National Institute for Health and Care Excellence

Draft for consultation

Barrett's Oesophagus

4.1 Evidence review for the clinical and cost effectiveness of endoscopic treatments in Barrett's Oesophagus (low grade dysplasia, indefinite dysplasia)

NICE guideline <number>

Evidence reviews underpinning recommendations 1.5.3 to 1.5.4 in the NICE guideline

August 2022

Draft for Consultation

These evidence reviews were developed by Guideline Development Team NGC

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ISBN:

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1.1 Review question

For adults with Barrett's Oesophagus with low grade or indefinite dysplasia, what is the clinical and cost effectiveness of endoscopic treatments?

1.1.1 Introduction

There is well established evidence that Low Grade dysplasia carries a risk of progression into cancer, although the rate of progression is relatively low. There are endoscopic treatment options for the eradication of low-grade dysplasia. This includes ablative technologies, the most common of which is radiofrequency ablation (RFA). These techniques deliver a mucosal burn to the Barrett's mucosa, with subsequent regrowth of healthy non dysplastic neo-squamous epithelium. This is not risk free, and carries risks of bleeding, perforation, and stricture formation. It often involves a course of treatments and requires the use of specialist disposable equipment. Consequently, it is important to determine the clinical and cost effectiveness of endoscopic treatment techniques for low grade dysplasia within Barrett's

1.1.2 Summary of the protocol

For full details see the review protocol in Appendix A.

Table 1: PICO characteristics of review question

Population	Inclusion: Adults, 18 years and over, with Barrett's oesophagus and dysplasia (low grade) or indefinite for dysplasia Exclusion: Non-dysplastic Barrett's oesophagus, stage 1 adenocarcinoma
Interventions	Endoscopic treatment alone: • Endoscopic ablation (radiofrequency ablation (RFA), argon plasma coagulation (APC), Cryotherapy) • Endoscopic resection (endoscopic mucosal resection (EMR), endoscopic submucosal dissection (ESD). Endoscopic treatment in combination: • Endoscopic ablation & endoscopic resection
Comparisons	• Different endoscopic modalities (e.g., RFA vs Cryotherapy, RFA vs APC) • Endoscopic surveillance
Outcomes	All outcomes are considered equally important for decision making and therefore have all been rated as critical: • Mortality (disease specific mortality and all-cause mortality) • Health related quality of life • Complete regression of Barrett's dysplasia and Barrett's oesophagus • Recurrence of dysplasia or neoplasia • Need for retreatment • Complications of treatment (bleeding, perforation, stricture, pain) • Rate of hospitalization • Progression to higher grade dysplasia and cancer

	• Conversion to non-endoscopic procedure Minimum follow up period of 1 year but to include longest follow up period available.
Study design	• RCT • If no RCT data is available, non-randomised studies if there is an active comparator within the study • Systematic review of RCT's Published NMAs and IPDs will be considered for inclusion.

1.1.3 Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual. Methods specific to this review question are described in the review protocol in appendix A and the methods document.

Declarations of interest were recorded according to NICE's conflicts of interest policy.

1.1.4 Effectiveness evidence

1.1.4.1 Included studies

Four studies (3 RCTs, 1 observational study) are included in the review;[1, 8-10] these are summarised in Table 2 below. Evidence from these studies is summarised in the clinical evidence summary below (Table 3).

All studies examined RFA compared with endoscopic surveillance with one study comparing RFA to a sham endoscopic procedure. The components of the sham endoscopic procedure were reviewed by the committee who noted it matched endoscopic surveillance and thus results for outcomes reported by more than one RCT were pooled together in meta-analysis.

Although RCT evidence was available for this comparison, there was an observational study identified that included long-term follow-up data for a population of one of the included RCTs (the SURF trial). The committee were interested to view this data for the purpose of decision-making and thus observational data from this study was included. There were no further observational studies for this comparison that were excluded.See also the study selection flow chart in Appendix C, study evidence tables in Appendix D, forest plots in **Error! Reference source not found.** and GRADE tables in Appendix F.

1.1.4.2 Excluded studies

One Cochrane review was identified{Bennett, 2020 #961}. The review could not be included as its population of interest was not relevant to this review protocol as it was set-out to include people with high-grade dysplasia and early cancer of different cellular cancer types, not limited to Barrett's oesophagus such as squamous cell carcinoma. The Cochrane review did not identify any studies for inclusion, further highlighting the limited availability of evidence in the area.

See the excluded studies list in Appendix I.

1.1.5 Summary of studies included in the effectiveness evidence

Table 2: Summary of studies included in the evidence review

Study	Intervention and comparison	Population	Outcomes	Comments
Barret 2021[1]	Radiofrequency ablation (RFA) (n=40) vs Endoscopic surveillance: annually (n=42)	Barrett's oesophagus patients with confirmed low-grade dysplasia (n=82) Mean age (SD): 62.3 (10.06) years France	Complete eradication of dysplasia Complete eradication of intestinal metaplasia Persistent low-grade dysplasia at 3 years (extracted as proxy for recurrence of dysplasia) Complications (including fever, chest pain, upper	Multicentre RCT (14 French centres) N=81 (98.8%) were on PPIs at inclusion Anti-reflux surgery had been performed in n=16 patients (19.5%). N=8 (9.8%) had prior endoscopic resection for high-grade dysplasia/ early adenocarcinoma.

Study	Intervention and comparison	Population	Outcomes	Comments
			GI bleeding, stricture) Progression to high-grade dysplasia or adenocarcinoma 3 years after randomisation	
Phoa 2014[8]	RFA (n=68); (double-dose PPI was given as maintenance therapy during the trial) vs Endoscopic surveillance (n=68):	Barrett's oesophagus patients with low-grade dysplasia (n=136) Mean age (SD): 63 (9.51) years The Netherlands, Belgium, UK, Ireland, Germany	Complete eradication of dysplasia Complete eradication of intestinal metaplasia Progression to high-grade dysplasia/ adenocarcinoma Adverse events (protocol outcome: complications) During a 3-year follow-up	Multicentre RCT (9 European centres): the Surveillance vs Radiofrequency Ablation (SURF) study) The trial was terminated early due to the superiority of ablation for the primary outcome (neoplastic progression) and the potential for safety issues if the trial continued. At point of termination, participants had completed at least 2 years of follow-up.
Pouw 2020[9]	RFA (n=68) Vs Endoscopic surveillance (n=68)	Barrett's oesophagus patients with low-grade dysplasia (n=136) The Netherlands, Belgium, UK, Ireland, Germany	Progression to high-grade dysplasia/ adenocarcinoma Follow-up: 73 months; additional median follow-up of 40 months (IQR 12-51) of the SURF study.	Retrospective cohort study of patients included in the SURF study. Further non-comparative data available: at long-term follow-up 15 patients from the surveillance group were offered RFA. Complete clearance of intestinal metaplasia was found in 75/83 patients and recurrence was found in 7/75.
Shaheen 2009[10]	RFA Vs	Patients with dysplastic Barrett's oesophagus (n=127; n=64 had	Complete eradication of dysplasia	Multicentre RCT (19 sites)

Study	Intervention and comparison	Population	Outcomes	Comments
	Sham endoscopic procedure	low-grade dysplasia and were included in this review) Mean age (range): 65.72 (41-78) USA	Complete eradication of intestinal metaplasia Progression to high-grade dysplasia/cancer At 12 months	Includes people with high-grade dysplasia but randomisation and results were stratified by grade of dysplasia; only results relevant to the low-grade dysplasia population are presented in the present review.

1 See Appendix D for full evidence tables.

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1.1.6 Summary of the effectiveness evidence

Table 3: Clinical evidence summary: RFA versus endoscopic surveillance/sham endoscopic procedure (RCT data)

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with endoscopic surveillance	Risk difference with RFA
Complete eradication of dysplasia	272 (3 RCTs)	⊕⊕⊕⊕ High	RR 3.06 (2.26 to 4.14)	268 per 1,000	551 more per 1,000 (337 more to 841 more)
Complete eradication of intestinal metaplasia	264 (3 RCTs)	⊕⊕◯◯ LOW [b]	OR 27.86 (16.47 to 47.14)	0 per 1,000	720 more per 1,000 (650 more to 790 more) [a]
Complications	213 (2 RCTs)	⊕⊕⊕⊕ High	OR 9.19 (3.67 to 22.98)	0 per 1,000	190 more per 1,000 (110 more to 270 more) [a]
Progression to high-grade dysplasia/cancer	213 (2 RCTs)	⊕◯◯◯ Very low [b,c]	RR 0.17 (0.02 to 1.36)	269 per 1,000	223 fewer per 1,000 (263 fewer to 97 more)
Progression to high-grade dysplasia	64 (1 RCT)	⊕◯◯◯ Very low [c,d]	RR 0.35 (0.06 to 1.94)	136 per 1,000	89 fewer per 1,000 (128 fewer to 128 more)
Progression to cancer	200 (2 RCTs)	⊕◯◯◯ Very Low [e,f]	Risk difference =0.05 (-0.11, 0.00)	67 per 1,000	50 fewer per 1,000 (from 110 fewer to 0 more) [g]
Persistent low-grade dysplasia (at 3	77 (1 RCT)	⊕⊕⊕◯ Moderate [c]	RR 0.60 (0.38 to 0.94)	675 per 1,000	270 fewer per 1,000 (419 fewer to 41 fewer)

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with endoscopic surveillance	Risk difference with RFA
years; proxy for recurrence)					

a. Due to zero events in one arm, based on risk difference calculated as: 0.72 (95%CI 0.65, 0.79) for complete eradication of intestinal metaplasia; 0.19 (95% CI 0.11 to 0.27) for complications.

b. Downgraded by 2 increments because the confidence intervals across studies show minimal overlap and Heterogeneity, I^2>70%, unexplained by subgroup analysis.

c. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs; default MIDs for dichotomous outcomes: 0.8 and 1.25

d. Downgraded by 1 increment as the evidence was at high risk of bias

e. Downgraded by 1 increment for inconsistency due to zero events in both arms of one study but not the other study.

f. Downgraded by 2 increments for imprecision due to xero events in both arms of one study, calculated <80% using OIS (optimal information size) https://www.stat.ubc.ca/~rollin/stats/ssize/b2.html indicating very serious imprecision

g. Due to zero events in both arms of one study, based on the risk difference calculated as: -0.05 (-0.11, 0.00)

Table 4: Clinical evidence summary: RFA versus endoscopic surveillance (observational data; long-term follow-up)

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with endoscopic surveillance (obs.data; long-term follow-up)	Risk difference with RFA
Progression to high-grade dysplasia/cancer	136 (1 observational study)	⨁◯◯◯ Very low[a]	RR 0.04 (0.01 to 0.31)	338 per 1,000	325 fewer per 1,000 (335 fewer to 233 fewer)

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with endoscopic surveillance (obs.data; long-term follow-up)	Risk difference with RFA
Progression to cancer	136 (1 observational study)	⨁◯◯◯ Very low[a],[b]	RR 0.14 (0.02 to 1.13)	103 per 1,000	89 fewer per 1,000 (101 fewer to 13 more)

a. Downgraded by 1 increment as the evidence was at high risk of bias

b. Downgraded by 1 increment if the confidence interval crossed one MID; default MIDs for dichotomous outcomes: 0.8 and 1.25

See Appendix F for full GRADE tables.

1.1.7 Economic evidence

1.1.7.1 Included studies

Two health economic studies with the relevant comparison were included in this review.[2, 7] They are summarised in the health economic evidence profile below (Table 5) and the health economic evidence table in Appendix H.

1.1.7.2 Excluded studies

No relevant health economic studies were excluded due to assessment of limited applicability or methodological limitations.

See also the health economic study selection flow chart in Appendix G.

1.1.8 Summary of included economic evidence

Table 5: Health economic evidence profile: radiofrequency ablation versus endoscopic surveillance

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects	Cost effectiveness	Uncertainty
Esteban 2018[2] (Spain)	Partially applicable[(a)]	Potentially serious limitations[(b)]	• Probabilistic semi-Markov model based on data from literature • Cost-utility analysis (QALYs) • Population: People with LGD in BO • Comparators: 1.Annual endoscopic surveillance 2.Radiofrequency ablation (RFA) • Time horizon: 15 years	£7,682[(c)]	0.56 QALYs	£13,718 per QALY gained	One-way sensitivity analyses were conducted, some of the parameters most impacting the cost per QALY gained were: • the time horizon between 5-25 years; ICER: £12,998-£19,135 • the starting age between 55-75 years; ICER: £13,136-£19,154 • the cost of RFA procedures by 25% either way; ICER: £9,180- £18,242, • the utility of the cured state by 0.03 either way; ICER: £11,036-£17,954
Phoa 2017 [7] (The Netherlands)	Partially applicable[(d)]	Potentially serious limitations[(e)]	• Probabilistic model based on Within-RCT analysis (SURF/Phoa 2014 [8]) • Cost-effectiveness analysis (cost per patient progression to neoplasia prevented)	£5,974[(f)]	0.25 progression to neoplasia prevented	£23,896 per progression to neoplasia prevented 95% CI: £14,152 to £47,975	Bootstrapping was used to calculate confidence intervals. Sensitivity analysis was not conducted.

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects	Cost effectiveness	Uncertainty
			Population: Patients with BO containing LGD • Comparators: 1.Endoscopic surveillance 2.Radiofrequency ablation Time horizon: 3 years				

Abbreviations: 95% CI= 95% confidence interval; BO= Barrett's oesophagus; LGD= low-grade dysplasia; RCT= randomised controlled trial; SURF= surveillance versus radiofrequency ablation

(a) The Spanish NHS perspective may not be entirely relevant to the UK NHS. Future costs and outcomes are not discounted in line with the NICE reference case. QALYS are not captured using the EQ-5D measure.

(b) Resource use associated with treatment was based on expert clinical opinion. Drug costs associated with symptomatic control of Barrett's oesophagus do not seem to have been included. Study was funded by a pharmaceutical company.

(c) 2013 Euros converted to UK pounds[6]. Cost components incorporated: drug costs (radiotherapy and chemotherapy including administration costs, procedure costs, follow-up costs, treatment complication costs

(d) Management of BO in The Netherlands may not be reflective of current UK practice. Time horizon may not be sufficiently long to capture the consequences of interventions.

(e) A cost-utility analysis was not conducted. The reported ICER is very close to the lower 95% CI level and suggests that the data from the probabilistic analysis is skewed.

(f) 2012 US dollars converted to UK pounds[6]. Cost components incorporated: Endoscopic therapy after neoplastic progression, surgical treatment of neoplastic progression, medication after neoplastic progression, treatment of adverse events after neoplastic progression

1.1.9 Economic model

This area was not prioritised for new cost-effectiveness analysis.

1.1.10 Unit costs

Relevant unit costs are provided below to aid consideration of cost effectiveness.

Table 6: Unit cost for therapeutic endoscopic procedures in adults

Resource	Unit costs	Source
FE20Z Therapeutic Endoscopic Upper Gastrointestinal Tract Procedures, 19 years and over,	£993	NHS Reference Costs 2019/20{NHS England, #1132}

1.1.11 Evidence statements

Economic

- One cost utility analysis reported that radiofrequency ablation was cost effective compared to annual endoscopic surveillance (ICER: £13,718). This study was graded as partially applicable with potentially serious limitations.
- One cost-effectiveness analysis compared radiofrequency ablation to endoscopic surveillance and reported that the cost per progression to neoplasia prevented was £23,896. This study was graded as partially applicable with potentially serious limitations.

1.1.12 The committee's discussion and interpretation of the evidence

1.1.12.1. The outcomes that matter most

The committee considered the outcomes of mortality (disease specific and all-cause mortality), health-related quality of life, complete regression of Barrett's dysplasia and Barrett's oesophagus, recurrence of dysplasia or neoplasia, need for retreatment, complications of treatment (such as bleeding, perforation, stricture, pain), rate of hospitalisation, progress to higher grade dysplasia and cancer and conversion to non-endoscopic procedure after treatment. For purposes of decision making, all outcomes were considered equally important and were therefore rated as critical. No evidence was identified for the outcomes of health-related quality of life, need for treatment, rate of hospitalisation and conversion to non-endoscopic procedure.

1.1.12.2 The quality of the evidence

Two RCT's compared radiofrequency ablation (RFA) to endoscopic surveillance and one RCT to a sham endoscopic procedure. The components of endoscopic surveillance and sham endoscopic procedure were the same, and where the same outcomes were being reported across studies results from the three RCTs were pooled together in meta-analysis. The quality of the evidence varied across outcomes ranging from very low to high. The quality of the evidence was high for complete eradication of dysplasiaand complications outcomes. The quality of the evidence for the outcome persistent low-grade dysplasia was moderate as it was downgraded for imprecision in the effect estimate. The quality of the evidence for the outcome progression to cancer was low because it was downgraded for imprecision and inconsistency (due to zero events in both arms of one of the two studies pooled together in the meta-analysis) and low for the outcome of complete eradication of intestinal metaplasia downgraded for very serious inconsistency unexplained by sub-group analysis. The quality of evidence for progression to high-grade dysplasia/cancer and progression to high-grade dysplasia outcomes was very low. The former was downgraded for inconsistency (due to heterogeneity in the two studies pooled together in the meta-analysis), the latter for risk of bias (due to baseline differences in the use of aspirin and NSAIDS). Both

outcomes were downgraded for imprecision in the effect estimates resulting in a very low-quality rating.

