National Institute for Health and Care Excellence

Draft for consultation

Barrett's oesophagus

4.2 Evidence review for the clinical and cost effectiveness of endoscopic treatments in Barrett's Oesophagus (high-grade dysplasia, stage 1 adenocarcinoma)

NICE guideline <number>

Evidence reviews underpinning recommendations 1.5.1 to 1.5.2 and research recommendations in the NICE guideline

August 2022

Draft for consultation

These evidence reviews were developed by Guideline Development Team NGC

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1.1 Review question

For adults with high-grade dysplasia and stage 1 adenocarcinoma, what is the clinical and cost effectiveness of endoscopic treatments alone or in combination?

1.1.1 Introduction

There is well established evidence that High Grade Dysplasia is a pre-malignant change that invariably progresses to cancer. There are endoscopic treatment options, including endoscopic resection (ER) and the ablation techniques of radiofrequency ablation (RFA), cryo-ablation and argon plasma coagulation (APC). These techniques are being used in current clinical practice, either alone or in combination. ER involves removal of the dysplastic mucosa whereas the ablation techniques destroy the dysplastic tissue using either heat or cold with the intention of allowing healing by regrowth of non dysplastic neo-squamous epithelium. Often a course of treatments are required. These are not risk free, with bleeding, perforation and stricture formation all recognised complications. Consequently, it is important to determine the clinical and cost effectiveness of endoscopic treatment techniques for high 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 with Barrett's Oesophagus, 18 years and over, with high grade dysplasia or stage 1 adenocarcinoma Exclusion: adults with non and low grade dysplastic, indefinite dysplasia Barrett's and those beyond stage 1 oesophageal adenocarcinoma
Interventions	• Endoscopic resection (Endoscopic Mucosal Resection (EMR), Endoscopic Submucosal Dissection (ESD)) • Endoscopic ablation (Radio Frequency ablation (RFA), Argon Plasma Coagulation (APC), cryotherapy) • Endoscopic resection and ablation

Comparisons	• Different technique of endoscopic resection or ablation e.g.:
	  ○ Resection technique vs resection technique
	  ○ Ablation technique vs ablation technique
	  ○ Mixed technique (endoscopic resection and ablation) vs different mixed technique
	• Oesophagectomy
	• 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) • Treatment related mortality • Health related quality of life (any validated score) • Complete regressions of dysplasia or Barrett's oesophagus • Recurrence of Barrett's dysplasia or neoplasia • Need for retreatment • Complications of treatment (e.g., bleeding, pain infection, perforation, stricture) • Length of hospital stay • Conversion of endoscopic treatment to surgery Minimum length of follow up of 1 year but to also include longest follow up period available.
Study design	• RCT • If no RCT data is available, non-randomised studies will be considered if the study is comparative with another technique. • Systematic Reviews of RCTs 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

Eight studies (6 RCTs, 2 observational studies) were included in the review; [8, 9, 13-18] these are summarised in Table 2 below. Evidence from these studies is summarised in the clinical evidence summary below (Table 3).

The studies compared different endoscopic treatments. Observational studies were included for comparisons where no RCT evidence was identified. RCT evidence was identified comparing: Argon plasma coagulation (APC) to surveillance; endoscopic resection (ER) combined with APC to ER combined with radiofrequency ablation (RFA); ER using a cap with ER with Multi-band mucosectomy (MBM); RFA with sham endoscopic procedure; endoscopic submucosal dissection (ESD) with endoscopic mucosal resection (EMR); focal ER combined with stepwise radical ER (SRER) with focal ER combined with RFA.

Observational evidence was identified comparing EMR combined with RFA with RFA alone and RFA with cryotherapy.

See also the study selection flow chart in Appendix C, study evidence tables in Appendix D, forest plots in Appendix E and GRADE tables in Appendix F.

1.1.4.2 Excluded studies

There was one Cochrane review identified[5]. The review could not be included as it included carcinoma, including squamous cell carcinoma and not limited to Barrett's oesophagus. The review had no included studies but included a meta-analysis of 5 excluded studies that did not meet all the Cochrane review's inclusion criteria. These were independently cross-checked for inclusion in the present review. None met the review protocol as they included interventions not included in the protocol of the current review.

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
Li 2016 [8]	EMR+RFA (n=406) Vs RFA alone (n=857)	Patients with high-grade dysplasia (n=1054) or intramucosal carcinoma (IM) (n=209); Total n=1263 Mean age (SD): 66.59 (10.34) years USA	Treatment related mortality Complete eradication of dysplasia Complete eradication of intestinal metaplasia Recurrence of Intestinal metaplasia Complications of treatment (stricture, GI	US RFA Patient Registry Retrospective observational study; multicentre registry including people who had RFA preceded by EMR. Patients with EMR before RFA had worse pre-treatment histology (IMC, 38% vs 6%), shorter BE segment (mean 4.6 vs 5.4 cm) and were less likely to be

Study	Intervention and comparison	Population	Outcomes	Comments
			bleeding, hospitalisation) Number of RFA sessions required (protocol outcome: need for treatment) At mean (SD) follow-up time: 2.86 (1.53) years for EMR+RFA, 2.76 (1.66) years for RFA alone	taking twice-daily PPIs (74% vs 81%) Outcomes stratified by baseline grade of dysplasia
Manner 2014 [9]	APC (n=33) Vs Surveillance (n=30) PPI (esomeprazole) was administered in both treatment groups (dosage adjusted to the patients' 24-hour PH-metry finding 40 or 80 mg per day)	Patients in whom focal early Barrett's neoplasia (high-grade neoplasia, n=40 or mucosal cancer, n=23) had been curatively resected by endoscopy (n=63) Mean age (SD; range): 63 (1; 42-79) years Germany	Recurrence (of neoplasia) 2-year follow-up; Mean follow-up (SD, range): ablation group= 28.2 (13.7, 0-44) months; surveillance group= 24.7 (14.8; 0-45) months	RCT
Peerally 2019[13]	ER + APC (n=40) Vs ER+ RFA (n=36) High-dose PPI (twice daily) was administered to all patients.	Patients with high-grade dysplasia (n=58) or T1a cancer (n=18); Total n=76 Mean age: 69.7 years UK	Clearance of high-grade dysplasia/cancer Clearance of Barrett's oesophagus Adverse events (stricture, GI bleeding) (protocol outcome: complications of treatment) 12 months	Multicentre pilot RCT: Barrett's Randomised Intervention for Dysplasia by Endoscopy (BRIDE study); 6 tertiary-care referral centres N=65 completed the trial Study also reports QoL (EQ-5D, QLQ-C30, chest-pain, dysphagia) but not in an extractable format: graph format with no specific scores reported
Pouw 2011[14]	ER-cap; n=42	Patients with Barrett's	Complications of treatment:	RCT

Study	Intervention and comparison	Population	Outcomes	Comments
	Vs ER with Multi-band mucosectomy (MBM); n=42	oesophagus with biopsy proven high-grade dysplasia (n=19) and/or early cancer (n=52); Total n=84 Median age (IQR): 70 (63.3-76) years The Netherlands	bleeding, perforation During the procedure and 0-48 hours later.	Perforations occurring in the ER-cap group were reported as moderate; perforation occurring in the MBM group was reported as severe Complication severity: moderate (4-10 days hospitalisation, need for repeat endoscopic intervention), severe (>10 days of hospitalisation, intensive care unit admission, need for surgery), fatal (death attributable to procedure <30 days or longer with continuous hospitalization)
Shaheen 2009[15]	RFA Vs Sham endoscopic procedure All patients received 40 mg of esomeprazole twice daily throughout the trial	Patients with dysplastic Barrett's oesophagus (n=127; n=63 had high-grade dysplasia and were included in this review) Mean age (range): 66.37 (49-80) USA	Complete eradication of dysplasia Complete eradication of intestinal metaplasia At 12 months	Multicentre RCT (19 sites) Includes people with low-grade dysplasia but randomisation and results were stratified by grade of dysplasia; only results relevant to the high-grade dysplasia population are presented in the present review.
Terheggen 2017[16]	ESD (n=20) Vs EMR (n=20) PPI was orally administered in double standard during the study period.	Barrett's oesophagus patients with high-grade intraepithelial neoplasia (HGIN, N=9) or early adenocarcinoma (EAC) (n=31); Total n=40 Mean age (SD): 64.5 (11.52) years	Complete resection of high-grade intraepithelial neoplasia or adenocarcinoma Curative resection (histologically complete resection of HGIN/ mucosal EAC or EAC with low-risk	RCT Pre-treatment histology: ESD: n=5 high-grade intraepithelial neoplasia, n=15 adenocarcinoma; EMR: n=4 high-grade intraepithelial neoplasia, n=16 adenocarcinoma

