/62 (87%)	Surgery 31/32 (97%)	RR = 0.90 (0.79 to 1.05); ARR = 0.09; NNH = −10.2 (−infinity to 4.74)	Not serious	Not serious	Not serious	Not serious	Not serious	++ (Low)
Primary outcome 2. Complete eradication of Barrett's oesophagus or intestinal metaplasia										
Schembre et al. (2008)[a]	Cohort	35/62 (56%)	Surgery 31/32 (97%)	RR = 0.58 (0.45 to 0.72); ARR = −0.40; NNH = −2.47 (−1.86 to −4.07)	Not serious	Not serious	Not serious	Not serious	Not serious	++ (Low)
Peters et al. (2005a, 2005b)[b]; May et al. (2002a, 2002b)[c]; Pech et al. (2008)[d]	Uncontrolled	90.0–96.6%			3 studies of n = 34, n = 115 and n = 349					+ (Very low)
Primary outcome 5. Progression of disease to cancer										
Schembre et al. (2008)[a]	Cohort	4/62 (6%)	0/32 (0%)	ARR = −0.06 (−0.16 to 0.05); NNT = −15.5 (−infinity to -6.45)	Not serious	Not serious	Not serious	Not serious	Not serious	++ (Low)
Pech et al. (2008)[d]	Uncontrolled	74/349 (21.2%)[e]			Large case series with n = 486; relevant population n = 349					+ (Very low)
Primary outcome 6. Overall survival										
Greenstein et al. (2008)[f]	Cohort	84% (n = 47)	No therapy 64% (n = 119)	RR = 1.31 (1.07 to 1.57); ARR = 0.20; NNT = 5 (3.15 to 26.45)	Serious	Not serious	Not serious	Not serious	Not serious	+ (Very low)
Prasad et al. (2009)[g]	Cohort	83% (n = 132)	Surgery 95% (n = 46)	0.87 (0.78 to 0.96); ARR = −0.12; NNH = −8.33 (−4.71 to −28.19)	Not serious	Not serious	Not serious	Not serious	Not serious	++ (Low)
Schembre et al. (2008)[a]	Cohort	89% (n = 62)	Surgery 93% (n = 32)	RR = 0.96 (0.87 to 1.05); ARR=0.04; NNT = 25 (-23.58 to infinity)	Not serious	Not serious	Not serious	Not serious	Not serious	++ (Low)

Study	Design	Treatment	Placebo	Relative risk (RR, 95% confidence interval [CI]); absolute risk reduction (ARR); number needed to treat (NNT) or to harm (NNH, 95%CI)	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Quality
Das et al. (2008)[h]	Cohort	Endotherapy group versus surgery group: overall survival hazard ratio (HR) = 0.89 (95% CI 0.51 to 1.56, p = 0.68); cancer-free survival = 56 versus 59 months (p=0.41)			Not serious	Not serious	Not serious	Not serious	Not serious	++ (Low)
Pech et al. (2008)[d]	Uncontrolled	84% survival at 5 years using Kaplan–Meier analysis			Large case series with n = 486; relevant population n = 349					++ (Low)
May et al. (2002a, 2002b)	Uncontrolled	98% at 1 year, 95% at 2 years and 88% at 3 years calculated using life tables			Large case series n = 115; follow-up 34±10 months					++ (Low)
Adverse outcome 7. Major adverse events										
Prasad et al. (2009)	Cohort	0/132 (0%)	Surgery 17/46 (36.96%)	ARR = 0.37 NNT = 2.70 (1.94 to 4.08)i	Not serious	Not serious	Not serious	Not serious	Not serious	++ (Low)
Schembre et al. (2008)[a]	Cohort	5/62 (8%)	4/32 (13%)	RR = 1.05 (0.92 to 1.29); ARR = 0.04; NNT = 22.55 (−12.76 to infinity)[j]	Not serious	Not serious	Not serious	Not serious	Not serious	++ (Low)
Peters et al. (2005a; 2005b)	Uncontrolled	1/34 (2.94%)[k]			Case series n = 34; follow-up 30 months					+ (Very low)
Adverse outcome 8. Minor adverse events										
Schembre et al. (2008)[a]	Cohort	20/62 (32%)	Surgery 26/32 (81.25%)	RR = 3.61 (1.86 to 7.75); ARR = 0.49; NNT = 2.04 (1.55 to 3.49)[l]	Not serious	Not serious	Not serious	Not serious	Not serious	++ (Low)
May et al. (2002a, 2002b)	Uncontrolled	11/115 (9.57%)[m]			Large case series n = 115; follow-up 34±10 months					+ (Very low)
Adverse outcome 10.: Photosensitivity										
Peters et al. (2005a; 2005b)	Uncontrolled	2/34 (5.88%)			Small case series n = 34; follow-up 30 months					+ (Very low)
Adverse outcome 11. Cardiac complications										
Peters et al. (2005a; 2005b)	Uncontrolled	1/34 (2.94%)			Small case series n = 34; median follow-up 30 months					+ (Very low)

[a] Cohort study analysing retrospectively two institutional review board approved databases n = 117; intervention was photodynamic therapy, endoscopic resection, argon plasma coagulation or any combination with median follow-up of 20 months (range 6–84 months) for endotherapy arm and 48 months (range 6–88 months) for surgery arm. Survival adjusted at 4 years but method used is not mentioned; there was no significant difference between groups (p = 0.47).

[b] n = 34; intervention was endoscopic mucosal resection followed by photodynamic therapy and argon plasma coagulation with a median follow-up of 30 months (22–31 months).

[c] n = 115; intervention was initial argon plasma coagulation followed by endoscopic mucosal resection or endoscopic mucosal resection with photodynamic therapy with a follow-up of 34 ± 10 months (range 24–60 months).

[d] This is a large well-documented single-centre prospective case series with n = 486 but relevant population was 349 with high-grade intestinal metaplasia or early adenocarcinoma; intervention was laser ablation followed by endoscopic resection, photodynamic therapy, endoscopic mucosal resection with photodynamic therapy or argon plasma coagulation with a median follow-up of 63 months (interquartile range 49.5–80.0 months).

[e] Metachronous lesions were detected in 74 patients at a median of 15 months. 63/74 achieved complete remission after repeat treatment; 3 were referred for surgery; 2 received ongoing therapy; 2 died. Recurrence-free rate was 77% after 5 years. The rate of apparent long-term eradication achieved was calculated as 94.5% (330 of 349 patients).

[f] A retrospective analysis of cases from a national registry (n = 166) of local procedures (n = 47) versus no therapy (n = 119) with a median follow-up of 17 months (range 1–69 months). Survival was calculated at 4 years. Local endoscopic therapies included relevant ablative therapies but also others outside this scope. Local therapies were excisional biopsy (19), photodynamic therapy (11), local destruction (6), laser (5), polypectomy (3), electrocautery (1) and cryoablation (1).

[g] Survival calculated at 5 years. Using Cox proportional hazards modelling, overall survival was comparable between the two groups after adjusting for age, sex, length of Barrett's oesophagus, Charlson comorbidity score, and the propensity score, whereas cancer-free survival was superior in the surgical group (overall survival HR = 1.54 (95% CI 0.64 to 3.75) p = 0.33; cancer-free survival HR = 2.64 (95% CI 1.70 to 4.08) p < 0.001).

[h] A retrospective analysis of cases from a national registry: n = 621 of endotherapy (n = 99) versus surgery (n = 643) with a mean follow-up of 23.9 months for the endotherapy group and 25.3 months for the surgery group. The significant variables associated with mortality using the Cox proportional hazards model were higher age at diagnosis (HR = 1.06 [95% CI 1.03 to, 1.08], p < 0.001) and absence of exposure to radiation therapy (HR = 0.32 [95% CI 0.21 to 0.48], p < 0.001).

[i] Major adverse events for the surgery arm were postoperative complications such as anastomotic leaks, anastomotic strictures, cardiopulmonary complications, and feeding jejunostomy leaks. Three patients were readmitted within 90 days of surgery for medical and surgical issues. The median length of hospital stay was 8 days (interquartile range 7–13 days; range, 5–57 days).

[j] Major adverse events for the endotherapy arm were death (1), bleeding (2), and prolonged hospital stay (3); those for the surgery arm were anastomatic leak (1), chyle leak (2) and deep vein thrombosis (1); p = 0.50.

[k] Major adverse event was haematemesis in 1 patient, 1 week after the photodynamic therapy.

[l] Minor adverse events for the endotherapy arm were stricture (13) and photosensitivity (4); and for the surgery arm were pneumonia (2), atrial fibrillation (6), wound infection (3), stricture (15) and pneumothorax (1); p < 0.001.

[m] Minor complications: 11 including stenosis (3), bleeding (5), odynophagia (1) and photosensitive reaction-sunburn (2).

2.2.2 Evidence statements

2.2.2.1 Nine studies, including four two-arm controlled observational studies, considered the use of different ablative therapies or endoscopic mucosal resection for the treatment of Barrett's oesophagus.

Primary outcomes

2.2.2.2 Two overlapping large case series (Manner et al. 2006, 2007; n = 111, 131) did not state a follow-up period but showed a rate of complete ablation of Barrett's oesophagus of 79.39%.

2.2.2.3 The other seven studies had a follow-up of more than 12 months.

2.2.2.4 Schembre et al. (2008; n = 117, 20-month median follow-up) did not find a significant difference in eradication of dysplasia for the endotherapy arm (87%) versus the surgery arm (97%, RR = 0.90, 95% confidence interval [CI] 0.79 to 1.05). However, it showed a significant difference in the complete ablation of Barrett's oesophagus: 56% in the endotherapy arm compared with 97% in the surgery arm (RR = 0.58, 95% CI 0.45–0.72). The study also showed 6% progression to cancer in the endotherapy arm compared with 0% in the surgery arm (ARR = −0.06, 95% CI −0.005 to 0.1).

2.2.2.5 Three uncontrolled studies (May et al. 2002a, 2002b; n = 115; Pech et al. 2008; n = 486, relevant population = 349; Peters et al. 2005a, 2005b; n = 34) found 90–96.6% complete ablation of Barrett's oesophagus using endotherapy.

2.2.2.6 Overall survival was studied in four cohort studies (Das et al. 2008; Greenstein et al. 2008; Prasad et al. 2009; Schembre et al. 2008).

2.2.2.7 Prasad et al. (2009; n = 178, 64-month median follow-up) found overall survival at 5 years of 83% for endotherapy and 95% for surgery (RR = 0.87, 95% CI 0.79 to 0.96). After adjusting for age,

sex and length of Barrett's oesophagus segment, the hazard ratio [HR] was 1.54 (95% CI 0.64 to 3.75, p = 0.33).

2.2.2.8 *Schembre et al. (2008) found the survival for the two arms to be 89% for endotherapy and 93% for surgery (RR = 0.96, 95% CI 0.87–1.05) but the adjusted difference in overall survival at 4 years was not statistically significant (p = 0.47).*

2.2.2.9 *Das et al. (2008; n = 621, 24.6-month mean follow-up) showed that the relative hazard (RH) for oesophageal-cancer-specific mortality in the endotherapy group was not different from that in the surgery group (RH 0.89, 95% CI 0.51 to 1.56, p = 0.68). The median cancer-free survival (calculated by Kaplan–Meier estimate) in the endotherapy group (56 months) was not significantly different from that in the surgically treated group (59 months, p = 0.41). Significant variables associated with mortality using the Cox proportional hazards model were higher age at diagnosis (HR = 1.06, 95% CI 1.03 to 1.08, p < 0.001) and absence of exposure to radiation therapy (HR = 0.32, 95% CI 0.21 to 0.48, p < 0.001).*

2.2.2.10 *Greenstein et al. (2008, n = 166) calculated 4-year survival after local therapy as 84% compared with 64% for no therapy (RR = 1.3, 95% CI 1.07 to 1.57).*

Adverse events

2.2.2.11 *Manner et al. (2006, 2007) reported a 0.76–0.96% rate of strictures requiring treatment and 10.69–11.71% of patients had other adverse events (chest pain, fever, cough, cardiac arrhythmia, gas accumulation in the gastrointestinal wall and neuromuscular irritation).*

2.2.2.12 *Prasad et al. (2009) showed a 36.96% rate of major adverse events for the surgery arm versus 0% in the endotherapy arm. Schembre et al. (2008) reported a 13% rate of major adverse events for the surgery arm versus 8% in the endotherapy arm.*

Other major complications were seen in the case series, including photosensitivity reactions (5.88%; only in studies that treated with photodynamic therapy) and cardiac complications (2.94%).

2.2.3 Health economic modelling

Methods

A search for cost-effectiveness studies identified eight relevant papers that examined ablation therapy in people with Barrett's oesophagus with high-grade dysplasia. These were reviewed with quality checklists to assess their applicability and limitations to the decision problem. For further information, you may wish to refer to the full health economic analysis, including completed checklists (appendix 6). None of the studies were assessed to be of high quality or applicable to the decision problem and all have limitations.

Given the absence of an appropriate analysis, a new cost-effectiveness model was constructed. The population included in the model was 60-year old men and women with high-grade dysplasia. The analysis was run over a 50-year time horizon. The new analysis includes the following interventions: endoscopic mucosal resection, radiofrequency ablation, photodynamic therapy, argon plasma coagulation, combinations of endoscopic mucosal resection and ablative therapies, surgery (for high-grade dysplasia) and surveillance. All treatments were compared with no surveillance.

