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

Full guideline

Draft for consultation, March 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.

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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 or intramucosal cancer (including T1a); however, it is associated with significant mortality and morbidity. Consequently less invasive surgical techniques such as endoscopic resection and ablative treatments have been developed and are being used as alternatives. 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.

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 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

1.1 List of all recommendations

Key principles of care

1.1.1 Confirm diagnosis of Barrett's oesophagus with high-grade dysplasia or intramucosal cancer at a specialist centre, ensuring full staging.

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 individual preferences, fitness and general health.

Endoscopic resection

1.1.3 Consider using endoscopic resection alone to treat localised lesions.

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

1.1.5 Consider repeated endoscopic resection with further pathological assessment for suspected residual or recurrent disease.

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 resection in combination with ablative therapies

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

1.1.8 If using endoscopic 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 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 decision about their care.

1.1.10 Give patients the multidisciplinary team's views on the range of appropriate treatments.

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

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

1.2 Care pathway

The algorithm will be added when the recommendations have been finalised.

1.3 Overview

1.3.1 Endoscopic 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

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

the oesophagus becoming similar to that of the stomach and small intestine (Garside 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 resection and ablation are currently used to treat Barrett's oesophagus. Endoscopic 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 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 2009; Green 2009, Rees 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

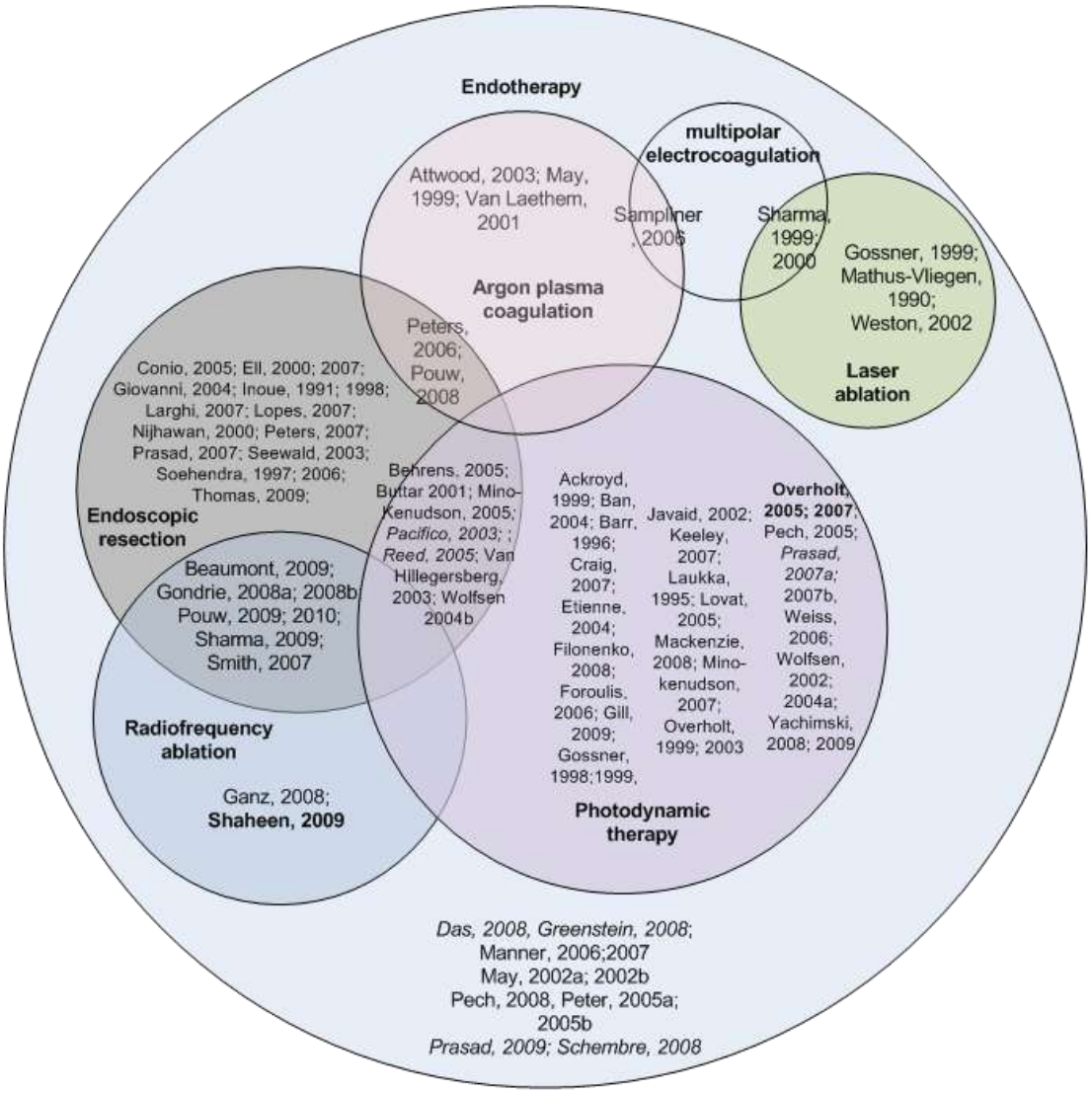
'Barrett's oesophagus: ablative therapy for the treatment of Barrett's oesophagus' (NICE clinical guideline [XX]) is a NICE short clinical guideline. The primary outcomes and adverse outcomes that were considered in this guideline are listed in table 1. All results from the included studies (relative risk or risk ratio [RR], absolute risk reduction [ARR], number-needed-to-treat to benefit [NNTB] and number-needed-to-treat to harm [NNTH]) are presented in 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 (CR-D/CA)	7	Major adverse events
2	Complete eradication of intestinal metaplasia/Barrett's oesophagus (CR-IM/BO)	8	Minor adverse events
3	Complete eradication of high-grade dysplasia or cancer (CR-HGD/CA)	9	Stricture or stenosis requiring treatment
4	Reduction in length of Barrett's oesophagus	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

Figure 1 Evidence map



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

2.2 Endoscopic therapies

2.2.1 Evidence review

Through systematic searching, 1888 articles were identified. Of these, nine studies investigating the clinical effectiveness of different endoscopic therapies (endoscopic resection combined with different ablative therapies) for the treatment of high-grade dysplastic Barrett's oesophagus or early adenocarcinoma were eligible for inclusion[3]. The evidence from these studies is summarised in the GRADE profiles below.

GRADE profile 1 Endoscopic therapies with follow-up not stated

Endoscopic therapies- Studies with follow-up not stated										
No. of studies	**Design**	**Treatment**	**Placebo**	**Risk**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Quality**
Primary Outcome 2: Complete eradication of Barrett's / intestinal metaplasia										
1(M07)	Uncontrolled study	104/131 (79.39%)			Single centre study, mainly looking at safety with N=215 but relevant population of 131					⊕ VERY LOW
No. of studies	**Design**	**Treatment**	**Placebo**	**Risk**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Quality**
Adverse Outcome 8: Minor adverse events										
2[4]	Uncontrolled studies	10.69–11.71%[5]			Two studies from the same centre with N=111 and 131					⊕ VERY LOW
Adverse Outcome 9: Stricture or stenosis requiring dilation										
2[6]	Uncontrolled studies	0.76–0.96%			Two studies from the same centre with N=111 and 131					⊕ VERY LOW
(M07): Manner 2007										

[3] For the full review protocol, see appendix 2, for the full search strategies, see appendix 3; for the inclusion and exclusion criteria, study selection flowcharts and list of excluded studies see appendix 4.
[4] Manner (2006, 2007): Studies used argon plasma coagulation after prior treatment with endoscopic resection or endoscopic resection + photodynamic therapy.
[5] Manner (2006): 13 cases of minor adverse events occurred (chest pain [7] and fever [6]) out of the relevant population of 111. Manner (2007): 14 cases of minor adverse events occurred (pain, dysphagia, cough after argon plasma coagulation, cardiac arrhythmia, gas accumulation in the gastrointestinal wall, neuromuscular irritation).
[6] Manner (2006, 2007): Studies used argon plasma coagulation after prior treatment with endoscopic resection or endoscopic resection + photodynamic therapy.