Study	Intervention and comparison	Population	Outcomes	Comments
		Germany	superficial submucosal invasion) Adverse events (perforation, mediastinitis, temporary chest discomfort, severe adverse events) Up to 30 days after the procedure Complete remission of neoplasia after initial resection Complete remission of intestinal neoplasia Recurrent neoplasia Conversion of endoscopic treatment to surgery (Referral to elective surgery) >30 day follow-up (mean (SD) follow-up was 22.6 (7.8) months for the ESD and 23.6 (5) months for the EMR group.	Severe adverse events: that caused prolongation of hospitalisation and/or its management required additional therapeutic interventions, 30-day mortality
Thota 2018[17]	RFA (n=73) Vs Cryotherapy (cryo-spray; n=81)	Barrett's oesophagus patients with dysplasia or intramucosal carcinoma; N=154 USA	Mortality (all-cause and disease specific) Complete eradication of intestinal metaplasia Complete eradication of dysplasia	Retrospective observational study Indirectness: Includes 23/154 (15%) had low-grade dysplasia at baseline

Study	Intervention and comparison	Population	Outcomes	Comments
			Recurrence 2-year follow up	
van Vilsteren 2011[18]	Focal ER (ER-cap technique) + Stepwise radical ER (SRER) (n=25) Vs Focal ER (ER-cap technique) + RFA (n=22)	Barrett's oesophagus patients with high-grade dysplasia (n=19) or early cancer (n=28); Total n=55 Median age (range): 68 (45-88) years Germany, The Netherlands	Complete histological response for neoplasia (CR-neoplasia) Complete histological response for intestinal metaplasia (CR-IM) Recurrence Complications (severe, moderate, mild) Median (IQR) follow-up from initial treatment 24 (18-29) months; from final treatment sessions 18 (11-23) months	Multi-centre RCT (3 centres) Recurrence notes was of early cancer, requiring ER.

See Appendix D for full evidence tables.

1.1.6 Summary of the effectiveness evidence

Table 3: Clinical evidence summary: EMR + RFA versus RFA alone in people with high-grade dysplasia/intramucosal carcinoma

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with RFA alone	Risk difference with EMR+RFA
Mortality (treatment-related)	1263 (1 observational study)	⨁◯◯◯ Very low[a]	not estimable	0 per 1,000	0 fewer per 1,000 (0 fewer to 0 fewer)
Recurrence of intestinal metaplasia	831 (1 observational study)	⨁◯◯◯ Very low[a,b]	RR 1.06 (0.79 to 1.41)	195 per 1,000	12 more per 1,000 (41 fewer to 80 more)
Number of RFA sessions required	994 (1 observational study)	⨁◯◯◯ Very low[a]	-	The mean number of RFA sessions required was 0	MD 0.5 lower (0.76 lower to 0.24 lower)

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

b. 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; for continuous outcomes: 0.5*SD of the control group (1.05 for number of RFA sessions required)

Table 4: **Clinical evidence summary: EMR + RFA versus RFA alone in people with high-grade dysplasia**

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with RFA alone	Risk difference with EMR+RFA
Complete eradication of dysplasia in people with HGD	832 (1 observational study)	⊕◯◯◯ Very low[a]	RR 1.03 (0.99 to 1.07)	914 per 1,000	27 more per 1,000 (9 fewer to 64 more)
Complete eradication of intestinal metaplasia in people with HGD	832 (1 observational study)	⊕◯◯◯ Very low[a]	RR 1.02 (0.95 to 1.09)	830 per 1,000	17 more per 1,000 (41 fewer to 75 more)
Complications (any) in people with HGD	1054 (1 observational study)	⊕◯◯◯ Very low[a,b]	RR 1.38 (0.89 to 2.14)	75 per 1,000	28 more per 1,000 (8 fewer to 85 more)
Stricture in people with HGD	1054 (1 observational study)	⊕◯◯◯ Very low[a,b]	RR 1.11 (0.69 to 1.79)	75 per 1,000	8 more per 1,000 (23 fewer to 59 more)
Bleeding in people with HGD	1054 (1 observational study)	⊕◯◯◯ Very low[a,b]	RR 1.19 (0.32 to 4.46)	10 per 1,000	2 more per 1,000 (7 fewer to 35 more)
Hospitalisation in	1054 (1	⊕◯◯◯ Very low[a,b]	RR 2.03 (0.79 to 5.17)	14 per 1,000	14 more per 1,000 (3 fewer to 57 more)

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with RFA alone	Risk difference with EMR+RFA
people with HGD	observational study)				

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

b. 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

Table 5: Clinical evidence summary: EMR + RFA versus RFA alone in people with intramucosal carcinoma

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with RFA alone	Risk difference with EMR+RFA
Complete eradication of dysplasia in people with intramucosal carcinoma	162 (1 observational study)	⨁◯◯◯ Very low[a]	RR 0.95 (0.90 to 1.01)	1,000 per 1,000	50 fewer per 1,000 (100 fewer to 10 more)
Complete eradication of intestinal metaplasia in people with intramucosal carcinoma	162 (1 observational study)	⨁◯◯◯ Very low[a,b]	RR 0.87 (0.77 to 0.97)	943 per 1,000	123 fewer per 1,000 (217 fewer to 28 fewer)

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with RFA alone	Risk difference with EMR+RFA
Complications (any) in people with intramucosal carcinoma	209 (1 observational study)	⨁◯◯◯ Very low[a,b]	RR 1.43 (0.31 to 6.52)	36 per 1,000	16 more per 1,000 (25 fewer to 201 more)
Stricture in people with intramucosal carcinoma	209 (1 observational study)	⨁◯◯◯ Very low[a,b]	RR 1.43 (0.31 to 6.52)	36 per 1,000	16 more per 1,000 (25 fewer to 201 more)
Bleeding in people with intramucosal carcinoma	209 (1 observational study)	⨁◯◯◯ Very low[a,c]	not estimable[d]	0 per 1,000	0 fewer per 1,000 (0 fewer to 0 fewer)
Hospitalisation in people with intramucosal carcinoma	209 (1 observational study)	⨁◯◯◯ Very low[a,c]	not estimabled	0 per 1,000	0 fewer per 1,000 (0 fewer to 0 fewer)

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

b. 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

c. Downgraded by 1 increment due to serious imprecision as there were zero events in both arms and sample size was >70 but <350

d. zero events in both arms

Table 6: Clinical evidence summary: APC versus surveillance in people with high-grade neoplasia/ mucosal cancer

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Surveillance	Risk difference with APC
Recurrence of neoplasia follow-up: Mean follow-up (SD): ablation group= 28.2 (13.7) months; surveillance group= 24.7 (14.8) months	63 (1 RCT)	⊕⊕⊕⊕ High	RR 0.08 (0.01 to 0.60)	367 per 1,000	337 fewer per 1,000 (363 fewer to 147 fewer)

Table 7: Clinical evidence summary: ER+APC versus ER+RFA in people with high-grade dysplasia/T1a cancer