Surveillance of Barrett's oesophagus: exploring uncertainty through systematic review, expert workshop and economic modelling (Garside et al. 2006, published in Health Technology Assessment; hereafter referred to as the HTA report) provided the basis for the model and was adapted to include the interventions. This model includes a person's actual health state (no Barrett's oesophagus, non-dysplastic Barrett's oesophagus, low-grade dysplasia, high-grade dysplasia, asymptomatic cancer and symptomatic cancer) and a diagnostic category based on endoscopic surveillance. Treatment with endotherapies for high-grade dysplasia occurs in the first cycle, with the option of additional treatments if the condition progresses to high-grade dysplasia in the future. If a condition progresses to cancer, the

treatment is assumed to be oesophagectomy after which people enter post-surgery states.

The standard surveillance schedule used in the model was as follows:

- no Barrett's oesophagus – no surveillance
- non-dysplastic Barrett's oesophagus – every 2 years
- low-grade dysplasia – every 6 months
- high-grade dysplasia – every 3 months.

For active treatments a different schedule was used:

- surveillance every 3 months for the first year
- every 6 months for the second year
- every year thereafter until the fifth year post-treatment

Patients then reverted to the standard schedule, except for those with no Barrett's oesophagus who had surveillance every 5 years.

Transitions for the natural history were obtained from the HTA report. The HTA report assumed that people can progress or regress through Barrett's oesophagus only in a stepwise manner. However, the Guideline Development Group considered that people could potentially progress or regress in larger increments (opposite to stepwise). Therefore, a Bayesian dirichlet methodology was used, which allowed the inclusion of these transitions without using invalidated data sources. In some cases the transitions from the HTA report were updated with more recent publications and papers identified from clinical searches. For example, the probability of recurrence of cancer after surgery for high-grade dysplasia was obtained from Prasad et al. (2009). Full details are in appendix 6.

Treatment effects were calculated using the outcomes 'complete ablation of dysplasia' and, if available, 'complete ablation of Barrett's oesophagus'. Since no meta-analysis or evidence synthesis was possible, the highest quality study with the reported outcome was chosen. The selected studies are summarised in table 2.

Table 2 Studies included in cost-effectiveness model

Treatment	Study	Study type	Outcome for complete eradication of dysplasia
Endoscopic mucosal resection	Ell et al. (2007)	Case series	99% of cohort
Radiofrequency ablation	Shaheen et al. (2009)	Randomised, controlled	RR = 4.25 compared with placebo
Photodynamic therapy	Overholt et al. (2005, 2007)	Randomised, controlled	RR = 4.11 compared with placebo
Endoscopic mucosal resection and argon plasma coagulation	Peters et al. (2006)	Case series	89.9% of cohort
Endoscopic mucosal resection and radiofrequency ablation	Sharma et al. (2009); Gondrie et al. (2008a, 2008b)	Case series	79–100% of cohort (midpoint of 89.5% used)
Endoscopic mucosal resection and photodynamic therapy	Van Hillegersberg (2003)	Case series	50–100% of population (midpoint of 75% used)

Ideally, relative risk should be used to incorporate the treatment effectiveness into the model. Unfortunately this was available only for radiofrequency ablation and photodynamic therapy alone. Therefore, the placebo arm from Overholt et al. (2007) was used to calculate relative risks for the treatments that did not have a reported relative risk. If available, the 'complete ablation of Barrett's oesophagus' outcome was used to determine how many people transitioned to 'no Barrett's oesophagus' compared with 'non-dysplastic Barrett's oesophagus'. The Guideline Development Group acknowledged that since Ell et al. (2007) was conducted in a high volume and highly specialist centre, it was unlikely to represent the true effectiveness of endoscopic mucosal resection in the NHS setting. Therefore, the Group concluded that the effectiveness of endoscopic mucosal resection should be reduced to 85%.

Perforations, strictures and photosensitivity reactions were the only included adverse events with cost and quality-of-life outcomes. The probabilities for these events were obtained from the clinical studies. Perforations were treated with surgery and transited to the post-surgery states. Strictures and photosensitivity reactions affected costs and quality of life but not treatment pathways.

Utilities for health states, treatment and adverse events were obtained from published sources. No EQ-5D values were available and therefore values based on visual analogue scale and time trade-off methods were used. Costs for procedures were obtained from NHS reference costs, drug costs from the 'British national formulary' 58 and costs for palliative care came from published papers. Full details of chosen utilities and costs are presented in appendix 6.

Both deterministic (using only point estimates) and probabilistic analyses (using a range of values and simulation to account for uncertainty) were conducted to examine cost effectiveness. Additional analysis included cost-effectiveness acceptability curves (which assess the probability that a treatment is cost effective at a particular cost per quality-adjusted life year [QALY]; for example, £30,000 per QALY), and cost-effectiveness acceptability frontiers (which assess the probability that a treatment is the optimum choice compared with all valid comparators at a cost per QALY). Finally, value of information analysis was conducted. Value of information analysis places a value on how much resolving the uncertainty in the cost-effectiveness analysis is worth to society and also which areas of uncertainty should be prioritised for research.

The overall deterministic results are presented in table 3; however, more detailed results will be outlined later.

Table 3 Deterministic cost-effectiveness analyses over a 50-year period

Intervention	QALYs	Cost (£)	Incremental QALYs	Incremental cost (£)	ICER (£)
No surveillance	7.89	8782	-	-	-
Surveillance	8.27	22,233	0.38	13,450	35,277
Surgery	9.18	15.971	1.29	7189	5560
Endoscopic mucosal resection and surveillance	8.73	20.464	0.84	11,682	13,846
Radiofrequency ablation and surveillance	8.92	34.522	1.04	25,740	24,829
Photodynamic therapy and surveillance	8.87	31.480	0.99	22.698	23.002
Endoscopic mucosal resection and radiofrequency ablation and surveillance	9.23	27.644	1.35	18.862	13.990
Endoscopic mucosal resection and photodynamic therapy and surveillance	9.18	31.233	1.30	22.451	17.327
Endoscopic mucosal resection and argon plasma coagulation and surveillance	9.13	24.047	1.24	15.265	12.300
ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year					

The analysis suggests that surgery is the most cost-effective treatment option. However, surgery is a highly invasive treatment, which many patients may not be able to tolerate or would not choose. Additionally, surveillance does not appear to be cost effective; therefore, it was considered that the ablative therapies should be compared with 'no surveillance' only. In view of the majority of the clinical data being cohort and other types of lower quality information it was considered inappropriate to compare across treatments. This guideline considers the treatment options for patients whom, for one reason or another, are not considered candidates for surgery. Therefore, for these individuals the correct incremental comparisons are against a baseline of no surveillance, not surgery. Therefore cost-effectiveness acceptability frontier results will not be presented as they would be misleading.

The probabilistic results (which accounts for uncertainty in individual inputs) are presented in table 4 below:

Table 4 Probabilistic cost-effectiveness analyses over a 50-year period

Intervention	QALYs	Cost (£)	Incremental QALYs	Incremental cost (£)	ICER (£)
No surveillance	8.44	7249	0.00	0	-
Surveillance	8.50	22,741	0.05	15,491	283,009
Surgery	9.25	15,855	0.81	8606	10,612
Endoscopic mucosal resection and surveillance	8.98	20,993	0.54	13,743	25,662
Radiofrequency ablation and surveillance	9.15	24,740	0.70	17,490	24,823
Photodynamic therapy and surveillance	9.09	32,437	0.65	25,188	38,681
Endoscopic mucosal resection and radiofrequency ablation and surveillance	9.44	23,136	1.00	15,887	15,916
Endoscopic mucosal resection and photodynamic therapy and surveillance	9.38	32,598	0.94	25,348	26,946
Endoscopic mucosal resection and argon plasma coagulation and surveillance	9.33	23,924	0.89	16,675	18,745
ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year					

The result for surveillance is significantly different to the deterministic result. This is because the simulated incremental benefits for surveillance vary between -3 and 3 QALYs. This averages to an overall near zero benefit. The result of this is that a relatively large cost gets divided by a small incremental QALY. This produces an exponentially large and volatile incremental cost effectiveness ratio (ICER). Further details are provided in appendix 6. The inclusion of surveillance with the ablative therapies is also the reason that the probabilistic results for the ablative therapies are generally higher than the deterministic results. If the treatment is associated with a low rate of complete ablation it results in more people undertaking an intensive surveillance

strategy. Hence the uncertainty in the results increases. This particularly affects PDT since it is associated with the lowest rate.

The Guideline Development Group considered that potential flaws in the structure of the model could mean that the value of surveillance could have been underestimated, such as the grouping of high-grade dysplasia and intramucosal cancer into one state. In addition, the effectiveness of surveillance strategies in Barrett's oesophagus has not been systematically reviewed. Therefore, the Group considered that no definitive conclusions could be made on the value of surveillance. However, the addition of surveillance to the endoscopic therapies causes the estimates of cost effectiveness to become very uncertain. The removal of surveillance post-treatment reduces the ICERs considerably (see appendix 6 for more details). Therefore, the uncertainty is being driven by the uncertainty around the value of surveillance rather than the treatment. In this case, given the poor quality of the evidence, the probabilistic results are likely to be the most representative of the true cost effectiveness; however, these results may be overestimated because of the uncertainty around surveillance.

The results of the value-of-information analysis indicated that research into ablative therapies for Barrett's oesophagus would be very valuable. Expected value of perfect information analysis assesses how much it is worth to society for all the uncertainty in the analysis to be resolved. This analysis showed that the value of the uncertainty in the analysis is approximately £58 million. Expected value of perfect parameter information analysis prioritises areas for research and showed that research into the entire natural history of Barrett's oesophagus and the clinical effectiveness of the ablative therapies would be of particular value.

2.2.4 Evidence to recommendations

The Guideline Development Group agreed that there was sufficient evidence (both in terms of overall survival and complete eradication of Barrett's oesophagus) to support the use of endoscopic mucosal resection as an alternative to surgery for high-grade dysplastic Barrett's oesophagus and intramucosal cancer. The Group considered that it is an important form of

treatment for people with comorbidities who are unable to undergo surgery. The Group also agreed that endoscopic therapies should be offered as an option to appropriate patients to accommodate their preference as part of the treatment decision, and that a multidisciplinary team should assess the person. Therefore, the Group felt that it was important that – before any treatment – all patients should have their diagnosis confirmed at a specialist centre, and full staging should be mandatory. This principle was supported by the evidence because all studies considered in the evidence review were undertaken at specialist centres.

2.2.5 Recommendation

Recommendation 1.1.2

Offer endoscopic therapy as an alternative to oesophagectomy to people with high-grade dysplasia and intramucosal cancer (T1a), taking into account individual preferences, fitness and general health.

2.3 Endoscopic mucosal resection

2.3.1 Evidence review

Through systematic searching, 1888 articles were identified and 1524 articles did not meet the inclusion criteria at the abstract and title stage and 364 articles were ordered as full articles[6]. Of these, 12 studies that treated high-grade dysplastic Barrett's oesophagus or early adenocarcinoma using endoscopic mucosal resection alone were eligible for analysis. The quality of evidence found was very low. The evidence is summarised in the GRADE profiles 3 and 4.

[6] See appendix 4 for the inclusion and exclusion criteria, study selection flowcharts and list of excluded studies

GRADE profile 3 Endoscopic mucosal resection alone for studies with less than 12 months' follow-up

Study	Design	Treatment	Placebo	Risk	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Quality
Primary outcome 1. Complete eradication of dysplasia										
Prasad et al. (2007c)	Uncontrolled	2/4 (50%)			Series of 4 individual case reports					+ (Very low)
Primary outcome 2. Complete eradication of Barrett's oesophagus or intestinal metaplasia										
Prasad et al. (2007c); Thomas et al. (2009); Soehendra et al. (1997); Seewald et al. (2003)	Uncontrolled	25–100%			4 studies of n = 4, n = 16, n = 7 and n = 12					+ (Very low)
Adverse outcome 9. Stricture or stenosis requiring treatment										
Seewald et al. (2003); Soehendra et al. (2006)	Uncontrolled	16.67–70%[a]			2 studies of n = 12 and n = 10					+ (Very low)
Adverse outcome 12. Perforations										
Peters et al. (2007)	Uncontrolled	1/93 (1.08%)			Study looking at safety of different endoscopic mucosal resection techniques					+ (Very low)
Adverse outcome 14. Bleeding										
Seewald et al. (2003); Thomas et al. (2009); Soehendra et al. (2006); Peters et al. (2007)	Uncontrolled studies	12.90–26%			4 studies of n = 12, n = 16, n = 12 and n = 93					+ (Very low)

a The use of different techniques of endoscopic mucosal resection caused the variation of stricture rates, with the low-end of the range corresponding to focal endoscopic mucosal resection and the higher end to circumferential endoscopic resection.