GRADE profile 2 Endoscopic therapies with follow-up of 12 months or more

Endoscopic therapies - Studies with 12 months or more follow-up										
No. of studies	**Design**	**Treatment**	**Placebo**	**Relative risk [RR] (95%CI)] [ARR; NNTB (95%CI)]**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other consideration**	**Quality**
Primary outcome 1: Complete eradication of dysplasia/ cancer (CR-D/ CA)										
1(S)	Cohort study	54/62 (87%)	Surgery 31/32 (97%)	RR=0.90 (0.79, 1.05); ARR=0.098; NNTB=-10.2 (-4.74, 24.79)	N	N	N	N	N	⊕⊕ LOW
Primary outcome 2: Complete eradication of Barrett's/ intestinal metaplasia (CR-IM/BO)										
1(S)	Cohort study	35/62 (56%)	Surgery 31/32 (97%)	RR=0.58 (0.45, 0.72); [ARR=-0.404; NNTB= -2.47(-1.86, -4.07)]	N	N	N	N	N	⊕⊕ LOW
3[7]	Uncontrolled studies	90%-96.6%			3 studies with of N=34, 115 and 349					⊕ VERY LOW
Primary outcome 5: Progression of disease to cancer										
1(S)	Cohort study	4/62 (6%)	0/32 (0%)	[ARR=-0.06(-0.16, 0.05) NNTB=-15.5 (-6.45, 21.67)]	N	N	N	N	N	⊕⊕ LOW
1 (P)	Uncontrolled study	74/349 (21.2%)[8]			Large case series with N=486 and relevant population of 349					⊕ VERY LOW
Primary outcome 6: Overall survival										
1 (G)	Cohort study	84% (n=47)	No therapy 64% (n=119)	RR=1.31 (1.07, 1.57); [ARR=0.2; NNTB=5 (3.15, 26.45)][9]	S[10]	N	N	N	N	⊕ VERY LOW
1 (Pr)	Cohort study	83% (n=132)	Surgery 95% (n=46)	RR= 0.87(0.79, 0.99); [ARR=-0.12 NNTB=-8.33(-4.84, -93)][11]	N	N	N	N	N	⊕⊕ LOW

[7] Peters (2005a, 2005b): N = 34; intervention was endoscopic resection followed by photodynamic therapy and argon plasma coagulation with a follow-up of median 30 months (22–31 months); May (2002a, 2002b): N = 115; intervention was initial argon plasma coagulation followed by endoscopic resection or endoscopic resection + photodynamic therapy with a follow-up of 34 ± 10 months (range 24–60 months); Pech (2008): This is a large single-centre well-documented 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 resection + photodynamic therapy or argon plasma coagulation with a follow-up of median 63 months (inter-quartile range 49.5–80.0 months).

[8] Pech (2008): Metachronous lesions were detected in 74 patients at a median of 15 months. 63/74 achieved complete remission after repeat treatment; 3 referred for surgery; 2 received ongoing therapy; 2 died. Recurrence-free rate was 77% after 5 years.

[9] Greenstein (2008): Survival calculated at 4 years.

[10] Greenstein (2008): Local endoscopic therapies include relevant ablative therapies but also additional endotherapies outside of this scope. For further details refer to footnote about study.

Endoscopic therapies - Studies with 12 months or more follow-up										
1(S)	Cohort study	89% (n=62)	Surgery 93% (n=32)	RR=0.87 (0.79, 0.99) [ARR=-0.12; NNTB=-8.33(-4.84, -93.2)][12]	N	N	N	N	N	⊕⊕ LOW
1 (D)	Cohort study	Endotherapy group vs. surgery group : Overall survival, RH=0.89, 95% CI 0.51–1.56, p=0.68) Cancer free survival=56 vs. 59 months (p=0.41)[13]			N	N	N	N	N	⊕⊕ LOW
1 (P)	Uncontrolled study	84%[14]			Large case series with N=486 and relevant population of 349					⊕ VERY LOW
1 (M)	Uncontrolled study	1 yr=98%, 2yr=95% and 3 yr=88%[15]			Large case series N=115 and follow-up 34±10 months					⊕ VERY LOW
No. of studies	**Design**	**Treatment**	**Placebo**	**Relative risk [RR] (95%CI)] [ARR; NNTB (95%CI)]**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other consideration**	**Quality**
Adverse outcome 7: Major adverse events										
1 (Pr)	Cohort study	0/132 (0%)	Surgery 17/46 (36.96%)	[ARR=0.369 NNTB=-2.70 (1.94, 4.08)][16]	N	N	N	N	N	⊕⊕ LOW
1 (S)	Cohort study	5/62 (8%)	4/32 (13%)	RR=1.05 (0.92, 1.29) [ARR=0.044; NNTB= 22.55 (-12.76, 4.77)][17]	N	N	N	N	N	⊕⊕ LOW
1 (Pe)	Uncontrolled study	1/34 (2.94%)[18]			case series N=34; with a follow-up of 30 months					⊕ VERY LOW
Adverse outcome 8: Minor adverse events										
1 (S)	Cohort study	20/62 (32%)	Surgery 26/32	RR= 3.61(1.86, 7.75)	N	N	N	N	N	⊕⊕ LOW

[11] Prasad 2009: 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 BE segment, Charlson comorbidity score, and the propensity score, whereas cancer-free survival was superior in the surgical group (overall survival HR = 1.54 (95% CI 0.64–3.75) p = 0.33; cancer-free survival HR = 2.64 (95% CI 1.70–4.08) p < 0.001).

[12] Schembre (2008): Survival adjusted at 4 years but method used is not mentioned; there was no significant difference (p = 0.47).

[13] Das (2008): The significant variables associated with mortality using the Cox proportional hazards model were higher age at diagnosis (HR = 1.06 [95% CI 1.03, 1.08], p < 0.001) and absence of exposure to radiation therapy (HR = 0.32 [95% CI 0.21, 0.48], p < 0.001).

[14] Pech (2008): Survival at 5 years using Kaplan–Meier analysis.

[15] May (2002a, 2002b): Survival analysis calculated using life tables.

[16] Prasad (2009): 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 hospitalisation was 8 days (IQR, 7–13 days; range, 5–57 days).

[17] Schembre (2008): Major adverse events for the endotherapy arm were death (1), bleeding (2), and prolonged hospitalisation (3); those for the surgery arm were anastomatic leak (1), chyle leak (2) and DVT (1); p = 0.50.

[18] Peters (2005a, 2005b): Major adverse event was hematemesis in 1 patient 1 week after the photodynamic therapy.

Endoscopic therapies - Studies with 12 months or more follow-up										
			(81.25%)	[ARR=0.49; NNTH=2.04 (1.55, 3.49)][19]						
1 (M)	Uncontrolled study	11/115 (9.57%)[20]			Large case series N=115 and follow-up 34±10 months					⊕ VERY LOW
Adverse outcome 10: Photosensitivity										
1 (Pe)	Uncontrolled study	2/34 (5.88%)			case series N=34; with a follow-up of 30 months					⊕ VERY LOW
Adverse outcome 11: Cardiac complications										
1 (Pe)	Uncontrolled study	1/34 (2.94%)			Small case series N=34; with a follow-up of median 30 months					⊕ VERY LOW
N = No serious; S = Serious; VS = Very serious; RR: relative risk; ARR: absolute risk reduction; CI: confidence intervals NNTB/ NNTH: number-needed-to-treat to benefit/ number-needed-to-treat to harm (S): Schembre 2008[21] ; (P): Pech 2008; (G): Greenstein 2008[22]; (D): Das 2008[23]; (Pr): Prasad 2009; (Pe): Peters 2005a; 2005b; (M): May 2002a; 2002b										

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 resection for the treatment of Barrett's oesophagus.

Primary outcomes

2.2.2.2 Two overlapping large case series (Manner 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.

[19] Schembre (2008): 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); $p < 0.001$.
[20] May (2002a, 2002b): Minor complications: 11 included stenosis (3), bleeding (5), odynophagia (1) and photosensitive reaction-sunburn (2).
[21] Schembre (2008): 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 a follow-up of median 20 months (range 6–84 months) for endotherapy arm and median 48 months (range 6–88 months) for surgery arm.
[22] Greenstein (2008): 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). Local therapies: excisional biopsy (19), photodynamic therapy (11), local destruction (6), laser (5), polypectomy (3), electrocautery (1) and cryoablation (1).
[23] Das (2008): 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.

2.2.2.4 Schembre (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 0.1 to −0.005).

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

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

2.2.2.7 Prasad (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 0.99). 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 (2008) found the survival for the two arms to be 89% for endotherapy and 93% for surgery (RR = 0.87, 95% CI 0.79–0.99) but the adjusted difference in overall survival at 4 years was not statistically significant (p = 0.47).

2.2.2.9 Das (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 (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 (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 (2009) showed a 36.96% rate of major adverse events for the surgery arm versus 0% in the endotherapy arm. Schembre (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. Completed checklists are available in 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 resection, radiofrequency ablation, photodynamic therapy, argon plasma coagulation, combinations of endoscopic 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
Endocopic resection	Ell et al. 2007	Case series	99% of cohort
Radiofrequency ablation	Shaheen et al. 2009	RCT	RR = 4.25
Photodynamic therapy	Overholt et al. 2005, 2007	RCT	RR = 4.11
Endoscopic resection and argon plasma coagulation	Peters et al. 2006	Case series	89.9% of cohort
Endoscopic 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 resection and photodynamic therapy	Van Hillegersberg 2003	Case series	50–100% of population (midpoint of 75% used)
RCT, randomised controlled trial			

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 highly specialist centre, it was unlikely to represent the true effectiveness of endoscopic resection in the NHS setting. Therefore, the Group concluded that the effectiveness of endoscopic 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 Cost-effectiveness analyses over a 50-year period

Intervention	Utility	Cost	Incremental utility	Incremental cost	Incremental cost-effectiveness ratio (ICER)
No surveillance	7.91	£9,095	0.00	£0	–
Surveillance	8.32	£18,211	0.40	£9,116	£22,756
Surgery	9.18	£15,971	1.26	£6,876	£5,438
Endoscopic resection and surveillance	9.47	£15,142	1.56	£6,047	£3,886
Radiofrequency ablation and surveillance	10.16	£29,174	2.24	£20,079	£8,947
Photodynamic therapy and surveillance	9.95	£26,346	2.04	£17,251	£8,470
Endoscopic resection and radiofrequency ablation and surveillance	10.69	£21,765	2.77	£12,670	£4,573
Endoscopic resection and photodynamic therapy and surveillance	10.75	£24,835	2.83	£15,740	£5,558
Endoscopic resection and argon plasma coagulation and surveillance	10.52	£17,928	2.61	£8,833	£3,390

The analysis suggests that surgery is the most cost-effective treatment option for ablative therapies. 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 generally poor quality of the clinical data, making comparisons between the ablative treatments was thought to be inappropriate. 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. Therefore, the Group considered that no definitive conclusions could be made on the value of 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. This analysis indicated that all parameters in the analysis could benefit from research, but that the entire natural history of Barrett's oesophagus is of particular importance and that the clinical effectiveness of the ablative therapies is also 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 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 endotherapy 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 resection

2.3.1 Evidence review

Through systematic searching, 1888 articles were found; of these, 12 studies that treated high-grade dysplastic Barrett's oesophagus or early adenocarcinoma using endoscopic resection alone were eligible for analysis. The evidence is summarised in the GRADE profiles 3 and 4.