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with ER+RFA	Risk difference with ER+APC
Clearance of high-grade dysplasia/ cancer follow-up: 12 months	65 (1 RCT)	⊕⊕⊕◯ Moderate[a]	RR 1.06 (0.84 to 1.33)	794 per 1,000	48 more per 1,000 (127 fewer to 262 more)
Clearance of BE on endoscopy follow-up: 12 months	65 (1 RCT)	⊕⊕◯◯ Low[a]	RR 0.87 (0.54 to 1.39)	559 per 1,000	73 fewer per 1,000 (257 fewer to 218 more)
Stricture follow-up: 12 months	73 (1 RCT)	⊕⊕◯◯ Low[a]	RR 0.97 (0.21 to 4.51)	83 per 1,000	3 fewer per 1,000 (66 fewer to 293 more)
GI bleeding follow-up: 12 months	73 (1 RCT)	⊕⊕◯◯ Low[a]	RR 1.95 (0.18 to 20.53)	28 per 1,000	26 more per 1,000 (23 fewer to 543 more)

a. 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

Table 8: Clinical evidence summary: ER-cap versus MBM in people with high-grade dysplasia/ early cancer

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with MBM	Risk difference with ER-cap
Clinically not relevant bleeding (during the procedure, 0-48 hours later)	84 (1 RCT)	⨁⨁◯◯ Low[a,b]	RR 1.29 (0.81 to 2.06)	405 per 1,000	117 more per 1,000 (77 fewer to 429 more)
Perforation (during the procedure, 0-48 hours later)	84 (1 RCT)	⨁◯◯◯ Very low[a,b]	RR 3.00 (0.33 to 27.69)	24 per 1,000	48 more per 1,000 (16 fewer to 635 more)

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

b. 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

Table 9: Clinical evidence summary: RFA vs sham endoscopic procedure in people with high-grade dysplasia

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with sham endoscopic procedure	Risk difference with RFA
Complete eradication of dysplasia at 12 months	58 (1 RCT)	⨁⨁⨁◯ Moderate[a]	RR 4.47 (1.85 to 10.82)	200 per 1,000	694 more per 1,000 (170 more to 1,964 more)
Complete eradication of intestinal metaplasia at 12 months	58 (1 RCT)	⨁⨁◯◯ Low[a,b]	OR 25.08 (8.55, 73.57)	0 per 1,000	820 more per 1,000

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with sham endoscopic procedure	Risk difference with RFA
					(680 more to 960 more)c

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

b. Downgraded by 1 increment if the confidence interval did not cross MIDs but was judged to be very wide.
c. Calculated based on risk difference of 0.82 (95% CI 0.68, 0.96)

Table 10: Clinical evidence summary: ESD versus EMR in people with high-grade intraepithelial neoplasia/ early adenocarcinoma

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with EMR	Risk difference with ESD
Complete resection of high-grade intraepithelial neoplasia or oesophageal adenocarcinoma	34 (1 RCT)	⊕⊕⊕⊕ High	RR 5.00 (1.28 to 19.50)	118 per 1,000	471 more per 1,000 (33 more to 2,176 more)
Curative resection	34 (1 RCT)	⊕⊕⊕◯ Moderate[a]	RR 4.50 (1.14 to 17.83)	118 per 1,000	412 more per 1,000 (16 more to 1,980 more)
Complete remission of neoplasia after initial resection	33 (1 RCT)	⊕⊕⊕⊕ High	RR 1.00 (0.84 to 1.18)	941 per 1,000	0 fewer per 1,000 (151 fewer to 169 more)

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with EMR	Risk difference with ESD
(mean (SD) follow-up: ESD 22.6 (7.8) months, EMR 23.6 (5) months)					
Complete remission of intestinal neoplasia (mean (SD) follow-up: ESD 22.6 (7.8) months, EMR 23.6 (5) months)	33 (1 RCT)	⨁⨁◯◯ Low[a]	RR 0.64 (0.30 to 1.35)	588 per 1,000	212 fewer per 1,000 (412 fewer to 206 more)
Recurrence of neoplasia (mean (SD) follow-up: ESD 22.6 (7.8) months, EMR 23.6 (5) months)	33 (1 RCT)	⨁⨁◯◯ Low[a]	OR 7.87 (0.16, 397.12)	0 per 1,000	60 more per 1,000 (90 fewer to 220 more) b
Patients referred for elective surgery	40 (1 RCT)	⨁⨁◯◯ Low[a]	RR 1.33 (0.34 to 5.21)	150 per 1,000	50 more per 1,000 (99 fewer to 632 more)

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with EMR	Risk difference with ESD
Perforation (up to 30 days after the procedure)	40 (1 RCT)	⨁⨁◯◯ Low[a]	OR 7.79 (0.47, 129.11)	0 per 1,000	100 more per 1,000 (50 fewer to 250 more) b

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with EMR	Risk difference with ESD
Mediastinitis (up to 30 days after the procedure)	40 (1 RCT)	⨁⨁◯◯ Low[a]	OR 7.39 (0.15, 372.38)	0 per 1,000	50 more per 1,000 (80 fewer to 180 more) b
Temporary chest discomfort (up to 30 days after the procedure)	40 (1 RCT)	⨁⨁◯◯ Low[a]	RR 1.50 (0.28 to 8.04)	100 per 1,000	50 more per 1,000 (72 fewer to 704 more)

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with EMR	Risk difference with ESD
Severe adverse events (up to 30 days after the procedure)	40 (1 RCT)	⨁⨁◯◯ Low[a]	OR 7.79 (0.47, 129.11)	0 per 1,000	100 more per 1,000 (50 fewer to 250 more) b
30-day mortality	40 (1 RCT)	⨁⨁◯◯ Low[c]	not estimable	0 per 1,000	0 fewer per 1,000 (0 fewer to 0 fewer)

a. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs; For dichotomous outcomes default MIDs: 0.8 and 1.25
b. Calculated based on risk difference due to zero events in one arm; risk difference (95% CI) was 0.06 (-0.09 to 0.22) for recurrence of neoplasia, 0.10 (-0.05 to 0.25) for perforation, 0.05 (-0.08 to 0.18) for mediastinitis, 0.10 (-0.05 to 0.25) for severe adverse events
c. Downgraded by 2 increments for very serious imprecision as sample size was <70 and there were zero events in both arms

Table 11: Clinical evidence summary: RFA versus cryotherapy in people with dysplasia/ intramucosal cancer

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with cryotherapy	Risk difference with RFA
Mortality (all cause) follow-up: 2 years	152 (1 observational study)	⨁◯◯◯ Very low[a,b,c]	RR 0.14 (0.02 to 1.08)	100 per 1,000	86 fewer per 1,000 (98 fewer to 8 more)
Complete eradication of metaplasia	152 (1 observati	⨁◯◯◯ Very low[a,b,c]	RR 1.62 (1.19 to 2.20)	413 per 1,000	256 more per 1,000 (78 more to 495 more)

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with cryotherapy	Risk difference with RFA
follow-up: 2 years	onal study)				
Mortality (due to cancer) follow-up: 2 years	152 (1 observational study)	⨁◯◯◯ Very low[a,b,c]	RR 0.28 (0.03 to 2.43)	50 per 1,000	36 fewer per 1,000 (49 fewer to 72 more)
Complete eradication of dysplasia follow-up: 2 years	152 (1 observational study)	⨁◯◯◯ Very low[a,b,c]	RR 1.11 (0.96 to 1.28)	788 per 1,000	87 more per 1,000 (32 fewer to 221 more)
Recurrence of disease follow-up: 2 years	126 (1 observational study)	⨁◯◯◯ Very low[a,b,c]	RR 0.78 (0.31 to 1.96)	143 per 1,000	31 fewer per 1,000 (99 fewer to 137 more)

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

b. Downgraded by 1 increment because the evidence included an indirect population: people with low-grade dysplasia