GRADE profile 4 Endoscopic mucosal resection alone for studies with 12 months' or more follow-up

Study	Design	Treatment	Placebo	Risk	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Quality
Primary outcome 1. Complete eradication of dysplasia										
Ell et al. (2000; 2007)[a]	Uncontrolled	99/100 (99%)[b]			Large case series, with 2 published papers.					+ (Very low)
Primary outcome 2. Complete eradication of Barrett's oesophagus or intestinal metaplasia										
Nijhawan and Wang (2000); Lopes et al. (2007); Giovanni et al. (2004); Larghi et al. (2007)	Uncontrolled	44–87.50%			4 studies of n =25, n = 41,n = 21 and n = 24					+ (Very low)
Primary outcome 6. Overall survival										
Ell et al. (2000; 2007)[a]	Uncontrolled	100/100 (100%); estimate 98%[c]			Large case series, with 2 published papers					+ (Very low)
Inoue (1991, 1998)	Uncontrolled	95%[d]			Large study, n = 142; 9-year follow-up					+ (Very low)
Adverse outcome 7. Major adverse events										
Ell et al. (2000; 2007)[a]	Uncontrolled	0/100 (0%)[e]			Large case series, with 2 published papers					+ (Very low)
Adverse outcome 8. Minor adverse events										
Ell et al. (2000; 2007)[a]	Uncontrolled	11/100 (11%)[f]			Large case series, with 2 published papers					+ (Very low)
Adverse outcome 9. Stricture or stenosis needing treatment										
Inoue (1991, 1998)	Case series	1/142 (0.70%)			Large study, n = 142; 9-year follow-up					+ (Very low)
Lopes et al. (2007); Conio et al. (2005); Larghi et al. (2007)	Uncontrolled	2.44–12.5%			3 studies of n = 41, n = 39 and n = 24					+ (Very low)

Study	Design	Treatment	Placebo	Risk	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Quality
Adverse outcome 12. Perforations										
Inoue (1998)	Uncontrolled	1/142 (0.70%)			Large study, n = 142; 9-year follow-up					+ (Very low)
Lopes et al. (2007)	Uncontrolled	2/41 (4.88%)			n = 41					+ (Very low)
Adverse outcome 14. Bleeding										
Larghi et al. (2007); Conio et al. (2005); Giovanni et al. (2004); Lopes et al. (2007).	Uncontrolled	8.33–19.51%			4 studies of n = 24, n = 39, n = 21 and n = 41					+ (Very low)

[a] Data are taken from a specialist, high-volume centre.

[b] Time to complete remission range 1–18 months, mean = 1.9 months, standard deviation = 2.1 months.

[c] At follow-up range 2–83 months, mean = 36.7 months, standard deviation = 15.4 months, median 33 months, 100% survival was seen; the life table estimate was 98% at 5 years.

[d] Survival at 5 years.

[e] Major adverse events: strictures, perforations, bleeding or death.

[f] Minor adverse events: haemorrhage post-endoscopic mucosal resection requiring treatment with epinephrine (adrenaline).

2.3.2 Evidence statements

2.3.2.1 Four small case series (n = 4, n = 7, n = 12 and n = 16) studied the use of endoscopic mucosal resection alone on the ablation of Barrett's oesophagus with less than 12 months' follow-up.

2.3.2.2 Two large studies (Ell et al. 2000, 2007; n = 100) and (Inoue 1991, 1998; N = 142) and six small case series studied the use of endoscopic mucosal resection alone on the ablation of Barrett's oesophagus with more than 12 months' follow-up.

Primary outcomes

2.3.2.3 The four small case series with less than 12 months' follow-up showed 25–100% complete ablation of Barrett's oesophagus, and Prasad et al. (2007c) showed 50% complete eradication of dysplasia.

2.3.2.4 Ell et al. (2007) showed a 99% eradication of dysplasia and cancer and estimated a 98% 5-year overall survival and Inoue (1998) showed 95% overall survival at 5 years.

2.3.2.5 Four small case series with more than 12 months' follow-up showed 44–87.50% complete ablation of Barrett's oesophagus.

Adverse events

2.3.2.6 The four small case series with less than 12 months' follow-up showed 16.67–70% cases with strictures needing treatment, 1.08% cases of perforations and 12.90–26% cases of bleeding, with the higher rate of strictures seen with circumferential endoscopic resection.

2.3.2.7 Major adverse events for studies with more than 12 months' follow-up included 0.7–12.5% cases of strictures requiring treatment (the higher rate of strictures was seen with circumferential endoscopic resection) and 0.7–4.88% cases of perforations. Minor adverse

events included 11% cases of haemorrhage after resection requiring treatment with adrenaline and 8.33–19.51% cases of bleeding.

2.3.3 Health economic modelling

The results of the cost-effectiveness analysis for endoscopic mucosal resection are summarised in table 5.

Table 5 Cost effectiveness of endoscopic mucosal resection

Parameter	Outcome
Deterministic ICER	£13,846
Probabilistic ICER	£25,662
Probability of being cost effective at £20,000 per QALY	35.5%
Probability of being cost effective at £30,000 per QALY	44.4%
ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year	

These results suggest that endoscopic mucosal resection is cost effective compared with no surveillance. However, there is considerable uncertainty in the decision, as suggested by the 44% probability of being cost effective at £30,000.

2.3.4 Evidence to recommendations

The Guideline Development Group felt that due to the high rate of strictures after circumferential endoscopic resection, it should only be used with care. Consequently there was consensus around using endoscopic mucosal resection alone for localised lesions only. The Group considered the use of endoscopic resection alone, though the evidence was of very low quality as the Ell at al. (2007) series had long-term follow-up (median 33 months). The Group also discussed that caution should be exercised over the data obtained in a study by Ell et al. (2007) that show 99% eradication of dysplasia and/or cancer using endoscopic mucosal resection alone. This high rate was established at a specialist high-volume centre and reproduction in the UK would be very difficult. The Group discussed the cost-effectiveness results for endoscopic mucosal resection and acknowledged that the results were highly uncertain and were based on poor clinical data. The Group concluded that if

endoscopic mucosal resection was restricted to specialist centres and was used to treat only localised lesions, then its cost effectiveness would improve. Consequently, endoscopic mucosal resection was deemed a cost-effective option for the treatment of Barrett's oesophagus.

2.3.5 Recommendations

Recommendation 1.1.3
Consider using endoscopic mucosal resection alone to treat localised lesions.

Recommendation 1.1.4
Use circumferential endoscopic mucosal resection with care because of the high incidence of stricture formation.

Recommendation 1.1.5
If residual or recurrent disease is suspected, consider additional or repeated therapies (either endoscopic mucosal resection (also referred to as endoscopic resection) with further pathological assessment or ablative therapies [RFA, APC or PDT]) with appropriate follow-up.

2.4 Ablative therapies

2.4.1 Evidence review

Through systematic searching, 1888 articles were identified; 364 of these met the inclusion criteria at the abstract and title stage and ordered as full articles[7]. Of these, 11 studies that treated high-grade dysplastic Barrett's oesophagus or early intramucosal cancer using ablative therapies alone were eligible for inclusion. The quality of evidence found was predominantly very low. The 11 studies comprised:

- three studies that used argon plasma coagulation alone for ablation (see GRADE profile 5)
- three studies that used laser alone for ablation (see GRADE profile 6)

[7] See appendix 4 for the inclusion and exclusion criteria, study selection flowcharts and list of excluded studies

- two studies that used laser ablation with multipolar electrocoagulation (see GRADE profile 7)
- one study that used argon plasma coagulation with multipolar electrocoagulation for ablation (see GRADE profile 8)
- two studies that used radiofrequency ablation alone for ablation (see GRADE profile 9).

Both these radiofrequency ablation-alone studies (Shaheen et al. 2009; Ganz et al. 2008) had some participants that had received endoscopic mucosal resection before radiofrequency ablation. In the paper by Shaheen et al. (2009), the authors stated that the participants included could have received endoscopic mucosal resection up to 8 weeks before the study. As this was done prior to randomisation this should have been balanced in both arms, the specific numbers that received endoscopic mucosal resection in each arm, however are not stated in the paper. In the study by Ganz et al. (2008) 17% of the participants had received endoscopic mucosal resection before radiofrequency ablation.

For photodynamic therapy alone, 28 articles relating to 24 studies were eligible for inclusion. A randomised controlled trial by Ragunath et al. (2005), which compared the effectiveness of argon plasma coagulation with photodynamic therapy, was eligible but was removed from the analysis on consensus from the Guideline Development Group. The study had 26 participants but only three were of the correct population (with high-grade dysplasia) of which one was treated with argon plasma coagulation versus two with photodynamic therapy. However, no outcome data were available for the patient treated with argon plasma coagulation after 12 months of follow-up because the individual dropped out of the study.

The photosensitisers used for photodynamic therapy in the included studies are listed in table 6 and the evidence from the included studies is summarised in the GRADE profile 10. An indirect comparison was drawn to determine the clinical effectiveness of radiofrequency ablation alone compared with photodynamic therapy alone using the Altman and Bland (2003) method.

Table 6 Drugs used for photodynamic therapy in the included studies

Study	Type of photosensitiser used
Ackroyd et al. (1999)	5-aminolaevulinic acid 30 mg/kg
Ban et al. (2004)	Porfirmer sodium 2 mg/kg
Barr et al. (1996)	5-aminolaevulinic acid 30 mg/kg
Craig et al. (2007)	Porfirmer sodium 2 mg/kg
Etienne et al. (2004)	Temoporfin or meta-tetrahydroxyphenyl chlorine
Filonenko et al. (2008)	Haematoporphyrin derivative, sulfonated aluminium phtalocyanine, natural chlorophyll-a derivative or 5-aminolaevulinic acid
Foroulis and Thorpe (2006)	Porfirmer sodium 2 mg/kg
Gill et al. (2009)	Porfirmer sodium 2 mg/kg
Gossner et al. (1998)	5-aminolaevulinic acid 30 mg/kg
Gossner et al. (1999b)	5-aminolaevulinic acid 30 mg/kg or intravenous meta-tetrahydroxyphenyl chlorine
Javaid et al. (2002)	Meta-tetrahydroxyphenyl chlorine
Keeley et al. (2007)	Porfirmer sodium 2 mg/kg
Laukka and Wang (1995)	Low-dose haematoporphyrin derivative
Lovat et al. (2005)	Meta-tetrahydroxyphenyl chlorine
Mackenzie et al. (2008)	5-aminolaevulinic acid 30 mg/kg
Mino-Kenudson et al. (2007)	Porfirmer sodium 2 mg/kg
Overholt et al. (1999, 2003 and 2005, 2007)	Porfirmer sodium 2 mg/kg
Pech et al. (2005)	5-aminolaevulinic acid 30 mg/kg
Prasad et al. (2007a)	26 patients – haematoporphyrin derivative (94 mg/kg); 103 patients – porfimer sodium (2 mg/kg)
Prasad et al. (2007b)	26 patients – hematoporphyrin derivative (94 mg/kg); 105 patients – porfimer sodium (2 mg/kg)
Weiss et al. (2006)	Porfirmer sodium 2 mg/kg
Wolfsen et al. (2002, 2004a)	Porfirmer sodium 2 mg/kg
Yachimski et al. (2008, 2009)	Porfirmer sodium 2 mg/kg

GRADE profile 5 Argon plasma coagulation alone for studies with 12 months of follow-up or longer

Study	Design	Treatment	Placebo	Risk	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Quality
Primary outcome 1: Complete eradication of dysplasia or cancer										
Van Laethem et al. (2001)	Uncontrolled	8/10 (80%)			n = 10					+ (Very low)
Primary outcome 2. Complete eradication of Barrett's oesophagus or intestinal metaplasia										
Attwood et al. (2003); May et al. (1999); Van Laethem et al. (2001)	Uncontrolled	50–76%			3 studies of n = 3, n = 10 and n = 29					+ (Very low)
Primary outcome 5. Progression of disease to cancer										
Attwood et al. (2003)	Uncontrolled	4/29 (13.79%)			n = 29					+ (Very low)
Primary outcome 6. Overall survival										
Attwood et al. (2003)[a]; Van Laethem et al. (2001)[b]	Uncontrolled	90% at 2 years; 82% at 5 years			2 studies of n = 29 and n = 10					+ (Very low)
Adverse outcome 9. Stricture or stenosis needing dilation										
Attwood et al. (2003)	Uncontrolled	0/29 (0%)			n = 29					+ (Very low)
Adverse outcome 12. Perforations										
Attwood et al. (2003)	Uncontrolled	1/29 (3.49%)			n = 29					+ (Very low)

[a] Survival analysis using Kaplan–Meier and life tables but using the general UK population for comparison and up to 5 years showing 82% survival.

[b] Mortality was 1/10 after follow-up of 24 months.