GRADE profile 3

Endoscopic resection alone for studies with less than 12 months follow-up										
No. of studies	**Design**	**Treatment**	**Placebo**	**Risk**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other consideration**	**Quality**
Primary outcome 1: Complete eradication of dysplasia										
1(Pr)	Uncontrolled study	2/4 (25%)			Series of 4 individual case reports					⊕ VERY LOW
Primary outcome 2: Complete eradication of Barrett's oesophagus/ intestinal metaplasia										
4[24]	Uncontrolled studies	25–100%			4 studies with of N=4, 16, 7 and 12					⊕ VERY LOW
No. of studies	**Design**	**Treatment**	**Placebo**	**Risk**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other consideration**	**Quality**
Adverse outcome 9: Stricture or stenosis requiring treatment										
2[25]	Uncontrolled studies	16.67–70%[26]			2 studies with N=12 and 10 respectively					⊕ VERY LOW
Adverse outcome 12: Perforations										
1(Pe)	Uncontrolled study	1/93 (1.08%)			Study looking at safety of different ER techniques					⊕ VERY LOW
Adverse outcome 14: Bleeding										

[24] Prasad (2007); Thomas (2009); Soehendra (1997); Seewald (2003).
[25] Seewald (2003); Soehendra (2006).
[26] The use of different techniques of endoscopic resection caused the variation of stricture rates, with the low-end of the range corresponding to focal endoscopic resection and the higher end to circumferential endoscopic resection.

Endoscopic resection alone for studies with less than 12 months follow-up										
No. of studies	**Design**	**Treatment**	**Placebo**	**Risk**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other consideration**	**Quality**
4[27]	Uncontrolled studies	12.90–26%			4 studies with of N=12, 16, 12 and 93					⊕ VERY LOW
(Pr): Prasad 2007 (Pe): Peters 2007										

GRADE profile 4

Endoscopic resection alone for studies with 12 months or more follow-up										
No. of studies	**Design**	**Treatment**	**Placebo**	**Risk**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other consideration**	**Quality**
Primary outcome 1: Complete eradication of dysplasia										
1(E)	Uncontrolled study	99/100 (99%)[28]			Large case series, with 2 published papers.					⊕ VERY LOW
Primary outcome 2: Complete eradication of Barrett's/ intestinal metaplasia										
4[29]	Uncontrolled studies	44–87.50%			4 studies with of N=25, 41, 21and 24					⊕ VERY LOW
Primary Outcome 6: Overall Survival										
1(E)	Uncontrolled study	100/100 (100%); estimate 98%[30]			Large case series, with 2 published papers					⊕ VERY LOW
1(I)	Uncontrolled study	95%[31]			Large study, N=142; 9 year follow up					⊕ VERY LOW
No. of studies	**Design**	**Treatment**	**Placebo**	**Risk**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other consideration**	**Quality**
Adverse Outcome 7: Major adverse events										
1(E)	Uncontrolled study	0/100 (0%)[32]			Large case series, with 2 published papers					⊕ VERY LOW
Adverse Outcome 8: Minor adverse events										
1(E)	Uncontrolled study	11/100 (11%)[33]			Large case series, with 2 published papers					⊕ VERY LOW
Adverse Outcome 9: Stricture or stenosis requiring treatment										
1(I)	Case series	1/142 (0.70%)			Large Study, N=142; 9 year follow-up					⊕ VERY LOW
3[34]	Uncontrolled studies	2.44–12.5%			3 studies with of N= 41, 39 and 24					⊕ VERY LOW

[27] Seewald (2003); Thomas (2009); Soehendra (2006); Peters (2007).
[28] Time to complete remission range 1–18 months, mean = 1.9, SD = 2.1.
[29] Nijhamwan (2000); Lopez (2007); Giovanni (2004); Larghi (2007).
[30] At follow-up range 2–83 months, mean = 36.7, SD = 15.4, median 33 months, 100% survival was seen; the life table estimate was 98% at 5 years.
[31] Survival at 5 years.
[32] Major adverse events: strictures, perforations, bleeding or death.
[33] Minor adverse events: haemorrhage post-endoscopic resection requiring treatment with epinephrine.
[34] Lopez (2007); Conio (2005); Larghi (2007).

Endoscopic resection alone for studies with 12 months or more follow-up										
No. of studies	**Design**	**Treatment**	**Placebo**	**Risk**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other consideration**	**Quality**
Adverse Outcome 12: Perforations										
1(I)	Uncontrolled study	1/142 (0.70%)			Large Study, N=142; 9 year follow-up					⊕ VERY LOW
1 (Lo)	Uncontrolled study	2/41 (4.88%)			N=41					⊕ VERY LOW
Adverse Outcome 14: Bleeding										
4[35]	Uncontrolled studies	8.33–19.51%			4 studies with of N=24, 39, 21and 41					⊕ VERY LOW
(E): Ell, 2000; 2007[36] (I): Inoue 1998; (Lo): Lopez 2007										

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 resection alone on the ablation of Barrett's oesophagus with less than 12 months' follow-up.

2.3.2.2 Two large studies (Ell 2000, 2007; n = 100) and (Inoue 1991, 1998; N=142) and six small case series studied the use of endoscopic 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 (2007) showed 25% complete eradication of dysplasia.

2.3.2.4 Ell (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.

[35] Larghi (2007); Conio (2005); Giovanni (2004); Lopez (2007).
[36] Ell (2007): Data are taken from a specialist, high-volume centre.

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 resection are summarised in table 4.

Table 4 Cost effectiveness of endoscopic resection

Parameter	Outcome
Deterministic ICER	£13,571
Probabilistic ICER	£26,026
Probability of being cost effective at £20,000 per QALY	37.9%
Probability of being cost effective at £30,000 per QALY	47.7%
Probability of being optimum choice at £20,000 per QALY	1.7%
Probability of being optimum choice at £30,000 per QALY	2.3%
ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year	

These results suggest that endoscopic resection is cost effective compared with no surveillance. However, there is considerable uncertainty in the decision, as suggested by the 48% probability of being cost effective at £30,000. Compared with all other treatment options, it is unlikely to be the optimum choice.

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 resection alone for localised lesions only. The Group considered the use of ER 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 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 resection and acknowledged that the results were highly uncertain and were based on poor clinical data. The Group concluded that if endoscopic resection was restricted to specialist centres and was used to treat only localised lesions, then its cost effectiveness would improve and therefore endoscopic 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 resection alone to treat localised lesions.

Recommendation 1.1.4

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

Recommendation 1.1.5

Consider repeated endoscopic resection with further pathological assessment for suspected residual or recurrent disease.

2.4 Ablative therapies

2.4.1 Evidence review

Through systematic searching, 1888 articles were found; of these, 11 studies that treated high-grade dysplastic Barrett's oesophagus or early adenocarcinoma using ablative therapies alone were eligible for inclusion. Three studies used argon plasma coagulation alone for ablation and the evidence from those studies is summarised in GRADE profile 5. Three studies used laser alone for ablation and the evidence from those studies is summarised in GRADE profile 6. Two studies used laser ablation along with multipolar electrocoagulation for ablation and the evidence from those studies is summarised in GRADE profile 7. Only one study used argon plasma coagulation along with multipolar electrocoagulation for ablation and the evidence from that study is summarised in GRADE profile 8. Two studies used radiofrequency ablation alone for ablation and the evidence from those studies is summarised in GRADE profile 9. Both these radiofrequency ablation-alone studies (Shaheen 2009; Ganz 2008) had some participants that had received endoscopic resection before radiofrequency ablation. In Shaheen (2009) the author stated that the study participants could have received endoscopic resection up to 8 weeks before the study and in Ganz (2008) 17% of the participants had received endoscopic resection before radiofrequency ablation.

For photodynamic therapy alone, 28 articles relating to 24 studies were eligible for inclusion. One randomised controlled trial (Ragunath 2005) comparing the effectiveness of argon plasma coagulation with photodynamic therapy was eligible for inclusion 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 5 and the evidence from the included studies is summarised in the GRADE profile 10. An indirect comparison was done to determine the clinical effectiveness of radiofrequency ablation alone compared with photodynamic therapy alone using the Altman and Bland (2003) method.