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

Table 12: Clinical evidence summary: ER-cap + SRER versus ER-cap + RFA in people with high-grade dysplasia/early cancer

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with ER+RFA	Risk difference with ER+SRER
Complete histological response for neoplasia (median follow-up 24 months)	47 (1 RCT)	⊕⊕⊕◯ Moderate[a]	RR 1.05 (0.93 to 1.18)	955 per 1,000	48 more per 1,000 (67 fewer to 172 more)
Complete histological response for intestinal metaplasia (median follow-up 24 months)	47 (1 RCT)	⊕⊕⊕◯ Moderate[a]	RR 0.96 (0.83 to 1.12)	955 per 1,000	38 fewer per 1,000 (162 fewer to 115 more)
Recurrence (median follow-up 24 months)	47 (1 RCT)	⊕◯◯◯ Very low[a,b]	OR 6.55 (0.13, 332.93)	0 per 1,000	40 more per 1,000 (70 fewer to 150 more) c
Severe complications (perforation, stenoses)	47 (1 RCT)	⊕⊕⊕◯ Moderate[a]	OR 8.24 (1.51, 45.05)	0 per 1,000	240 more per 1,000 (60 more to 240 more) c
Moderate complications (early bleeding, stenoses, late bleeding)	47 (1 RCT)	⊕⊕⊕◯ Moderate[a]	RR 3.96 (1.58 to 9.93)	182 per 1,000	538 more per 1,000 (105 more to 1,624 more)

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with ER+RFA	Risk difference with ER+SRER
Mild complications (acute bleeding, acute non-transmural laceration)	47 (1 RCT)	⨁◯◯◯ Very low[a,b]	RR 1.47 (0.40 to 5.44)	136 per 1,000	64 more per 1,000 (82 fewer to 605 more)

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

b. 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

c. Calculated based on risk difference due to zero events in one arm; risk difference (95% CI) was 0.04 (-0.07 to 0.15) for recurrence, 0.24 (0.06 to 0.42) for severe complications

See Appendix F for full GRADE and/or GRADE-CERQual tables

1.1.7 Economic evidence

1.1.7.1 Included studies

Four health economic studies with the relevant comparison were included in this review. Three were published economic evaluations[1-3] and the fourth was the guideline model from CG106.[11] These are summarised in the health economic evidence profile below (Table 13,Table 14 and Table 15) 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 13: Health economic evidence profile: radiofrequency ablation versus oesophagectomy

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects	Cost effectiveness	Uncertainty
Boger 2010 [1] (UK)	Partially applicable[(a)]	Potentially serious limitations[(b)]	• Probabilistic model based on data taken from various literature • Cost-utility analysis (QALYs) Population: People with HGD in BO • Comparators: 1. Oesophagectomy 2. RFA followed by endoscopic surveillance, with oesophagectomy reserved for HGD recurrence or persistence Time horizon: 25 years (lifetime)	-£1,904[(c)]	0.4 QALYs	Intervention 2 dominates	Probability Intervention 2 cost effective (£20/£30K threshold): 85%/83% Various one-way sensitivity analyses were conducted testing extreme values, after which RFA remained cost effective oesophagectomy at a threshold of £20k per QALY.

Abbreviations: BO= Barrett's oesophagus; HGD= high grade dysplasia;; k= thousand; QALY= quality-adjusted life years; RCT= randomised controlled trial; RFA= radiofrequency ablation;

(a) QALYs were not captured using the EQ-5D scale

(b) Sources for costs are dated and not likely reflective of the current NHS. Model does not include the natural history of Barrett's oesophagus and therefore progression of Barrett's post-treatment is not adequately captured.

(c) 2009/10 costs in UK pounds. Cost components incorporated: surveillance, RFA, oesophagectomy, complications from oesophagectomy and dilatation, outpatient follow-up, palliation of untreatable adenocarcinoma

Table 14: Health economic evidence profile: endoscopic eradication therapy versus endoscopic surveillance

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects	Cost effectiveness	Uncertainty
Filby 2017 [3] (UK)	Partially applicable[(a)]	Potentially serious limitations[(b)]	• Probabilistic model based on natural history of Barrett's oesophagus from Inadomi 2009 [7]) • Cost-utility analysis (QALYs) • Population: People with HGD in BO • Comparators: 1. endoscopic surveillance until oesophageal cancer developed 2. Endoscopic eradication therapy Time horizon: Lifetime	£1,246[(c)]	0.979 QALYs	£1,272 per QALY gained	Probability Intervention 2 cost effective (£20/£30K threshold): 65%/63% Univariate analysis identified two areas likely to change the direction of results: 1. Proportion of patients having residual dysplasia following RFA. For the intervention to cross the £20k threshold, treatment efficacy would have to fall below 20% (base case efficacy: 92.6%). 2. HGD multiplier: In the model, when there are fewer people with HGD, there are more people with NDBO, LGD and OAC. For the ICER to cross over £20k, there would have to be less than half the proportion of patients staying in

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects	Cost effectiveness	Uncertainty
							the HGD health state each year.
Esteban 2018[2] (Spain)	Partially applicable[(d)]	Potentially serious limitations[(e)]	• Probabilistic semi-Markov model based on data from literature • Cost-utility analysis (QALYs) • Population: People with LGD in BO • Comparators: 1.Oesophagectomy 2.Radiofrequency ablation resection (RFA) • Time horizon: 15 years	-£12,182[(f)]	1.23 QALYs	Intervention 2 dominates	Probability Intervention 2 dominates Intervention 1: 100% Various one-way sensitivity analyses were conducted, for example changing the time horizon between 5-25 years, the age between 55-75 years, the discount rate between 0-5%, transition probabilities by 25% either way, among others. In all scenarios, RFA-EMR dominates oesophagectomy.

Abbreviations: BO= Barrett's oesophagus; ICER= incremental cost-effectiveness ratio; LGD= low-grade dysplasia; QALY= quality-adjusted life years; RCT= randomised controlled trial; RFA= Radiofrequency ablation

(a) QALYs were not captured using EQ-5D

(b) Sources for costs are unclear as well as which year they relate to. Sources for QALYs used in the model are unclear. Analysis was funded by a pharmaceutical company.

(c) UK pounds (year that costs relate to unclear). Cost components incorporated: surveillance, oesophagectomy, RFA, EMR, treatment for perforation and stricture, endoscopy and biopsy, PPIs and H2 receptor antagonists following surgery

(d) 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.

(e) 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.

(f) 2013 Euros converted to UK pounds[12]. Cost components incorporated: drug costs (radiotherapy and chemotherapy including administration costs, procedure costs, follow-up costs, treatment complication costs

(g)

Table 15. Health economic evidence profile: Surveillance and ablative treatments versus no surveillance

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects	Cost effectiveness	Uncertainty
NICE Barrett's oesophagus: ablative therapy clinical guideline 2010 (CG106) [11] (UK)	Partially applicable[a]	Potentially serious limitations[b]	• Probabilistic model based on meta-analysis of RCTs (CG106 [11]) • Cost-utility analysis (QALYs) • Population: People aged 60 years with HGD • Comparators: 1. No surveillance 2. Surveillance every three months for the first year, then every 6 months in second year, then annually in years 3-5, then every 5 years thereafter. 3. Surgery 4. EMR plus surveillance 5. RFA plus surveillance 6. EMR plus RFA plus surveillance 7. EMR plus APC plus surveillance • Time horizon: Lifetime	**2 versus 1:** £13,450 **3 versus 1:** £7,189 **4 versus 1:** £12,701 **5 versus 1:** £25,740 **6 versus 1:** £20,634 **7 versus 1:** £16,750	**2 versus 1:** 0.36 QALYS **3 versus 1:** 1.23 QALYS **4 versus 1:** 0.54 QALYS **5 versus 1:** 0.99 QALYS **6 versus 1:** 0.78 QALYS **7 versus 1:** 0.73 QALYS	**2 versus 1:** £283,009 per QALY gained **3 versus 1:** £10,612 per QALY gained **4 versus 1:** £25,662 per QALY gained **5 versus 1:** £24,823 per QALY gained **6 versus 1:** £15,916 per QALY gained **7 versus 1:** £18,745 per QALY gained	Probability of each intervention being cost effective versus intervention 1(£20K/30K threshold) **Int.** / **£20k** / **£30k** 2 / 11% / 17% 3 / 58% / 62% 4 / 36% / 44% 5 / 39% / 53% 6 / 55% / 70% 7 / 45% / 60%

Abbreviations: APC= argon plasma coagulation; CG= clinical guideline; EMR= endoscopic mucosal resection; HGD= high-grade dysplasia;ICER= incremental cost-effectiveness ratio; QALY= quality-adjusted life years; RCT= randomised controlled trial; RFA= radiofrequency ablation

(h) QALYs were not captured using the EQ-5D scale.