There was evidence from one observational study comparing RFA with endoscopic surveillance. The quality of evidence for outcomes of progression to high-grade dysplasia/cancer, and progression to cancer was very low as it was downgraded for risk of bias (due to potential selection bias), the latter was also downgraded for imprecision in the effect estimate.

1.1.12.3 Benefits and harms

Clinical evidence from three RCTs and one observational study showed a clinically important benefit of RFA compared to endoscopic surveillance across all outcomes examined, except for complications. RCT evidence showed a clinically important benefit of RFA over endoscopic surveillance for complete eradication of dysplasia and complete eradication of intestinal metaplasia.

Evidence from 3 RCTs showed a clinical benefit of RFA in terms of progression to high-grade dysplasia/cancer and for the separately reported outcomes progression to high-grade dysplasia and progression to cancer, although the committee noted evidence for the outcomes had been downgraded by two increments for very serious imprecision, based on the confidence intervals around of effect estimates. Although when drafting the protocol, the committee rated all outcomes as equally important, they noted the outcomes of progression to high-grade dysplasia and progression to cancer to be very important and more weight should be placed on the results of these outcomes. Therefore, they agreed it was appropriate to lower the default threshold used to assess clinical importance from 100 per 1,000 people treated to 50 per 1,000 people treated. For the outcomes of progression to high-grade dysplasia or cancer to be considered clinically important, an absolute risk difference of 50 fewer/more cases per 1,000 treated with the intervention compared to the control group should be present. Evidence from one observational study also showed a clinical benefit of RFA over surveillance for the outcome's progression to high-grade dysplasia/cancer and progression to cancer. The committee noted there was imprecision in the effect estimates of these outcomes across the RCT and observational evidence, slightly lowering confidence in the results, but this was overcome by the benefit of RFA over surveillance for progression to high-grade dysplasia and cancer being supported by three separate RCTs and one observational study.

In contrast, two RCTs showed a clinical benefit of endoscopic surveillance over RFA for the complication's outcome. The committee noted based on their clinical experience, RFA can result in some cases of minor bleeding, a stricture rate of approximately 5% which can easily be resolved and would infrequently result in more severe bleeding.

The committee agreed the evidence strongly supported RFA as protection against progression to high-grade dysplasia and cancer. Overall, they agreed that the benefit of protecting against progression to high-grade dysplasia and cancer outweighed the potential small risk of complications involved, especially as these are not likely to be severe. The committee agreed based on the evidence identified it was appropriate to make a recommendation supporting the use of RFA for people with low-grade oesophageal dysplasia. Based on clinical experience, the committee agreed that in order for RFA to be offered, the diagnosis of low-grade dysplasia should be first confirmed by two gastrointestinal pathologists. It was emphasised this reflects current practice as RFA is conducted in specialist centres, by highly experienced pathologists who would not consider RFA unless there is evidence for low-grade dysplasia from biopsies obtained from 2 separate endoscopiesy

The committee noted that only people with low-grade dysplasia were included in the studies and no evidence had been identified for people with indefinite dysplasia. They acknowledged that the efficacy of RFA is likely to be similar, but the benefit of treatment for people with

indefinite dysplasia may be much lower as the risk of progression to HGD/cancer is lower than for people with confirmed low-grade dysplasia. They emphasised evidence was not available to support this conclusion. Based on their clinical experience, the committee agreed that endoscopic surveillance at 6 monthly intervals was appropriate for people with indefinite dysplasia to enable the detection of progression to low-grade dysplasia. The committee believed this to be appropriate because in their clinical experience the risk of progression is approximately 3-5 times higher in people with indefinite dysplasia compared to people with non-dysplastic Barrett's oesophagus. Based on experience, the committee also noted that indefinite dysplasia is often associated with excessive inflammation of the oesophagus. Thus, they agreed that people with a diagnosis of indefinite dysplasia should also be manged by optimising the dosages of acid-suppressant medication.

The committee emphasised that in current practice low-grade dysplasia is managed with RFA and that the lack of evidence to support the use of other ablation modalities for treating low-grade dysplasia, such as cryotherapy or EMR, was not unexpected. Cryotherapy is a more recent treatment, and less research has been completed. Endoscopic resection treatment would not be usual in this population.

The committee discussed the psychological impact of having Barrett's oesophagus without receiving any intervention. They agreed that although no data for quality-of-life (QoL) had been identified, in their experience QoL of people with Barrett's oesophagus is likely to be worse without treatment. Decisions on treatment would be made in discussion with individual patients.

1.1.12.4 Cost effectiveness and resource use

Endoscopic treatment is a more costly and risky procedure than endoscopic surveillance. However, it is also associated with an improved quality of life. The frequency of surveillance after an endoscopic treatment is expected to reduce, so there is the potential for future cost savings.

Two economic evaluations were identified for this review.

One cost utility analysis took a Spanish NHS perspective comparing radiofrequency ablation (RFA) to annual endoscopic surveillance in people with low-grade dysplasia in Barrett's oesophagus. The model time horizon was 15 years. Future costs and health outcomes were discounted at 3% each year, which does not align with the NICE reference case. Costs were taken from national databases. Resource use associated with treatment were based on expert clinical opinion. QALYs were captured using a utility scale ranging from 1 to 0, with 1 representing perfect health and 0 representing death. The study was funded by a device manufacturing company.

The study reported that RFA was cost effective compared to annual endoscopic surveillance, with a cost per QALY gained of £13,718.

The other economic evaluation took a Dutch perspective. The population was patients with Barrett's oesophagus containing low-grade dysplasia. The study was based on the surveillance versus radiofrequency (SURF) trial with a follow-up period of three years. A cost effectiveness analysis was conducted where the health outcome was cost per event of progression to neoplasia prevented. Costs were evaluated from the perspective of the hospital provider, which is based in a national health service. Resource use was based on data from the SURF trial. A discount rate of 3% was applied to all costs, which is not exactly in line with the current NICE reference case. The analysis was funded by a device manufacturing company.

The committee noted that since quality of life data was not captured during the trial, it was not feasible to conduct a cost-utility analysis. It is difficult to decide on an acceptable threshold at which the cost per progression averted would represent value for money.

Furthermore, they noted that the time horizon of 3 years was far too short to adequately capture progression to neoplasia.

The committee discussed the clinical and economic evidence. A cost-utility analysis showed that RFA was cost-effective versus endoscopic surveillance while the clinical evidence demonstrated a clear clinical benefit with endoscopic ablation therapies over endoscopic surveillance. The committee agreed that a time horizon of 15 years was sufficiently long to capture the costs and effects. They also agreed that a cost per QALY gained below the threshold of £20,000 per QALY gained enable a decision to be made. The committee therefore decided to offer radiofrequency ablation to individuals with low-grade dysplasia confirmed by expert pathologists and by two endoscopies. This recommendation is not expected to have any significant impact on NHS resource use since it corresponds to current practice.

In the absence of any evidence in people with indefinite dysplasia, the cost effectiveness of endoscopic treatment in this group is uncertain. The committee were unable to make any recommendation for this group and therefore issued a research recommendation.

1.1.13 Recommendations supported by this evidence review

This evidence review supports recommendations, 1.5.3, 1.5.4 and the research recommendation on endoscopic treatments alone and in combination.

1.1.14 References

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Appendices

Appendix A – Review protocols

Review protocol for endoscopic treatment in Barrett's oesophagus (low grade dysplasia or indefinite dysplasia)

ID	Field	Content
0.	PROSPERO registration number	
1.	Review title	The clinical and cost effectiveness of different endoscopic treatments for adults with Barrett's Oesophagus (low grade dysplasia or indefinite dysplasia)
2.	Review question	For adults with Barrett's Oesophagus with low grade or indefinite dysplasia, what is the clinical and cost effectiveness of endoscopic treatments?
3.	Objective	To assess the efficacy and cost effectiveness of different endoscopic treatments, in adults with Barrett's Oesophagus and low grade dysplasia
4.	Searches	The following databases (from inception) will be searched: • Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews (CDSR) • Embase • MEDLINE • Epistemonikus Searches will be restricted by: • English language studies • Human studies

		• Letters and comments are excluded Other searches: • Inclusion lists of systematic reviews will be checked by the reviewers The searches may be re-run 6 weeks before the final committee meeting and further studies retrieved for inclusion if relevant. The full search strategies will be published in the final review. Medline search strategy to be quality assured using the PRESS evidence-based checklist (see methods chapter for full details).
5.	Condition or domain being studied	Barrett's Oesophagus
6.	Population	Inclusion: Adults, 18 years and over, with Barrett's oesophagus and dysplasia (low grade) or indefinite for dysplasia Exclusion: Non-dysplastic Barrett's oesophagus stage 1 adenocarcinoma

7.	Intervention	• Endoscopic treatment alone
		  ○ Endoscopic ablation (RFA, APC, Cryotherapy)
		  ○ Endoscopic resection (EMR, ESD)

		• Endoscopic treatment in combination ○ Endoscopic ablation & endoscopic resection
8.	Comparator	• Different endoscopic modalities (e.g. RFA vs Cryotherapy, RFA vs APC) • Endoscopic surveillance
9.	Types of study to be included	• RCT • If no RCT data is available, non-randomised studies if there is an active comparator within the study • Systematic review of RCT's Published NMAs and IPDs will be considered for inclusion.
10.	Other exclusion criteria	Non-English language studies. Non comparative cohort studies Before and after studies Conference abstracts will be excluded as it is expected there will be sufficient full text published studies available.
11.	Context	The treatment of adults with Barrett's Oesophagus can be performed through endoscopic treatment alone or in combination. This review aims to assess whether endoscopic treatment is more clinically and cost effective alone or in combination with other treatments
12.	Primary outcomes (critical outcomes)	All outcomes are considered equally important for decision making and therefore have all been rated as critical: • Mortality (disease specific mortality and all cause mortality) • Health related quality of life • Recurrence of dysplasia or neoplasia • Need for retreatment • Complications of treatment (bleeding, perforation, stricture, pain)

		• Rate of hospitalization • Progression to higher grade dysplasia and cancer • Conversion to non-endoscopic procedure Minimum follow up period of 1 year but to include longest follow up period available.
14.	Data extraction (selection and coding)	All references identified by the searches and from other sources will be uploaded into EPPI reviewer and de-duplicated. This review will make use of the priority screening functionality within the EPPI-reviewer software. 10% of the abstracts will be reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer. The full text of potentially eligible studies will be retrieved and will be assessed in line with the criteria outlined above. A standardised form will be used to extract data from studies (see Developing NICE guidelines: the manual section 6.4). 10% of all evidence reviews are quality assured by a senior research fellow. This includes checking: • papers were included /excluded appropriately • a sample of the data extractions • correct methods are used to synthesise data • a sample of the risk of bias assessments Disagreements between the review authors over the risk of bias in particular studies will be resolved by discussion, with involvement of a third review author where necessary. Study investigators may be contacted for missing data where time and resources allow.
15.	Risk of bias (quality) assessment	Risk of bias will be assessed using the appropriate checklist as described in Developing NICE guidelines: the manual.

		For Intervention reviews the following checklist will be used according to study design being assessed: Systematic reviews: Risk of Bias in Systematic Reviews (ROBIS) Randomised Controlled Trial: Cochrane RoB (2.0) Nonrandomised study, including cohort studies: Cochrane ROBINS-I Case control study: CASP case control checklist
16.	Strategy for data synthesis	Pairwise meta-analyses will be performed using Cochrane Review Manager (RevMan5). Fixed-effects (Mantel-Haenszel) techniques will be used to calculate risk ratios for the binary outcomes where possible. Continuous outcomes will be analysed using an inverse variance method for pooling weighted mean differences. Heterogeneity between the studies in effect measures will be assessed using the I^2 statistic and visually inspected. An I^2 value greater than 50% will be considered indicative of substantial heterogeneity. Sensitivity analyses will be conducted based on pre-specified subgroups using stratified meta-analysis to explore the heterogeneity in effect estimates. If this does not explain the heterogeneity, the results will be presented pooled using random-effects. GRADEpro will be used to assess the quality of evidence for each outcome, taking into account individual study quality and the meta-analysis results. The 4 main quality elements (risk of bias, indirectness, inconsistency and imprecision) will be appraised for each outcome. Publication bias is tested for when there are more than 5 studies for an outcome. The risk of bias across all available evidence was evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group http://www.gradeworkinggroup.org/ Where meta-analysis is not possible, data will be presented, and quality assessed individually per outcome.

		If sufficient data is available, WinBUGS will be used for network meta-analysis, if possible, given the data identified.		
17.	Analysis of sub-groups	Stratification: Low-grade dysplasia vs indefinite for dysplasia Subgrouping: If serious or very serious heterogeneity (I2>50%) is present, sub-grouping will occur according to the following strategies: None		
18.	Type and method of review	☒	Intervention	
		☐	Diagnostic	
		☐	Prognostic	
		☐	Qualitative	
		☐	Epidemiologic	
		☐	Service Delivery	
		☐	Other (please specify)	
19.	Language	English		
20.	Country	England		
21.	Anticipated or actual start date			
22.	Anticipated completion date			
23.		Review stage	Started	Completed

	Stage of review at time of this submission	Preliminary searches	☐	☐
		Piloting of the study selection process	☐	☐
		Formal screening of search results against eligibility criteria	☐	☐
		Data extraction	☐	☐
		Risk of bias (quality) assessment	☐	☐
		Data analysis	☐	☐
24.	Named contact	5a. Named contact National Guideline Centre 5b Named contact e-mail @nice.org.uk 5e Organisational affiliation of the review National Institute for Health and Care Excellence (NICE) and National Guideline Centre		
25.	Review team members	From the National Guideline Centre: Norma O Flynn Gill Ritchie Amy Crisp		

		Lina Gulhane Muksitur Rahman Stephen Deed Melina Vasileiou Maheen Qureshi
26.	Funding sources/sponsor	This systematic review is being completed by the National Guideline Centre which receives funding from NICE.
27.	Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.
28.	Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: [NICE guideline webpage].
29.	Other registration details	
30.	Reference/URL for published protocol	
31.	Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: • notifying registered stakeholders of publication • publicising the guideline through NICE's newsletter and alerts

		• issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.	
32.	Keywords	Barrett's Oesophagus	
33.	Details of existing review of same topic by same authors		
34.	Current review status	☒	Ongoing
		☐	Completed but not published
		☐	Completed and published
		☐	Completed, published and being updated
		☐	Discontinued
35..	Additional information		
36.	Details of final publication	www.nice.org.uk	

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2

3

1 Health economic review protocol

Review question	All questions – health economic evidence
Objectives	To identify health economic studies relevant to any of the review questions.
Search criteria	• Populations, interventions and comparators must be as specified in the clinical review protocol above. • Studies must be of a relevant health economic study design (cost–utility analysis, cost-effectiveness analysis, cost–benefit analysis, cost–consequences analysis, comparative cost analysis). Studies must not be a letter, editorial or commentary, or a review of health economic evaluations. (Recent reviews will be ordered although not reviewed. The bibliographies will be checked for relevant studies, which will then be ordered.) • Unpublished reports will not be considered unless submitted as part of a call for evidence. • Studies must be in English.
Search strategy	A health economic study search will be undertaken for all years using population-specific terms and a health economic study filter – see appendix B below.
Review strategy	Studies not meeting any of the search criteria above will be excluded. Studies published before 2006, abstract-only studies and studies from non-OECD countries or the USA will also be excluded. Studies published in 2006 or later, that were included in the previous guidelines, will be reassessed for inclusion and may be included or selectively excluded based on their relevance to the questions covered in this update and whether more applicable evidence is also identified. Each remaining study will be assessed for applicability and methodological limitations using the NICE economic evaluation checklist which can be found in appendix H of Developing NICE guidelines: the manual (2014).[5] **Inclusion and exclusion criteria** • If a study is rated as both 'Directly applicable' and with 'Minor limitations' then it will be included in the guideline. A health economic evidence table will be completed and it will be included in the health economic evidence profile. • If a study is rated as either 'Not applicable' or with 'Very serious limitations' then it will usually be excluded from the guideline. If it is excluded then a health economic evidence table will not be completed and it will not be included in the health economic evidence profile. • If a study is rated as 'Partially applicable', with 'Potentially serious limitations' or both then there is discretion over whether it should be included.

Where there is discretion

The health economist will make a decision based on the relative applicability and quality of the available evidence for that question, in discussion with the guideline committee if required. The ultimate aim is to include health economic studies that are helpful for decision-making in the context of the guideline and the current NHS setting. If several studies are considered of sufficiently high applicability and methodological quality that they could all be included, then the health economist, in discussion with the committee if required, may decide to include only the most applicable studies and to selectively exclude the remaining studies. All studies excluded on the basis of applicability or methodological limitations will be listed with explanation in the excluded health economic studies appendix below.

The health economist will be guided by the following hierarchies.

Setting:

- UK NHS (most applicable).
- OECD countries with predominantly public health insurance systems (for example, France, Germany, Sweden).
- OECD countries with predominantly private health insurance systems (for example, Switzerland).
- Studies set in non-OECD countries or in the USA will be excluded before being assessed for applicability and methodological limitations.