Table 5 Drugs used for photodynamic therapy in the included studies

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

GRADE profile 5

Argon plasma coagulation alone for studies with 12 months or more follow-up										
No. of studies	**Design**	**Treatment**	**Placebo**	**Risk**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other consideration**	**Quality**
Primary outcome 1: Complete eradication of dysplasia/cancer										
1 (L)	Uncontrolled study	8/10 (80%)			N=10					⊕ VERY LOW
Primary outcome 2: Complete eradication of Barrett's / intestinal metaplasia										
3[37]	Uncontrolled studies	50–76%			3 studies with of N=3, 10 and 29					⊕ VERY LOW
Primary outcome 5: Progression of disease to cancer										
1(A)	Uncontrolled study	4/29 (13.79%)			N=29					⊕ VERY LOW
Primary outcome 6: Overall survival										
2[38]	Uncontrolled studies	90% at 2 years – 82% at 5 years			2 studies with N=29 and 10					⊕ VERY LOW
No. of studies	**Design**	**Treatment**	**Placebo**	**Risk**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other consideration**	**Quality**
Adverse Outcome 9: Stricture or stenosis requiring dilation										
1(A)	Uncontrolled study	0/29 (0%)			N=29					⊕ VERY LOW
Adverse Outcome 12: Perforations										
1(A)	Uncontrolled study	1/29 (3.49%)			N=29					⊕ VERY LOW
(L): Laetham, 2001 (A): Attwood 2003										

[37] Attwood (2003); May (1999); Laetham (2001).

[38] Attwood (2003): Survival analysis using Kaplan–Meier and life tables but using the general UK population for comparison and up to 5 years showing 82% survival; Laetham (2001): Mortality was 1/10 after follow-up of 24 months.

GRADE profile 6

Laser Therapies alone for studies with 12 months or more follow up										
No. of studies	**Design**	**Treatment**	**Placebo**	**Risk**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other consideration**	**Quality**
Primary Outcome 2: Complete eradication of Barrett's / intestinal metaplasia (CR-IM/BO)										
2[39]	Uncontrolled studies	78.6–100%			2 studies with of N=14 and 10 respectively					⊕ VERY LOW
Primary Outcome 3: Complete eradication of high grade dysplasia/ cancer (CR-HGD/CA)										
1(W)	Uncontrolled study	14/14 (100%)			N=14					⊕ VERY LOW
No. of studies	**Design**	**Treatment**	**Placebo**	**Risk**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other consideration**	**Quality**
Adverse Outcome 9: Stricture or stenosis requiring dilation										
1(W)	Uncontrolled study	2/14 (14.28%)			N=14					⊕ VERY LOW
Adverse Outcome 12: Perforations										
1(MV)	Uncontrolled study	0/21 (0%)			N=21					⊕ VERY LOW
Adverse Outcome 13: Chest Pain and/ or retrosternal pain										
2[40]	Uncontrolled studies	30–33.33%			2 studies with of N=10 and 14 respectively					⊕ VERY LOW
Adverse Outcome 14: Bleeding										
2[41]	Uncontrolled studies	7.14–14.9%			2 studies with of N=14 and 21 respectively					⊕ VERY LOW
(W): Weston 2000; (MV): Mathus-Vliegen 1990										

[39] Weston (2000); Grossner (1999).
[40] Grossner (1999); Weston (2000).
[41] Weston (2000); Mathus-Vliegen (1990).

GRADE profile 7

Laser + Multipolar electrocoagulation for studies with 12 months or more follow-up										
No. of studies	**Design**	**Treatment**	**Placebo**	**Risk**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other consideration**	**Quality**
Primary Outcome 2: Complete eradication of Barrett's / intestinal metaplasia										
2[42]	Uncontrolled studies	33.3–37.5%			2 studies with N=6 and 8 respectively with 12 months and 3.4 years follow-up					⊕ VERY LOW

GRADE profile 8

Multipolar electrocoagulation + Argon plasma coagulation for studies with 12 months or more follow up										
No. of studies	**Design**	**Treatment**	**Placebo**	**Risk**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other consideration**	**Quality**
Primary Outcome 5: Progression of disease to cancer										
1(S)	Uncontrolled study	3/3 (100%[43])			N=3, mean 14.3 months follow-up					⊕ VERY LOW
(S): Sampliner 2006										

GRADE profile 9

Radiofrequency ablation alone for studies of more than 12 months follow up										
No. of studies	**Design**	**Treatment**	**Placebo**	**Relative risk RR (95% CI) [ARR] NNTB (95% CI)**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other consideration**	**Quality**
Primary outcome 1: Complete eradication of dysplasia/ cancer										
1(Sh)	RCT	34/42 (81%)	4/21(19%)	RR = 4.25 (1.98,10.66) [ARR=0.62]; NNTB=1.62 (1.28, 2.69)	N	N	N	N	N	⊕⊕⊕⊕ HIGH
1(G)	Uncontrolled study	74/92 (80.4%)			Large case series, patient registry from 16 institutions, N=142 but efficacy data on 92					⊕ VERY LOW
Primary outcome 2: Complete eradication of intestinal metaplasia/ Barrett's oesophagus										

[42] Sharma (1999, 2000).
[43] Sampliner (2006): The case series specifically reported only those cases that progressed to adenocarcinoma.

Radiofrequency ablation alone for studies of more than 12 months follow up

No. of studies	Design	Treatment	Placebo	Relative risk RR (95% CI) [ARR] NNTB (95% CI)	Limitations	Inconsistency	Indirectness	Imprecision	Other consideration	Quality
1(Sh)	RCT	31/42 (74%)	0/21 (0%)	[ARR=0.74; NNTB=1.35 (1.18, 1.78)	N	N	N	N	N	⊕⊕⊕⊕ HIGH
1(G)	Uncontrolled study	50/92 (54.3%)			Large case series, patient registry from 16 institutions, N=142 but efficacy data on 92					⊕ VERY LOW
Primary outcome 3: Complete eradication of high grade dysplasia/ cancer										
1(G)	Uncontrolled study	83/92 (90.2%)			Large case series, patient registry from 16 institutions, N=142 but efficacy data on 92					⊕ VERY LOW
Primary outcome 5: Progression of disease to cancer										
1(Sh)	RCT	1/42 (2%)	4/21(19%)	RR=0.125 (0.019, 0.784) [ARR=0.167]; NNTB=6.0 (2.62, 40.22)	N	N	N	S[44]	N	⊕⊕⊕ MODERATE
No. of studies	**Design**	**Treatment**	**Placebo**	**Relative risk RR (95%CI) [ARR] NNTH (95%CI)**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Quality**
Adverse outcome 7: Major adverse event										
1(Sh)	RCT	1/42 (2.38%)	0/21 (0%)	[ARR=-0.024]; NNTH=42 (-8.03, 7.45)[45] **NS**	N	N	N	N	N	⊕⊕⊕⊕ HIGH
Adverse outcome 13: Chest pain and/ or retrosternal pain										
1(Sh)	RCT	2/42 (4.76%)	0/21 (0%)	[ARR=-0.048]; NNTH=21 (-6.28, 8.9)[46] **NS**	N	N	N	N	N	⊕⊕⊕⊕ HIGH

N = No serious; S = Serious; VS = Very serious;
RR: relative risk; ARR: absolute risk reduction; CI: confidence intervals
NNTB/ NNTH: number-needed-to-treat to benefit/ number-needed-to-treat to harm
(Sh): Shaheen, 2009; (G): Ganz, 2008[47]

[44] Shaheen (2009): 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.
[45] Shaheen (2009): one patient in the radiofrequency ablation arm had an upper gastrointestinal haemorrhage.
[46] Shaheen (2009): one patient had chest pain after 8 days and patient had chest discomfort and nausea immediately after the procedure; 0–100 VAS score for some patients only: radiofrequency ablation (n = 41) median 22 versus 0 control (n = 20).
[47] Shaheen (2009): The authors state that study participants could receive endoscopic resection up to 8 weeks prior to the study but the majority of the patients received radiofrequency ablation alone. Ganz (2008): The authors state that 17% of the participants had received endoscopic resection before radiofrequency ablation.

GRADE profile 10

Photodynamic Therapy alone for studies of 12 months or more follow up										
No. of studies	**Design**	**Treatment (photosensitiser used for photodynamic therapy)**	**Placebo**	**Relative risk [RR] (95%CI)] [ARR; NNTB (95%CI)]**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other consideration**	**Quality**
Primary outcome 1: Complete eradication of dysplasia/ cancer										
1(O)	RCT	81/138 (58.7%) (porfirmer sodium)	10/70 (14.3%)	RR=4.11 (2.36, 7.45) [ARR=0.44; NNTB=2.25 (1.81, 3.16)]	N	N	N	N	N	⊕⊕⊕⊕ HIGH
1 (O99)	Case Series	64/85 (75.3%) (porfirmer sodium)			Single centre standard case series with subgroups for dysplasia					⊕ VERY LOW
3[48]	Case series	51.5% - 100% (porfirmer sodium, 5-ALA or 5-ALA or mTHPC)			Three studies: N=7, 32 and 33 patients with follow-up 12.8-60 mths					⊕ VERY LOW
Primary outcome 2: Complete eradication of intestinal metaplasia/ Barrett's oesophagus										
1 (O99)	Case Series	36/85 (42.5%) (porfirmer sodium)			Single centre case series with N=100 but analysis on 85					⊕ VERY LOW
1(W)	Case Series	57/102 (55.8%) (porfirmer sodium)			Single centre study focusing on PDT complications, N=102					⊕ VERY LOW
1 (Y09)	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
5[49]	Case series	8.3% - 61.5%[50] (3 studies with porfirmer sodium, and 1 with mTHPC and 5-ALA each)			Five studies, N = 19, 24, 28, 48 and 52 patients, with follow-up of 18.5 months to 7 years					⊕ VERY LOW
Primary outcome 3: Complete eradication of high grade dysplasia/ cancer										
1(O)	RCT	106/138 (76.8%) (porfirmer sodium)	27/70 (38.6%)	RR=1.99 (1.49, 2.76) [ARR=0.38; NNTB=2.61(1.97, 4.11)]	N	N	N	N	N	⊕⊕⊕⊕ HIGH
7[51]	Case series	38.5% - 100% (3 studies with porfirmer sodium, 1 with 5-ALA, 1 with temoporfin or mTHPC, 1 with 5-ALA or mTHPC, and 1 with HpD or sulfonated aluminium phtalocyanine or Radachlorin or 5-ALA)			Seven studies: N = 5-50 with follow-up 12 months to 11 years					⊕ VERY LOW
Primary outcome 4: Reduction in length of Barrett's Oesophagus										
1(L)	Case series	2.4±0.9 cm (1-5 rang); reduction by 10%-50% (Low-dose HpD)			Small study with N=5 and follow-up of 1 year					⊕ VERY LOW

[48] Ban (2004); Gossner (1998); Javaid (2002).
[49] Craig (2007); Lovat (2005); Mackenzie (2008); Mino-Kenudson (2007); Wolfsen (2002).
[50] The 8.3% rate was seen in Mackenzie (2008), which was a dose escalation study, excluding it changes the range to 36.8–61.5%.
[51] Barr (1996); Etienne (2004); Filonenko (2008); Foroulis (2009); Gossner (1999); Keeley (2007); Weiss (2006).