(i) Source of natural history data for Barrett's progression is dated. Sources for costs are dated and not likely reflective of current NHS costs. The study authors advise against making data comparisons and ranking treatments due to the poor quality of data informing the modelling.

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 16: 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

1.1.11 Evidence statements

Economic

- One cost utility analysis reported that endoscopic eradication therapy was cost effective versus endoscopic surveillance (ICER: £1,272). This study was graded as being partially applicable with potentially serious limitations.
- One cost utility analysis reported that endoscopic mucosal resection plus radiofrequency ablation plus surveillance, endoscopic mucosal resection plus argon plasma coagulation plus surveillance and surgery were cost effective versus no surveillance (ICERs: £15,916, £18,745 and £10,612, respectively). This study was graded as being partially applicable with potentially serious limitations.
- One cost utility analysis reported that radiofrequency ablation followed by endoscopic surveillance dominated oesophagectomy. This study was graded as being partially applicable with potentially serious limitations.
- One cost utility analysis reported that radiofrequency ablation dominated oesophagectomy. This study was graded as being 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 outcomes considered for this review were mortality (disease specific mortality and all-cause mortality), treatment related mortality, health related quality of life, complete regressions of dysplasia or Barrett's oesophagus, recurrence of Barrett's dysplasia or neoplasia, need for retreatment, complications of treatment (such as bleeding, pain infection, perforation, stricture), length of hospital stay, conversion of endoscopic treatment to surgery. For purposes of decision making, all outcomes were considered equally important and were therefore rated as critical by the committee. No evidence was identified for the outcomes of quality of life and length of hospital stay.

1.1.12.2 The quality of the evidence

The quality of the evidence differed across comparisons ranging from very low to high for different outcomes.

The quality of the evidence for endoscopic mucosal resection + radiofrequency ablation (EMR+RFA) versus RFA alone was very low as evidence came from an observational study that was downgraded for risk of bias (due to baseline differences in participants in the intervention groups) and due to imprecision in the effect estimates.

The majority of the evidence for endoscopic resection + argon plasma coagulation (ER+APC) versus endoscopic resection+ radiofrequency ablation (ER+RFA) and ER-cap versus ER with Multi-band mucosectomy (MBM) was low as the evidence was downgraded for imprecision in the effect estimates with evidence for the latter comparison also downgraded for risk of bias that was due to a lack of clarity over how outcomes were measured *(*complications were recorded only if considered 'clinically significant' and this was not defined) and a difference in level of expertise in endoscopists that could act as a confounding factor impacting on the results).

The quality of the evidence for RFA versus sham endoscopic procedure ranged from low to moderate, being downgraded for risk of bias (due to baseline differences in the intervention groups in terms of the number of people with subsquamous metaplasia, multifocal dysplasia, current use of aspirin or NSAIDS in each group and lack of clarity over how eligible participants were derived) and for imprecision due to the confidence interval around the effect estimate being very wide.

The quality of the evidence for APC versus surveillance was high. The quality of the evidence for endoscopic submucosal dissection (ESD) versus EMR ranged from low to high, being occasionally downgraded due to imprecision where the confidence interval crossed agreed minimal important difference (MIDs).

The quality of the evidence for RFA versus cryotherapy was very low as the evidence came from a single observational study downgraded for risk of bias (due to baseline differences between groups, and lack of randomisation with patients given interventions that could be confounding), indirectness (due to the inclusion of people with low-grade dysplasia) and imprecision in the effect estimates.

Evidence quality for endoscopic resection-cap + stepwise radical endoscopic resection (ER-cap +SRER) versus ER-cap + RFA ranged from very low to moderate as it was downgraded for risk of bias (due to potential selection bias of participants and the ER taking place before randomisation for some participants and after for others); potential selection bias as limited details on recruitment provided and occasionally imprecision in the effect estimates.

1.1.12.3 Benefits and harms

Clinical evidence for EMR+RFA versus RFA alone suggested there was no clinically important difference for the majority of the outcomes examined. Evidence from a sub-group analysis of participants with intramucosal carcinoma, showed a clinically important benefit of the RFA alone for the outcome of complete eradication of intestinal metaplasia. However, the committee noted the evidence came from a single observational study and was of very low quality. The committee noted there was no clinically important difference in complications as well as the number of hospitalisations between participants with intramucosal carcinoma who had EMR combined with RFA and those who had RFA alone. Based on the evidence and their clinical experience, the committee agreed that people with intramucosal carcinoma should receive endoscopic resection. In addition, evidence of no clinically important difference in the aforementioned outcomes was taken to show that EMR does not compromise subsequent treatment with RFA and combination of the two treatments does not result in an increased risk of complications.

Clinical evidence from one RCT suggested there is a clinically important benefit of APC over surveillance for the outcome of recurrence of neoplasia in people with high-grade dysplasia or mucosal cancer after initial endoscopic resection. There was evidence from once RCT indicating there was no clinically important difference between ER when combined with APC compared to when combined with RFA across outcomes, including clearance of high-grade dysplasia/cancer or of Barrett's oesophagus and complications. There was a high event rate achieved in both comparison groups in terms of clearance of high-grade dysplasia/cancer at 12 months and clearance of Barrett's oesophagus on endoscopy. This was interpreted by the

committee to indicate the effectiveness of both treatments. Similarly, there was a very low event rate for both comparison groups in terms of complications including stricture and GI bleeding, supporting the safety of both treatments. Based on the two aforementioned comparisons, the committee noted that the APC can be equally effective to the RFA in terms of reducing the risk of recurring oesophageal lesions in people who have received an endoscopic resection for high-grade dysplasia or T1a adenocarcinoma, noting that for very long segments of Barrett's oesophagus, RFA may be more practical as APC has a smaller ablation catheter. Considering there is no evidence of superiority of one ablation technique over the other, the committee agreed that more research for APC vs RFA is required.

Clinical evidence from one RCT showed a clinically important benefit of MBM over the ER-cap in terms of 'clinically not relevant bleeding' and no clinical difference in perforation during the procedure. The committee emphasised based on their experience that the ER-cap is considered less favourable in clinical practice and has decreased in popularity because MBM is easier to use and has a shorter procedural time.

Clinical evidence from one RCT showed a clinically important benefit of RFA compared to sham endoscopic procedure in people with high-grade dysplasia in terms of complete eradication of dysplasia and complete eradication of intestinal metaplasia. The committee noted this was in line with their experience and supported the effectiveness of RFA. Clinical evidence from one observational study also showed a clinically important benefit of RFA compared to cryotherapy in terms of all-cause mortality and complete eradication of metaplasia and no clinical difference in terms of mortality due to cancer, complete eradication of dysplasia and recurrence of the disease.