Health economic study type:

- Cost–utility analysis (most applicable).
- Other type of full economic evaluation (cost–benefit analysis, cost-effectiveness analysis, cost–consequences analysis).
- Comparative cost analysis.
- Non-comparative cost analyses including cost-of-illness studies will be excluded before being assessed for applicability and methodological limitations.

Year of analysis:

- The more recent the study, the more applicable it will be.

Studies published in 2006 or later (including any such studies included in the previous guidelines) but that depend on unit costs and resource data entirely or predominantly from before 2006 will be rated as ‘Not applicable’.

- Studies published before 2006 (including any such studies included in the previous guidelines) will be excluded before being assessed for applicability and methodological limitations.

Quality and relevance of effectiveness data used in the health economic analysis:

- The more closely the clinical effectiveness data used in the health economic analysis match with the outcomes of the studies included in the clinical review the more useful the analysis will be for decision-making in the guideline.

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Appendix B – Literature search strategies

The literature searches for this review are detailed below and complied with the methodology outlined in Developing NICE guidelines: the manual.[5]

For more information, please see the Methodology review published as part of the accompanying documents for this guideline.

B.1 Clinical search literature search strategy

Searches were constructed using a PICO framework where population (P) terms were combined with Intervention (I) and in some cases Comparison (C) terms. Outcomes (O) are rarely used in search strategies as these concepts may not be indexed or described in the title or abstract and are therefore difficult to retrieve. Search filters were applied to the search where appropriate.

Table 4: Database parameters, filters and limits applied

Database	Dates searched	Search filter used
Medline (OVID)	1946 – 26 April 2022	Randomised controlled trials Systematic review studies Exclusions (animal studies, letters, comments, editorials, case studies/reports) English language
Embase (OVID)	1974 – 26 April 2022	Randomised controlled trials Systematic review studies Exclusions (animal studies, letters, comments, editorials, case studies/reports, conference abstracts) English language
The Cochrane Library (Wiley)	Cochrane Database of Systematic Reviews to Issue 4 of 12, April 2022 Cochrane Central Register of Controlled Trials to Issue 4 of 12, April 2022	Exclusions (clinical trials, conference abstracts)
Epistemonikos (The Epistemonikos Foundation)	Inception to 26 April 2022	Systematic review Exclusions (Cochrane reviews)

Medline (Ovid) search terms

1.	exp Barrett esophagus/
2.	barrett*.ti,ab.
3.	(speciali* adj3 (epithel* or oesophag* or esophag* or mucos*)).ti,ab.

4.	(column* adj3 (epithel* or oesophag* or esophag* or mucos* or lined or lining or metaplas*)).ti,ab.
5.	(intestin* adj2 metaplas*).ti,ab.
6.	or/1-5
7.	Precancerous conditions/
8.	(dysplasia* or precancer* or pre-cancer* or premalign* or pre-malign* or preneoplast* or pre-neoplastic* or preneoplasia* or pre-neoplasia* or neoplasm* or cancer* or carcinoma* or adenocarcinom* or adenoma* or tumour* or tumor* or malignan* or metaplas* or metast* or nodul* or node* or lump* or lymphoma*).ti,ab.
9.	7 or 8
10.	exp Esophagus/
11.	Esophageal Mucosa/
12.	(oesophag* or esophag* or intramucosal* or intra-mucosal*).ti,ab.
13.	or/10-12
14.	9 and 13
15.	exp Esophageal Neoplasms/
16.	6 or 14 or 15
17.	letter/
18.	editorial/
19.	news/
20.	exp historical article/
21.	Anecdotes as Topic/
22.	comment/
23.	case report/
24.	(letter or comment*).ti.
25.	or/17-24
26.	randomized controlled trial/ or random*.ti,ab.
27.	25 not 26
28.	animals/ not humans/
29.	exp Animals, Laboratory/
30.	exp Animal Experimentation/
31.	exp Models, Animal/
32.	exp Rodentia/
33.	(rat or rats or mouse or mice or rodent*).ti.
34.	or/27-33
35.	16 not 34
36.	limit 35 to english language
37.	Endoscopy/
38.	(Endoscop* adj2 (treatment* or therap* or eradicat* or remov*)).ti,ab,kf.
39.	endotherap*.ti,ab,kf.
40.	EET.ti,ab.
41.	Endoscopic Mucosal Resection/
42.	(Endoscop* adj3 (resect* or dissect*)).ti,ab,kf.
43.	EndoRotor.ti,ab,kf.
44.	(EMR or ESD).ti,ab.
45.	Ablation Techniques/
46.	exp Light Coagulation/

47.	exp Electrocoagulation/
48.	exp Radiofrequency Ablation/
49.	Photochemotherapy/
50.	Laser Therapy/
51.	Cryotherapy/
52.	Cryosurgery/
53.	ablati*.ti,ab,kf.
54.	(laser adj2 (treatment* or therap*)).ti,ab,kf.
55.	(photodynamic or photo dynamic or thermocoagulation or thermo coagulation or photocoagulation or photo coagulation or electrocoagulation or electro coagulation or photochemotherap* or photo chemotherap* or electrocauter* or thermoablati*).ti,ab,kf.
56.	(cryotherap* or cryosurg* or cryoablati* or cryoballoon* or cryospray*).ti,ab,kf.
57.	(argon plasma or Hybrid-APC or HybridAPC).ti,ab,kf.
58.	Barrx.ti,ab,kf.
59.	(RFA or APC or HPAC or CBA or PDT or MPEC).ti,ab.
60.	or/37-59
61.	36 and 60
62.	Meta-Analysis/
63.	Meta-Analysis as Topic/
64.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
65.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
66.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
67.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
68.	(search* adj4 literature).ab.
69.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
70.	cochrane.jw.
71.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
72.	or/62-71
73.	randomized controlled trial.pt.
74.	controlled clinical trial.pt.
75.	randomi#ed.ab.
76.	placebo.ab.
77.	randomly.ab.
78.	clinical trials as topic.sh.
79.	trial.ti.
80.	or/73-79
81.	61 and (72 or 80)

Embase (Ovid) search terms

1.	exp Barrett esophagus/
2.	barrett*.ti,ab.
3.	(speciali* adj3 (epithel* or oesophag* or esophag* or mucos*)).ti,ab.
4.	(column* adj3 (epithel* or oesophag* or esophag* or mucos* or lined or lining or metaplas*)).ti,ab.
5.	(intestin* adj2 metaplas*).ti,ab.

6.	or/1-5
7.	Precancer/
8.	(dysplasia* or precancer* or pre-cancer* or premalign* or pre-malign* or preneoplast* or pre-neoplastic* or preneoplasia* or pre-neoplasia* or neoplasm* or cancer* or carcinoma* or adenocarcinom* or adenoma* or tumour* or tumor* or malignan* or metaplas* or metast* or nodul* or node* or lump* or lymphoma*).ti,ab.
9.	7 or 8
10.	exp Esophagus/
11.	Esophagus Mucosa/
12.	(oesophag* or esophag*).ti,ab.
13.	or/10-12
14.	9 and 13
15.	exp Esophagus Tumor/
16.	6 or 14 or 15
17.	letter.pt. or letter/
18.	note.pt.
19.	editorial.pt.
20.	case report/ or case study/
21.	(letter or comment*).ti.
22.	(conference abstract or conference paper).pt.
23.	or/17-22
24.	randomized controlled trial/ or random*.ti,ab.
25.	23 not 24
26.	animal/ not human/
27.	nonhuman/
28.	exp Animal Experiment/
29.	exp Experimental Animal/
30.	animal model/
31.	exp Rodent/
32.	(rat or rats or mouse or mice or rodent*).ti.
33.	or/25-32
34.	16 not 33
35.	limit 34 to english language
36.	*Endoscopy/
37.	(Endoscop* adj2 (treatment* or therap* or eradicat* or remov*)).ti,ab,kf.
38.	endotherap*.ti,ab,kf.
39.	EET.ti,ab.
40.	Endoscopic Mucosal Resection/
41.	(Endoscop* adj3 (resect* or dissect*)).ti,ab,kf.
42.	EndoRotor.ti,ab,kf.
43.	(EMR or ESD).ti,ab.
44.	exp ablation therapy/
45.	laser coagulation/
46.	electrocoagulation/
47.	argon plasma coagulation/
48.	exp photochemotherapy/
49.	Laser Therapy/

50.	Cryotherapy/
51.	Cryosurgery/
52.	cryoablation/
53.	ablati*.ti,ab,kf.
54.	(laser adj2 (treatment* or therap*)).ti,ab,kf.
55.	(photodynamic or photo dynamic or thermocoagulation or thermo coagulation or photocoagulation or photo coagulation or electrocoagulation or electro coagulation or photochemotherap* or photo chemotherap* or electrocauter* or thermoablati*).ti,ab,kf.
56.	(cryotherap* or cryosurg* or cryoablati* or cryoballoon* or cryospray*).ti,ab,kf.
57.	(argon plasma or Hybrid-APC or HybridAPC).ti,ab,kf.
58.	Barrx.ti,ab,kf.
59.	(RFA or APC or HPAC or CBA or PDT or MPEC).ti,ab.
60.	or/36-59
61.	35 and 60
62.	random*.ti,ab.
63.	factorial*.ti,ab.
64.	(crossover* or cross over*).ti,ab.
65.	((doubl* or singl*) adj blind*).ti,ab.
66.	(assign* or allocat* or volunteer* or placebo*).ti,ab.
67.	crossover procedure/
68.	single blind procedure/
69.	randomized controlled trial/
70.	double blind procedure/
71.	or/62-70
72.	Systematic Review/
73.	Meta-Analysis/
74.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
75.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
76.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
77.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
78.	(search* adj4 literature).ab.
79.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
80.	cochrane.jw.
81.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
82.	or/72-81
83.	61 and (71 or 82)

Cochrane Library (Wiley) search terms

#1.	MeSH descriptor: [Barrett Esophagus] explode all trees
#2.	barrett*:ti,ab
#3.	speciali* near/3 (epithel* or oesophag* or esophag* or mucos*):ti,ab
#4.	column* near/3 (epithel* or oesophag* or esophag* or mucos* or lined or lining or metaplas*):ti,ab
#5.	(intestin* near/2 metaplas*):ti,ab
#6.	(or #1-#5)

#7.	MeSH descriptor: [Precancerous Conditions] explode all trees
#8.	(dysplasia* or precancer* or pre-cancer* or premalign* or pre-malign* or preneoplast* or pre-neoplastic* or preneoplasia* or pre-neoplasia* or neoplasm* or cancer* or carcinoma* or adenocarcinom* or adenoma* or tumour* or tumor* or malignan* or metaplas* or metast* or nodul* or node* or lump* or lymphoma*):ti,ab
#9.	#7 or #8
#10.	MeSH descriptor: [Esophagus] explode all trees
#11.	MeSH descriptor: [Esophageal Mucosa] explode all trees
#12.	(oesophag* or esophag* or intramucosal* or intra-mucosal*):ti,ab
#13.	(or #10-#12)
#14.	#9 and #13
#15.	MeSH descriptor: [Esophageal Neoplasms] explode all trees
#16.	#6 or #14 or #15
#17.	MeSH descriptor: [Endoscopy] this term only
#18.	(Endoscop* near/2 (treatment* or therap* or eradicat* or remov*)):ti,ab,kw
#19.	endotherap*:ti,ab,kw
#20.	EET:ti,ab
#21.	MeSH descriptor: [Endoscopic Mucosal Resection] this term only
#22.	(Endoscop* near/3 (resect* or dissect*)):ti,ab,kw
#23.	EndoRotor:ti,ab,kw
#24.	(EMR or ESD):ti,ab
#25.	MeSH descriptor: [Ablation Techniques] this term only
#26.	MeSH descriptor: [Light Coagulation] explode all trees
#27.	MeSH descriptor: [Electrocoagulation] explode all trees
#28.	MeSH descriptor: [Radiofrequency Ablation] explode all trees
#29.	MeSH descriptor: [Photochemotherapy] this term only
#30.	MeSH descriptor: [Laser Therapy] this term only
#31.	MeSH descriptor: [Cryotherapy] this term only
#32.	MeSH descriptor: [Cryosurgery] this term only
#33.	ablati*:ti,ab,kw
#34.	(laser near/2 (treatment* or therap*)):ti,ab,kw
#35.	(photodynamic or photo dynamic or thermocoagulation or thermo coagulation or photocoagulation or photo coagulation or electrocoagulation or electro coagulation or photochemotherap* or photo chemotherap* or electrocauter* or thermoablati*):ti,ab,kw
#36.	(cryotherap* or cryosurg* or cryoablati* or cryoballoon* or cryospray*):ti,ab,kw
#37.	(argon plasma or Hybrid APC or HybridAPC):ti,ab,kw
#38.	Barrx:ti,ab,kw
#39.	(RFA or APC or HPAC or CBA or PDT or MPEC):ti,ab
#40.	(or #17-#39)
#41.	#16 and #40
#42.	conference:pt or (clinicaltrials or trialsearch):so
#43.	#41 not #42

Epistemonikos search terms

1.	(title:(Barrett* OR "oesophageal adenocarcinoma*" OR "esophageal adenocarcinoma*" OR "oesophageal cancer*" OR "esophageal cancer*" OR "oesophageal carcinoma*" OR "esophageal carcinoma*" OR "oesophageal metaplas*" OR "esophageal dysplas*" OR "column* epithel*" OR "intestin* metaplas*" OR "intestin* dysplas*") OR abstract:(Barrett* OR "oesophageal adenocarcinoma*" OR "esophageal

	adenocarcinoma*" OR "oesophageal cancer*" OR "esophageal cancer*" OR "oesophageal carcinoma*" OR "esophageal carcinoma*" OR "oesophageal metaplas*" OR "esophageal dysplas*" OR "column* epithel*" OR "intestin* metaplas*" OR "intestin* dysplas*")) AND (title:("endoscopic treatment*" OR "endoscopic therap*" OR "endoscopic eradicat*" OR "endoscopic remov*" OR endotherap* OR "endoscopic mucosal resection" OR "endoscopic submucosal dissection" OR EndoRotor OR ablati* OR "laser treatment*" OR "laser therap*" OR photodynamic OR "photo dynamic" OR thermocoagulation OR "thermo coagulation" OR photocoagulation OR "photo coagulation" OR electrocoagulation OR "electro coagulation" OR photochemotherap* OR "photo chemotherap*" OR electrocauter* OR thermoablati* OR cryotherap* OR cryosurg* OR cryoablati* OR cryoballoon* OR cryospray* OR "argon plasma" OR "Hybrid-APC" OR HybridAPC OR Barrx) OR abstract:("endoscopic treatment*" OR "endoscopic therap*" OR "endoscopic eradicat*" OR "endoscopic remov*" OR endotherap* OR "endoscopic mucosal resection" OR "endoscopic submucosal dissection" OR EndoRotor OR ablati* OR "laser treatment*" OR "laser therap*" OR photodynamic OR "photo dynamic" OR thermocoagulation OR "thermo coagulation" OR photocoagulation OR "photo coagulation" OR electrocoagulation OR "electro coagulation" OR photochemotherap* OR "photo chemotherap*" OR electrocauter* OR thermoablati* OR cryotherap* OR cryosurg* OR cryoablati* OR cryoballoon* OR cryospray* OR "argon plasma" OR "Hybrid-APC" OR HybridAPC OR Barrx)

B.2 Health Economics literature search strategy

Health economic evidence was identified by conducting searches using terms for a broad Barrett's Oesophagus population. The following databases were searched: NHS Economic Evaluation Database (NHS EED - this ceased to be updated after 31st March 2015), Health Technology Assessment database (HTA - this ceased to be updated from 31st March 2018) and The International Network of Agencies for Health Technology Assessment (INAHTA). Searches for recent evidence were run on Medline and Embase from 2014 onwards for health economics, and all years for quality-of-life studies.