GRADE profile 6 Laser therapies alone for studies with 12 months of follow-up or longer

Study	Design	Treatment	Placebo	Risk	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Quality
Primary outcome 2. Complete eradication of Barrett's oesophagus or intestinal metaplasia										
Weston and Sharma (2002); Gossner et al. (1999a)	Uncontrolled	78.6–100%			2 studies of n = 14 and n = 10, respectively					+ (Very low)
Primary outcome 3. Complete eradication of high-grade dysplasia or cancer										
Weston and Sharma (2002)	Uncontrolled	14/14 (100%)			n = 14					+ (Very low)
Adverse outcome 9. Stricture or stenosis needing dilation										
Weston and Sharma (2002)	Uncontrolled	2/14 (14.28%)			n = 14					+ (Very low)
Adverse outcome 12. Perforations										
Mathus-Vliegen and Tytgat (1990)	Uncontrolled	0/21 (0%)			n = 21					+ (Very low)
Adverse outcome 13. Chest pain or retrosternal pain										
Gossner et al. (1999a); Weston and Sharma (2002)	Uncontrolled	30–33.33%			2 studies of n = 10 and n = 14, respectively					+ (Very low)
Adverse outcome 14. Bleeding										
Weston and Sharma (2002); Mathus-Vliegen and Tytgat(1990)	Uncontrolled	7.14–14.9%			2 studies of n = 14 and n = 21, respectively					+ (Very low)

GRADE profile 7 Laser and multipolar electrocoagulation for studies with 12 months of follow-up or longer

Study	Design	Treatment	Placebo	Risk	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Quality
Primary outcome 2. Complete eradication of Barrett's oesophagus or intestinal metaplasia										
Sharma et al. (1999, 2000)	Uncontrolled	33.3–37.5%			2 studies of n = 6 and n = 8, respectively with 12 months' and 3.4 years' follow-up					+ (Very low)

GRADE profile 8 Multipolar electrocoagulation and argon plasma coagulation for studies with 12 months of follow–up or longer

Study	Design	Treatment	Placebo	Risk	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Quality
Primary outcome 5. Progression of disease to cancer										
Sampliner et al. (2006)	Uncontrolled	3/3 (100%)[a]			n = 3, mean 14.3 months' follow-up					+ (Very low)

[a] The case series specifically reported only those cases that progressed to adenocarcinoma.

GRADE profile 9 Radiofrequency ablation alone for studies of 12 months of follow-up or longer

Study	Design	Treatment	Placebo	Relative risk (RR, 95% confidence interval [CI]); absolute risk reduction (ARR); number needed to treat (NNT) or to harm (NNH, 95% CI)	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Quality
Primary outcome 1. Complete eradication of dysplasia or cancer										
Shaheen et al. (2009)	Randomised controlled	34/42 (81%)	4/21(19%)	RR = 4.25 (1.98 to 10.66); ARR = 0.62; NNT = 1.62 (1.28 to 2.69)	Not serious	Not serious	Not serious	Not serious	Not serious	++++ (High)
Ganz et al. (2008)[a]	Uncontrolled	74/92 (80.4%)			Large case series, patients' registry from 16 institutions, n = 142; efficacy data n = 92					+ (Very low)
Primary outcome 2. Complete eradication of Barrett's oesophagus or intestinal metaplasia										
Shaheen et al. (2009)	Randomised controlled	31/42 (74%)	0/21 (0%)	ARR = 0.74; NNT = 1.35 (1.18 to 1.78)	Not serious	Not serious	Not serious	Not serious	Not serious	++++ (High)
Ganz et al. (2008)[a]	Uncontrolled	50/92 (54.3%)			Large case series, patients' registry from 16 institutions, n = 142; efficacy data n = 92					+ (Very low)
Primary outcome 3. Complete eradication of high-grade dysplasia or cancer										
Ganz et al. (2008)[a]	Uncontrolled	83/92 (90.2%)			Large case series, patients' registry from 16 institutions, n = 142; efficacy data n = 92					+ (Very low)
Primary outcome 5. Progression of disease to cancer										
Shaheen et al. (2009)	Randomised controlled	1/42 (2%)	4/21(19%)	RR = 0.13 (0.019 to 0.784); ARR = 0.17; NNT = 6.0 (2.62 to 40.22)	Not serious	Not serious	Not serious	Serious[b]	Not serious	+++ (Moderate)
Adverse outcome 7. Major adverse event										
Shaheen et al. (2009)	Randomised controlled	1/42 (2.38%)	0/21 (0%)	ARR = -0.02; NNH = 42 (−8.03 to 74.50)[c]	Not serious	Not serious	Not serious	Not serious	Not serious	++++ (High)

Study	Design	Treatment	Placebo	Relative risk (RR, 95% confidence interval [CI]); absolute risk reduction (ARR); number needed to treat (NNT) or to harm (NNH, 95% CI)	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Quality
Adverse outcome 13. Chest pain or retrosternal pain										
Shaheen et al. (2009)	Randomised controlled	2/42 (4.76%)	0/21 (0%)	ARR = −0.05; NNH = 21 (−6.28 to 89.43)[d]	Not serious	Not serious	Not serious	Not serious	Not serious	++++ (High)

[a] The authors state that 17% of participants received endoscopic mucosal resection before radiofrequency ablation.

[b] The outcome was downgraded for imprecision due to the large range of the confidence intervals. The authors also stated that only one more person getting cancer in the radiofrequency ablation arm could have moved the relative risk in favour of the sham procedure arm.

[c] One patient in the radiofrequency ablation arm had an upper gastrointestinal haemorrhage.

[d] One patient had chest pain after 8 days and another patient had chest discomfort and nausea immediately after the procedure. Visual analogue scale score (0–100) for some patients only: radiofrequency ablation (n = 41) median 22 versus 0 for control (n = 20).

GRADE profile 10 Photodynamic therapy alone for studies with 12 months of follow-up or longer

Study	Design	Treatment (photosensitiser used for photodynamic therapy)	Placebo	Relative risk (RR, 95% confidence interval [CI]); absolute risk reduction (ARR); number needed to treat (NNT) or to harm (NNH, 95% CI)	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Quality
Primary outcome 1.Complete eradication of dysplasia or cancer										
Overholt et al. (2005, 2007)	Randomised controlled	81/138 (58.7%; (porfirmer sodium)	10/70 (14.3%)	RR = 4.11 (2.36 to 7.45); ARR = 0.44; NNT = 2.25 (1.81 to 3.16)	Not serious	Not serious	Not serious	Not serious	Not serious	++++ (High)
Overholt et al. (1999)	Case series	64/85 (75.3%; porfirmer sodium)			Single centre standard case series with subgroups for dysplasia					+ (Very low)
Ban et al. (2004); Gossner et al. (1998); Javaid et al. (2002)	Case series	51.5–100% (porfirmer sodium, 5-aminolaevulinic acid or meta-tetrahydroxyphenyl chlorine)			3 studies n = 7, n = 32 and n = 33 with follow-up 12.8–60 months					+ (Very low)
Primary outcome 2. Complete eradication of Barrett's oesophagus or intestinal metaplasia										
Overholt et al. (1999)	Case series	36/85 (42.5%) (porfirmer sodium)			Single centre case series of n =100; analysis of n = 85					+ (Very low)
Wolfsen et al. (2004a)	Case series	57/102 (55.8%) (porfirmer sodium)			Single centre study of complications of photodynamic therapy n = 102					+ (Very low)
Yachimski et al. (2009)	Case series	45/116 (38.8%) (porfirmer sodium)			Study looking at predictors for complete ablation (using data from a single large urban teaching hospital), n = 116					+ (Very low)
Craig et al. (2007); Lovat et al. (2005); Mackenzie et al. (2008); Mino-Kenudson et al. (2007); Wolfsen et al. (2002)	Case series	8.3–61.5%[a] (3 studies with porfirmer sodium, and 1 each with meta-tetrahydroxyphenyl chlorine and 5-aminolaevulinic acid)			5 studies n = 19, n = 24, n = 28, n = 48 and n = 52, with follow-up of 18.5 months to 7 years					+ (Very low)

Study	Design	Treatment (photosensitiser used for photodynamic therapy)	Placebo	Relative risk (RR, 95% confidence interval [CI]); absolute risk reduction (ARR); number needed to treat (NNT) or to harm (NNH, 95% CI)	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Quality
Primary outcome 3. Complete eradication of high-grade dysplasia or cancer										
Overholt et al. (2005, 2007)	Randomised controlled	106/138 (76.8%; porfirmer sodium)	27/70 (38.6%)	RR = 1.99 (1.49 to 2.76); ARR = 0.38; NNT = 2.61 (1.97 to 4.11)	Not serious	Not serious	Not serious	Not serious	Not serious	++++ (High)
Barr et al. (1996); Etienne et al. (2004); Filonenko et al. (2008); Foroulis and Thorpe (2006); Gossner et al. (1999b); Keeley et al. (2007); Weiss et al. (2006)	Case series	38.5–100% (3 studies with porfirmer sodium, 1 with 5-aminolaevulinic acid, 1 with temoporfin or meta-tetrahydroxyphenyl chlorine, 1 with 5-aminolaevulinic acid or meta-tetrahydroxyphenyl chlorine, and 1 with haematoporphyrin derivative or sulfonated aluminium phtalocyanine or radachlorin or 5-aminolaevulinic acid)			7 studies n = 5–50 with follow-up 12 months to 11 years					+ (Very low)
Primary outcome 4. Reduction in length of Barrett's oesophagus										
Laukka and Wang (1995)	Case series	2.4±0.9 cm (1–5 range); reduction by 10–50% (low-dose haematoporphyrin derivative)			Small study with n = 5 and follow-up of 1 year					+ (Very low)
Primary outcome 5. Progression of disease to cancer										
Overholt et al. (2005, 2007)	Randomised controlled	21/138 (15.2%; porfirmer sodium)	20/70 (28.6%)	RR = 0.53 (0.31 to 0.91); ARR = 0.134; NNT = 7.49 (3.83 to 55.62)	Not serious	Not serious	Not serious	Not serious	Not serious	++++ (High)
Primary outcome 6. Overall survival										
Prasad et al. (2007a)	Cohort	118/129 (91.47%; porfirmer sodium or haematoporphyrin derivative)	Surgery 64/70 (91.43%)	RR = 1.0 (0.92 to 1.12)[b]; ARR = 0.00	Not serious	Not serious	Not serious	Not serious	Not serious	++ (Low)
Overholt et al. (2003)	Case series	77/89 (81.5%[c]; porfirmer sodium)			Single centre case series with mean follow-up of 50.7 months and n = 103; relevant population n = 89					+ (Very low)

Study	Design	Treatment (photosensitiser used for photodynamic therapy)	Placebo	Relative risk (RR, 95% confidence interval [CI]); absolute risk reduction (ARR); number needed to treat (NNT) or to harm (NNH, 95% CI)	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Quality
Adverse outcome 8. Minor adverse events										
Ackroyd et al. (1999); Etienne et al. (2004); Foroulis and Thorpe (2006); Gossner et al. (1998); Keeley et al. (2007); Laukka and Wang (1995); Mackenzie et al. (2008); Pech et al. (2005); Weiss et al. (2006)	Case series	3.22–75%[d] (4 studies with 5-aminolaevulinic acid, 3 with porfirmer sodium, 1 with low-dose haematoporphyrin derivative and 1 with temoporfin or meta-tetrahydroxyphenyl chlorine)			7 studies n = 5–66 patients with follow-up of 12–45 months					+ (Very low)
Adverse outcome 9. Stricture or stenosis needing treatment										
Overholt et al. (2005, 2007)	Randomised controlled	49/133 (36.8%; porfirmer sodium)	0/69 (0%)	ARR = 0.37; NNH = 2.71	Not serious	Not serious	Not serious	Not serious	Not serious	++++ (High)
Prasad et al. (2007)b;	Case series	35/131(26.72%; porfirmer sodium or haematoporphyrin derivative)			Single centre study, studying stricture after photodynamic therapy n = 131					+ (Very low)
Overholt et al. (2003)	Case series	27/89 (30.3%; porfirmer sodium)			Single centre case series with mean follow-up of 50.7 months n = 103; relevant population n = 89					+ (Very low)
Wolfsen et al. (2004a)	Case series	20/102 (20%; porfirmer sodium)			Single centre study focusing on complications of photodynamic therapy n = 102, with a mean follow-up time: 18.5 (range, 1-56) months					+ (Very low)
Yachimski et al. (2008)	Case series	37/160 courses of photodynamic therapy (23.12%; porfirmer sodium)			Study looking at predictors for stricture (using data from a single large urban teaching hospital) n = 116					+ (Very low)

Study	Design	Treatment (photosensitiser used for photodynamic therapy)	Placebo	Relative risk (RR, 95% confidence interval [CI]); absolute risk reduction (ARR); number needed to treat (NNT) or to harm (NNH, 95% CI)	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Quality
Craig et al. (2007); Etienne et al. (2004); Foroulis and Thorpe (2006); Gill et al. (2009); Gossner et al. (1999b); Javaid et al. (2002); Lovat et al. (2005); Mackenzie et al. (2008); Weiss et al. (2006)	Case series	0–50%[e] (4 with porfirmer sodium, 2 with meta-tetrahydroxyphenyl chlorine, 2 with 5-aminolaevulinic acid, and one with temoporfin or meta-tetrahydroxyphenyl chlorine)			9 studies: n = 6–31 with follow-up of up to 45 months					+ (Very low)
Adverse outcome 10. Photosensitivity										
Overholt et al. (2005, 2007)	Randomised controlled	92/133 (69%; porfirmer sodium)	0/69 (0%)	ARR = 0.691; NNH = 1.45	Not serious	Not serious	Not serious	Not serious	Not serious	++++ (High)
Wolfsen et al. (2004a)	Case series	18/102 (18%; porfirmer sodium)			Single centre study focusing on complications of photodynamic therapy, n = 102, with a mean follow-up time: 18.5 (range, 1-56) months					+ (Very low)
Etienne et al. (2004); Filonenko et al. (2008); Foroulis and Thorpe (2006); Gossner et al. (1998); Keeley et al. (2007); Laukka and Wang (1995); Lovat et al. (2005); Mackenzie et al. (2008); Weiss et al. (2006); Wolfsen et al. (2002).	Case series	0–100%; 4 with porfirmer sodium, 2 with 5-aminolaevulinic acid, 1 with temoporfin or meta-tetrahydroxyphenyl chlorine, 1 with meta-tetrahydroxyphenyl chlorine, 1 with low-dose haematoporphyrin derivative and 1 with haematoporphyrin derivative or sulfonated aluminium phtalocyanine or Radachlorin or 5-aminolaevulinic acid)			10 studies n = 5–50 with follow-up ranging from 12 months to 11 years.					+ (Very low)
Adverse outcome 11. Cardiac complications										
Overholt et al. (2003)	Case series	3/89 (3.37%; porfirmer sodium)			Single centre case series with mean follow-up of 50.7 months n = 103; relevant population n = 89					+ (Very low)

Study	Design	Treatment (photosensitiser used for photodynamic therapy)	Placebo	Relative risk (RR, 95% confidence interval [CI]); absolute risk reduction (ARR); number needed to treat (NNT) or to harm (NNH, 95% CI)	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Quality
Wolfsen et al. (2004a)	Case series	2/102 (2%; porfirmer sodium)			Single centre study focusing on complications of photodynamic therapy n = 102, with a mean follow-up time: 18.5 (range, 1-56) months					+ (Very low)
Weiss et al. (2006); Wolfsen et al. (2002)	Case series	4.16–5.88% (porfirmer sodium)[f]			2 studies n = 17 and n = 48, with follow-up of 21 months and 18.5 months, respectively					+ (Very low)
Adverse outcome 13. Chest pain or retrosternal pain										
Overholt et al. (2005, 2007)	Randomised controlled	27/133 (20%; porfirmer sodium)	0/69 (0%)	ARR = 0.203; NNH = 4.93	Not serious	Not serious	Not serious	Not serious	Not serious	++++ (High)
Wolfsen et al. (2004a)	Case series	Photodynamic therapy 15/102 (15%; porfirmer sodium)			Single centre study focusing on complications of photodynamic therapy n = 102					+ (Very low)

[a] The 8.3% rate was seen in Mackenzie et al. (2008), which was a dose escalation study, excluding it changes the range to 36.8–61.5%.