There was evidence from one RCT showing a clinically important benefit of ESD compared to EMR in terms of complete resection of high-grade intraepithelial neoplasia or oesophageal adenocarcinoma and curative resection, but no clinically important difference in terms of complete remission of neoplasia after initial resection, recurrence of neoplasia and number of patients referred for elective surgery. In contrast, a clinically important benefit was shown in EMR over ESD for severe adverse events (perforation and mediastinitis) and temporary chest discomfort. The committee noted the clinically important benefits shown were contradictory and, based on their clinical experience, emphasised that ESD may offer an advantage in a sub-group of individuals with Barrett's oesophagus related neoplasia (lesions larger than 15mm, poorly lifting tumours and lesions at risk for submucosal invasion) but there was no reason to select it over EMR for small slightly elevated lesions because ESD is a complex procedure and is associated with more complications. The committee emphasised, based on their experience that endoscopic resection performed with EMR or ESD is less invasive, has fewer complications and is more likely to result in a better quality of life after treatment due to preserved anatomy compared to oesophagectomy and therefore should be offered as first-line treatment to people with T1a oesophageal adenocarcinoma. Nevertheless, they agreed that clinical consultation should be offered to people with stage I oesophageal adenocarcinoma to discuss and evaluate the suitability of treatment options including endoscopic resection and oesophagectomy.

Evidence from one RCT showed a clinically important benefit of stepwise-radical endoscopic resection (SRER) compared with ER+RFA in terms of severe and moderate complications. The evidence showed there was no clinically important difference between ER+SRER compared with ER+RFA across outcomes including complete histological response of neoplasia, complete histological response of intestinal metaplasia, recurrence, and mild complications. The committee noted this evidence was limited to one study and there was imprecision in the effect estimates of some outcomes thereby lowering confidence in the findings and the extent to which conclusions could be drawn from this study. The committee

also noted that SRER is not widely used in current practice and the evidence did not justify a recommendation for its use.

Overall, the committee agreed based on the evidence and their clinical experience that endoscopic treatment either using a combination of endoscopic resection and endoscopic ablation or endoscopic ablation alone is effective in treating people with high-grade dysplasia and preventing progression to adenocarcinoma. Based on their clinical experience, the committee agreed that high-grade dysplasia when associated with neoplastic visible lesions at endoscopy as well as T1a oesophageal adenocarcinoma should be endoscopically resected and the residual Barrett's oesophagus should then be treated with endoscopic ablation, with the largest body of evidence supporting use of RFA over other ablation techniques. The committee discussed the need for further research comparing the different ablation modalities, particularly APC and cryotherapy as the evidence is limited, and agreed to make a research recommendation to help determine the most clinically and cost-effective endoscopic modality.

1.1.12.4 Cost effectiveness and resource use

Surgery is a costlier and riskier procedure than endoscopic treatment. It is unclear whether there is an improved quality of life after surgery compared to endoscopic treatment, and if so, whether the extra cost justifies the improved outcomes.

Endoscopic treatment is a more costly and risky procedure than endoscopic surveillance. However, they are also associated with an improved quality of life. The frequency of surveillance after an endoscopic treatment is expected to reduce compared to surveillance only, so there is potential for future cost savings. Four economic evaluations were identified. All were in a population with high-grade dysplasia; one study included both people with high-grade dysplasia and intramucosal cancer as a single population but justified this action as something frequently done in practice. All four studies sourced utility values from literature sources, which were subsequently used to calculate QALYs. These utilities were not captured using the EQ-5D measure, which is NICE's preferred methodology. For this reason, all studies were graded as partially applicable.

Endoscopic eradication therapy versus endoscopic surveillance

The first study compared endoscopic eradication therapy (endoscopic mucosal resection and radiofrequency ablation) to endoscopic surveillance (Filby 2017). The perspective was that of the UK NHS. The frequency of surveillance was one surveillance session every 3–5 years for non-dysplastic Barrett's oesophagus, two sessions per year for low-grade dysplasia and three sessions per year for high-grade dysplasia. Sources of costs were based on the UK, though the citations were incorrectly referenced meaning the exact source and year were not known. The analysis was also funded by a device manufacturing company. For these reasons, the study was graded as having potentially serious limitations. Endoscopic eradication therapy was cost effective versus endoscopic surveillance with a cost per QALY of £1,272.

Ablation therapy versus no surveillance

The second study was the economic analysis of the NICE 2010 Barrett's oesophagus ablative therapy clinical guideline (CG106), which took a UK NHS perspective. This analysis compared each of the following to no surveillance:

i. endoscopic surveillance,
ii. surgery,
iii. endoscopic mucosal resection (EMR) plus surveillance,
iv. radiofrequency ablation (RFA) plus surveillance,
v. EMR plus RFA plus surveillance and
vi. EMR plus argon plated coagulation (APC) plus surveillance.

The frequency of surveillance was every three months for the first year, every six months in the second, annually in years 3-5 and every 5 years thereafter. The model applied a lifetime horizon. Sources for the natural history of Barrett's oesophagus and costs were dated. It was therefore graded as having potentially serious limitations. The results suggested than EMR plus RFA plus surveillance, EMR plus APC plus surveillance and surgery were cost effective versus no surveillance with costs per QALYs of £15,916, £18,745 and £10,612, respectively.

Radiofrequency ablation versus oesophagectomy

The developers advised that comparisons between treatments should be avoided in the CG106 model. This is because there is a high degree of uncertainty in the treatment effectiveness as, with the exception of for radiofrequency ablation, data for all other interventions were taken from non-comparative, non-randomised studies. However, in a full incremental analysis, surgery was the most cost-effective intervention overall.

The third study compared radiofrequency ablation followed by endoscopic surveillance to oesophagectomy (Boger 2010). The perspective was that of the UK NHS. Data for treatment effects were dated as they were taken from the period spanning 1999 to 2009 and therefore not reflective of current practice. Sources for costs were also dated. It was therefore graded as having potentially serious limitations. Radiofrequency ablation plus surveillance dominated oesophagectomy, being cheaper and more effective.

The final study took a Spanish NHS perspective, again comparing radiofrequency ablation (RFA) to oesophagectomy. The model time horizon was 15 years. Future costs and health outcomes were discounted at 3% each year, which does not exactly align with the NICE reference case. Costs were taken from national databases. Resource use associated with treatment were based on expert clinical opinion. The study was funded by a device manufacturing company. Radiofrequency ablation dominated oesophagectomy, being cheaper and more effective.

The committee queried the difference in results between Boger 2010 and CG106 regarding the cost effectiveness of RFA plus surveillance versus surgery, given that both were based on the UK NHS perspective. Radiofrequency ablation dominated oesophagectomy in Boger

2010 and vice versa in CG106. Part of the reason for this is different assumptions around the frequency of surveillance post radiofrequency ablation; in Boger 2010 annual surveillance was conducted for the first five years post-treatment, and further surveillance would continue based on disease progression, while in CG106 post-treatment surveillance was identical to pre-treatment surveillance. In the committee's opinion, this assumption from CG106 was implausible.

The committee members are aware of recent data from long-term prospective studies that support the notion that surveillance intervals post endoscopic ablation can and should be extended, which would improve the cost utility of RFA plus surveillance over surgery. However, there was no evidence available looking at the frequency of surveillance post-treatment in Barrett's in comparative studies. The committee agreed that research in this field is needed as it represents a cost-saving opportunity for the NHS and therefore made a research recommendation (see Evidence Review Q7.1 optical frequency and duration of endoscopic and radiological follow up).

There was also a noticeable difference in utilities between studies; Boger 2010 reported an incremental utility gain of 0.02 favouring RFA plus surveillance while CG106 reported an incremental utility gain of 0.093 favouring surgery. The committee commented that they would expect a higher utility gain with RFA plus surveillance over surgery post-intervention, with the utility for post-surgery being unusually high in their estimation. One committee member further commented that the model assumption that patients with RFA plus surveillance would receive PPIs but not patients electing for surgery was false as it is common for patients' post-surgery to continue taking PPIs. The committee therefore decided that the analysis from CG106 was flawed, being biased in favour of surgery.