Table 5: Database parameters, filters and limits applied

Database	Dates searched	Search filters and limits applied
Medline (OVID)	Health Economics 1 January 2014 – 29 April 2022	Health economics studies Quality of life studies Exclusions (animal studies, letters, comments, editorials, case studies/reports) English language
	Quality of Life 1946 – 29 April 2022	
Embase (OVID)	Health Economics 1 January 2014 – 29 April 2022	Health economics studies Quality of life studies Exclusions (animal studies, letters, comments, editorials, case studies/reports, conference abstracts) English language
	Quality of Life 1974 – 29 April 2022	

Database	Dates searched	Search filters and limits applied
NHS Economic Evaluation Database (NHS EED) (Centre for Research and Dissemination - CRD)	Inception –31st March 2015	
Health Technology Assessment Database (HTA) (Centre for Research and Dissemination – CRD)	Inception – 31st March 2018	
The International Network of Agencies for Health Technology Assessment (INAHTA)	Inception - 29 April 2022	English language

Medline (Ovid) search terms

1.	exp Barrett esophagus/
2.	barrett*.ti,ab.
3.	(speciali* adj3 (epithel* or oesophag* or esophag* or mucos*)).ti,ab.
4.	(column* adj3 (epithel* or oesophag* or esophag* or mucos* or lined or lining or metaplas*)).ti,ab.
5.	or/1-4
6.	Precancerous conditions/
7.	(dysplasia* or precancer* or pre-cancer* or premalign* or pre-malign* or preneoplast* or pre-neoplastic* or preneoplasia* or pre-neoplasia* or neoplasm* or cancer* or carcinoma* or adenocarcinom* or adenoma* or tumour* or tumor* or malignan* or metaplas* or metast* or nodul* or node* or lump* or lymphoma*).ti,ab.
8.	6 or 7
9.	exp Esophagus/
10.	Esophageal Mucosa/
11.	(oesophag* or esophag* or intramucosal* or intra-mucosal*).ti,ab.
12.	or/9-11
13.	8 and 12
14.	exp Esophageal Neoplasms/
15.	5 or 13 or 14
16.	letter/
17.	editorial/
18.	news/
19.	exp historical article/
20.	Anecdotes as Topic/
21.	comment/
22.	case report/
23.	(letter or comment*).ti.
24.	or/16-23

25.	randomized controlled trial/ or random*.ti,ab.
26.	24 not 25
27.	animals/ not humans/
28.	exp Animals, Laboratory/
29.	exp Animal Experimentation/
30.	exp Models, Animal/
31.	exp Rodentia/
32.	(rat or rats or mouse or mice or rodent*).ti.
33.	or/26-32
34.	15 not 33
35.	limit 34 to English language
36.	economics/
37.	value of life/
38.	exp "costs and cost analysis"/
39.	exp Economics, Hospital/
40.	exp Economics, medical/
41.	Economics, nursing/
42.	economics, pharmaceutical/
43.	exp "Fees and Charges"/
44.	exp budgets/
45.	budget*.ti,ab.
46.	cost*.ti.
47.	(economic* or pharmaco?economic*).ti.
48.	(price* or pricing*).ti,ab.
49.	(cost* adj2 (effectiv* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
50.	(financ* or fee or fees).ti,ab.
51.	(value adj2 (money or monetary)).ti,ab.
52.	or/36-51
53.	quality-adjusted life years/
54.	sickness impact profile/
55.	(quality adj2 (wellbeing or well being)).ti,ab.
56.	sickness impact profile.ti,ab.
57.	disability adjusted life.ti,ab.
58.	(qal* or qtime* or qwb* or daly*).ti,ab.
59.	(euroqol* or eq5d* or eq 5*).ti,ab.
60.	(qol* or hql* or hqol* or h qol* or hrqol* or hr qol*).ti,ab.
61.	(health utility* or utility score* or disutilit* or utility value*).ti,ab.
62.	(hui or hui1 or hui2 or hui3).ti,ab.
63.	(health* year* equivalent* or hye or hyes).ti,ab.
64.	discrete choice*.ti,ab.
65.	rosser.ti,ab.

66.	(willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab.
67.	(sf36* or sf 36* or short form 36* or shortform 36* or shortform36*).ti,ab.
68.	(sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab.
69.	(sf12* or sf 12* or short form 12* or shortform 12* or shortform12*).ti,ab.
70.	(sf8* or sf 8* or short form 8* or shortform 8* or shortform8*).ti,ab.
71.	(sf6* or sf 6* or short form 6* or shortform 6* or shortform6*).ti,ab.
72.	or/53-71
73.	35 and (52 or 72)

Embase (Ovid) search terms

1.	exp Barrett esophagus/
2.	barrett*.ti,ab.
3.	(speciali* adj3 (epithel* or oesophag* or esophag* or mucos*)).ti,ab.
4.	(column* adj3 (epithel* or oesophag* or esophag* or mucos* or lined or lining or metaplas*)).ti,ab.
5.	or/1-4
6.	Precancer/
7.	(dysplasia* or precancer* or pre-cancer* or premalign* or pre-malign* or preneoplast* or pre-neoplastic* or preneoplasia* or pre-neoplasia* or neoplasm* or cancer* or carcinoma* or adenocarcinom* or adenoma* or tumour* or tumor* or malignan* or metaplas* or metast* or nodul* or node* or lump* or lymphoma*).ti,ab.
8.	6 or 7
9.	exp Esophagus/
10.	Esophagus Mucosa/
11.	(oesophag* or esophag*).ti,ab.
12.	or/9-11
13.	8 and 12
14.	exp Esophagus Tumor/
15.	5 or 13 or 14
16.	letter.pt. or letter/
17.	note.pt.
18.	editorial.pt.
19.	case report/ or case study/
20.	(letter or comment*).ti.
21.	(conference abstract or conference paper).pt.
22.	or/16-21
23.	randomized controlled trial/ or random*.ti,ab.
24.	22 not 23
25.	animal/ not human/
26.	nonhuman/
27.	exp Animal Experiment/
28.	exp Experimental Animal/
29.	animal model/
30.	exp Rodent/
31.	(rat or rats or mouse or mice or rodent*).ti.
32.	or/24-31

33.	15 not 32
34.	limit 33 to English language
35.	health economics/
36.	exp economic evaluation/
37.	exp health care cost/
38.	exp fee/
39.	budget/
40.	funding/
41.	budget*.ti,ab.
42.	cost*.ti.
43.	(economic* or pharmaco?economic*).ti.
44.	(price* or pricing*).ti,ab.
45.	(cost* adj2 (effectiv* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
46.	(financ* or fee or fees).ti,ab.
47.	(value adj2 (money or monetary)).ti,ab.
48.	or/35-47
49.	quality-adjusted life years/
50.	"quality of life index"/
51.	short form 12/ or short form 20/ or short form 36/ or short form 8/
52.	sickness impact profile/
53.	(quality adj2 (wellbeing or well being)).ti,ab.
54.	sickness impact profile.ti,ab.
55.	disability adjusted life.ti,ab.
56.	(qal* or qtime* or qwb* or daly*).ti,ab.
57.	(euroqol* or eq5d* or eq 5*).ti,ab.
58.	(qol* or hql* or hqol* or h qol* or hrqol* or hr qol*).ti,ab.
59.	(health utility* or utility score* or disutilit* or utility value*).ti,ab.
60.	(hui or hui1 or hui2 or hui3).ti,ab.
61.	(health* year* equivalent* or hye or hyes).ti,ab.
62.	discrete choice*.ti,ab.
63.	rosser.ti,ab.
64.	(willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab.
65.	(sf36* or sf 36* or short form 36* or shortform 36* or shortform36*).ti,ab.
66.	(sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab.
67.	(sf12* or sf 12* or short form 12* or shortform 12* or shortform12*).ti,ab.
68.	(sf8* or sf 8* or short form 8* or shortform 8* or shortform8*).ti,ab.
69.	(sf6* or sf 6* or short form 6* or shortform 6* or shortform6*).ti,ab.
70.	or/49-69
71.	34 and (48 or 70)

NHS EED and HTA (CRD) search terms

#1.	MeSH DESCRIPTOR Barrett Esophagus EXPLODE ALL TREES
#2.	(barrett*)
#3.	(speciali*) AND (epithel* or oesophag* or esophag* or mucos*)

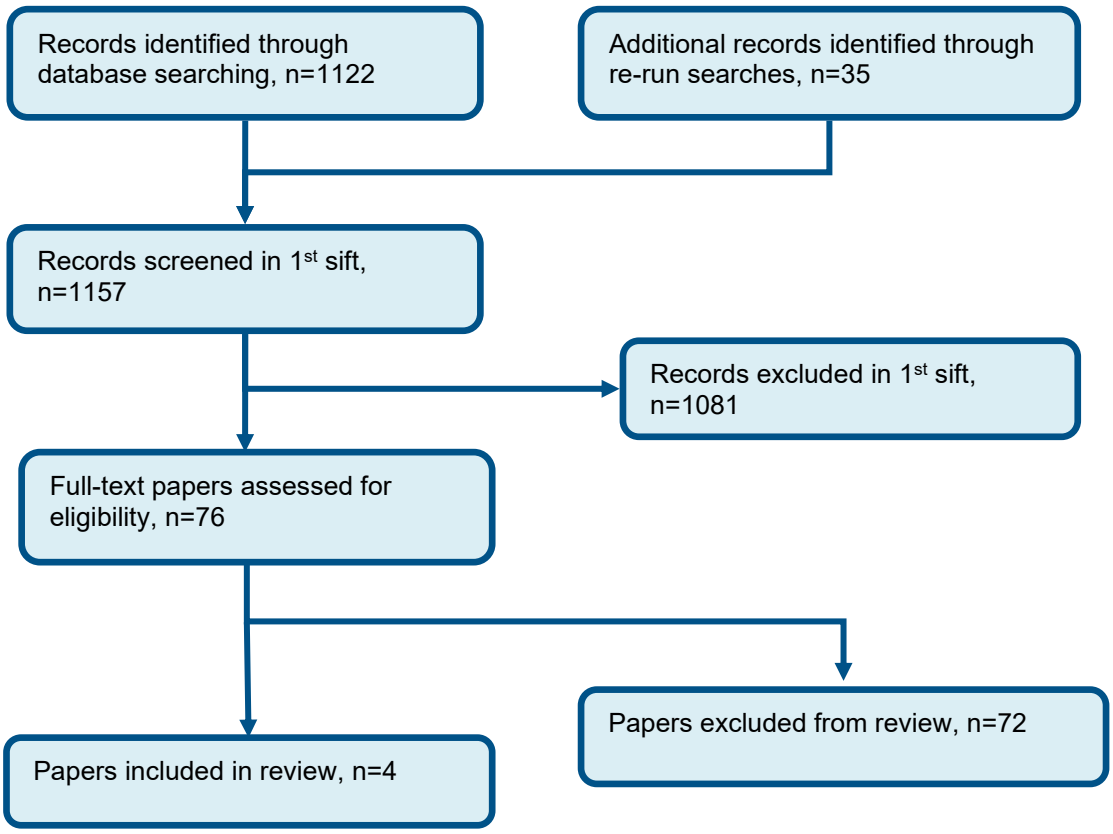
#4.	(column*) AND (epithel* or oesophag* or esophag* or mucos* or lined or lining or metaplas*)
#5.	#1 OR #2 OR #3 OR #4
#6.	MeSH DESCRIPTOR Precancerous Conditions EXPLODE ALL TREES
#7.	((dysplasia* or precancer* or pre-cancer* or premalign* or pre-malign* or preneoplast* or pre-neoplastic* or preneoplasia* or pre-neoplasia* or neoplasm* or cancer* or carcinoma* or adenocarcinom* or adenoma*or tumour* or tumor* or malignan* or metaplas* or metast* or nodul* or node* or lump* or lymphoma*))
#8.	#6 OR #7
#9.	MeSH DESCRIPTOR Esophagus EXPLODE ALL TREES
#10.	MeSH DESCRIPTOR Esophageal Mucosa EXPLODE ALL TREES
#11.	(oesophag* or esophag* or intramucosal* or intra-mucosal*)
#12.	#9 OR #10 OR #11
#13.	#8 AND #12
#14.	#5 OR #13
#15.	MeSH DESCRIPTOR Esophageal Neoplasms EXPLODE ALL TREES
#16.	#14 OR #15

INAHTA search terms

1.	("Barrett Esophagus"[mh]) OR (Barrett*) OR (Esophageal Neoplasms)[mh]

Appendix C – Effectiveness evidence study selection

Figure 1: Flow chart of clinical study selection for the review of: Endoscopic treatments (low grade dysplasia, indefinite dysplasia)



Appendix D – Effectiveness evidence

RCT evidence

Barret, 2021

Bibliographic Reference	Barret, M.; Pioche, M.; Terris, B.; Ponchon, T.; Cholet, F.; Zerbib, F.; Chabrun, E.; Le Rhun, M.; Coron, E.; Giovannini, M.; Caillol, F.; Laugier, R.; Jacques, J.; Legros, R.; Boustiere, C.; Rahmi, G.; Metivier-Cesbron, E.; Vanbiervliet, G.; Bauret, P.; Escourrou, J.; Branche, J.; Jilet, L.; Abdoul, H.; Kaddour, N.; Leblanc, S.; Bensoussan, M.; Prat, F.; Chaussade, S.; Endoscopic radiofrequency ablation or surveillance in patients with Barrett's oesophagus with confirmed low-grade dysplasia: a multicentre randomised trial; Gut; 2021; vol. 70 (no. 6); 1014-1022

Study details

Secondary publication of another included study- see primary study for details	Primary study
Other publications associated with this study included in review	None
Trial name / registration number	Trial registration number NCT01360541
Study type	Randomised controlled trial (RCT)
Study location	France
Study setting	French centres

Study dates	22 December 2010 - 17 December 2014
Sources of funding	This study was funded by the Programme Hospitalier de Recherche Clinique 2009 and the French Ministry of Health (PHRC 00-89). This work was led under scientific caution of the Société Française d'Endoscopie Digestive (French Digestive Endoscopy Society).
Inclusion criteria	• Patients aged 18–80 years were included if they had a histologically confirmed Barrett's oesophagus with at least 1 cm high circumferential extension and/or 3 cm high non-circumferential extension (ie, at least C1M1 or C0M3 according to the Prague classification16). • A confirmed diagnosis of low-grade dysplasia (LGD) in the past 5 months, no visible lesion and LGD as worst histology (no concomitant high-grade dysplasia (HGD) or early adenocarcinoma).
Exclusion criteria	Exclusion criteria were: • Presence of a Barrett's oesophagus with a C or M>12 cm length • Presence of a visible lesion • Contraindication to proton pump inhibitor (PPI) or anaesthesia • History of oesophageal or gastric surgical resection, oesophageal radiation therapy, oesophageal ablation therapy, oesophageal stricture, severe (Los Angeles grade C or D) peptic oesophagitis, oesophageal varices, systemic sclerosi • Estimated life expectancy <2 years
Recruitment / selection of participants	Not stated
Intervention(s)	• Patients were randomly assigned to Ablation group. • The first radio frewuency ablation (RFA) procedure was performed within 3 months after randomisation, using the BarrX system (Medtronic, Minnesota, USA) under conscious sedation by propofol or general anaesthesia with endotracheal intubation, according to the anaesthesiologist's choice, with one to two nights' hospital admission. • The balloon-based, circumferential and the focal, endoscope attached RFA electrodes (HALO360 and HALO90, respectively, Medtronic) were used depending on the circumferential extension of the BO. • Double-dose PPIs were prescribed during the month following the treatment, and then PPIs were resumed at the usual dose.

	• After complete eradication of the BO or reaching the maximal number of four RFA sessions, a follow-up OGD with biopsies was scheduled at 12, 24 and 36 months after randomisation.
Comparator	Patients were randomly assigned to Endoscopic surveillance group. In the surveillance group, a second oesophagogastroduodenoscopy (OGD) was scheduled 12, 24 and 36 months after the randomisation, with the same modalities as the initial OGD.
Number of participants	N=82
Duration of follow-up	3 years
Additional comments	• The analysis of primary outcome 'prevalence of Low grade dysplasia (LGD) 3 years after randomisation' required to introduce a modified intention-to-treat (mITT) population for the main outcome measurement, since all patients with neoplastic progression beyond LGD (ie, HGD and EAC) dropped out of the study and had to be excluded from the calculation of potential patients harbouring LGD. Thus, the mITT population was made of the randomised patient population, excluding patients with neoplastic progression during the study • Considering the possible benefit of Radiofrequency ablation in LGD remission and the absence of neoplastic progression, we also reported the rates of Complete eradication of Dysplasia and Complete eradication of Intestinal metaplasia, allowing to include all the study patients in the intention-to-treat (ITT) population • In the ITT population, all patients with neoplastic progression or lost to follow-up were considered as treatment failure

Study arms

Radiofrequency Ablation (N = 40)

Endoscopic Surveillance (N = 42)

Characteristics

Arm-level characteristics

Characteristic	**Radiofrequency Ablation (N = 40)**	**Endoscopic Surveillance (N = 42)**
Age (Mean (SD)) Mean (SD)	62.8 (10.2)	61.8 (9.9)
Men (%) Sample size	n = 36 ; % = 90	n = 40 ; % = 95.5
History of Barrett's oesophagus (Mean (SD)) Mean (SD)	6.1 (5.6)	5.5 (5)
History of Low-grade Dysplasia (Mean (SD)) Mean (SD)	2.2 (3.2)	2.2 (2.4)
Endoscopic resection for High-grade Dysplasia or early adenocarcinoma (%)	n = 2 ; % = 5	n = 6 ; % = 14.3

Characteristic	Radiofrequency Ablation (N = 40)	Endoscopic Surveillance (N = 42)
Sample size		

Outcomes

Study timepoints

3 year

Primary outcome

Outcome	Radiofrequency Ablation, 3 year, N = 37	Endoscopic Surveillance, 3 year, N = 40
Persistent Low-grade Dysplasia (%) No of events	n = 15 ; % = 40.5	n = 27 ; % = 67.5
Complete eradication of dysplasia (n (%)) No of events	n = 21 ; % = 56.8	n = 10 ; % = 25
Complete eradication of intestinal metaplasia (n (%)) No of events	n = 14 ; % = 37.8	n = 0 ; % = 0
Neoplastic progression (n (%)) No of events	n = 4 ; % = 10.8	n = 11 ; % = 26.2

Outcome	Radiofrequency Ablation, 3 year, N = 37	Endoscopic Surveillance, 3 year, N = 40
Complications of treatment (n (%)) Number of people with adverse events No of events	n = 7 ; % = 18.9	n = 0 ; % = 0