[b] Overall survival at a median follow-up of 59.27 months.

[c] Survival analysis using Kaplan–Meier curves at mean follow-up of 50.65 months.

[d] Ackroyd et al. (1999; n = 10; 24 months' follow-up) 10% nausea for 24 hours; Etienne et al. (2004) (n = 12; 34 months' follow-up) 25% had hiccups; Foroulis and Thorpe (2006; n = 31; 14 months' follow-up) 3.22% epigastric pain and nausea and 16.12% symptomatic oesophagitis; Gossner et al. (1998; n = 32; 30 months' follow-up) 46.9% nausea; Keeley et al. (2007; n = 50; 28.1 months' follow-up) 6% had pleural effusion; Laukka and Wang (1995; n = 5; 12 months' follow-up) nausea, epigastric pain and anorexia 40%; Mackenzie et al. (2008; n = 24; 45 months' follow-up) 75% had nausea and vomiting; Pech et al. (2005; n = 66; 37 months' follow-up) 40% had vomiting, nausea and chest pain; Weiss et al. (2006; n = 17; 21 months' follow-up) 11.8% had pleural effusion.

[e] The 50% stricture rate was seen in Craig et al. (2007) (using porfirmer sodium) and 0% was seen in Mackenzie et al. (2008) and Gossner et al. (1999b) using 5-aminolaevulinic acid. The 0% rate was found in two studies: Gossner et al. (1998) n = 32 with 1–30 months' follow-up and Mackenzie (2008) n = 24 with a median follow-up of 45 months, both using 5-aminolaevulinic acid. The 100% rate was found in one study: Filonenko (2008) n = 48 with 3–11 years' follow-up using haematoporphyrin derivative, sulfonated aluminium phtalocyanine, natural chlorophyll-a derivative or 5-aminolaevulinic acid.

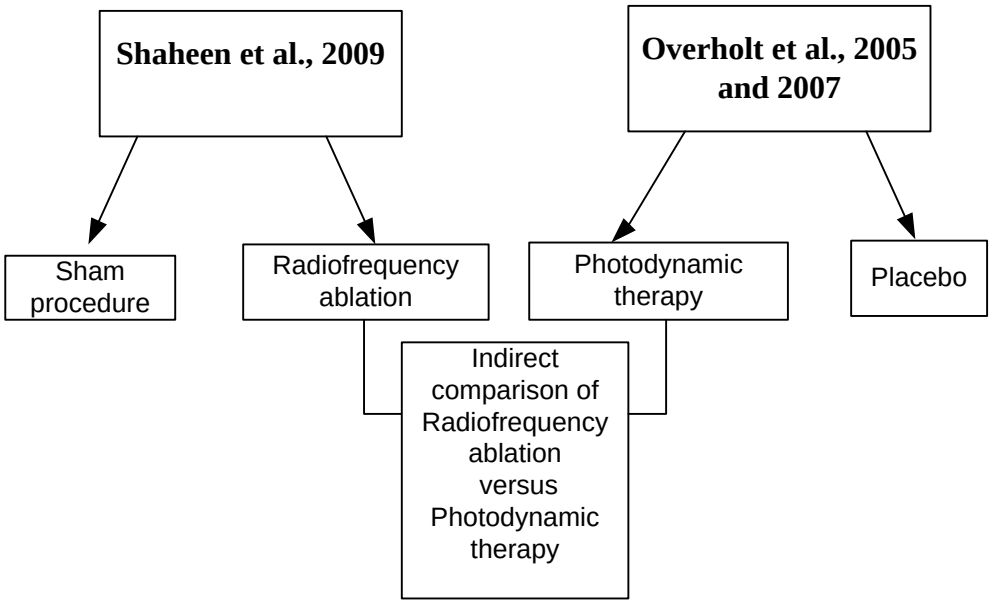
[f] Weiss et al. (2006), one patient had atrial fibrillation; Wolfsen et al. (2002) one patient had atrial fibrillation and one had recurrent congestive heart failure.

Indirect comparison for radiofrequency ablation versus photodynamic therapy

Methods

An indirect comparison of two interventions can be made by the comparing them with a common control group. For this guideline the simplest scenario was considered, where we compared two interventions (radiofrequency ablation and photodynamic therapy) and got indirect evidence of effectiveness of radiofrequency ablation versus photodynamic therapy by using the estimates of their effect in relation to the control from their individual randomised controlled trials (Shaheen et al. 2009; Overholt et al. 2005, 2007; figure 2, table 7).

Figure 2 Schematic representation of the indirect comparison between radiofrequency ablation and photodynamic therapy



The statistical method used for the indirect comparison was taken from Altman and Bland (2003), in which relative risks were analysed on the log scale because the distributions of the log ratios tend to be closer to normal distribution compared with the ratios themselves. The assumptions for this particular indirect comparison were: that the control arms for the two randomised controlled trials were comparable – that is, the sham procedure in the study by Shaheen et al. (2009) was equivalent to the placebo arm of the

study by Overholt et al. (2005, 2007); that the populations in the two randomised controlled trials were similar; and that their sample size was sufficient to make the comparison.

Table 7 Randomised controlled trials included for the indirect comparison

Parameters	**Shaheen et al. (2009)**	**Overholt et al. (2005, 2007)**
Population	Total n = 127; but only population with high-grade dysplasia used for analysis n = 63: radiofrequency ablation (n = 42) versus sham procedure (n = 21). All received omeprazole	Total n = 208; all with high-grade dysplasia: photodynamic therapy and omeprazole (n = 138) versus omeprazole alone (n = 70)
Intervention	Circumferential radiofrequency ablation	Photodynamic therapy (with porfirmer sodium)
Comparator	Sham procedure	Placebo
Outcomes used for indirect comparison	Complete eradication of dysplasia	

The individual relative risks for complete eradication of dysplasia against the control arm for Shaheen et al. (2009) and Overholt et al. (2005, 2007) were 4.25 (95% CI 1.98 to 10.66) and 4.11 (95% CI 2.36 to 7.45) respectively. The ratio of relative risks (RRR) for radiofrequency ablation versus photodynamic therapy was calculated as 1.034 (95% CI 0.37 to 2.87). Therefore, there was no significant difference between the clinical effectiveness of radiofrequency ablation compared with photodynamic therapy in the complete eradication of dysplasia (table 8). It is important to note that although some of the participants in the study by Shaheen et al. (2009) did have prior endoscopic mucosal resection, the numbers should be balanced in both arms because this was before randomisation and, therefore, should not affect the relative risk calculation and in turn the ratio of relative risks.

Table 8 Calculations of the indirect comparison

Parameters	Shaheen et al. (2009)	Overholt et al. (2005, 2007)
RR (95% CI)	4.25 (1.98 to 10.66)	4.11 (2.36 to 7.45)
Log RR[8]	1.45 (0.68 to 2.37)	1.41 (0.86 to 2.01)
Standard error of log RR	0.43	0.30
Difference[9](95% CI)	0.03 (−0.99, 1.05)	
Standard error of the difference	0.52	
RRR (95% CI)	1.03 (0.37 to 2.87)	
CI, confidence interval; RR, relative risk; RRR, ratio of relative risks		

2.4.2 Evidence statements

Argon plasma coagulation alone

2.4.2.1 Three small case series (n = 3, 10 and 29) were included that showed a 50–76% ablation of Barrett's oesophagus and a 13.79% progression of cancer rate.

2.4.2.2 Survival estimated at 5 years by Attwood et al. (2003; n = 29, mean 37 months' follow-up) was 82% and Van Laethem et al. (2001; n = 10, median 24 months' follow-up) noted a 90% survival at 24 months. Attwood et al. (2003) also noted a 3.49% rate of perforations.

Laser ablation alone

2.4.2.3 Three small case series (n = 10, 14 and 21) were included and showed 78.6–100% ablation of Barrett's oesophagus. The rate of strictures requiring treatment was 14.28% with 30–33.33% cases of chest pain and 7.14–14.9% cases of bleeding.

[8] Log values are obtained by taking the natural logarithms of the values.

[9] Difference (d) is the difference between the log relative risks.

Laser ablation and multipolar electrocoagulation alone

2.4.2.4 Two small case series (n = 6 and 8, median 12 and 40.8 months' follow-up, respectively) by Sharma et al. (1999, 2000) showed poor eradication of Barrett's oesophagus (33.3–37.5%).

Multipolar electrocoagulation and argon plasma coagulation alone

2.4.2.5 Only one case series (Sampliner et al. 2006; n = 3) was obtained; the article reported only those cases that progressed to adenocarcinoma, therefore all three cases progressed to cancer.

Radiofrequency ablation alone

2.4.2.6 One high-quality randomised controlled trial (Shaheen et al. 2009) with a follow-up of 12 months, was included that studied radiofrequency ablation alone (n = 42) compared with a sham procedure (n = 21). The study showed 81% eradication of dysplasia for the radiofrequency ablation arm compared with 19% in the sham arm (RR = 4.25, 95% CI 1.98 to 10.66); complete eradication of Barrett's oesophagus was 74% in the radiofrequency ablation arm compared with 0% in the sham arm (NNT = 1.35, 95% CI 1.18 to 1.78). The progression of dysplasia to cancer was 2% in the radiofrequency ablation arm versus 18% in the sham arm (RR = 0.125; 95% CI 0.19–0.78).

2.4.2.7 One patient (2.38%) had an upper gastrointestinal haemorrhage and two people (4.76%) had chest pain in the radiofrequency ablation arm.

2.4.2.8 One large case series (Ganz et al. 2008; n = 142) showed 80.4% eradication of dysplasia, 54.3% complete ablation of Barrett's oesophagus and 90.2% eradication of high-grade dysplasia after a median follow-up of 12 months.

Photodynamic therapy alone

Primary outcomes

2.4.2.9 One randomised controlled trial with 5-year follow-up (Overholt et al. 2005, 2007; n = 208) showed improved complete eradication of

dysplasia using photodynamic therapy with porfimer sodium (58.7%) compared with omeprazole alone (14.3%, RR = 4.11, 95% CI 2.36 to 7.45).

2.4.2.10 *Three case series (n = 7, 32 and 33) with follow-up from 1 to 5 years showed a 51.5–100% rate of complete eradication of dysplasia and/or cancer, with the 100% rate seen in the study using 5-aminolaevulinic acid (Gossner et al. 1998; n = 32).*

2.4.2.11 *Seven case series (n = 19, 24, 28, 48, 52, 100, 102 and 116) showed a 36.8–61.5% rate of complete ablation of Barrett's oesophagus with a follow-up of 18.5 months to seven years. One dose-escalation study (Mackenzie et al. 2008, n = 24) showed an 8.3% rate of complete ablation of Barrett's oesophagus at a follow-up of 45 months.*

2.4.2.12 *One randomised controlled trial (Overholt et al. 2005, 2007; n = 208) showed improved complete eradication of high-grade dysplasia using photodynamic therapy with porfimer sodium (76.8%) compared with omeprazole alone (38.6%, RR = 1.99, 95% CI 1.49 to 2.76).*

2.4.2.13 *Seven case series (n = 5, 6, 17, 28, 31, 48 and 50) showed a complete eradication of high-grade dysplasia and/ or cancer rate of 38.5–100% at a follow-up of 15 months to 11 years.*

2.4.2.14 *One randomised controlled trial (Overholt et al. 2005, 2007; n = 208) showed a reduced rate of progression to cancer at 5 years for photodynamic therapy with porfimer sodium (15.2%) compared with omeprazole alone (28.6%, RR = 0.53, 95% CI 0.31 to 0.91).*

2.4.2.15 *One cohort study (Prasad et al. 2007a; n = 199) did not find a significant difference in overall survival between people with high-grade dysplasia treated with photodynamic therapy (predominantly porfimer sodium) or with surgery (RR = 1.0, 95% CI 0.92 to 1.12) at median follow-up of 59 months.*

2.4.2.16 One case series (Overholt et al. 2003; n = 103) found the overall survival for people treated with photodynamic therapy using porfimer sodium to be 81.5% at mean follow-up of 51 months.