Primary outcome 5: Progression of disease to cancer										
1(O)	RCT	21/138 (15.2%) (porfirmer sodium)	20/70 (28.6%)	RR=0.53 (0.31, 0.91) [ARR=0.134; NNTB=7.49(3.83, 55.62)]	N	N	N	N	N	⊕⊕⊕⊕ HIGH
Primary outcome 6: Overall Survival										
1(Pr)	Cohort study	118/129 (91.47%) (porfirmer sodium or HpD)	Surgery 64/70 (91.43%)	RR= 1.0 (0.92, 1.12)[52] [ARR=0.0; NNTH=2257.5 (-12.95, 10.27)] **NS**	N	N	N	N	N	⊕⊕ LOW
1(O03)	Case Series	77/89 (81.5%)[53] (porfirmer sodium)			Single centre case series with follow up of mean 50.7 months and N=103 but relevant is 89					⊕ VERY LOW
No. of studies	**Design**	**Treatment (photosensitiser used for photodynamic therapy)**	**Placebo**	**Relative risk [RR] (95%CI)] [ARR; NNTB (95%CI)]**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other consideration**	**Quality**
Adverse outcome 8: Minor adverse events										
7[54]	Case series	3.22%-75%[55] (4 studies with 5-ALA, 3 with porfirmer sodium, 1 with low-dose HpD and 1 with temoporfin or mTHPC)			Seven studies: N = 5-66 patients with a follow – up of 12 -45 months.					⊕ VERY LOW
Adverse outcome 9: Stricture or stenosis requiring treatement										
1(O)	RCT	49/133 (36.8%) (porfirmer sodium)	0/69 (0%)	RR= N.A. [ARR=0.368;NNTH=2.71]	N	N	N	N	N	⊕⊕⊕⊕ HIGH
1(P)	Case series	PDT 35/131(26.72%) (porfirmer sodium or HpD)			Single centre study, studying stricture post PDT, N=131					⊕ VERY LOW
1(O03)	Case Series	27/89 (30.3%) (porfirmer sodium)			Single centre case series with follow up of mean 50.7 months and N=103 but relevant is 89					⊕ VERY LOW
1(W)	Case Series	20/102 (20%) (porfirmer sodium)			Single centre study focusing on PDT complications, N=102					⊕ VERY LOW
1 (Y08)	Case Series	37/160 courses of PDT (23.12%) (porfirmer sodium)			Study looking at predictors for stricture (using data from a single large urban teaching hospital),					⊕ VERY LOW

[52] Prasad (2007a): Overall survival at a median follow-up of 59.27 months.
[53] Overholt (2003): Survival analysis using Kaplan–Meier curves at mean follow-up of 50.65 months.
[54] Ackroyd (1999); Etienne (2004); Foroulis (2009); Gossner (1998); Keeley (2007); Laukka (1995); Mackenzie (2008); Pech (2005); Weiss (2006).
[55] Ackroyd (1999) (N = 10; 24 months follow-up) 10% nausea for 24 hours; Etienne (2004) (N = 12; 34 months follow-up) 25% had hiccups; Foroulis (2009) (N = 31; 14 months follow-up) 3.22% epigastric pain and nausea and 16.12% symptomatic oesophagitis; Gossner (1998) (N = 32; 30 months follow-up) 46.9% nausea; Keeley (2007) (N = 50; 28.1 months follow-up) 6% had pleural effusion; Laukka (1995) (N = 5; 12 months follow-up) nausea, epigastric pain and anorexia 40%; Mackenzie (2008) (N = 24; 45 months follow-up) 75% had nausea and vomiting; Pech (2005) (N = 66; 37 months follow-up) 40% had vomiting nausea and chest pain; Weiss (2006) (N = 17; 21 months follow-up) 11.8% pleural effusions.

					N=116					
9[56]	Case series	0% - 50%[57] (4 with porfirmer sodium, 2 with mTHPC, 2 with 5-ALA , and one with temoporfin or mTHPC)			Nine studies: N = 6-31 with a follow up of up to 45 months					⊕ VERY LOW
Adverse outcome 10: Photosensitivity										
1(O)	RCT	92/133 (69%) (porfirmer sodium)	OM 0/69 (0%)	RR= N.A. [ARR=0.691;NNTH=1.45]	N	N	N	N	N	⊕⊕⊕⊕ HIGH
1(W)	Case Series	18/102 (18%) (porfirmer sodium)			Single centre study focusing on PDT complications, N=102					⊕ VERY LOW
10[58]	Case series	0% - 100%[59] 4 with porfirmer sodium, 2 with 5-ALA, 1 with temoporfin or mTHPC, 1 with mTHPC, 1 with low-dose HpD and 1 with HpD or sulfonated aluminium phtalocyanine or Radachlorin or 5-ALA)			Ten studies: N = 5-50 with a follow-up ranging from 12 months to 11 years.					⊕ VERY LOW
Adverse outcome 11: Cardiac complications										
1(O03)	Case Series	3/89 (3.37%) (porfirmer sodium)			Single centre case series with follow up of mean 50.7 months and N=103 but relevant is 89					⊕ VERY LOW
1(W)	Case Series	2/102 (2%) (porfirmer sodium)			Single centre study focusing on PDT complications, N=102					⊕ VERY LOW
2[60]	Case series	4.16% - 5.88% (porfirmer sodium)			Two studies: N = 17 and 48, with a follow-up of 21 months and 18.5 months respectively.					⊕ VERY LOW
Adverse outcome 13: Chest pain and/ or retrosternal pain										
1(O)	RCT	27/133 (20%) (porfirmer sodium)	0/69 (0%)	RR= N.A. [ARR=0.203;NNTH=4.93]	N	N	N	N	N	⊕⊕⊕⊕ HIGH
1(W)	Case Series	PDT 15/102 (15%) (porfirmer sodium)			Single centre study focusing on PDT complications, N=102					⊕ VERY LOW

N = No serious; S = Serious; VS = Very serious; **NS**: not statistically significant
RR: relative risk; ARR: absolute risk reduction; CI: confidence intervals
NNTB/ NNTH: number-needed-to-treat to benefit/ number-needed-to-treat to harm
(L): Laukka, 1995; (O): Overholt 2005; 2007; (O99): Overholt, 1999; (O03): Overholt, 2003; (Pr): Prasad, 2007a; (P): Prasad 2007b; (W): Wolfsen, 2004a; (Y08): Yachimski, 2008; (Y09): Yachimski, 2009

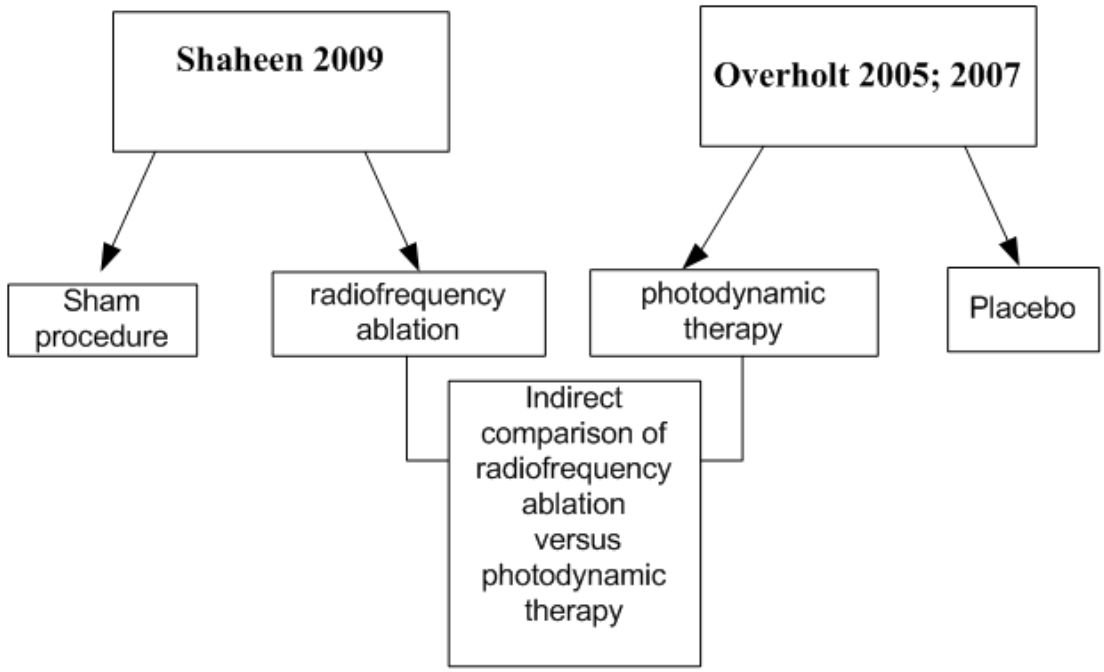
[56] Craig (2007); Etienne (2004); Foroulis (2009); Gill (2009); Gossner (1999); Javaid (2002); Lovat (2005); Mackenzie (2008); Weiss (2006).
[57] The 50% stricture rate was seen in Craig (2007) (using porfirmer sodium) and 0% was seen in Mackenzie (2008) and Gossner (1999) using 5-ALA.
[58] Etienne (2004); Filonenko (2008); Foroulis (2009); Gossner (1998); Keeley (2007); Laukka (1995); Lovat (2005); Mackenzie (2008); Weiss (2006); Wolfsen (2002).
[59] The 0% rate was found in two studies: Gossner (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-ALA. The 100% rate was found in one study: Filonenko (2008) N = 48 with 3–11 years follow-up using HpD, Photosens [sulfonated aluminium phtalocyanine], Radachlorin [natural chlorophill-a derivative] or 5-ALA.
[60] Weiss (2006) (atrial fibrillation in one patient); Wolfsen (2002) (atrial fibrillation in one patient and recurrent congestive heart failure in one patient).