Complete eradication of dysplasia - Polarity - Higher values are better
Complete eradication of intestinal metaplasia - Polarity - Higher values are better
Neoplastic progression - Polarity - Lower values are better
Complications of treatment - Polarity - Lower values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Primaryoutcome-PersistentLow-gradeDysplasia-NoOfEvents-Radiofrequency Ablation-Endoscopic Surveillance-t3

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low

Section	Question	Answer
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Primaryoutcome-Completeeradicationofdysplasia-NoOfEvents-Radiofrequency Ablation-Endoscopic Surveillance-t3

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Primaryoutcome-Completeeradicationofintestinalmetaplasia-NoOfEvents-Radiofrequency Ablation-Endoscopic Surveillance-t3

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Primaryoutcome-Neoplasticprogression-NoOfEvents-Radiofrequency Ablation-Endoscopic Surveillance-t3

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low

Section	Question	Answer
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Primaryoutcome-Complicationsoftreatment-NoOfEvents-Radiofrequency Ablation-Endoscopic Surveillance-t3

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low

Section	Question	Answer
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Phoa, 2014

Bibliographic Reference	Phoa, K. N.; van Vilsteren, F. G.; Weusten, B. L.; Bisschops, R.; Schoon, E. J.; Ragunath, K.; Fullarton, G.; Di Pietro, M.; Ravi, N.; Visser, M.; Offerhaus, G. J.; Seldenrijk, C. A.; Meijer, S. L.; ten Kate, F. J.; Tijssen, J. G.; Bergman, J. J.; Radiofrequency ablation vs endoscopic surveillance for patients with Barrett esophagus and low-grade dysplasia: a randomized clinical trial; JAMA; 2014; vol. 311 (no. 12); 1209-17

Study details

Secondary publication of another included study- see primary study for details	Primary study
Other publications associated with this study included in review	Pouw 2020

Trial name / registration number	Trial name: SURF (Surveillance versus Radiofrequency Ablation study) trialregister.nl Identifier: NTR1198
Study type	Randomised controlled trial (RCT)
Study location	Europe
Study setting	Barrett treatment centers
Study dates	June 2007 and June 2011
Sources of funding	This investigator-initiated trial was supported, in part, by Covidien GI Solutions (formerly BÂRRX Medical) and by the Maag Lever Darm Stichting grant WO 07-60 from the Dutch Digestive Diseases Foundation. Covidien GI Solutions provided ablation devices and access to a central electronic data management system.
Inclusion criteria	Eligible patients had undergone upper endoscopy and biopsy within the previous 18 months demonstrating Barrett esophagus containing low-grade dysplasia.
Exclusion criteria	• Prior endoscopic treatment for Barrett esophagus. • History of high-grade dysplasia, adenocarcinoma or active secondary malignancy • Estimated life expectancy less than 2 years (according to the enrolling physician). • Age of 18 years or younger or 85 years and older.
Recruitment / selection of participants	Not stated
Intervention(s)	• Patients were randomly assigned to receive endoscopic radiofrequency ablation (ablation). • 1 month after randomization, patients assigned to ablation were treated with a circumferential device (HALO360+ system) or a focal device (HALO90; both from Covidien GI Solutions [formerly BÂRRX Medical]) according to extent of disease and investigator preference. • Subsequent ablation sessions occurred every 3 months, until complete endoscopic and histological eradication of Barrett esophagus or a maximum of 2 circumferential and 3 focal sessions. • At each ablation session, the gastroesophageal junction was ablated circumferentially, irrespective of its endoscopic appearance.

	• All procedures were performed on an outpatient basis using midazolam plus fentanyl, midazolam plus pethidine, or propofol. • During the trial, the ablation group received double-dose proton pump inhibition as maintenance therapy. A histamine (H2) receptor antagonist and sucralfate suspension were added for 2 weeks after each therapeutic endoscopy
Population subgroups	None
Comparator	• Patients were randomly assigned to endoscopic surveillance (control group). • Patients assigned to the control group underwent high-resolution endoscopy at 6 and 12 months after the baseline qualifying endoscopy and annually thereafter until 3 years after randomization. • At each follow-up endoscopy, 4-quadrant biopsy samples were obtained from every 2-cm interval of Barrett epithelium.
Number of participants	N=136
Duration of follow-up	Median follow up: 36 months
Additional comments	• The modified intention-to-treat population included all randomized patients meeting all study criteria. • If residual columnar epithelium persisted after the maximum allowable number of ablations, a single session of endoscopic resection or argon plasma coagulation (for ≤4 Barrett esophagus islands, ≤5 mm in size) was allowed per protocol.

Study arms

Radiofrequency Ablation (N = 68)

Control (N = 68)

Characteristics

Arm-level characteristics

Characteristic	Radiofrequency Ablation (N = 68)	Control (N = 68)
Age (Mean (SD)) Standardised Mean (SD)	63 (10)	63 (9)
Men (Percentage) Sample size	n = 55 ; % = 81	n = 61 ; % = 90
White race (Percentage) Sample size	n = 66 ; % = 97	n = 66 ; % = 97
BMI (Mean (SD)) Mean (SD)	26.8 (3.7)	27.9 (4.8)
Circumferential Barrett esophagus Median (IQR)	2 (0 to 6)	2 (1 to 4)
Barrett surveillance endoscopies prior to baseline Median (IQR)	5 (3 to 8)	5 (3 to 7)
Barrett surveillance endoscopies with dysplasia prior to baseline Median (IQR)	2 (1 to 4)	2 (1 to 3)

Outcomes

Primary outcome

Outcome	Radiofrequency Ablation, , N = 68	Control, , N = 68
Progression to high-grade dysplasia or cancer (%) No of events	n = 1 ; % = 1.5	n = 18 ; % = 26.5
Progression to cancer (%) No of events	n = 1 ; % = 1.5	n = 6 ; % = 8.8
Complete eradication of dysplasia during follow-up (%) 63 people who had complete eradication after treatment analysed in the study but for this review used total 68 for analysis to capture those who did not show eradication No of events	n = 62 ; % = 98.4	n = 19 ; % = 27.9
Complications of treatment (%) 2 people had serious adverse events including bleeding and hospitalisation for abdominal pain, stricture, fever and 12 had adverse events (non-serious) including pain and stricture; one patient had both serious adverse events and adverse events, thus total with events is 13 people No of events	n = 13 ; % = 19.12	n = 0 ; % = 0

Progression to high-grade dysplasia or cancer - Polarity - Lower values are better
Progression to cancer - Polarity - Lower values are better
Complete eradication of dysplasia during follow-up - Polarity - Higher values are better
Complications of treatment - Polarity - Lower values are better

Complete eradication of intestinal metaplasia

Outcome	Radiofrequency Ablation, , N = 60	Control, , N = 68
Complete eradication of intestinal metaplasia during follow-up No of events	n = 54 ; % = 90	n = 0 ; % = 0

Complete eradication of intestinal metaplasia during follow-up

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Primaryoutcome-Progressiontohigh-gradedysplasiaorcancer-NoOfEvents-Radiofrequency Ablation-Control

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Low

Section	Question	Answer
Overall bias and Directness	Overall Directness	Directly applicable

Primaryoutcome-Progressiontocancer-NoOfEvents-Radiofrequency Ablation-Control

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Primaryoutcome-Completeeradicationofdysplasiaduringfollow-up-NoOfEvents-Radiofrequency Ablation-Control

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Primaryoutcome-Complicationsoftreatment-NoOfEvents-Radiofrequency Ablation-Control

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low

Section	Question	Answer
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Completeeradicationofintestinalmetaplasia-Completeeradicationofintestinalmetaplasiaduringfollow-up-NoOfEvents-Radiofrequency Ablation-Control

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low

Section	Question	Answer
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Shaheen, 2009

Bibliographic Reference	Shaheen, N. J.; Sharma, P.; Overholt, B. F.; Wolfsen, H. C.; Sampliner, R. E.; Wang, K. K.; Galanko, J. A.; Bronner, M. P.; Goldblum, J. R.; Bennett, A. E.; Jobe, B. A.; Eisen, G. M.; Fennerty, M. B.; Hunter, J. G.; Fleischer, D. E.; Sharma, V. K.; Hawes, R. H.; Hoffman, B. J.; Rothstein, R. I.; Gordon, S. R.; Mashimo, H.; Chang, K. J.; Muthusamy, V. R.; Edmundowicz, S. A.; Spechler, S. J.; Siddiqui, A. A.; Souza, R. F.; Infantolino, A.; Falk, G. W.; Kimmey, M. B.; Madanick, R. D.; Chak, A.; Lightdale, C. J.; Radiofrequency ablation in Barrett's esophagus with dysplasia; New England Journal of Medicine; 2009; vol. 360 (no. 22); 2277-88

Study details

Secondary publication of another included study- see primary study for details	Primary study
Other publications associated with this study included in review	None

Study type	Randomised controlled trial (RCT)
Study location	19 sites in the United states
Study setting	The academic investigators collected data at each study site, and the sponsor, BÂRRX Medical, managed the database.
Study dates	Not stated
Sources of funding	• Supported by BÂRRX Medical. • Study medication was provided by AstraZeneca. • Statistical analysis and data management were supported by a grant (P30 DK034987) from the National Institutes of Health
Inclusion criteria	Patients between 18 and 80 years of age and who had endoscopically evident, non-nodular, dysplastic Barrett's esophagus of no more than 8 cm in length
Exclusion criteria	Exclusion criteria were pregnancy, active esophagitis or stricture precluding passage of the endoscope, a history of esophageal cancer, esophageal varices, uncontrolled coagulopathy, or a life expectancy of less than 2 years, as judged by the site investigator.
Recruitment / selection of participants	Patients meeting inclusion criteria; unclear how original number of eligible patients was derived; recruitment not specified Samples from eligible patients with a diagnosis of dysplastic Barrett's oesophagus underwent review by a study pathologist at a central laboratory. If the readings were concordant, the patient was deemed to be eligible for the study and was assigned an entry grade of dysplasia. If the readings were discordant, a second masked review was performed, with assignment by concordance.
Intervention(s)	RFA: • The entire segment of Barrett's esophagus was ablated. • Randomization was stratified according to the grade of dysplasia (low-grade or high-grade) and the length of Barrett's esophagus (<4 cm or 4 to 8 cm), as viewed on endoscopy • Patients in the ablation group could receive up to four ablation sessions, performed at baseline and at 2, 4, and 9 months. Patients with low-grade dysplasia underwent biopsy procedures at 6 and 12 months; those with high-grade dyspla-sia underwent such procedures at 3, 6, 9, and 12 months. • All patients underwent upper endoscopy, esophageal intubation with a study catheter, measurement of the esophageal inner diameter,15 and periprocedural assignment to a study group with the use of a computer-generated block-randomization sequence.

	• All patients received 40 mg of esomeprazole (which was provided by AstraZeneca) twice daily through-out the trial.
Population subgroups	None
Comparator	Sham endoscopic procedure (control group): After completion of all 12-month assessments, patients in the control group were offered open-label radiofrequency ablation. All patients received 40 mg of esomeprazole (which was provided by AstraZeneca) twice daily throughout the trial.
Number of participants	N= 127; 64 with low-grade dysplasia included in the present review
Duration of follow-up	12 months
Indirectness	None
Additional comments	• The study population for the primary intention-to-treat analysis included all patients who underwent randomization. In this analysis, patients who were lost to follow-up were regarded as having had a failure of treatment for the primary outcome. • A secondary per-protocol analysis was performed in patients who completed the 12-month visit. • The intention-to-treat population, calculated how many patients would need to be treated to prevent one outcome failure, according to the variable being assessed.

Study arms

RFA (N = 42)

Sham endoscopic procedure (N = 22)

Characteristics

Arm-level characteristics

Characteristic	RFA (N = 42)	Sham endoscopic procedure (N = 22)
% Female Sample size	n = 9 ; % = 21	n = 3 ; % = 14
Mean age (SD) Mean (SD)	66.3 (1.4)	64.6 (1.9)
Race: white No of events	n = 40 ; % = 95	n = 22 ; % = 100
Length of Barrett's oesophagus (cm) Mean (SD)	4.6 (0.4)	4.6 (0.5)
Subsquamous intestinal metaplasia Sample size	n = 11 ; % = 26	n = 8 ; % = 36

Characteristic	RFA (N = 42)	Sham endoscopic procedure (N = 22)
Current use of NSAID or aspirin Sample size	n = 20 ; % = 48	n = 7 ; % = 32

Outcomes

Study timepoints

- 12 month

Complete eradication of dysplasia/ intestinal metaplasia

Outcome	RFA, 12 month, N = 40	Sham endoscopic procedure, 12 month, N = 19
Complete eradication of dysplasia No of events	n = 38 ; % = 95	n = 5 ; % = 26
Complete eradication of intestinal metaplasia No of events	n = 34 ; % = 85	n = 1 ; % = 5

Progression to HGD/cancer

Outcome	RFA, 12 month, N = 42	Sham endoscopic procedure, 12 month, N = 22
Progression to high-grade dysplasia No of events	n = 2 ; % = 5	n = 3 ; % = 14

Outcome	RFA, 12 month, N = 42	Sham endoscopic procedure, 12 month, N = 22
Progression to cancer No of events	n = 0 ; % = 0	n = 0 ; % = 0

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Completeeradicationofdysplasia/intestinalmetaplasia-Completeeradicationofdysplasia-NoOfEvents-RFA-Sham endoscopic procedure-t12

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Some concerns *(difference in use of aspirin and NSAIDS)*
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns

Section	Question	Answer
Overall bias and Directness	Overall Directness	Directly applicable

Completeeradicationofdysplasia/intestinalmetaplasia-Completeeradicationofintestinalmetaplasia-NoOfEvents-RFA-Sham endoscopic procedure-t12

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Some concerns *(difference in use of aspirin and NSAIDS)*
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

ProgressiontoHGD/cancer-Progressiontohigh-gradedysplasia-NoOfEvents-RFA-Sham endoscopic procedure-t12

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Some concerns *(difference in use of aspirin and NSAIDS)*
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

ProgressiontoHGD/cancer-Progressiontocancer-NoOfEvents-RFA-Sham endoscopic procedure-t12

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low

Section	Question	Answer
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Some concerns *(difference in use of aspirin and NSAIDS)*
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

Observational evidence

Pouw, 2020

Bibliographic Reference	Pouw, R. E.; Klaver, E.; Phoa, K. N.; van Vilsteren, F. G.; Weusten, B. L.; Bisschops, R.; Schoon, E. J.; Pech, O.; Manner, H.; Ragunath, K.; Fernandez-Sordo, J. O.; Fullarton, G.; Di Pietro, M.; Januszewicz, W.; O'Toole, D.; Bergman, J. J.; Radiofrequency ablation for low-grade dysplasia in Barrett's esophagus: long-term outcome of a randomized trial; Gastrointestinal Endoscopy; 2020; vol. 92 (no. 3); 569-574

Study details

Secondary publication of	Secondary publication of another included study

another included study- see primary study for details	
Other publications associated with this study included in review	Phoa 2014
Trial name / registration number	Trial name: SURF (Surveillance versus Radiofrequency Ablation study) Clinical trial registration number: NTR1198
Study type	Retrospective cohort study
Study location	Europe
Study setting	Hospitals
Study dates	May 2013 until December 2017
Inclusion criteria	Patients with Barrett's esophagus with at least 1 diagnosis of LGD confirmed by an expert central pathology panel within 18 months before randomization
Exclusion criteria	• Previous endoscopic treatment for BE • History of HGD or esophageal adenocarcinoma • Active secondary malignancy • Estimated life expectancy <2 years • Age <18 years or >85 years.
Recruitment / selection of participants	Not stated
Intervention(s)	• Patients were randomly assigned to receive endoscopic radiofrequency ablation (ablation). • 1 month after randomization, patients assigned to ablation were treated with a circumferential device (HALO360+ system) or a focal device (HALO90; both from Covidien GI Solutions [formerly BÂRRX Medical]) according to extent of disease and investigator preference.