Adverse outcomes

2.4.2.17 One randomised controlled trial (Overholt et al. 2005, 2007; n = 208) showed a rate of strictures or stenoses needing treatment of 36.8% for photodynamic therapy using porfimer sodium after a median follow-up of 5 years.

2.4.2.18 Four large case series (n = 89, 102, 116 and 131) showed a stricture or stenosis rate (requiring treatment) of 20–30% with porfimer sodium after a median follow-up of 12–50.7 months.

2.4.2.19 Nine smaller case series (n = 6, 7, 11, 12, 17, 19, 24, 28 and 31) showed a stricture or stenosis rate (needing treatment) of 0–50% after a median follow-up of 12 to 45 months with the 0% rate seen in the two studies that used 5-aminolaevulinic acid.

2.4.2.20 One randomised controlled trial (Overholt et al. 2005, 2007; n = 208) showed a photosensitivity reaction rate of 69% for the photodynamic therapy arm (using porfimer sodium).

2.4.2.21 Ten case series (n = 5, 17, 19, 24, 28, 31, 32, 48, 48 and 50) showed a photosensitivity reaction rate of 0–100%. The 0% rate was found in two studies using 5-aminolaevulinic acid and the 100% rate was found in one study that used any one of four different photosensitisers (haematoporphyrin derivative, sulfonated aluminium phtalocyanine, natural chlorophyll-a derivative or 5-aminolaevulinic acid).

2.4.2.22 Four case series (n = 17, 48, 89 and 102) showed a cardiac complications rate of 2–5.88%, using porfimer sodium.

2.4.2.23 Nine case series (n = 5, 10, 17, 24, 31, 32, 48, 50 and 66) reported a 3–40% minor adverse events rate of epigastric pain, symptomatic

oesophagitis, hiccups, pleural effusions or anorexia and a 10–75% rate of nausea and/or vomiting.

Indirect comparison of radiofrequency ablation versus photodynamic therapy

2.4.2.24 No significant difference was seen between the clinical effectiveness of radiofrequency ablation compared with photodynamic therapy in complete eradication of dysplasia (RRR = 1.034, 95% CI 0.37 to 2.87).

2.4.3 Health economic modelling

Ablative therapies alone

The results of the cost-effectiveness analysis are summarised in table 9.

Table 9 Cost-effectiveness results for radiofrequency ablation and photodynamic therapy

	Radiofrequency ablation	**Photodynamic therapy**
Deterministic ICER	£24,757	£22,990
Probabilistic ICER	£24,823	£38,681
Probability of being cost effective at £20,000 per QALY	39%	20.1%
Probability of being cost effective at £30,000 per QALY	53.4%	33.3%
ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year		

These results suggest that radiofrequency ablation is cost effective compared with no surveillance. However, there is considerable uncertainty in the decision, as suggested by the 53% probability of being cost effective at £30,000. Cost-effectiveness estimates for photodynamic therapy vary between £23,000 and £39,000 per QALY compared with no surveillance. This range suggests that photodynamic therapy could be cost effective, but that under the current analysis it is probably not a cost-effective use of NHS resources. However, if post treatment surveillance is removed the probabilistic ICER is reduced to £21,760 per QALY gained. Therefore, the uncertainty in the ICER for photodynamic therapy is driven by the addition of surveillance. Therefore, if the benefits of surveillance have been underestimated the cost

effectiveness estimates for photodynamic therapy would have been overestimated.

2.4.4 Evidence to recommendations

The Guideline Development Group felt that the quality of evidence for the use of argon plasma coagulation, laser ablation and multipolar electrocoagulation alone or in combination with each other was very low and failed to show clinical effectiveness and that these treatments should not be used in normal practice. However, the Group considered that these ablative therapies may need further evaluation in clinical research studies.

There was discussion around the studies by Shaheen et al. (2009) and Ganz et al. (2008) being categorised as radiofrequency ablation alone, because both studies included some participants who had received endoscopic mucosal resection before radiofrequency ablation. The Guideline Development Group came to a consensus that because the majority of the participants had received only radiofrequency ablation, they should be regarded as radiofrequency ablation alone studies. The majority of the discussion about radiofrequency ablation alone surrounded the study by Shaheen et al. (2009) and so the Group considered that any recommendations for radiofrequency ablation alone should be made specific to the population that participated within that study: people with flat high-grade dysplastic Barrett's oesophagus. The Group noted that the cost-effectiveness estimates were consistently around £25,000 per QALY gained. The Group understood that there was great uncertainty over the consumable costing because no NHS list price was available. However, the Group considered that this factor had been captured by the probabilistic analysis and that radiofrequency ablation was a cost-effective use of resources.

Similar recommendations were made for the use of photodynamic therapy alone because the indirect comparison between radiofrequency ablation and photodynamic therapy showed no statistically significant difference between the clinical effectiveness of the two ablative techniques for complete eradication of dysplasia. The Guideline Development Group supported the use of photodynamic therapy alone, despite the significantly higher adverse-

event profile when compared with radiofrequency ablation alone, since the randomised controlled trial conducted by Overholt et al. (2005, 2007) was the only high-quality long-term study available with a follow-up of 5 years. The Group also felt that the evidence suggested a reduced rate of strictures and photosensitivity when 5-aminolaevulinic acid was used as the photosensitiser instead of porfirmer sodium.

The depth of ablation was not covered as an outcome for the ablative therapies as the Group felt that the question was more around which technique to use between radiofrequency ablation or photodynamic therapy etc. Radiofrequency ablation has a standard depth of ablation set by the manufacturer and photodynamic therapy though has a greater depth of ablation (that does not differ by the photosensitiser used) has a higher rate of complications associated with the greater depth. Clinicians do not control the depth, therefore the Group felt that the recommendations implicitly cover depth with the consideration of complications.

The Group considered the cost-effectiveness analysis and acknowledged that the results suggested that photodynamic therapy was not cost effective. However, the Group noted that when post-treatment surveillance was removed the ICER for photodynamic therapy was reduced to £22,000 per QALY gained. The Group considered that since the benefit of surveillance may have been underestimated the cost effectiveness of photodynamic therapy is likely to have been overestimated. The Group concluded that if the additional benefits of reduced cancer progression and the true benefits of surveillance were accounted for, the cost effectiveness of photodynamic therapy would be lower than £30,000 per QALY gained. Additionally, the Group considered that when restricted to flat lesions and specialist centres, photodynamic therapy would represent a cost-effective use of resources.

2.4.5 Recommendations

Recommendation 1.1.6

Consider using radiofrequency ablation alone or photodynamic therapy alone for flat high-grade dysplasia taking into account the evidence of their long-term efficacy, cost and complication rates.

Recommendation 1.1.7

Do not use argon plasma coagulation, laser ablation or multipolar electrocoagulation alone, or in combination with each other, unless as part of a clinical trial.

2.5 Endoscopic resection in combination with ablative therapies

2.5.1 Evidence review

Through systematic searching, 1888 articles were found; 364 of these met the inclusion criteria at the abstract and title stage and were ordered as full articles[10]. Of these, seven studies that treated high-grade dysplastic Barrett's oesophagus or early adenocarcinoma using endoscopic mucosal resection in combination with an ablative therapy were eligible for inclusion. The quality of evidence found was very low. Two studies used argon plasma coagulation in combination with endoscopic mucosal resection for ablation and the evidence from those studies is summarised in GRADE profiles 11 and 12. Five studies used radiofrequency ablation in combination with endoscopic mucosal resection and the evidence from those studies is summarised in GRADE profile 13.

Seven studies were eligible for inclusion that used endoscopic mucosal resection in combination with photodynamic therapy. The photosensitisers used for photodynamic therapy in these studies are listed in table 10 and the evidence from these studies is summarised in GRADE profile 14.

[10] See appendix 4 for the inclusion and exclusion criteria, study selection flowcharts and list of excluded studies

Table 10 List of photosensitisers used in included studies of endoscopic mucosal resection and photodynamic therapy

Study	Type of photosensitiser
Behrens et al. (2005)	5-aminolaevulinic acid 30 mg/kg
Buttar et al. (2001)	Porphyrin-based photosensitisers
Mino-Kenudson et al. (2005)	Not stated
Pacifico et al. (2003)	Either porfirmer sodium (23 of 24 participants) or haematoporphyrin derivative (1 of 24 participants)
Reed et al. (2005)	Not stated
Van Hillegersberg et al. (2003)	5-aminolaevulinic acid 30 mg/kg
Wolfsen et al. (2004b)	Porfirmer sodium 2 mg/kg

GRADE profile 11 Endoscopic mucosal resection and argon plasma coagulation for studies with less than 12 months' follow-up

Study	Design	Treatment	Placebo	Risk	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Quality
Primary outcome 2. Complete eradication of Barrett's oesophagus or intestinal metaplasia										
Peters et al. (2006)	Uncontrolled	33/37 (89.19%)			n = 37, 11 months' follow-up					+ (Very low)
Primary outcome 3. Complete eradication of high-grade dysplasia or cancer										
Peters et al. (2006)	Uncontrolled	37/37 (100%)			n = 37, 11 months' follow-up					+ (Very low)
Adverse outcome 9. Stricture or stenosis needing treatment										
Peters et al. (2006)	Uncontrolled	10/39 (25.64%)			n = 39[a]					+ (Very low)
Adverse outcome 12. Perforations										
Peters et al. (2006)	Uncontrolled	1/37 (2.70%)			n = 37					+ (Very low)
Adverse outcome 14. Bleeding										
Peters et al. (2006)	Uncontrolled	1/37 (2.70%)			n = 37					+ (Very low)

[a] The study had enrolled 39 participants but 2 discontinued treatment due to unrelated comorbidity. Both had symptomatic stenosis needing endoscopic boulenage treatment from initial endotherapy. Argon plasma coagulation treatment was given to 34 of the 37 remaining participants.

GRADE profile 12 Endoscopic mucosal resection and argon plasma coagulation for studies with 12 months of follow-up or longer

Study	Design	Treatment	Placebo	Risk	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Quality
Primary outcome 2. Complete eradication of Barrett's oesophagus or intestinal metaplasia										
Pouw et al. (2008)	Uncontrolled	23/34 (67.65%)			n = 34[a], median 23 months' follow-up (interquartile range 15-41 months)					+ (Very low)
Primary outcome 3. Complete eradication of high-grade dysplasia or cancer										
Pouw et al. (2008)	Uncontrolled	34/34 (100%)[b]			n = 34, median 23 months' follow-up (interquartile range 15-41 months)					+ (Very low)

[a] Argon plasma coagulation treatment was given to 12 out of 34 participants.

[b] After a median follow-up of 23 months all patients were free of high-grade intestinal metaplasia and early cancer, but two patients had additional endoscopic mucosal resection and one had curative surgical resection.

GRADE profile 13 Endoscopic mucosal resection and radiofrequency ablation for studies with 12 months of follow-up or longer

Study	Design	Treatment	Placebo	Risk	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Quality
Primary outcome 1. Complete eradication of dysplasia or cancer										
Sharma et al. (2009); Gondrie et al. (2008a, 2008b)	Uncontrolled	79–100%			Small studies of n = 24, 12 with median follow-up of 14–24 months					+ (Very low)
Primary outcome 2. Complete eradication of Barrett's oesophagus or intestinal metaplasia										
Beaumont et al. (2009); Gondrie et al. (2008a, 2008b); Pouw et al. (2009, 2010); Smith et al. (2007); Sharma et al. (2009)	Uncontrolled	20/24 (83.3%)			Small single-arm studies, n = 8–24 with median follow-up of 12-24 months					+ (Very low)
Primary outcome 3. Complete eradication of high-grade dysplasia or cancer										
Beaumont et al. (2009); Smith et al. (2007); Sharma et al. (2009)	Uncontrolled	90–100%			Three small studies, n = 8–24 with median follow-up of 12–22 months					+ (Very low)
Adverse outcome 7. Major adverse events										
Pouw et al. (2009, 2010)	Uncontrolled	1/24 (4.16%)[a]			Small single-arm cohort, n = 24 with median follow-up of 22 months					+ (Very low)
Adverse outcome 9. Stricture or stenosis needing treatment										
Pouw et al. (2009, 2010)	Uncontrolled	1/24 (4.16%)			Small single-arm cohort, n = 24 with median follow up of 22 months					+ (Very low)
Adverse outcome 12. Perforations										
Pouw et al. (2009, 2010)	Uncontrolled	1/24 (4.16%)			Small single-arm cohort, n = 24 with median follow-up of 22 months					+ (Very low)

[a] The major adverse event of melena was observed in one patient 2 weeks after focal ablation.