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 2009; Overholt 2005, 2007; figure 2, table 6).

Figure 2 Schematic representation of the indirect comparison done for radiofrequency ablation versus 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 both the control arms for the two randomised controlled trials were comparable – that is, the sham procedure in the Shaheen (2009) study was equivalent to the placebo arm of the Overholt

(2005, 2007) study; that the populations in the two randomised controlled trials were similar enough; and that their sample size was large enough to make the comparison.

Table 6 Randomised controlled trials included for the indirect comparison

Parameters	Shaheen (2009)	Overholt (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	Radiofrequency ablation done circumferentially	Photodynamic therapy done 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 (2009) and Overholt (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 7).

Table 7 Calculations of the indirect comparison

Parameters	Shaheen (2009)	Overholt (2005, 2007)
RR (95% CI)	4.25 (1.98 to 10.66)	4.11 (2.36 to 7.45)
Log RR[61]	1.45 (0.68 to 2.37)	1.41 (0.86 to 2.01)
Standard error of log RR	0.43	0.30
Difference[62](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, n = 10 and n = 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 (2003; n = 29, mean 37 months' follow-up) was 82% and Laetham (2001; n = 10, median 24 months' follow-up) noted a 90% survival at 24 months. Attwood (2003) also noted a 3.49% rate of perforations.

Laser ablation alone

2.4.2.3 Three small case series (n = 10, n = 14 and n = 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.

Laser ablation and multipolar electrocoagulation alone

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

[61] Log values are obtained by taking the natural logarithms of the values.
[62] Difference (d) is the difference between the log relative risks.

Multipolar electrocoagulation and argon plasma coagulation alone

2.4.2.5 Only one case series (Sampliner 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 2009) 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 (NNTB = 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 2008) showed 80.4% eradication of dysplasia, 54.3% complete ablation of Barrett's oesophagus and 90.2% eradication of high-grade dysplasia.

Photodynamic therapy alone

Primary outcomes

2.4.2.9 One randomised controlled trial with 5-year follow-up (Overholt 2005, 2007) 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 Four case series 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 1998).

2.4.2.11 *Seven case series showed a 36.8–61.5% rate of complete ablation of Barrett's oesophagus. One dose-escalation study (Mackenzie 2008) showed an 8.3% rate of complete ablation of Barrett's oesophagus.*

2.4.2.12 *One randomised controlled trial (Overholt 2005, 2007) 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).*

2.4.2.13 *One cohort study (Prasad 2007a) 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.*

2.4.2.14 *One case series (Overholt 2003) 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

2.4.2.15 *One randomised controlled trial (Overholt 2005, 2007) 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.*

2.4.2.16 *Four large case series (n = 89, 102, 116,131) showed a stricture or stenosis rate (requiring treatment) of 20–30% with porfimer sodium after a median follow-up of 45–50 months.*

2.4.2.17 *Nine smaller case series showed a stricture or stenosis rate (needing treatment) of 0–50% after a median follow-up of 45 months with the 0% rate seen in the two studies that used 5-aminolaevulinic acid.*

2.4.2.18 One randomised controlled trial (Overholt 2005, 2007) showed a photosensitivity reaction rate of 69% for the photodynamic therapy arm (using porfimer sodium).

2.4.2.19 Eleven case series 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 chlorophill-a derivative or 5-aminolaevulinic acid).

2.4.2.20 Seven case series 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

2.4.2.21 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 0.37–2.87).

2.4.3 Health economic modelling

Ablative therapies alone

The results of the cost-effectiveness analysis are summarised in table 8.

Table 8 Cost-effectiveness results for radiofrequency ablation and photodynamic therapy

	Radiofrequency ablation	Photodynamic therapy
Deterministic ICER	£24,757	£22,990
Probabilistic ICER	£25,558	£39,739
Probability of being cost effective at £20,000 per QALY	34.4%	20.6%
Probability of being cost effective at £30,000 per QALY	47.1%	33.6%
Probability of being optimum choice at £20,000 per QALY	0.6%	0%
Probability of being optimum choice at £30,000 per QALY	0.7%	0.1%
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 £38,000 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. It is also associated with a 33% probability of being cost effective and a very low probability of being an optimum choice.

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 inclusion of the Shaheen (2009) and Ganz (2008) studies categorised as radiofrequency ablation alone, because both studies included some participants who had received endoscopic 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 Shaheen (2009) study 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 varied between £21,000 and £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 Overholt (2005, 2007) randomised controlled trial 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 Group considered the cost-effectiveness analysis and acknowledged that the results suggested that photodynamic therapy was not cost effective. However, the Group considered that the analysis had not captured all the clinical benefits of photodynamic therapy, such as deeper penetration into the mucosa, which meant that recurrence of cancer was reduced, thus improving its cost effectiveness. 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 Endscopic resection in combination with ablative therapies

2.5.1 Evidence review

Through systematic searching, 1888 articles were found; of these, seven studies that treated high-grade dysplastic Barrett's oesophagus or early adenocarcinoma using endoscopic resection in combination with an ablative therapy were eligible for inclusion. Two studies used argon plasma coagulation in combination with endoscopic 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 resection and the evidence from those studies is summarised in GRADE profile 13.

Seven studies were eligible for inclusion that used endoscopic resection in combination with photodynamic therapy alone. The photosensitisers used for photodynamic therapy in these studies are listed in table 9 and the evidence from these studies is summarised in GRADE profile 14.

Table 9 List of photosensitisers used in included studies of endoscopic resection and photodynamic therapy

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

GRADE profile 11

Endoscopic resection + Argon plasma coagulation for studies with less than 12 months follow-up										
No. of studies	**Design**	**Treatment**	**Placebo**	**Risk**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other consideration**	**Quality**
Primary outcome 2: Complete eradication of Barrett's/ intestinal metaplasia										
1 (Pe)	Uncontrolled study	33/37 (89.19%)			N=37, 11 months follow-up					⊕ VERY LOW
Primary outcome 3: Complete eradication of high grade dysplasia/ cancer										
1 (Pe)	Uncontrolled study	37/37 (100%)			N=37, 11 months follow-up					⊕ VERY LOW
No. of studies	**Design**	**Treatment**	**Placebo**	**Risk**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other consideration**	**Quality**
Adverse outcome 9: Stricture or stenosis requiring treatment										
1 (Pe)	Uncontrolled study	10/39 (25.64%)			N=39[63]					⊕ VERY LOW
Adverse outcome 12: Perforations										
1 (Pe)	Uncontrolled study	1/37 (2.70%)			N=37					⊕ VERY LOW
Adverse outcome 14: Bleeding										
1 (Pe)	Uncontrolled study	1/37 (2.70%)			N=37					⊕ VERY LOW

[63] Peters (2006): The study had enrolled 39 participants but 2 discontinued treatment due to unrelated comorbidity. Both suffered symptomatic stenosis requiring endoscopic boulenage treatment from initial endotherapy. Argon plasma coagulation treatment was given to 34 out of the 37 remaining participants.