Conclusions

Overall, the committee thought that EMR plus RFA was likely to be cost effective compared both to no treatment and to other interventions and should be offered to patients. This represents current practice and is therefore unlikely to substantially alter NHS resource use.

1.1.13 Recommendations supported by this evidence review

This evidence review supports recommendations 1.5.1 and 1.5.2, 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 (high grade dysplasia, stage 1 adenocarcinoma)

ID	Field	Content
0.	PROSPERO registration number	CRD42021272034
1.	Review title	The clinical and cost effectiveness of different endoscopic treatments alone or in combination for adults with stage 1 adenocarcinoma
2.	Review question	For adults with stage 1 adenocarcinoma, what is the clinical and cost effectiveness of endoscopic treatments alone or in combination?
3.	Objective	To assess the efficacy and cost effectiveness of different endoscopic treatments alone or in combination, in adults with stage 1 adenocarcinoma
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 • Epistemonikas 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 (high grade) & stage 1 adenocarcinoma
6.	Population	Inclusion: Adults with Barrett's Oesophagus, 18 years and over, with high grade dysplasia or stage 1 adenocarcinoma Exclusion: adults with non and low grade dysplastic, indefinite dysplasia Barrett's and those beyond stage 1 oesophageal adenocarcinoma
7.	Intervention	• Endoscopic resection (Endoscopic Mucosal Resection, Endoscopic Submucosal Dissection)

		• Endoscopic ablation (Radio Frequency ablation (RFA), Argon Plasma Coagulation (APC), cryotherapy) • Endoscopic resection and ablation •

8.	Comparator	• Different technique of endoscopic resection or ablation e.g.:
		  ○ Resection technique vs resection technique
		  ○ Ablation technique vs ablation technique
		  ○ Mixed technique (endoscopic resection and ablation) vs different mixed technique
		• Oesophagectomy
		• Endoscopic surveillance

9.	Types of study to be included	• RCT • If no RCT data is available, non-randomised studies will be considered if the study is comparative with another technique. • Systematic Reviews of RCTs 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 stage 1 adenocarcinoma 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) • Treatment related mortality • Health related quality of life (any validated score) • Recurrence of Barrett's dysplasia or neoplasia • Need for retreatment • Complications of treatment (e.g. bleeding, pain infection, perforation, stricture) • Length of hospital stay • Conversion of endoscopic treatment to surgery Minimum length of follow up of 1 year but to also 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: High grade dysplasia / T1a vs T1b Subgrouping: If serious or very serious heterogeneity (I2>50%) is present, sub-grouping will occur according to the following strategies: Histopathological risk factors (Lymphovascular invasion and grade of differentiation (1-2 vs 3)) High grade dysplasia vs T1a T1b (SM1,2,3)	
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.	Stage of review at time of this submission	Review stage	Started / Completed
		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 Vimal Bedia Stephen Deed Muksitur Rahman 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	

APC (N = 33)

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). [12] **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.

1

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.[10]

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 17: 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 18: 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*)

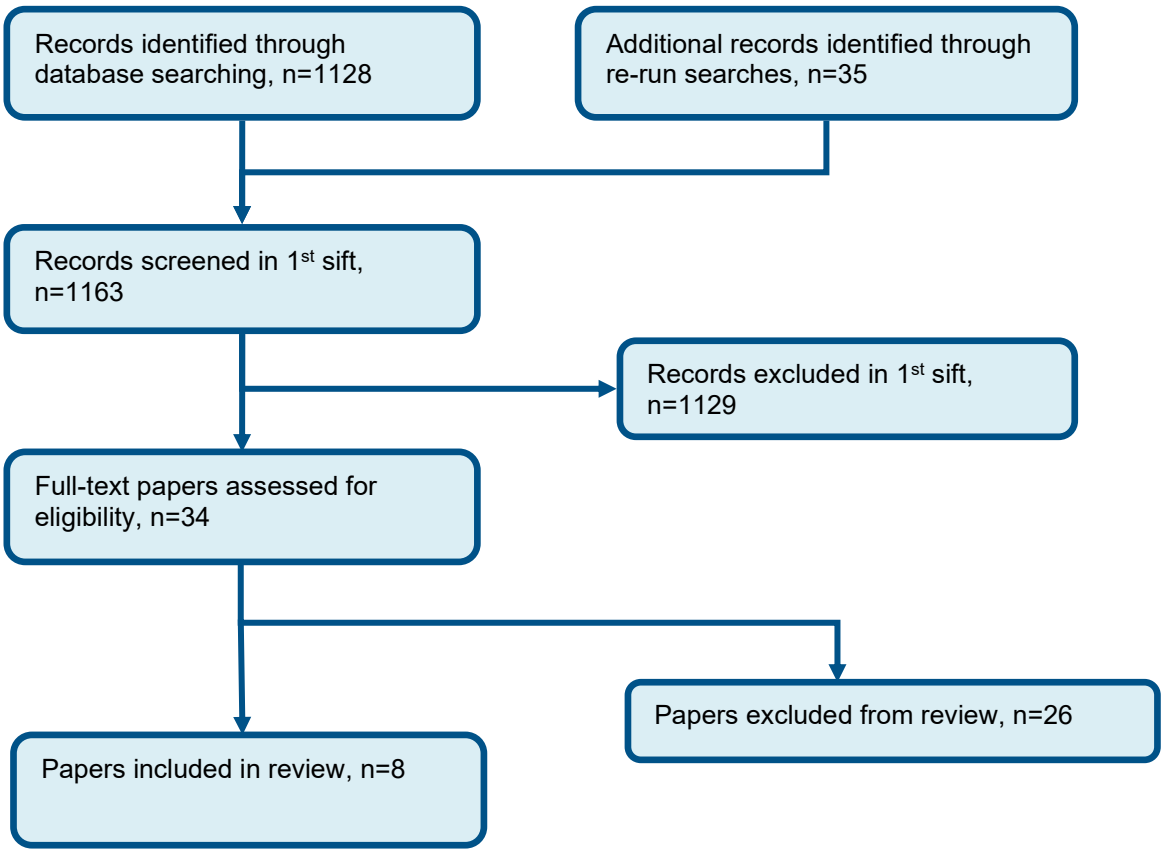
#4.	(column*) AND (epithel* or oesophag* or esophag* or mucos* or lined or lining or metaplas*)
#5.	#1 OR #2 OR #3 OR #4
#6.	MeSH DESCRIPTOR Precancerous Conditions EXPLODE ALL TREES
#7.	((dysplasia* or precancer* or pre-cancer* or premalign* or pre-malign* or preneoplast* or pre-neoplastic* or preneoplasia* 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 treatment in high-grade dysplasia/ stage 1 adenocarcinoma



Appendix D – Effectiveness evidence

RCT studies

Manner, 2014

Bibliographic Reference	Manner, H.; Rabenstein, T.; Pech, O.; Braun, K.; May, A.; Pohl, J.; Behrens, A.; Vieth, M.; Ell, C.; Ablation of residual Barrett's epithelium after endoscopic resection: a randomized long-term follow-up study of argon plasma coagulation vs. surveillance (APE study); Endoscopy; 2014; vol. 46 (no. 1); 6-12

Study details

Study type	Randomised controlled trial (RCT)
Study location	Wiesbaden, Germany
Study setting	Department of Internal Medicine II at the HSK Hospital
Study dates	August 2006 to June 2009
Sources of funding	Astra Zeneca
Inclusion criteria	age 18≥, written consent to participate in the study, complete remission from early Barrett's neoplasia (negative biopsies from resection site and ≥4 biopsies every 2cm in the Barrett's remainder, initial Barrett's length before endoscopic resection ≥3cm, residual Barrett's length after endoscopic resection ≥2cm, histological diagnosis of Barrett's only made if detection of specialised intestinalised columnar epithelium
Exclusion criteria	Concomitant disease: presence of malignant tumor/renal insufficiency requiring dialysis/ life expectancy <1 year; treatment related coagulation disturbances (phenprocoumon treatment/therepeutic heparinization/ lysis treatment at time of study); abnormal laboratory tests revealing coagulation disturbance (Quick's value under 50%/ thrombocyte count below 50/nL); previous attempts of Barrett's ablation; endoscopic treatment period for early neoplasia >12 months; insufficient wound healing or squamous re-epithelisation in the area of previous endoscopic resection