	• Subsequent ablation sessions occurred every 3 months, until complete endoscopic and histological eradication of Barrett esophagus or a maximum of 2 circumferential and 3 focal sessions. • At each ablation session, the gastroesophageal junction was ablated circumferentially, irrespective of its endoscopic appearance. • All procedures were performed on an outpatient basis using midazolam plus fentanyl, midazolam plus pethidine, or propofol. • During the trial, the ablation group received double-dose proton pump inhibition as maintenance therapy. A histamine (H2) receptor antagonist and sucralfate suspension were added for 2 weeks after each therapeutic endoscopy
Comparator	• Patients were randomly assigned to endoscopic surveillance (control group). • Patients assigned to the control group underwent high-resolution endoscopy at 6 and 12 months after the baseline qualifying endoscopy and annually thereafter until 3 years after randomization. • At each follow-up endoscopy, 4-quadrant biopsy samples were obtained from every 2-cm interval of Barrett epithelium.
Number of participants	N=136
Duration of follow-up	Median follow-up of 73 months

Study arms

Radiofrequency Ablation (N = 68)

Endoscopic surveillance (N = 68)

Characteristics

Arm-level characteristics

Characteristic	Radiofrequency Ablation (N = 68)	Endoscopic surveillance (N = 68)
Age (Mean (SD)) Mean (SD)	63 (10)	63 (9)
Men (%) Sample size	n = 55 ; % = 81	n = 61 ; % = 90
White race (n (%)) Sample size	n = 66 ; % = 97	n = 66 ; % = 97
BMI (Mean (SD)) Mean (SD)	26.8 (3.7)	27.9 (4.8)
Circumferential Barrett esophagus Median (IQR)	2 (0 to 6)	2 (1 to 4)

Characteristic	Radiofrequency Ablation (N = 68)	Endoscopic surveillance (N = 68)
Barrett surveillance endoscopies prior to baseline Median (IQR)	5 (3 to 8)	5 (3 to 7)
Barrett surveillance endoscopies with dysplasia prior to baseline Median (IQR)	2 (1 to 4)	2 (1 to 3)

Outcomes

Study timepoints

- 40 month

Primary outcome

Outcome	Radiofrequency Ablation, 40 month, N = 68	Endoscopic surveillance, 40 month, N = 68
Progression to high-grade dysplaisa or cancer (n (%)) No of events	n = 1 ; % = 1.5	n = 23 ; % = 33.8
Progression to cancer (n (%)) No of events	n = 1 ; % = 1.5	n = 7 ; % = 10.3
Regression of Low-grade dysplasia (n (%))	n = 0 ; % = 0	n = 15 ; % = 22

Outcome	Radiofrequency Ablation, 40 month, N = 68	Endoscopic surveillance, 40 month, N = 68
No of events		

Progression to high-grade dysplaisa or cancer - Polarity - Lower values are better
Progression to cancer - Polarity - Lower values are better

Critical appraisal - ROBINS-I checklist

Primaryoutcome-Progressiontohigh-gradedysplaisaorcancer-NoOfEvents-Radiofrequency Ablation-Endoscopic surveillance-t40

Section	Question	Answer
1. Bias due to confounding	Risk of bias judgement for confounding	Low
2. Bias in selection of participants into the study	Risk of bias judgement for selection of participants into the study	Serious
3. Bias in classification of interventions	Risk of bias judgement for classification of interventions	Low
4. Bias due to deviations from intended interventions	Risk of bias judgement for deviations from intended interventions	Low
5. Bias due to missing data	Risk of bias judgement for missing data	Low
6. Bias in measurement of outcomes	Risk of bias judgement for measurement of outcomes	Low
7. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Low

Section	Question	Answer
Overall bias	Risk of bias judgement	Serious *(uneven groups, selection bias)*
Overall bias	Directness	Directly applicable

Primaryoutcome-Progressiontocancer-NoOfEvents-Radiofrequency Ablation-Endoscopic surveillance-t40

Section	Question	Answer
1. Bias due to confounding	Risk of bias judgement for confounding	Low
2. Bias in selection of participants into the study	Risk of bias judgement for selection of participants into the study	Serious
3. Bias in classification of interventions	Risk of bias judgement for classification of interventions	Low
4. Bias due to deviations from intended interventions	Risk of bias judgement for deviations from intended interventions	Low
5. Bias due to missing data	Risk of bias judgement for missing data	Low
6. Bias in measurement of outcomes	Risk of bias judgement for measurement of outcomes	Low
7. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Low
Overall bias	Risk of bias judgement	Serious *(uneven groups, selection bias)*

Section	Question	Answer
Overall bias	Directness	Directly applicable

Primaryoutcome-RegressionofLow-gradedysplasia-NoOfEvents-Radiofrequency Ablation-Endoscopic surveillance-t40

Section	Question	Answer
1. Bias due to confounding	Risk of bias judgement for confounding	Low
2. Bias in selection of participants into the study	Risk of bias judgement for selection of participants into the study	Serious
3. Bias in classification of interventions	Risk of bias judgement for classification of interventions	Low
4. Bias due to deviations from intended interventions	Risk of bias judgement for deviations from intended interventions	Low
5. Bias due to missing data	Risk of bias judgement for missing data	Low
6. Bias in measurement of outcomes	Risk of bias judgement for measurement of outcomes	Low
7. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Low
Overall bias	Risk of bias judgement	Serious *(uneven groups, selection bias)*
Overall bias	Directness	Directly applicable

Appendix E – Forest plots

RFA versus endoscopic surveillance/sham endoscopic procedure (RCT data)

Figure 2: Complete eradication of dysplasia (at 12months; during/after 3-year follow-up)

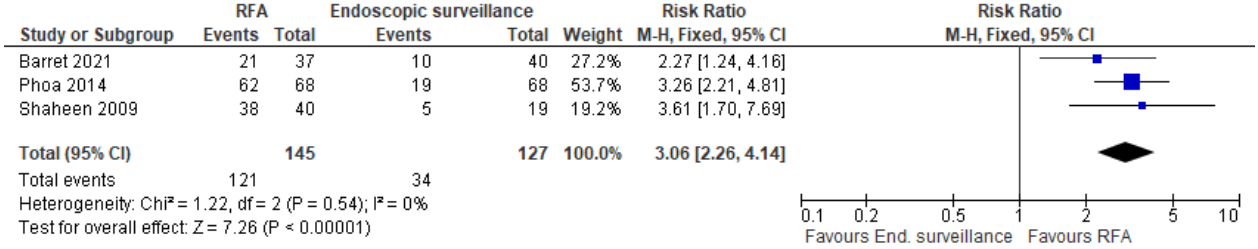


Figure 3: Complete eradication of intestinal metaplasia (at 12 months; during/after 3-year follow-up)

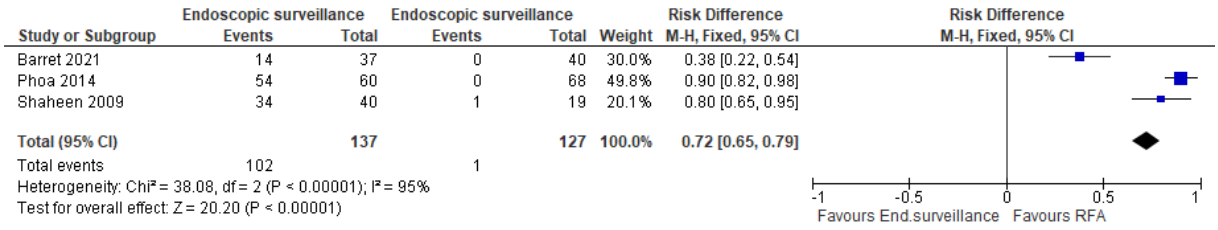


Figure 4: Complications

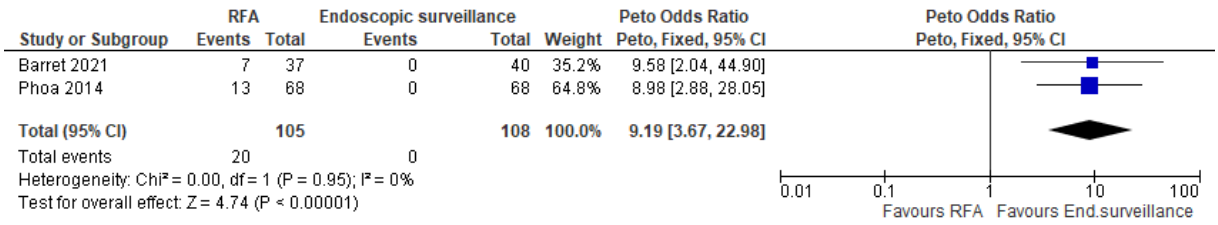


Figure 5: Progression to high-grade dysplasia/cancer

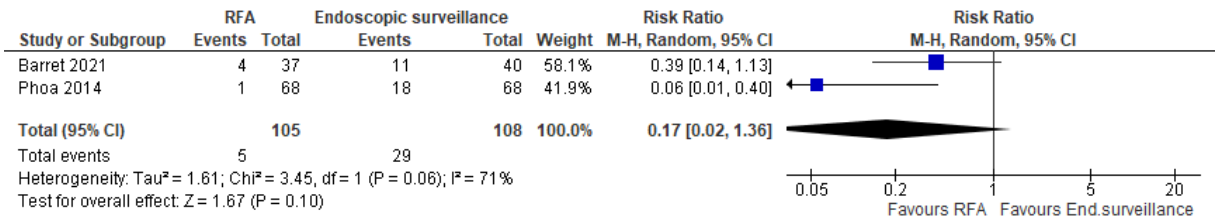


Figure 6: Progression to high-grade dysplasia

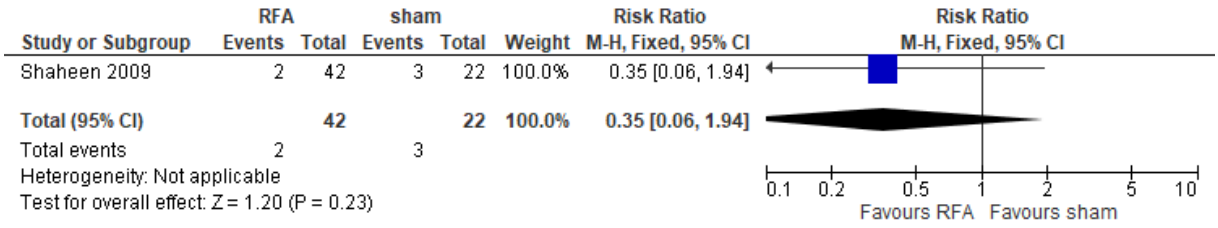


Figure 7: Progression to cancer

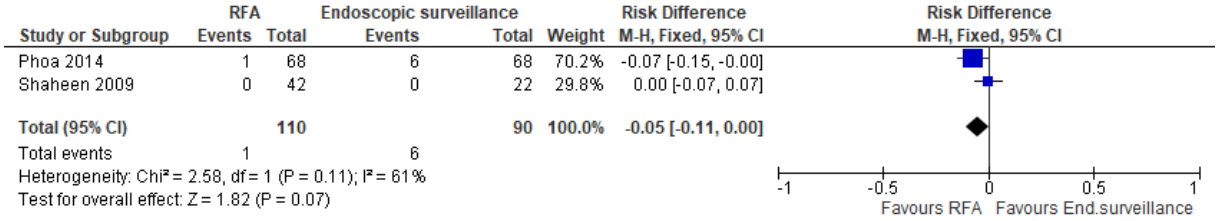


Figure 8: Persistence of low-grade dysplasia (at 3-year follow-up)

RFA versus endoscopic surveillance (observational data; long-term follow-up)

Figure 9: Progression to high-grade dysplasia/cancer

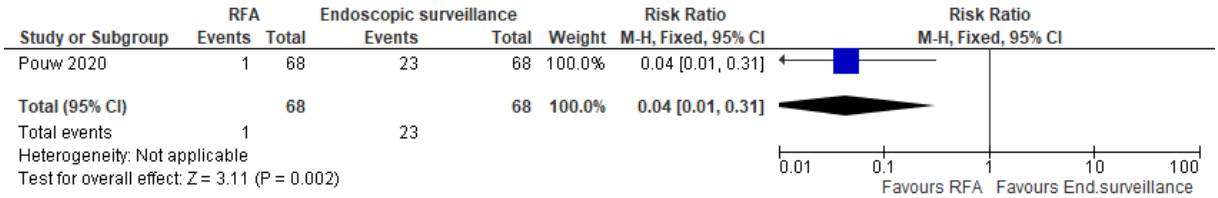
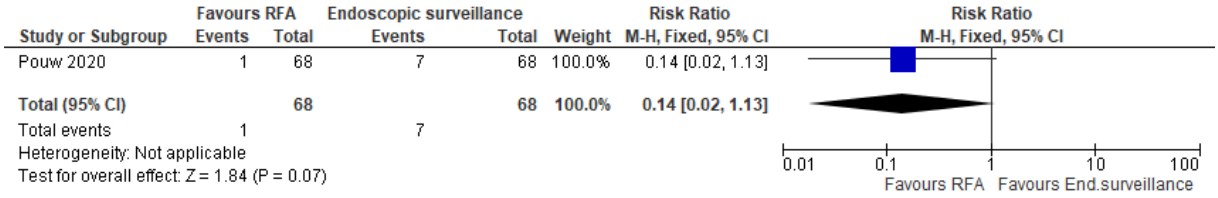


Figure 10: Progression to cancer


Favours RFA
Endoscopic surveillance
Risk Ratio
Risk Ratio
Study or Subgroup
Events
Total
Events
Total
Weight
M-H, Fixed, 95% CI
M-H, Fixed, 95% CI
Pouw 2020
1
68
7
68
100.0%
0.14 [0.02, 1.13]
Total (95% CI)
68
68
100.0%
0.14 [0.02, 1.13]
Total events
1
7
Heterogeneity: Not applicable
Test for overall effect: Z = 1.84 (P = 0.07)
0.01
0.1
1
10
100
Favours RFA
Favours End.surveillance

Appendix F – GRADE tables

Clinical evidence profile: RFA versus endoscopic surveillance/sham endoscopic procedure (RCT data)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RFA	endoscopic surveillance	Relative (95% CI)	Absolute (95% CI)		
Complete eradication of dysplasia												
3	randomised trials	not serious	not serious	not serious	not serious	none	121/145 (83.4%)	34/127 (26.8%)	**RR 3.06** (2.26 to 4.14)	**521 more per 1,000** (from 337 more to 841 more)	⨁⨁⨁⨁ High	CRITICAL
Complete eradication of intestinal metaplasia												
3	randomised trials	not serious	very serious[b]	not serious	not serious	none	102/137 (74.5%)	1/127 (0.0%)	**OR 27.86** (16.47 to 47.14)	**720 more per 1,000** (from 650 more to 790 more)[a]	⨁⨁◯◯ Low	CRITICAL
Complications												
2	randomised trials	not serious	not serious	not serious	not serious	none	20/105 (19.0%)	0/108 (0.0%)	**OR 9.19** (3.67 to 22.98)	**190 more per 1,000** (from 110 more to 270 more)[a]	⨁⨁⨁⨁ High	CRITICAL
Progression to high-grade dysplasia/cancer												
2	randomised trials	not serious	very serious[b]	not serious	very serious[c]	none	5/105 (4.8%)	29/108 (26.9%)	**RR 0.17** (0.02 to 1.36)	**223 fewer per 1,000** (from 263 fewer to 97 more)	⨁◯◯◯ Very low	CRITICAL
Progression to high-grade dysplasia												
1	randomised trials	serious[d]	not serious	not serious	very serious[c]	none	2/42 (4.8%)	3/22 (13.6%)	**RR 0.35** (0.06 to 1.94)	**89 fewer per 1,000** (from 128 fewer to 128 more)	⨁◯◯◯ Very low	CRITICAL
Progression to cancer												
2	randomised trials	not serious	Serious [e]	not serious	very serious [f]	none	1/110 (0.9%)	6/90 (6.7%)	**Risk difference -0.05 (-0.11, 0.00)**	**50 fewer per 1,000** (from 110fewer to 0 more)[g]	⨁◯◯◯ Very low	CRITICAL
Persistent low-grade dysplasia (at 3 years; proxy for recurrence)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RFA	endoscopic surveillance	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	not serious	not serious	not serious	Serious [c]	none	15/37 (40.5%)	27/40 (67.5%)	**RR 0.60** (0.38 to 0.94)	**270 fewer per 1,000** (from 419 fewer to 41 fewer)	⨁⨁⨁◯ Moderate	CRITICAL

a. Due to zero events in one arm, based on risk difference calculated as: 0.72 (95%CI 0.65, 0.79) for complete eradication of intestinal metaplasia; 0.19 (95% CI 0.11 to 0.27) for complications.
b. Downgraded by 1 increment because the confidence intervals across studies show minimal overlap and Heterogeneity, I2>70%, p=0.06, unexplained by subgroup analysis.
c. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs; default MIDs for dichotomous outcomes: 0.8 and 1.25
d. Downgraded by 1 increment as the evidence was at high risk of bias
e. Downgraded by 1 increment for inconsistency due to zero events in both arms of one study but not the other study.

f. Downgraded by 2 increments for imprecision due to xero events in both arms of one study, calculated <80% using OIS (optimal information size) https://www.stat.ubc.ca/~rollin/stats/ssize/b2.html indicating very serious imprecision
g. Due to zero events in both arms of one study, based on the risk difference calculated as: -0.05 (-0.11, 0.00)