(Pe): Peters 2006

GRADE profile 12

Endoscopic resection + Argon plasma coagulation for studies with 12 months or more follow-up										
No. of studies	**Design**	**Treatment**	**Placebo**	**Risk**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other consideration**	**Quality**
Primary Outcome 2: Complete eradication of Barrett's/ intestinal metaplasia										
1 (Po)	Uncontrolled study	23/34 (67.65%)			N=34[64] median 23 months follow-up (IQR 15-41months)					⊕ VERY LOW
Primary Outcome 3: Complete eradication of high grade dysplasia/ cancer										
1 (Po)	Uncontrolled study	34/34 (100%)[65]			N=34, median 23 months follow-up (IQR 15-41months)					⊕ VERY LOW
(Po): Pouw 2008										

GRADE profile 13

Endoscopic resection + Radiofrequency ablation for studies of more than 12 months follow up										
No. of studies	**Design**	**Treatment**	**Placebo**	**Risk**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other consideration**	**Quality**
Primary Outcome 1: Complete eradication of dysplasia/ cancer										
2[66]	Uncontrolled studies	79–100%			Small studies with N = 24, 12 with follow-up median 14-24 months					⊕ VERY LOW
Primary Outcome 2: Complete eradication of Barrett's / intestinal metaplasia (CR-IM/BO):										
5[67]	Uncontrolled studies	20/24 (83.3%)			Small single arm studies, N=8-24 with follow up of median 12-24 months.					⊕ VERY LOW
Primary Outcome 3: Complete eradication of high grade dysplasia/ cancer (CR-HGD/CA)										
3[68]	Uncontrolled studies	90–100%			Three small studies, N =8-24 with median follow-up of 12-22 months					⊕ VERY LOW
Adverse Outcome 7: Major adverse events										
(P)	Uncontrolled study	1/24 (4.16%)[69]			Small single arm cohort, N=24 with follow up of median 22 months.					⊕ VERY LOW

[64] Pouw (2008): Argon plasma coagulation treatment was given to 12 out of 34 participants.
[65] Pouw (2008): 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 resection and one had curative surgical resection.
[66] Sharma (2009) and Gondrie (2008a, 2008b).
[67] Beaumont (2009); Gondrie (2008a, 2008b); Pouw (2009, 2010); Smith (2006); Sharma (2009).
[68] Beaumont (2009); Smith (2006); Sharma (2009).
[69] Pouw (2009, 2010): The major adverse event of melena was observed in one patient 2 weeks after focal ablation.

Endoscopic resection + Radiofrequency ablation for studies of more than 12 months follow up										
No. of studies	**Design**	**Treatment**	**Placebo**	**Risk**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other consideration**	**Quality**
Adverse Outcome 9: Stricture or stenosis requiring treatment										
(P)	Uncontrolled study	1/24 (4.16%)			Small single arm cohort, N=24 with follow up of median 22 months.					⊕ VERY LOW
Adverse Outcome 12: Perforations										
(P)	Uncontrolled study	1/24 (4.16%)			Small single arm cohort, N=24 with follow up of median 22 months.					⊕ VERY LOW
(P): Pouw, 2009; 2010										

GRADE profile 14

Endoscopic resection + Photodynamic therapy for studies with 12 months or more follow up										
No. of studies	**Design**	**Treatment (photosensitiser used for photodynamic therapy)**	**Placebo**	**Relative risk [RR] (95%CI)] [ARR; NNTB (95%CI)]**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Quality**
Primary outcome 1: Complete eradication of Dysplasia/cancer (CR-D/ CA)										
5[70]	Uncontrolled studies	50%-100%			5 Studies of N=3, 12, 44, 17 and 3 with median follow up					⊕ VERY LOW
Primary outcome 2: Complete eradication of Barrett's / intestinal metaplasia (CR-IM/BO):										
5[71]	Uncontrolled studies	50-100%[72] (2 with 5-ALA, 1 with porphyrin based photosensitizers, 1 with porfirmer sodium and 1 not stated)			5 Studies of N=3, 12, 44, 17 and 3					⊕ VERY LOW
Primary outcome 6: Overall Survival										
1(P)	cohort	22/24 (91.67%) ((porfirmer sodium or 1 with HpD)	Surgery 62/64 (96.88%)	RR=0.95 ((0.76,1.05) [ARR=-0.05; NNTB=-19.2 (-4.32, 22.8)] **NS**[73]	N	N	N	N	N	⊕⊕ LOW

[70] Behrens (2005); Buttar (2001); Mino-Kenudson (2005); Van Hillegersberg (2003); Wolfsen (2004).

[71] Behrens (2005); Buttar (2001); Mino-Kenudson (2005); Van Hillegersberg (2003); Wolfsen (2004). Mino-Kenudson (2005) was a study of 18 patients but the relevant population was 12 patients.

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

[73] Pacifico (2003): The median follow-up was 12 ± 2 months for the endoscopic resection + photodynamic therapy arm and 19 ± 3 months for the surgery arm.

Endoscopic resection + Photodynamic therapy for studies with 12 months or more follow up											
1(R)	cohort	47/47 (100%) (not stated)	Surgery: 48/49 (97.96%) Observation: 19/19 (100%)	Surgery RR=1.02 (0.92, 1.11); ARR=-0.02; **NS** NNTB=48.8 (-17.6, 9.29) Surgical group=83% (at 5 years and 64% (at 10 years)[74]	N	S[75]	N	N	N	⊕ VERY LOW
No. of studies	**Design**	**Treatment (photosensitiser used for photodynamic therapy)**	**Placebo**	**Relative risk [RR] (95%CI)] [ARR; NNTB (95%CI)]**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Quality**
Adverse outcome 7: Major adverse events										
1(P)	cohort	0/24 (0%) (porfirmer sodium or 1 with HpD)	Surgery 19/64 (29.69%)	ARR=0.3 (0.3_0.57) NNTB=3.67 (2.39_6.77)[76]	N	N	N	N	N	⊕⊕ LOW
1(R)	cohort	0/47 (0%) (not stated)	Surgery 2/49 (4.08%)	ARR=0.04 (-0.03, 0.14) NNTB=24.5 (-27.0, 7.25)[77] **NS**	N	S	N	N	N	⊕ VERY LOW
Adverse outcome 9: Stricture or stenosis requiring treatment										
1(P)	cohort	2/24 (8.33%) (porfirmer sodium or 1 with HpD)	Surgery 10/64 (15.63%)	RR=0.53 (0.13, 1.91) ARR=0.0.07; NNTB= 13.71(-8.57, 4.91) **NS**	N	N	N	N	N	⊕⊕ LOW
1(Bu)	Uncontrolled study	5/17 (29.41%) (porphyrin based photosensitizers)			N=17, median 13 months follow-up					⊕ VERY LOW
Adverse outcome 10: Photosensitivity										
1(P)	cohort	2/24 (8.33%) (porfirmer sodium or 1 with HpD)	Surgery 0/64 (0%)	[ARR=-0.08 (-0.26,-0.02) NNTH=12(-4, 45)] **NS**	N	N	N	N	N	⊕⊕ LOW
1(Bu)	Uncontrolled study	2/17 (11.76%) (porphyrin based photosensitizers)			N=17, median 13 months follow-up					⊕ VERY LOW
Adverse outcome 11: Cardiac complications										
1(P)	cohort	0/24 (0%) (porfirmer sodium or 1 with HpD)	Surgery 2/64 (3.13%)	[ARR=0.03 (-0.10, 0.11) NNTB=32 (-9.14, 9.23)] **NS**	N	N	N	N	N	⊕⊕ LOW

[74] Survival analysis done using Kaplan–Meier for the surgical group.
[75] Reed (2005): 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 nonsurgical groups, but can be estimated to be 13.5 months for endoscopic resection + photodynamic therapy group.
[76] Pacifico (2003): The 19 major adverse events in the surgery arm were: anastomatic leaks 5; wound infections 5; dumping syndrome 3; empyema 2; blood transfusions 2; aspiration 1; chylothorax 1.
[77] Reed (2005): The two major adverse events in the surgery arm were two anastomatic leaks.

Endoscopic resection + Photodynamic therapy for studies with 12 months or more follow up				
1(Bu)	Uncontrolled study	1/17 (5.88%) (porphyrin based photosensitizers)	N=17, median 13 months follow-up	⊕ VERY LOW
Adverse outcome 14: Bleeding				
1(Bu)	Uncontrolled study	1/17 (5.88%) (porphyrin based photosensitizers)	N=17, median 13 months follow-up	⊕ VERY LOW
N = No serious; S = Serious; VS = Very serious; **NS**: not statistically significant RR: relative risk; ARR: absolute risk reduction; CI: confidence intervals NNTB/ NNTH: number-needed-to-treat to benefit/ number-needed-to-treat to harm (Bu): Buttar 2001; (P) Pacifico, 2003[78]; (R) Reed, 2005				

2.5.2 Evidence statements

Endoscopic resection in combination with argon plasma coagulation

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

2.5.2.2 Peters (2006, n = 37, median 11 months' follow-up) performed endoscopic 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 (2008, n = 34, median 23 months' follow-up) performed endoscopic 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 resection and one had surgical resection).

[78] Pacifico (2003): Study with a follow-up of 12 ± 2 months for endoscopic resection + photodynamic therapy group versus 19 ± 3 months for surgery group. It studied the patient characteristics between the two groups and the only statistically significant difference found pulmonary comorbidities to be higher for the endoscopic resection + photodynamic therapy group.

Endoscopic 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 2010, n = 24).

Endoscopic 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 2003; Reed 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 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 2003; Reed 2005) showed major adverse events[79] 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 (NNTB = 3.67, 95% CI 2.39 to 6.77 for Pacifico 2003, and NNTB=24.5, 95% CI −27.0 to 7.25 for Reed 2005).

2.5.2.9 One cohort study (Pacifico 2003) showed a higher stricture or stenosis rate (needing treatment) for the surgery arm (15.63%)

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

compared with the photodynamic therapy arm (8.33%, using porfirmer sodium or haematoporphyrin derivative), but was not statistically significant (RR=0.53, 95% CI 0.13 to 1.91).

2.5.2.10 One cohort study (Pacifico 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 (number needed to harm = 12, 95% CI −4 to 45).

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

2.5.2.12 One case series (Buttar 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 resection and ablative therapies

The results of the cost-effectiveness analysis are summarised in table 10.