GRADE profile 14 Endoscopic mucosal resection and photodynamic therapy for studies with 12 months of follow-up or longer

Study	Design	Treatment (photosensitiser used for photodynamic therapy)	Placebo	Relative risk (RR, 95% confidence interval [CI]); absolute risk reduction (ARR); number needed to treat (NNT) or to harm (NNH, 95% CI)	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Quality
Primary outcome 1. Complete eradication of dysplasia or cancer										
Behrens et al. (2005); Buttar et al. (2001); Mino-Kenudson et al. (2005); Van Hillegersberg et al. (2003); Wolfsen et al. (2004b)	Uncontrolled	50–100%			5 studies of n = 3, n = 12, n = 44, n = 17 and n = 3					+ (Very low)
Primary outcome 2. Complete eradication of Barrett's oesophagus or intestinal metaplasia										
Behrens et al. (2005); Buttar et al. (2001); Mino-Kenudson et al. (2005); Van Hillegersberg et al. (2003); Wolfsen et al. (2004b)[a]	Uncontrolled	50–100%[b] (2 with 5-aminolaevulinic acid, 1 with porphyrin based photosensitisers, 1 with porfirmer sodium and 1 not stated)			5 studies of n = 3, n = 12, n = 44, n = 17 and n = 3					+ (Very low)
Primary outcome 6. Overall survival										
Pacifico et al. (2003)[c]	Cohort	22/24 (91.67%; porfirmer sodium or 1 with haematoporphyrin derivative)	Surgery, 62/64 (96.88%)	RR = 0.95 (0.76 to 1.05); ARR = −0.05; NNH = 19.2 harm (at least 22.8 to benefit and infinity to harm)[d]	Not serious	Not serious	Not serious	Not serious	Not serious	++ (Low)
Reed et al. (2005)	Cohort	47/47 (100%; not stated)	Surgery, 48/49 (97.96%); Observation, 19/19 (100%)	Surgery RR = 1.02 (0.92 to 1.11); ARR = −0.02 Surgical group =83% (at 5 years and 64% (at 10 years)[e]	Not serious	Serious[f]	Not serious	Not serious	Not serious	+ (Very low)

Study	Design	Treatment (photosensitiser used for photodynamic therapy)	Placebo	Relative risk (RR, 95% confidence interval [CI]); absolute risk reduction (ARR); number needed to treat (NNT) or to harm (NNH, 95% CI)	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Quality
Adverse outcome 7. Major adverse events										
Pacifico et al. (2003)[c]	Cohort	0/24 (0%; porfirmer sodium or 1 with haematoporphyrin derivative)	Surgery 19/64 (29.69%)	ARR = 0.29 (0.18 to 0.41), NNT = 3.68 (2.45 to 5.41)[g]	Not serious	Not serious	Not serious	Not serious	Not serious	++ (Low)
Reed et al. (2005)	Cohort	0/47 (0%; not stated)	Surgery 2/49 (4.08%)	ARR = 0.04 (-0.01 to 0.10), NNT = 24.5 (at least 10.4 to benefit, as few as 68.6 to harm)[h]	Not serious	Serious	Not serious	Not serious	Not serious	+ (Very low)
Adverse outcome 9. Stricture or stenosis needing treatment										
Pacifico et al. (2003)[c]	Cohort	2/24 (8.33%; porfirmer sodium or 1 with haematoporphyrin derivative)	Surgery 10/64 (15.63%)	RR= 0.53 (0.13 to 2.26) ARR=0.07 (-0.07 to 0.21) NNT =13.7 (at least 4.65 to benefit, as few as 14.4 to harm)	Not serious	Not serious	Not serious	Not serious	Not serious	++ (Low)
Buttar et al. (2001)	Uncontrolled	5/17 (29.41%; porphyrin based photosensitisers)			n = 17, median 13 months' follow-up					+ (Very low)
Adverse outcome 10. Photosensitivity										
Pacifico et al. (2003)[c]	Cohort	2/24 (8.33%; porfirmer sodium or 1 with haematoporphyrin derivative)	Surgery 0/64 (0%)	ARR = −0.08 (−0.26 to −0.02) NNH = 12 (4 to 45 to harm)	Not serious	Not serious	Not serious	Not serious	Not serious	++ (Low)
Buttar et al. (2001)	Uncontrolled	2/17 (11.76%; porphyrin based photosensitisers)			n = 17, median 13 months' follow-up					+ (Very low)
Adverse outcome 11. Cardiac complications										

Study	Design	Treatment (photosensitiser used for photodynamic therapy)	Placebo	Relative risk (RR, 95% confidence interval [CI]); absolute risk reduction (ARR); number needed to treat (NNT) or to harm (NNH, 95% CI)	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Quality
Pacifico et al. (2003)[c]	Cohort	0/24 (0%; porfirmer sodium or 1 with haematoporphyrin derivative)	Surgery 2/64 (3.13%)	ARR = 0.03 (−0.10 to 0.11); NNT = 32 (9.14 harm to infinity benefit)	Not serious	Not serious	Not serious	Not serious	Not serious	++ (Low)
Buttar et al. (2001)	Uncontrolled	1/17 (5.88%; porphyrin based photosensitisers)			n = =17, median 13 months' follow-up					+ (Very low)
Adverse outcome 14. Bleeding										
Buttar et al. (2001)	Uncontrolled	1/17 (5.88%; porphyrin based photosensitisers)			n = 17, median 13 months' follow-up					+ (Very low)

[a] Mino-Kenudson et al. (2005) was a study of 18 patients but the relevant population was 12 patients.

[b] The 100% rate was seen in Wolfsen et al. (2004b) using porfirmer sodium.

[c] Study with a follow-up of 12 ± 2 months for endoscopic mucosal resection with photodynamic therapy group versus 19 ± 3 months for surgery group. It studied patients' characteristics between the two groups and the only statistically significant difference was higher pulmonary comorbidities for the endoscopic mucosal resection with photodynamic therapy group.

[d] The median follow-up was 12 ± 2 months for the endoscopic mucosal resection with photodynamic therapy arm and 19 ± 3 months for the surgery arm.

[e] Survival analysis done using Kaplan–Meier for the surgical group.

[f] Study with a follow-up of 56 months for the surgical group, reviewed retrospectively from a database. Inconsistent as different outcomes were used for different groups. Only survival studied in all groups otherwise the focus is on the surgical group. No follow-up mentioned for non-surgical groups, but is estimated as 13.5 months for endoscopic mucosal resection with photodynamic therapy group.

[g] The 19 major adverse events in the surgery arm were: anastomatic leak n = 5; wound infection n = 5; dumping syndrome n = 3; empyema n = 2; blood transfusion n = 2; aspiration n = 1; chylothorax n = 1.

[h] The two major adverse events in the surgery arm were anastomatic leak n = 2.

2.5.2 Evidence statements

Endoscopic mucosal resection in combination with argon plasma coagulation

2.5.2.1 Two case series were included that had endoscopic mucosal resection and argon plasma coagulation therapy for ablation of Barrett's oesophagus.

2.5.2.2 Peters et al. (2006, n = 37, median 11 months' follow-up) performed endoscopic mucosal resection followed by argon plasma coagulation in 34 of 37 cases and showed 89.19% ablation of Barrett's oesophagus and a 100% eradication of high-grade dysplasia and cancer, but had 25.64% rate of strictures needing treatment, 2.7% perforations rate and 2.7% rate of bleeding.

2.5.2.3 Pouw et al. (2008, n = 34, median 23 months' follow-up) performed endoscopic mucosal resection followed by argon plasma coagulation in 12 of 34 cases and showed 67.65% ablation of Barrett's oesophagus and 100% eradication of high-grade dysplasia and cancer (but two patients had additional endoscopic mucosal resection and one had surgical resection).

Endoscopic mucosal resection in combination with radiofrequency ablation

2.5.2.4 Five uncontrolled studies were included that showed 54.3–83.3% ablation of Barrett's oesophagus, 79–100% eradication of dysplasia and cancer and 90–100% eradication of high-grade dysplasia and cancer, but one case each of melena, stricture and perforation (4.16%) was seen in one study (Pouw et al. 2010, n = 24).

Endoscopic mucosal resection and photodynamic therapy

Primary outcomes

2.5.2.5 Five case series showed a 50–100% rate of complete eradication of dysplasia and/or cancer at a follow-up of 13–36 months.

2.5.2.6 Five case series showed a 50–100% rate of complete ablation of Barrett's oesophagus, with the 100% ablation seen in a study using porfirmer sodium at a follow-up of 13–36 months.

2.5.2.7 Two cohort studies (Pacifico et al. 2003; Reed et al. 2005) did not find a significant difference for overall survival (at the end of study time) between people with high-grade dysplasia treated with endoscopic mucosal resection with or without photodynamic therapy compared with surgery (RR = 0.95, 95% CI 0.76 to 1.05 with a follow-up of 12–19 months and RR = 1.02, 95% CI 0.92 to 1.11 with a follow-up of 13.5–56 months).

Adverse outcomes

2.5.2.8 Two cohort studies (Pacifico et al. 2003; Reed et al. 2005) showed major adverse events[11] for people treated with surgery compared with no adverse events for people treated with photodynamic therapy, but only one study showed a statistically significant result (NNT = 3.68 , 95% CI 2.45 to 5.41 for Pacifico et al. [2003], and NNT = 24.5, 95% CI at least 10.4 to benefit, as few as 68.6 to harm for Reed et al. [2005]).

2.5.2.9 One cohort study (Pacifico et al. 2003) showed a higher stricture or stenosis rate (needing treatment) for the surgery arm (15.63%) compared with the photodynamic therapy arm (8.33%, using porfirmer sodium or haematoporphyrin derivative), but was not statistically significant (RR=0.53, 95% CI 0.73 to 1.91).

2.5.2.10 One cohort study (Pacifico et al. 2003) showed a photosensitivity reaction rate of 8.33% for the photodynamic therapy arm (using porfirmer sodium or haematoporphyrin derivative) compared with no photosensitivity seen in the surgery arm (NNH = 12, 95% CI 4 to 45).

11 The major adverse events in the surgery arm were anastomatic leaks, wound infections, dumping syndrome, empyema, blood transfusions, aspiration and chylothorax.

2.5.2.11 One cohort study (Pacifico et al. 2003) showed a cardiac complications rate of 3.13% for the surgery arm compared with none in the photodynamic therapy arm (NNH = 32, 95% CI −9.14 to 9.23).

2.5.2.12 One case series (Buttar et al. 2001) that used a porphyrin-based photosensitiser showed a stricture or stenosis rate (needing treatment) of 24.91%, a photosensitivity reaction rate of 11.76%, and cardiac complications rate and bleeding rate of 5.88% each.

2.5.3 Health economic modelling

Endoscopic mucosal resection and ablative therapies

The results of the cost-effectiveness analysis (see appendix 6 for more details) are summarised in table 11.

Table 11 Cost-effectiveness results for endoscopic mucosal resection plus ablative therapies

	Endoscopic mucosal resection and argon plasma coagulation	**Endoscopic mucosal resection and radiofrequency ablation**	**Endoscopic mucosal resection and photodynamic therapy**
Deterministic ICER	£12,233	£13,893	£17,305
Probabilistic ICER	£18,745	£15,916	£26,946
Probability of being cost effective at £20,000 per QALY	45.1%	55.4%	30.7%
Probability of being cost effective at £30,000 per QALY	60.4%	70%	48.6%
ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year			

These results suggested that endoscopic mucosal resection plus argon plasma coagulation or radiofrequency ablation combinations were cost effective compared with no surveillance. Endoscopic mucosal resection plus radiofrequency ablation was associated with the least uncertainty of being cost effective. Endoscopic mucosal resection plus argon plasma coagulation was also associated with low uncertainty. Endoscopic mucosal resection plus photodynamic therapy was associated with the highest estimates of cost

effectiveness of the three combinations and the highest uncertainty. This is because of the value chosen for the outcome complete ablation of dysplasia was the lowest of the combined endoscopic mucosal resection and ablative therapy options. Consequently, a greater proportion of the cohort receives intensive surveillance and, therefore, the uncertainty increases the ICER due to the surveillance component.

2.5.4 Evidence to recommendations

The Guideline Development Group considered that there was sufficient evidence to support the additional use of ablative therapies (argon plasma coagulation, radiofrequency ablation and photodynamic therapy) after endoscopic mucosal resection for the treatment of high-grade dysplastic Barrett's oesophagus or early adenocarcinoma. The Group discussed the varying adverse-event profiles for the different individual ablative therapies and considered that these should be taken into account when deciding on treatment options. The Group considered the cost-effectiveness estimates and noted that these suggested that endoscopic mucosal resection plus an ablative therapy represented a cost-effective use of resources. The Group acknowledged that the estimates were based on very poor data, but considered that they were sufficient to support a recommendation for the treatments.

2.5.5 Recommendation

Recommendation 1.1.8

If using endoscopic mucosal resection, consider following with an additional ablative therapy (radiofrequency ablation, argon plasma coagulation or photodynamic therapy) to completely remove residual flat dysplasia, taking into consideration the side-effect profiles.

2.6 Patients and carer support and information

2.6.1 Evidence review

Twelve studies about patients' information were identified and four were ordered at full text and only one (Hemminger 2002) met the inclusion criteria. The evidence from this study is summarised in table 12.