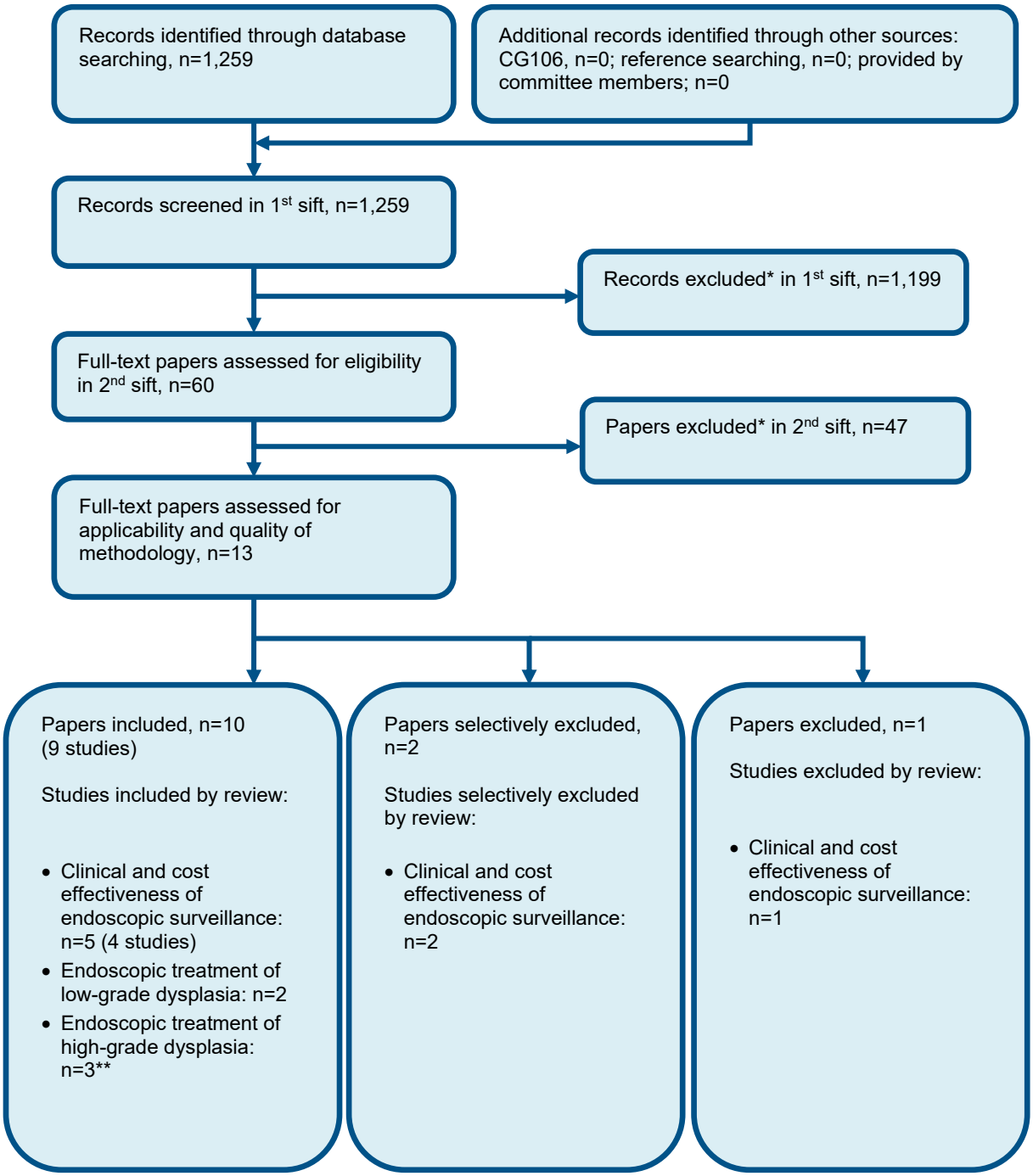
Clinical evidence profile: RFA versus endoscopic surveillance (observational data; long-term follow-up)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RFA	endoscopic surveillance (obs.data; long-term follow-up)	Relative (95% CI)	Absolute (95% CI)		
Progression to high-grade dysplasia/cancer												
1	observational studies	serious [a]	not serious	not serious	not serious	none	1/68 (1.5%)	23/68 (33.8%)	**RR 0.04** (0.01 to 0.31)	**325 fewer per 1,000** (from 335 fewer to 233 fewer)	⨁◯◯◯ Very low	CRITICAL
Progression to cancer												
1	observational studies	serious [a]	not serious	not serious	serious[b]	none	1/68 (1.5%)	7/68 (10.3%)	**RR 0.14** (0.02 to 1.13)	**89 fewer per 1,000** (from 101 fewer to 13 more)	⨁◯◯◯ Very low	CRITICAL

a. Downgraded by 1 increment due to serious risk of bias

b. Downgraded by 1 increment if the confidence interval crossed one MID; default MIDs for dichotomous outcomes: 0.8 and 1.25

Appendix G – Economic evidence study selection



* Non-relevant population, intervention, comparison, design or setting; non-English language
** One article identified was applicable to endoscopic treatment of low-grade dysplasia and endoscopic treatment for high-grade dysplasia, for the purposes of this diagram they have been included under endoscopic treatment of low-grade dysplasia only.

Appendix H – Economic evidence tables

Study	Esteban 2018[2]			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: Cost-utility analysis (health outcome: QALYs) **Study design:** Probabilistic semi-Markov model **Approach to analysis:** The natural history of BO was simulated in a cohort of patients undergoing one of two treatment options. There were six health states representing disease progression: 1. cured with a history of Barrett's (patients with neither dysplasia or intestinal metaplasia (IM) after successful treatment with RFA or oesophagectomy), 2. non-dysplastic Barrett's oesophagus (patients without dysplasia but with IM), 3. low-grade dysplasia, 4. high-grade dysplasia, 5. oesophageal adenocarcinoma 6. death. Model cycles were 1 year in length. **Perspective:** Spanish national health service	**Population:** People with LGD in BO **Cohort settings:** Start age: 65 Male: NR **Intervention 1:** Annual endoscopic surveillance* **Intervention 2:** RFA *Frequency of endoscopic surveillance was set by clinical experts and included 3-yearly intervals for cured patients with a history of Barrett's oesophagus, annually for patients with LGD, 6-monthly for patients with HGD and 3-monthly for people with OA.	**Total costs (mean per patient):** Intervention 1: £14,129 Intervention 2: £21,811 Incremental (2−1): £7,682 (95% CI: NR; p=NR) **Currency & cost year:** 2016 Euros, (presented here as 2016 UK pounds[(a)]) **Cost components incorporated:** drug costs (radiotherapy and chemotherapy including administration costs, procedure costs, follow-up costs, treatment complication costs	**QALYs (mean per patient):** Intervention 1: 9.15 Intervention 2: 9.71 Incremental (2−1): 0.56 (95% CI: NR; p=NR)	**ICER (Intervention 2 versus Intervention 1):** £13,718 per QALY gained (pa) 95% CI: NR **Analysis of uncertainty:** One-way sensitivity analyses were conducted, some of the parameters most impacting the cost per QALY gained were : the time horizon between 5-25 years; ICER: £12,998- £19,135 the starting age between 55-75 years; ICER: £13,136- £19,154 the cost of RFA procedures by 25% either way; ICER: £9,180- £18,242, the utility of the cured state by 0.03 either way; ICER: £11,036- £17,954

Time horizon: 15 years **Discounting:** Costs: 3%; Outcomes: 3%				
Data sources				
Health outcomes: The efficacy of treatment, defined as either the complete eradication of intestinal metaplasia (CE-IM) or the complete eradication of dysplasia (CE-D) were taken from Shaheen 2009 and Inadomi 2009.[4, 10] Transition probabilities between health states were taken from Hur 2012 and Imadomi 2009.[3, 4] **Quality-of-life weights:** QALYs derived from the EQ-5D were not available. Utilities were taken from literature based on a scale of 0 to 1, representing death and perfect health, respectively. **Cost sources:** Resource use data was based on a panel of three clinical experts. Unit costs were taken from two National databases (the Spanish Health Costs Database eSalud and the General Council of the Association of Official Pharmacists Database).				
Comments				
Source of funding: Study was funded by Covidien AG (now a Medtronic company). **Limitations:** The Spanish NHS perspective may not be entirely relevant to the UK NHS. Future costs and outcomes are not discounted in link with the NICE guideline. QALYS are not captured using the EQ-5D measure. Resource use associated with treatment was based on expert clinical opinion. Drug costs associated with symptomatic control of Barrett's oesophagus do not seem to have been included. Study was funded by a pharmaceutical company. **Other:** It was assumed that patients would not undergo a secondary RFA procedure, regardless of the success of the initial RFA.				
Overall applicability:(b) Partially applicable **Overall quality:**(c) Potentially serious limitations				

Abbreviations: 95% CI= 95% confidence interval; BO= Barrett's oesophagus; CE-D= complete eradication of dysplasia; CE-IM= complete eradication of intestinal metaplasia; CUA= cost–utility analysis; EQ-5D= Euroqol 5 dimensions;; HGD= high-grade dysplasia; ICER= incremental cost-effectiveness ratio; IM= intestinal metaplasia; LGD= low-grade dysplasia; NHS= national health service; NR= not reported; pa= probabilistic analysis; OA= oesophageal adenocarcinoma; QALYs= quality-adjusted life years; RFA= radiofrequency ablation; UK= United Kingdom

(a) Converted using 2016 purchasing power parities[6]

(b) Directly applicable / Partially applicable / Not applicable

(c) Minor limitations / Potentially serious limitations / Very serious limitations

Study	Phoa 2017[7]			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: Cost effectiveness analysis (health outcome: cost per patient progression to neoplasia prevented) **Study design:** Within-trial analysis (SURF) [8] **Approach to analysis:** Prospective analysis using patient-level data to model costs and outcomes over the trial follow-up period. **Perspective:** Dutch NHS **Follow-up:** 3 years **Discounting:** Costs: 3%; Outcomes: n/a	**Population:** Patients with BO containing LGD **Cohort settings:** Start age: 63 Male: 85% **Intervention 1:** Endoscopic surveillance **Intervention 2:** Radiofrequency ablation	**Total costs (mean per patient):** Intervention 1: £3,428 Intervention 2: £9,402 Incremental (2−1): £5,974 (95% CI: NR; p=NR) **Currency & cost year:** 2012/13 US dollars (presented here as 2013 UK pounds[(a)]) **Cost components incorporated:** Endoscopic therapy after neoplastic progression, surgical treatment of neoplastic progression, medication after neoplastic progression, treatment of adverse events after neoplastic progression	**Progression to neoplasia prevented (mean per patient):** Intervention 1: NR Intervention 2: NR Incremental (2−1): 0.25 (95% CI: NR; p=NR)	**ICER (Intervention 2 versus Intervention 1):** £23,896 per neoplasia prevented (pa) 95% CI: £14,152-£47,975) **Analysis of uncertainty:** Bootstrapping was conducted for confidence intervals. Sensitivity analysis was not conducted.
Data sources				
Health outcomes: Patients from the SURF trial were followed for 3 years to quantify their use of health care services, including therapeutic and surveillance endoscopies, treatment of adverse events, and medication. **Quality-of-life weights:** n/a **Cost sources:** Intervention costs were taken from the Academic Medical Hospital ledger 2012. Hospital stay costs were taken from the Dutch guideline for costing 2012. Drug costs were taken from the national drug costing manual called Medicijnkosten.				

Comments
Source of funding: SURF trial was funded in part by Covidien GI solutions and a grant from the Dutch Digestive Diseases Foundation. **Limitations:** Management of BO in The Netherlands may not be reflective of current UK practice. Time horizon may not be sufficiently long to capture the consequences of interventions on the selected health outcome. A cost-utility analysis was not conducted. **Other:**
Overall applicability:(c) Partially applicable **Overall quality:**(d) Potentially serious limitations

Abbreviations: 95% CI= 95% confidence interval; BO= Barrett's oesophagus; ICER= incremental cost-effectiveness ratio; LGD= low-grade dysplasia; n/a= not applicable; NHS= national health service; NR= not reported; pa= probabilistic analysis; SURF= surveillance versus radiofrequency ablation; UK= United Kingdom

(a) Converted using 2013 purchasing power parities[6]

(b) Figures were manually read from a graph

(c) Directly applicable / Partially applicable / Not applicable

(d) Minor limitations / Potentially serious limitations / Very serious limitations

Appendix I – Excluded studies

Clinical studies

Studies excluded from the clinical review

Study	Exclusion reason
(2017) Endoscopic mucosal resection (EMR) followed by radiofrequency ablation (RFA) in neoplastic Barrett's esophagus or Barrett early cancer is also economically superior to sole radical endoscopic resection. Tumor diagnostik und therapie 38(8): 501-506	- Study not reported in English
(2016) Effects of preceding endoscopic mucosal resection on the efficacy and safety of radiofrequency ablation for treatment of Barrett's esophagus: results from the United States Radiofrequency Ablation Registry. Diseases of the esophagus. 29 (6) (pp 537-543), 2016. Date of publication: 01 aug 2016.	- Population not relevant to this review protocol *High-grade dysplasia and intramucosal cancer; paper considered for inclusion in question 4.2*
(2020) Erratum: correction: argon plasma coagulation for Barrett's esophagus with low-grade dysplasia: a randomized trial with long-term follow-up on the impact of power setting and proton pump inhibitor dose (Endoscopy (2020)). Endoscopy	- Comparator in study does not match that specified in this review protocol *study compares APC of different power (watts) combined with different doses of PPI medication*
(2016) Recurrent intestinal metaplasia at the gastroesophageal junction following endoscopic eradication of dysplastic Barrett's esophagus may not be benign. Endoscopy international open. 4 (8) (pp E849-E858), 2016. Date of publication: 01 aug 2016.	- Population not relevant to this review protocol *Majority had high-grade dysplasia and intramucosal cancer; paper considered for inclusion in question 4.2*
Ackroyd, R., Tam, W., Schoeman, M. et al. (2004) Prospective randomized controlled trial of argon plasma coagulation ablation vs. endoscopic surveillance of patients with Barrett's esophagus after antireflux surgery. Gastrointestinal Endoscopy 59(1): 1-7	- Population not relevant to this review protocol *included people with and without low-grade dysplasia, the vast majority of which were confirmed to have normal squamous epithelium*
Ackroyd, R., Wijnhoven, B., Astill, D. et al. (2007) Five year results of prospective randomised controlled trial of argon plasma coagulation vs endoscopic surveillance of patients with Barrett's oesophagus after antireflux surgery. ANZ Journal of Surgery 77: a45	- Full text paper not available

Study	Exclusion reason
Agarwal, S., Alshelleh, M., Scott, J. et al. (2021) Comparative outcomes of radiofrequency ablation and cryoballoon ablation in dysplastic Barrett's esophagus: A propensity score-matched cohort study. Gastrointestinal Endoscopy 06: 06	- Population not relevant to this review protocol *majority had high-grade dysplasia/ intramucosal cancer; paper considered for inclusion in question 4.2*
Ali, S., Ali, A., Hussain, S. et al. (2020) Efficacy and Safety of Endoscopic Submucosal Dissection and Endoscopic Mucosal Resection in Barrett's Esophagus-Related Early Neoplasia: A Systematic Review and Pooled Comparative Analysis. Am. J. Gastroenterol. 115(suppl): S465-None	- Conference abstract
Almond, L. M.; Hodson, J.; Barr, H. (2014) Meta-analysis of endoscopic therapy for low-grade dysplasia in Barrett's oesophagus. British Journal of Surgery 101(10): 1187-95	- Systematic review used as source of primary studies
Alvarez Herrero, L., van Vilsteren, F. G., Pouw, R. E. et al. (2011) Endoscopic radiofrequency ablation combined with endoscopic resection for early neoplasia in Barrett's esophagus longer than 10 cm. Gastrointestinal Endoscopy 73(4): 682-90	- Population not relevant to this review protocol *Majority had high-grade dysplasia/cancer; paper considered for inclusion in question 4.2*
Arora, G., Basra, S., Roorda, A. K. et al. (2009) Radiofrequency ablation of Barrett's esophagus. European Surgery - Acta Chirurgica Austriaca 41(1): 19-25	- Conference abstract
Barr, H.; Stone, N.; Rembacken, B. (2005) Endoscopic therapy for Barrett's oesophagus. Gut 54(6): 875-84	- Review article but not a systematic review
Belghazi, K., Pouw, R. E., Koch, A. D. et al. (2019) Self-sizing radiofrequency ablation balloon for eradication of Barrett's esophagus: Results of an international multicenter randomized trial comparing 3 different treatment regimens. Gastrointestinal Endoscopy 90(3): 415-423	- Comparator in study does not match that specified in this review protocol *study comparing three different RFA regimens; population includes people with high-grade dysplasia/cancer*
Bennett, C, Green, S, DeCaestecker, J et al. (2020) Surgery versus radical endotherapies for early cancer and high-grade dysplasia in Barrett's oesophagus. Cochrane Database of Systematic Reviews	- Population not relevant to this review protocol *population does not meet protocol for this review as it includes people with high-grade dysplasia and early cancerof different cellular cancer types, not limited to Barrett's oesophagus such as squamous cell carcinoma.*