Table 10 Cost-effectiveness results for endoscopic resection plus ablative therapies

	Endoscopic resection and argon plasma coagulation	Endoscopic resection and radiofrequency ablation	Endoscopic resection and photodynamic therapy
Deterministic ICER	£12,233	£13,893	£17,305
Probabilistic ICER	£18,531	£16,050	£26,497
Probability of being cost effective at £20,000 per QALY	44.6%	50.4%	31.8%
Probability of being cost effective at £30,000 per QALY	60.6%	65.1%	47.2%
Probability of being optimum choice at £20,000 per QALY	4.6%	9.7%	1.3%
Probability of being optimum choice at £30,000 per QALY	6.2%	14.4%	2.9%
ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year			

These results suggested that endoscopic resection plus argon plasma coagulation or radiofrequency ablation combinations were cost effective compared with no surveillance. Endoscopic resection plus radiofrequency ablation was associated with the least uncertainty of being cost effective and in addition an 18% probability of being the optimum choice. Endoscopic resection plus argon plasma coagulation was also associated with low uncertainty but was unlikely to be the optimum choice. Endoscopic resection plus photodynamic therapy was associated with the highest estimates of cost effectiveness of the three combinations and the highest uncertainty. It was also highly unlikely to be the optimum choice.

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 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 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 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' 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 me the inclusion criteria and was included: 'Photodynamic therapy (PDT) with porfirmer sodium for Barrett's oesophagus (BO) and high grade dysplasia (HGD) – patients' perspective' (Hemminger 2002). The evidence from this included study is summarised in table 11.

Table 11 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 select 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 (pain on swallowing) or dysphagia (difficulty in swallowing).

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 decision about their care.

Recommendation 1.1.10

Give patients the multidisciplinary team's views on the range of appropriate treatments.

Recommendation 1.1.11

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

Recommendation 1.1.12

Advise patients who receive 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 case 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 (with a follow-up of at least five years) 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
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- 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)

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

Ablative

A term used to describe a procedure involving removal of a tissue or body part, or destruction of its function.

Abstract

Summary of a study, which may be published alone or as an introduction to a full scientific paper.

Cost-effectiveness model

An explicit mathematical framework, which is used to represent clinical decision problems and incorporate evidence from a variety of sources in order to estimate the costs and health outcomes.

Dysphagia

Difficulty in swallowing.

Dysplasia

Abnormal development or growth of tissues, organs, or cells. Dysplasia can be low grade or high grade. High- grade dysplasia represents a more advanced progression towards malignant transformation.

Effect (as in effect measure, treatment effect, estimate of effect, effect size)

The observed association between interventions and outcomes or a statistic to summarise the strength of the observed association.

Epithelium

A membranous cellular tissue that covers a free surface or lines a tube or cavity of an animal body and serves especially to enclose and protect the other parts of the body, to produce secretions and excretions, and to function in assimilation.

Evidence

Information on which a decision or guidance is based. Evidence is obtained from a range of sources including randomised controlled trials, observational studies, expert opinion (of clinical professionals and/or patients).

Incremental analysis

The analysis of additional costs and additional clinical outcomes with different interventions.

Incremental cost

The mean cost per patient associated with an intervention minus the mean cost per patient associated with a comparator intervention

Incremental cost effectiveness ratio (ICER)

The difference in the mean costs in the population of interest divided by the differences in the mean outcomes in the population of interest.

Incremental net benefit (INB)

The value (usually in monetary terms) of an intervention net of its cost compared with a comparator intervention. The INB can be calculated for a given cost-effectiveness (willingness to pay) threshold. If the threshold is £20,000 per QALY gained then the INB is calculated as: (£20,000 x QALYs gained) – Incremental cost.

Intention-to-treat analysis (ITT analysis)

An analysis of the results of a clinical study in which the data are analysed for all study participants as if they had remained in the group to which they were randomised, regardless of whether or not they remained in the study until the end, crossed over to another treatment or received an alternative intervention.

Life-years gained

Average years of life gained per person as a result of the intervention.

Metaplasia

Abnormal replacement of normal cells by malignant cells.

Mucosa

The mucous membrane, or the thin layer which lines body cavities and passages.

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 to benefit (NNTB)

NNTB is an epidemiological measure used in assessing the effectiveness of a health-care intervention, typically a treatment with medication. The NNTB is the number of patients who need to be treated in order to prevent one additional bad outcome (i.e. the number of patients that need to be treated for one to benefit compared with a control in a clinical trial). It is defined as the inverse of the absolute risk reduction. The ideal NNTB is 1, where everyone improves with treatment and no-one improves with control. The higher the NNTB, the less effective is the treatment.

Number needed to treat to harm (NNTH)

NNTH is an epidemiological measure that indicates how many patients need to be exposed to a risk-factor to cause harm in one patient that would not otherwise have been harmed. It is defined as the inverse of the attributable risk. Intuitively, the lower the number needed to harm, the worse the risk-factor.

Photosensitivity

Refers to any increase in the reactivity of the skin to sunlight.

Reference case

When estimating clinical and cost effectiveness in a technology appraisal, the reference case specifies the methods that are considered by NICE to be the

most appropriate for the Appraisal Committee's purpose and are also consistent with an NHS objective of maximising health gain from limited resources.

Reference standard

An agreed standard, for example for a test or treatment, against which other interventions can be compared.

Sensitivity analysis

A means of representing uncertainty in the results of economic evaluations. Uncertainty may arise from missing data, imprecise estimates or methodological controversy. Sensitivity analysis also allows for exploring the generalisability of results to other settings. The analysis is repeated using different assumptions to examine the effect on the results. One-way simple sensitivity analysis (univariate analysis): each parameter is varied individually in order to isolate the consequences of each parameter on the results of the study. Multi-way simple sensitivity analysis (scenario analysis): two or more parameters are varied at the same time and the overall effect on the results is evaluated. Threshold sensitivity analysis: the critical value of parameters above or below which the conclusions of the study will change are identified. Probabilistic sensitivity analysis: probability distributions are assigned to the uncertain parameters and are incorporated into evaluation models based on decision analytical techniques (For example, Monte Carlo simulation).

7.3 Abbreviations

5-ALA	5-aminolaevulinic acid
APC	Argon plasma coagulation
ARI	Absolute risk increase
ARR	Absolute risk reduction
BMI	Body mass index
BNF	British national formulary
BO	Barrett's oesophagus
CEAC	Cost-effectiveness acceptability curve
CEAF	Cost-effectiveness acceptability frontier
CI	Confidence interval

CLR	Complete local remission
CR-D/CR-CA	Complete eradication of dysplasia and or cancer
CR-IM/ CR-BO	Complete eradication of intestinal metaplasia or Barrett's oesophagus
ER	Endoscopic resection
EVPI	Expected value of perfect information
EVPPI	Expected value of perfect parameter information
GDG	Guideline development group
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HpD	Haematoporphyrin derivative
HR	Hazard ratio
ICER	Incremental cost-effectiveness ratio
IEN	Intraepithelial neoplasia
LET	Local endoscopic therapy
MPEC	Multipolar electrocoagulation
mTHPC	meta-Tetrahydroxyphenyl chlorine
NNTB	Number needed to treat to benefit
NNTH	Number needed to treat to harm
NPV	Negative predictive value
OD	Odds ratio
PDT	Photodynamic therapy
PPI	Proton pump inhibitor
PPV	Positive predictive value
QALY	Quality-adjusted life year
RCT	Randomised clinical trial
RFA	Radiofrequency ablation
ROC	Receiver operating characteristic
RR	Relative risk
RRR	Ratio of relative risk
RS	Reference standard
SD	Standard deviation

8 Contributors

8.1 The Guideline Development Group

Damien Longson (Chair)

Consultant Liaison Psychiatrist, Manchester Mental Health & Social Care Trust, Manchester

Hugh Barr
Professor of Upper Gastrointestinal Surgery, Gloucestershire Hospitals NHS Trust, Gloucester

Pradeep Bhandari
Consultant Gastroenterologist, Portsmouth Hospital NHS Trust, Portsmouth

Ricky Forbes-Young
Advanced Nurse Practitioner, Western General Hospital, Edinburgh

Janusz Jankowski
Professor of Gastroenterology & Endoscopy, Leicester Hospitals NHS Trust, Leicester

Laurence Lovat
Consultant Gastroenterologist & Senior Lecturer in Laser Medicine, UCL Hospitals NHS Trust, London

Robert Mason
Consultant Upper Gastrointestinal Surgeon, Guy's and St Thomas' Hospitals, London

Mimi McCord
Patient/Carer member

Andrea Nicholls
Advanced Nurse Practitioner, Leeds Teaching Hospitals Trust, Leeds

David Poller
Consultant Pathologist, Queen Alexandra Hospital, Portsmouth

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.

Kathryn Chamberlain
Project Manager

Nicole Elliott
Associate Director

Prashanth Kandaswamy
Technical Adviser (Health Economics)

Caroline Keir
Guideline Commissioning Manager

Hanna Lewin
Information Specialist

Jonathon Nyong
Assistant Technical Analyst

Beth Shaw
Technical Adviser

Tarang Sharma
Technical Analyst

Nicholas Staples
Guidelines Coordinator

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.

[Name; style = Unnumbered bold heading]
[job title, including name of hospital/university or other organisation, and city/county if relevant; style = NICE normal]

[Name; style = Unnumbered bold heading]

[job title, including name of hospital/university or other organisation, and city/county if relevant; style = NICE normal]

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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