Table 12 Adverse effects and patients' satisfaction of photodynamic ablation

Acute and chronic adverse effects	
The 'single worst' symptom after photodynamic therapy	Twelve of the 16 patients (75%) selected swallowing problems (odynophagia and/or dysphagia); two (12.5%) selected chest pain and another two (12.5%) patients said they had no problems after treatment.
Duration of sensitivity to sunlight	Duration ranged from 4 to 24 weeks (median of 6 weeks). Two patients had severe reactions that needed outpatient medical evaluation and treatment, eight patients needed medical treatment without a clinic visit, and six patients reported mild or no sunburn reactions.
Resuming regular diet and weight loss	A wide range of responses were reported. Some were able to eat normally almost immediately while others required an extended period of time (median of 4 weeks, range 0–12 weeks). All but two patients reported losing weight with a median weight loss of 6.8 kg (range 4.5–13.6 kg). Patients subsequently regained this weight.
Overall patients' satisfaction	
Faced with the same choice of surgery and photodynamic therapy, which would they choose?	All patients indicated they would again choose photodynamic therapy over surgery (this was a highly selected group of patients who are probably biased by their initial decision to avoid surgery).

2.6.2 Evidence statements

2.6.2.1 A qualitative survey in the form of a semi-structured questionnaire design reporting 16 of 18 patients (88.89%, 11 men and 5 women, median age 75 years; median response 27 months after treatment) treated with photodynamic therapy using porfimer sodium for Barrett's oesophagus with high-grade dysplasia.

2.6.2.2 The most common problem after treatment (75% participants) was odynophagia or dysphagia.

2.6.2.3 Swallowing problems lasted a median of 4 weeks and all but two patients reported weight loss (median 6.8 kg)

2.6.2.4 Skin photosensitivity persisted in all patients for a median of 6 weeks, but the maximum duration was 24 weeks.

2.6.2.5 If faced with a similar choice of endoscopic treatment versus surgery for Barrett's oesophagus, all patients in this single small study indicated they would choose photodynamic therapy.

2.6.3 Evidence to recommendations

Consensus-based recommendations were made by the Guideline Development Group after reviewing the limited available evidence that looked at patients' needs and satisfaction. The Group considered that proper and adequate information about possible long-term and repeated ablative treatment should be made available to the patient by the multidisciplinary team because this will help people to make an informed decision. The Group also agreed on the need for effective support before and after ablative therapy.

2.6.4 Recommendations

Recommendation 1.1.9

Give patients verbal and written information about their diagnosis, available treatments, patient support groups and the uncertainty of the long-term outcomes of ablative therapies. Give patients time to consider this information when making decisions about their care.

Recommendation 1.1.10
Discuss the multidisciplinary team's views on the range of appropriate treatments with the patient.

Recommendation 1.1.11
Offer patients the opportunity to see the same specialist healthcare team more than once to agree treatment.

Recommendation 1.1.12
Advise patients who have endoscopic therapy that they will need lifelong care and repeated endoscopies.

3 Research recommendations

We have made the following recommendations for research, based on our review of evidence, to improve NICE guidance in the future.

This guideline focuses on the use of ablative and excisional therapies to treat high-grade dysplasia or intramucosal cancer in patients with Barrett's oesophagus. Therefore, the natural history of Barrett's oesophagus, including oesophageal reflux disease, diagnosis and assessment, and progression to cancer was not reviewed systematically. The Guideline Development Group noted that treatment should only be considered after a confirmed diagnosis and full assessment, and they acknowledged that research to support diagnosis and prognosis was needed. The research recommendations below focus on treatment-related questions.

3.1 Progression to dysplasia

What is the likelihood of Barrett's oesophagus progressing to dysplasia and cancer? What are the significant influencing factors?

Why this is important
Surgical treatment of high-grade dysplasia is the most effective method of treatment; however, there are significant but rare adverse effects. Ablative and excisional therapies are also successful but have an increased risk of recurrence. It is therefore important to identify patients with the highest risk of developing high-grade dysplasia, both before and after surgery, or ablative and excisional therapies. Long-term observational studies are needed to

identify the risk of progression and predictive factors (for example age, sex, extent or distribution of disease, or previous treatments).

3.2 Markers of treatment success

Do anatomical, pathological and molecular markers indicate successful ablation of Barrett's oesophagus and/or the risk of recurrence of high-grade dysplasia after ablative and excisional treatment?

Why this is important

High-grade dysplasia in Barrett's oesophagus can recur after ablative and excisional therapies; however, it is not known if there are anatomical, pathological and molecular markers associated with the success of treatment or recurrence of high-grade dysplasia. Studies to identify markers associated with long-term treatment success are needed.

3.3 Effectiveness of treatment

What is the effectiveness of ablative and excisional therapies for the treatment of high-grade dysplasia or intramucosal cancer in Barrett's oesophagus?

Why this is important

Many cases were reviewed for this guideline; however, high quality evidence from randomised clinical trials on the benefit of ablative and excisional therapies was lacking. Randomised controlled trials (or well designed studies with a follow-up of at least 5 years or a central register) of ablative and excisional therapies compared with surgery, and compared with other ablative and excisional therapies are required to determine the relative benefits, costs, and impact on quality of life.

3.4 Follow-up after treatment

What is the most appropriate process of follow-up after the treatment of high-grade dysplasia or intramucosal cancer in Barrett's oesophagus?

Why this is important

Barrett's oesophagus can recur after ablative and excisional therapies. Evidence for the most appropriate follow-up is lacking so research should

establish how patients should be monitored after ablative and excisional therapies. This should include randomised controlled trials (with a follow-up of at least 5 years) to evaluate the effectiveness and optimal timing of different follow-up approaches such as universal surveillance, endoscopy if symptoms recur.

3.5 Information needs

What are the information needs of patients considering treatment for high-grade dysplasia or intramucosal cancer in Barrett's oesophagus?

Why this is important

Patients with Barrett's oesophagus deciding on the treatment of high-grade dysplasia or intramucosal cancer need information to make an informed choice. Substantial literature exists concerning their general information needs, but there is very little relating to the point of treatment choice.

Research is required into the delivery of information to patients who are considering ablative and excisional and other treatments for high-grade dysplasia in Barrett's oesophagus. This should include randomised controlled trials of different methods to support shared decision-making, with a process evaluation to identify barriers and facilitators for both patients and healthcare professionals.

4 Other versions of this guideline

This is the full guideline. It contains details of the methods and evidence used to develop the guideline. It is available from our website (www.nice.org.uk/guidance/CG[XX]Guidance). **[Note: these details will apply to the published full guideline.]**

Quick reference guide

A quick reference guide for healthcare professionals is available from www.nice.org.uk/guidance/CG[XX]QuickRefGuide

For printed copies, phone NICE publications on 0845 003 7783 or email publications@nice.org.uk (quote reference number N1[XXX]). **[Note: these details will apply when the guideline is published.]**

'Understanding NICE guidance'

A summary for patients and carers ('Understanding NICE guidance') is available from www.nice.org.uk/guidance/CG[XX]PublicInfo

For printed copies, phone NICE publications on 0845 003 7783 or email publications@nice.org.uk (quote reference number N1[XXX]). **[Note: these details will apply when the guideline is published.]**

We encourage NHS and voluntary sector organisations to use text from this booklet in their own information about Barrett's oesophagus.

5 Related NICE guidance

Published

- Endoscopic radiofrequency ablation for gastro-oesophageal reflux disease. NICE interventional procedure guidance 292 (2009). Available from www.nice.org.uk/guidance/IPG292
- Circumferential epithelial radiofrequency ablation for Barrett's oesophagus. NICE interventional procedure guidance 244 (2007). Available from www.nice.org.uk/guidance/IPG244 (currently under review)
- Endoscopic augmentation of the lower oesophageal sphincter using hydrogel implants for the treatment of gastro-oesophageal reflux disease. NICE interventional procedure guidance 222 (2007). Available from www.nice.org.uk/guidance/IPG222
- Photo-dynamic therapy for early oesophageal cancer. NICE interventional procedure guidance 200 (2006). Available from www.nice.org.uk/guidance/IPG200
- Thoracoscopically assisted oesophagectomy. NICE interventional procedure guidance 189 (2006). Available from www.nice.org.uk/guidance/IPG189

- Endoluminal gastroplication for gastro-oesophageal reflux disease. NICE interventional procedure guidance 115 (2005) Available from www.nice.org.uk/guidance/IPG115
- Dyspepsia: managing dyspepsia in adults in primary care. NICE clinical guideline 17 (2004). Available from www.nice.org.uk/guidance/CG17
- Endoscopic injection of bulking agents for gastro-oesophageal reflux disease. NICE interventional procedure guidance 55 (2004). Available from www.nice.org.uk/guidance/IPG55
- Photodynamic therapy for high-grade dysplasia in Barrett's oesophagus. NICE interventional procedure guidance 82 (2004). Available from www.nice.org.uk/guidance/IPG82 (currently under review)

In development

- Endoscopic submucosal dissection of oesophageal dysplasia and neoplasia. NICE interventional procedure guidance. Publication expected August 2010

6 Updating the guideline

NICE clinical guidelines are updated so that recommendations take into account important new information. New evidence is checked 3 years after publication, and healthcare professionals and patients are asked for their views; we use this information to decide whether all or part of a guideline needs updating. If important new evidence is published at other times, we may decide to do a more rapid update of some recommendations.

7 References, glossary and abbreviations

7.1 References

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7.2 Glossary

Cohort study

Also known as follow-up, incidence, longitudinal, or prospective study: an observational study in which a defined group of people (the cohort) is followed

over time. Outcomes are compared in subsets of the cohort who were exposed or not exposed (or exposed at different levels) to an intervention or other factor of interest.

Confidence interval

The range within which the 'true' values (for example, size of effect of an intervention) are expected to lie with a given degree of certainty (for example, 95% or 99%). (Note: confidence intervals represent the probability of random errors, but not systematic errors or bias).

Cost-effectiveness model

An explicit mathematical framework that is used to represent clinical decision problems and incorporates evidence from a variety of sources to estimate costs and health outcomes.

Guideline Development Group

A group of healthcare professionals, patients, carers and technical staff who develop the recommendations for a clinical guideline. The NICE Short Clinical Guidelines Team recruits the guideline development group, reviews the evidence and supports the guideline development group. The group writes draft guidance, and then revises it after a consultation with organisations registered as stakeholders.

Incremental cost

The mean cost of a treatment per patient minus the mean cost of a comparator treatment per patient.

Incremental cost effectiveness ratio (ICER)

The incremental cost of a treatment divided by the difference in the mean outcomes of the treatment versus the mean outcomes of the comparator treatment.

Multivariate model

A statistical model for analysis of the relationship between two or more predictor (independent) variables and the outcome (dependent) variable.

Number needed to treat (NNT) and number needed to harm (NNH)

This measures the impact of a treatment or intervention. It states how many patients need to be treated with the treatment in question to prevent an event which would otherwise occur. For example, if the NNT = 4, then 4 patients would have to be treated to prevent one bad outcome. The closer the NNT is to 1, the better the treatment is. Analogous to the NNT is the number needed to harm (NNH),which is the number of patients that would need to receive a treatment to cause one additional adverse event. For example, if the NNH = 4, then 4 patients would have to be treated for one bad outcome to occur.

Quality-adjusted life year (QALY)

A statistical measure, representing 1 year of life, with full quality of life.

Randomised controlled trial

A form of clinical trial to assess the effectiveness of medicines or procedures. Considered reliable because it tends not to be biased.

Relative risk (RR)

Also known as risk ratio; the ratio of risk in the intervention group to the risk in the control group. The risk (proportion, probability or rate) is the ratio of people with an event in a group to the total in the group. An RR of 1 indicates no difference between comparison groups. For undesirable outcomes, an RR that is less than 1 indicates that the intervention was effective in reducing the risk of that outcome.

Systematic review

Research that summarises the evidence on a clearly formulated question according to a pre-defined protocol using systematic and explicit methods to identify, select and appraise relevant studies, and to extract, collate and report their findings. It may or may not use statistical meta-analysis.

7.3 Abbreviations

ARR	Absolute risk reduction
CI	Confidence interval
GRADE	Grading of recommendations assessment, development and evaluation
HR	Hazard ratio
HTA	Health Technology Assessment
ICER	Incremental cost-effectiveness ratio
NNT	Number needed to treat
NNT	Number needed to harm
QALY	Quality-adjusted life year
RR	Relative risk
RRR	Ratio of relative risk

7.4 Appendices

Appendices 1 to 6 are filed as separate documents:

Appendix 1: Scope

Appendix 2: Review protocols

Appendix 3: Search strategies

Appendix 4: Clinical review methods

Appendix 5: EvidenceAppendix 6: Cost-effectiveness analysis

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8.1 The Guideline Development Group

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8.2 The Short Clinical Guidelines Technical Team

A short clinical guidelines technical team was responsible for this guideline throughout its development. It prepared information for the Guideline Development Group, drafted the guideline and responded to consultation comments. The following NICE employees made up the technical team for this guideline.

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8.3 The Guideline Review Panel

The Guideline Review Panel is an independent panel that oversees the development of the guideline and takes responsibility for monitoring adherence to NICE guideline development processes. In particular, the panel ensures that stakeholder comments have been adequately considered and responded to. The panel includes members from the following perspectives: primary care, secondary care, lay, public health and industry.

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8.4 Declarations of interest

A full list of all declarations of interest made by this Guideline Development Group is available on the NICE website (www.nice.org.uk).

8.5 Authorship and citation

Authorship of this document is attributed to the NICE Short Clinical Guidelines Technical Team and members of the Guideline Development Group under group authorship.

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