Study	Exclusion reason
	The Cochrane review did not include any studies, so no individual studies were checked for inclusion in the present review.
Bright, T., Watson, D. I., Tam, W. et al. (2007) Randomized trial of argon plasma coagulation versus endoscopic surveillance for barrett esophagus after antireflux surgery: late results. Annals of Surgery 246(6): 1016-20	- Population not relevant to this review protocol *people with non-dysplastic Barrett's oesophagus*
Cao, Y., Liao, C., Tan, A. et al. (2009) Meta-analysis of endoscopic submucosal dissection versus endoscopic mucosal resection for tumors of the gastrointestinal tract. Endoscopy 41(9): 751-7	- Systematic review used as source of primary studies
Caygill, C. P. J. and Gatenby, P. A. C. (2014) Randomised controlled trial: Radiofrequency ablation of Barrett's oesophagus with confirmed low-grade dysplasia reduces risk of development of high-grade dysplasia and adenocarcinoma. Evidence-Based Medicine 19(5): 185	- Duplicate reference [description of findings from RCT included in the present review: SURF trial]
Chadwick, G., Groene, O., Markar, S. R. et al. (2014) Systematic review comparing radiofrequency ablation and complete endoscopic resection in treating dysplastic Barrett's esophagus: A critical assessment of histologic outcomes and adverse events. Gastrointestinal Endoscopy 79(5): 718-731.e3	- Population not relevant to this review protocol *high-grade dysplasia and cancer; considered for inclusion in 4.2*
Cotton, C. C., Wolf, W. A., Overholt, B. F. et al. (2017) Late Recurrence of Barrett's Esophagus After Complete Eradication of Intestinal Metaplasia is Rare: Final Report From Ablation in Intestinal Metaplasia Containing Dysplasia Trial. Gastroenterology 153(3): 681-688.e2	- Population not relevant to this review protocol [mixed low-grade and high-grade dysplasia population with one relevant outcome of recurrence reported separately in the two populations but not in relation to the interventions.]
de Caestecker, J., Barr, H., Bhandari, P. et al. (2020) Randomized studies for Barrett's ablation: identifying the most cost-effective solutions by keeping an open mind. Gastrointestinal Endoscopy 91(5): 1218-1220	- Conference abstract
de Matos, M. V., da Ponte-Neto, A. M., de Moura, D. T. H. et al. (2019) Treatment of high-grade dysplasia and intramucosal carcinoma using radiofrequency ablation or endoscopic mucosal resection + radiofrequency ablation: Meta-analysis and systematic review. World	- Population not relevant to this review protocol *high-grade dysplasia/ carcinoma; paper considered for question 4.2*

Study	Exclusion reason
Journal of Gastrointestinal Endoscopy 11(3): 239-248	
De Souza, T. F., Artifon, E. L., Mestieri, L. H. et al. (2014) Systematic review and meta-analysis of endoscopic ablative treatment of Barrett's esophagus. Revista de Gastroenterologia del Peru 34(3): 217-24	- Systematic review used as source of primary studies
Desai, M., Rosch, T., Sundaram, S. et al. (2021) Systematic review with meta-analysis: the long-term efficacy of Barrett's endoscopic therapy-stringent selection criteria and a proposal for definitions. Alimentary Pharmacology & Therapeutics 54(3): 222-233	- Systematic review used as source of primary studies
Desai, M., Saligram, S., Gupta, N. et al. (2017) Efficacy and safety outcomes of multimodal endoscopic eradication therapy in Barrett's esophagus-related neoplasia: a systematic review and pooled analysis. Gastrointestinal Endoscopy 85(3): 482-495.e4	- Systematic review used as source of primary studies
Doosti-Irani, A., Mansournia, M. A., Rahimi-Foroushani, A. et al. (2017) Complications of stent placement in patients with esophageal cancer: A systematic review and network meta-analysis. PLoS ONE [Electronic Resource] 12(10): e0184784	- Systematic review used as source of primary studies
Dulai, G. S., Jensen, D. M., Cortina, G. et al. (2005) Randomized trial of argon plasma coagulation vs. multipolar electrocoagulation for ablation of Barrett's esophagus. Gastrointestinal Endoscopy 61(2): 232-40	- Population not relevant to this review protocol *non-dysplastic Barrett's oesophagus*
Faybush, E. M. and Sampliner, R. E. (2005) Randomized trials in the treatment of Barrett's esophagus. Diseases of the Esophagus 18(5): 291-7	- Systematic review used as source of primary studies
Fleischer, D. E., Overholt, B. F., Sharma, V. K. et al. (2008) Endoscopic ablation of Barrett's esophagus: a multicenter study with 2.5-year follow-up. Gastrointestinal Endoscopy 68(5): 867-876	Population not relevant to this review protocol [non-dysplastic Barrett's oesophagus]
Fleischer, D. E., Overholt, B. F., Sharma, V. K. et al. (2010) Endoscopic radiofrequency ablation for Barrett's esophagus: 5-year outcomes from a	- Conference abstract

Study	Exclusion reason
prospective multicenter trial. Endoscopy 42(10): 781-9	
Franchimont, D.; Van Laethem, J. L.; Deviere, J. (2003) Argon plasma coagulation in Barrett's esophagus. Gastrointestinal Endoscopy Clinics of North America 13(3): 457-66	- Review article but not a systematic review
Frei, N. F., Khoshiwal, A. M., Konte, K. et al. (2021) Tissue Systems Pathology Test Objectively Risk Stratifies Barrett's Esophagus Patients With Low-Grade Dysplasia. American Journal of Gastroenterology 116(4): 675-682	- No relevant outcomes
Green, S., Tawil, A., Barr, H. et al. (2009) Surgery versus radical endotherapies for early cancer and high grade dysplasia in Barrett's oesophagus. Cochrane Database of Systematic Reviews: cd007334	- Earlier publication of Cochrane review already excluded from this review.
Guo, H. M., Zhang, X. Q., Chen, M. et al. (2014) Endoscopic submucosal dissection vs endoscopic mucosal resection for superficial esophageal cancer. World Journal of Gastroenterology 20(18): 5540-7	- Systematic review used as source of primary studies
Gutschow, C. A., Schroder, W., Prenzel, K. et al. (2002) Impact of antireflux surgery on Barrett's esophagus. Langenbecks Archives of Surgery 387(34): 138-45	- Study does not contain an intervention relevant to this review protocol
Haidry, R. J., Butt, M. A., Dunn, J. M. et al. (2015) Improvement over time in outcomes for patients undergoing endoscopic therapy for Barrett's oesophagus-related neoplasia: 6-year experience from the first 500 patients treated in the UK patient registry. Gut 64(8): 1192-9	- Population not relevant to this review protocol *high-grade-dysplasia/cancer; considered for inclusion in 4.2*
Hamade, N., Desai, M., Thoguluva Chandrasekar, V. et al. (2019) Efficacy of cryotherapy as first line therapy in patients with Barrett's neoplasia: a systematic review and pooled analysis. Diseases of the Esophagus 32(11): 30	- Systematic review used as source of primary studies *review of studies with no comparison group*
Han, C. and Sun, Y. (2021) Efficacy and safety of endoscopic submucosal dissection versus endoscopic mucosal resection for superficial esophageal carcinoma: a systematic review and meta-analysis. Diseases of the Esophagus 34(4): 07	- Systematic review used as source of primary studies

Study	Exclusion reason
Kanzaki, H., Ishihara, R., Ohta, T. et al. (2013) Randomized study of two endo-knives for endoscopic submucosal dissection of esophageal cancer. American Journal of Gastroenterology 108(8): 1293-8	- Study does not contain an intervention relevant to this review protocol *comparison of two different endo-knifes for use during endoscopic submucosal resection*
Klair, J. S., Nagra, N., Law, J. K. et al. (2020) Outcomes of Radiofrequency Ablation VS Endoscopic Surveillance for Barrett's Esophagus with Low-Grade Dysplasia: A Systematic Review and Meta-Analysis. Gastrointest. Endosc. 91(6): AB403-None	- Conference abstract
Klair, J. S., Zafar, Y., Nagra, N. et al. (2021) Outcomes of Radiofrequency Ablation versus Endoscopic Surveillance for Barrett's Esophagus with Low-Grade Dysplasia: A Systematic Review and Meta-Analysis. Digestive Diseases 39(6): 561-568	- Systematic review used as source of primary studies
Knabe, M.; May, A.; Ell, C. (2015) Endoscopic Therapy of Early Carcinoma of the Oesophagus. Viszeralmedizin 31(5): 320-5	- Review article but not a systematic review
Komeda, Y.; Bruno, M.; Koch, A. (2014) EMR is not inferior to ESD for early Barrett's and EGJ neoplasia: An extensive review on outcome, recurrence and complication rates. Endoscopy International Open 2(2): E58-64	- Systematic review used as source of primary studies
Krishnamoorthi, R., Singh, S., Ragunathan, K. et al. (2016) Risk of recurrence of Barrett's esophagus after successful endoscopic therapy. Gastrointestinal Endoscopy 83(6): 1090-1106.e3	- Systematic review used as source of primary studies
Li, Y. M., Li, L., Yu, C. H. et al. (2008) A systematic review and meta-analysis of the treatment for Barrett's esophagus. Digestive Diseases & Sciences 53(11): 2837-46	- Systematic review used as source of primary studies
Liu, Y. Z., Lv, X. H., Deng, K. et al. (2020) Efficacy and safety of endoscopic submucosal tunnel dissection vs endoscopic submucosal dissection for early superficial upper gastrointestinal precancerous lesions and tumors: A meta-analysis. Journal of Digestive Diseases 21(9): 480-489	- Systematic review used as source of primary studies *review of studies with population not meeting protocol*

Study	Exclusion reason
Lu, J. X.; Liu, D. L.; Tan, Y. Y. (2019) Clinical outcomes of endoscopic submucosal tunnel dissection compared with conventional endoscopic submucosal dissection for superficial esophageal cancer: a systematic review and meta-analysis. Journal of Gastrointestinal Oncology 10(5): 935-943	- Systematic review used as source of primary studies
May, A., Gossner, L., Behrens, A. et al. (2003) A prospective randomized trial of two different endoscopic resection techniques for early stage cancer of the esophagus. Gastrointestinal Endoscopy 58(2): 167-75	- Population not relevant to this review protocol *Mixed population including people with squamous cell carcinoma*
Menon, D., Stafinski, T., Wu, H. et al. (2010) Endoscopic treatments for Barrett's esophagus: a systematic review of safety and effectiveness compared to esophagectomy. BMC Gastroenterology 10: 111	- Systematic review used as source of primary studies
Mochizuki, S., Uedo, N., Oda, I. et al. (2015) Scheduled second-look endoscopy is not recommended after endoscopic submucosal dissection for gastric neoplasms (the SAFE trial): a multicentre prospective randomised controlled non-inferiority trial. Gut 64(3): 397-405	- Comparator in study does not match that specified in this review protocol *and population does not meet protocol (people with solitary gastric neoplasm)*
Orman, E. S.; Li, N.; Shaheen, N. J. (2013) Efficacy and durability of radiofrequency ablation for Barrett's Esophagus: systematic review and meta-analysis. Clinical Gastroenterology & Hepatology 11(10): 1245-55	- Systematic review used as source of primary studies
Pandey, G., Mulla, M., Lewis, W. G. et al. (2018) Systematic review and meta-analysis of the effectiveness of radiofrequency ablation in low grade dysplastic Barrett's esophagus. Endoscopy 50(10): 953-960	- Systematic review used as source of primary studies
Peery, A. F. and Shaheen, N. J. (2011) Esophagus: Endoscopic therapy for flat, dysplastic Barrett esophagus. Nature Reviews Gastroenterology & Hepatology 8(4): 186-7	- Conference abstract
Peng, W., Tan, S., Ren, Y. et al. (2020) Efficacy and safety of endoscopic submucosal tunnel dissection for superficial esophageal neoplastic lesions: a systematic review and meta-analysis. Journal Of Cardiothoracic Surgery 15(1): 33	- Systematic review used as source of primary studies

Study	Exclusion reason
Phoa, K. N., Rosmolen, W. D., Weusten, Blam et al. (2017) The cost-effectiveness of radiofrequency ablation for Barrett's esophagus with low-grade dysplasia: results from a randomized controlled trial (SURF trial). Gastrointestinal Endoscopy 86(1): 120-129.e2	- Health economics paper based on study included in the present review
Pouw, R. E., van Vilsteren, F. G., Peters, F. P. et al. (2011) Randomized trial on endoscopic resection-cap versus multiband mucosectomy for piecemeal endoscopic resection of early Barrett's neoplasia. Gastrointestinal Endoscopy 74(1): 35-43	- Population not relevant to this review protocol *people with High-grade dysplasia/early cancer; paper considered for inclusion in question 4.2*
Qumseya, B. J., Wani, S., Desai, M. et al. (2016) Adverse Events After Radiofrequency Ablation in Patients With Barrett's Esophagus: A Systematic Review and Meta-analysis. Clinical Gastroenterology & Hepatology 14(8): 1086-1095.e6	- Systematic review used as source of primary studies
Qumseya, B. J., Wani, S., Gendy, S. et al. (2017) Disease Progression in Barrett's Low-Grade Dysplasia With Radiofrequency Ablation Compared With Surveillance: Systematic Review and Meta-Analysis. American Journal of Gastroenterology 112(6): 849-865	- Systematic review used as source of primary studies
Scholvinck, D. W., Kunzli, H. T., Kestens, C. et al. (2015) Treatment of Barrett's esophagus with a novel focal cryoablation device: a safety and feasibility study. Endoscopy 47(12): 1106-12	- Comparator in study does not match that specified in this review protocol *comparing ablations of different seconds (6, 8 or 10); non-randomised study with randomised controlled studies available.*
Shah, S., Roccato, M. K., Ji, S. S. et al. (2021) ID: 3522400 SIMPLIFED VERSUS STANDARD RADIOFREQUENCY ABLATION PROTOCOLS FOR DYSPLASTIC BARRETT'S ESOPHAGUS: A SYSTEMATIC REVIEW AND META-ANALYSIS. Gastrointest. Endosc. 93(6): AB292-None	- Duplicate reference
Shah, S., Roccato, M. K., Ji, S. et al. (2021) Simplified Versus Standard Radiofrequency Ablation Protocols for Barrett's Esophagus: A Systematic Review and Meta-Analysis. Techniques and Innovations in Gastrointestinal Endoscopy.	- Systematic review protocol

Study	Exclusion reason
Shaheen, N. J., Overholt, B. F., Sampliner, R. E. et al. (2011) Durability of radiofrequency ablation in Barrett's esophagus with dysplasia. Gastroenterology 141(2): 460-8	- Population not relevant to this review protocol *mixed population of low and high-grade dysplasia and results cannot be separated*
Sharma, P., Wani, S., Weston, A. P. et al. (2006) A randomised controlled trial of ablation of Barrett's oesophagus with multipolar electrocoagulation versus argon plasma coagulation in combination with acid suppression: long term results. Gut 55(9): 1233-9	- Population not relevant to this review protocol *Non-dysplastic Barrett's oesophagus*
Sharma, V. K., Kim, H. J., Das, A. et al. (2008) A prospective pilot trial of ablation of Barrett's esophagus with low-grade dysplasia using stepwise circumferential and focal ablation (HALO system). Endoscopy 40(5): 380-7	- No relevant outcomes
Sie, C., Bright, T., Schoeman, M. et al. (2013) Argon plasma coagulation ablation versus endoscopic surveillance of Barrett's esophagus: late outcomes from two randomized trials. Endoscopy 45(11): 859-65	- Review article but not a systematic review *presents results from 2 RCTs assessed separately for inclusion in the present review*
Tariq, R., Enslin, S., Hayat, M. et al. (2020) Efficacy of Cryotherapy as a Primary Endoscopic Ablation Modality for Dysplastic Barrett's Esophagus and Early Esophageal Neoplasia: A Systematic Review and Meta-Analysis. Cancer Control 27(1): 1073274820976668	- Systematic review used as source of primary studies
Visrodia, K., Zakko, L., Singh, S. et al. (2018) Cryotherapy for persistent Barrett's esophagus after radiofrequency ablation: a systematic review and meta-analysis. Gastrointestinal Endoscopy 87(6): 1396-1404.e1	- Systematic review used as source of primary studies
Wang, Y., Ma, B., Yang, S. et al. (2022) Efficacy and Safety of Radiofrequency Ablation vs. Endoscopic Surveillance for Barrett's Esophagus With Low-Grade Dysplasia: Meta-Analysis of Randomized Controlled Trials. Frontiers in Oncology 12: 801940	- Systematic review used as source of primary studies
Wronska, E., Polkowski, M., Orlowska, J. et al. (2021) Argon plasma coagulation for Barrett's esophagus with low-grade dysplasia: a randomized trial with long-term follow-up on the	- Comparator in study does not match that specified in this review protocol *compares APC of different strength (Watts) combined with different doses of PPI medication*

Study	Exclusion reason
impact of power setting and proton pump inhibitor dose. Endoscopy 53(2): 123-132	
Wronska, E., Polkowski, M., Orlowska, J. et al. (2021) Correction: Argon plasma coagulation for Barrett's esophagus with low-grade dysplasia: a randomized trial with long-term follow-up on the impact of power setting and proton pump inhibitor dose. Endoscopy 53(2): c2	- Duplicate reference
Yang, D., Zou, F., Xiong, S. et al. (2017) Endoscopic submucosal dissection for the management of barrett's early neoplasia: A systematic review and meta-analysis. Gastrointestinal Endoscopy: ab409	- Systematic review used as source of primary studies
Yang, D., Zou, F., Xiong, S. et al. (2018) Endoscopic submucosal dissection for early Barrett's neoplasia: a meta-analysis. Gastrointestinal Endoscopy 87(6): 1383-1393	- Comparator in study does not match that specified in this review protocol *no control group*
Zhang, L., Dong, L., Liu, J. et al. (2009) Argon plasma coagulation for Barrett's esophagus: A systematic review. Journal of Xi'an Jiaotong University (Medical Sciences) 30(5): 567-570	- Study not reported in English

Health Economic studies

Published health economic studies that met the inclusion criteria (relevant population, comparators, economic study design, published 2006 or later and not from non-OECD country or USA) but that were excluded following appraisal of applicability and methodological quality are listed below. See the health economic protocol for more details.

None.