Recruitment / selection of participants	From August 2006 to June 2009, patients in whom complete remission from early Barrett's cancer or high grade intraepithelial neoplasia had been achieved following endoscopic resection and who fulfilled the inclusion criteria.
Intervention(s)	Argon Plasma Coagulation (APC) ablation with concomitant proton pump inhibitor (PPI) treatment with esomeprazol. After baseline high-resolution video endoscopy with chromoendoscopy, the residual Barrett's mucosa was thermally ablated using APC, which is a clinically established contact-free thermal coagulation technique characterised by the flow of ionised argon gas. Power setting of 60W with gas flow of 1L/min was applied via prograde APC probes with a diameter of 2.3 mm. The ablation treatment was only carried out in hospitalised patients. The Barrett's mucosa was ablated dynamically in linear strips in the longitudinal or circumferential axis of the oesophagus until a visible coagulation effect was seen. Max number of APC sessions per hospital stay was two and the interval between two treatment sessions had to be at least 1 day. The max number of hospital stays was five, therefore max number of treatment sessions allowed was 10. If after that complete Barrett's ablation had not been achieved, a single additional APC session was allowed according to the study protocol. The interval between two hospital stays had to be between 4 and 8 weeks. The concomitant esomeprazole dosage was 2x40 mg daily during and for 3 weeks after APC ablation. Therefore a PPI dosage adjusted to the patients' 24-hour PH-metry finding was chosen (40 or 80 mg per day) for long term treatment. In the patients who initially received 40mg/day, the dosage was increased to 2x40mg daily if inadequate acid suppression had been noted on PH-metry. All endoscopic examinations were carried out by examiners who were experienced in using APC (over 50 APC treatments of Barrett's mucosa). Endoscopic ablation was carried out with the patients under analgesic sedation.
Comparator	Surveillance with concomitant PPI treatment: patients underwent check-up examinations at regular intervals. PPI dosage was adjusted to the patients' 24-hour PH-metry finding (40 or 80 mg per day)
Number of participants	63
Duration of follow-up	2-year follow-up; Mean follow-up (SD, range): ablation group= 28.2 (13.7, 0-44) months; surveillance group= 24.7 (14.8; 0-45) months

Study arms

Surveillance (N = 30)

Characteristics

Study-level characteristics

Characteristic	**Study (N = 63)**
% Female Sample size	n = 6 ; % = 9.52
Mean age (SD) Mean (SD)	63 (1)

Arm-level characteristics

Characteristic	**APC (N = 33)**	**Surveillance (N = 30)**
Previous characterisation of Barrett's neoplasia: HGIN/EAC (n (%)) Sample size	n = 21 ; % = 63.6	n = 19 ; % = 63.3
Previous characterisation of Barrett's neoplasia: EAC >2cm/multifocal neoplasia (n (%)) Sample size	n = 12 ; % = 36.4	n = 11 ; % = 36.7

Outcomes

Study timepoints

- 2 year (Mean follow-up (SD, range): ablation group= 28.2 (13.7, 0-44) months; surveillance group= 24.7 (14.8; 0-45) months)

Recurrence

Outcome	**APC, 2 year, N = 33**	**Surveillance, 2 year, N = 30**
Recurrence of neoplasia (n (%)) No of events	n = 1 ; % = 3	n = 11 ; % = 36.7

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

Recurrence-Recurrence-NoOfEvents-APC-Surveillance-t2

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

Peerally, 2019

Bibliographic Reference	Peerally, M. F.; Bhandari, P.; Ragunath, K.; Barr, H.; Stokes, C.; Haidry, R.; Lovat, L.; Smart, H.; Harrison, R.; Smith, K.; Morris, T.; de Caestecker, J. S.; Radiofrequency ablation compared with argon plasma coagulation after endoscopic resection of high-grade dysplasia or stage T1 adenocarcinoma in Barrett's esophagus: a randomized pilot study (BRIDE); Gastrointestinal Endoscopy; 2019; vol. 89 (no. 4); 680-689

Study details

Trial name / registration number	Barrett’s Randomised Intervention for Dysplasia by Endoscopy (BRIDE)
Study location	UK
Study setting	Six English tertiary-care referral centers for esophago-gastric cancer
Study dates	not specified
Sources of funding	National Institute for Health Research (NIHR) under its Research for Patient Benefit Programme (grant no. PB-PG-0711-25066)

Inclusion criteria	patients aged 18 to 85 years, histology HGD or T1a cancer with a maximum depth of invasion on ER of T1m3, EUS and CT or positron emission tomography-CT scan negative for locally advanced or metastatic disease (for histology-proven invasive cancer only).
Exclusion criteria	Histology more than T1m3, poorly differentiated histology, lymphatic or vascular invasion, short tongues (<2 cm) of BE completely removable by ER, no localized endoscopically identifiable abnormality, prior esophageal endoscopic therapy other than ER, existing stricture not dilatable to a level suitable for endoscopic treatment, history of mediastinal radiation, esophageal surgery (except fundoplication without adverse event), esophageal varices, or coagulopathy.
Recruitment / selection of participants	Potential participants identified at upper GI cancer multidisciplinary team meetings before ER (or after ER if done up to 6 months previously) were invited to participate.
Intervention(s)	Patients received up to 4 treatments every 2 months with APC or RFA after initial ER. All patients received high-dose (twice daily) proton pump inhibitors; ER was performed at entry if not done within the previous 6 months. If the latter, at initial trial endoscopy either further ER if appropriate or mapping biopsies were permitted but not APC or RFA. ER aimed to resect all visible lesions regardless of extent, including visible lesions at any subsequent treatment sessions; we did not limit ER size. All units used high-definition endoscopes, processors, and screens (5 units used Olympus H260 or 260Z with Lucera Spectrum [Olympus, Tokyo, Japan] processors and HD monitors, all with narrow-band imaging. The remaining unit used Pentax 7000 Epki-i10 with iScan [HOYA Corporation, PENTAX Lifecare Division, Tokyo, Japan]). ER was by either “cap and snare” (Olympus Optical Co Ltd, Tokyo, Japan) after submucosal lifting injection or Duette “band and snare” (Cook Ireland Ltd, Ireland)30 unfavourable ER histology resulted in withdrawal of the subject from the study. If a stricture occurred, dilation was allowed at any session to allow treatment. For RFA, either a circumferential balloon HALO ablator (Barrx Medical, Sunnyvale, Calif) at a 12J setting after an initial sizing balloon or focal HALO 90 ablator (Barrx) at a 15J setting were used at the local investigator’s discretion; HALO 60, Ultra, or TTS ablators were allowed if thought appropriate. The originally described technique of ablation (single hit for HALO 360, double for focal devices), cleaning, and further ablation were used with both the balloon and focal ablators, by using the same techniques and power settings as the EURO-125 and EURO-231 studies led by the Amsterdam group. At 12 months, diagnostic high-resolution endoscopy was performed, with targeted biopsies of any macroscopically abnormal areas and 4-quadrant biopsies at 2-cm intervals, including at the gastroesophageal mucosal junction, of the area still containing BE or of neosquamous epithelium, by using standard biopsy forceps with a 6-mm open span and the “turn and suck” technique. Trial biopsies were required only at exit from the trial. No ablation was offered as part of the trial at this time point, although after study completion, patients continued endoscopic treatment (ER and/or ablation) at the local investigators’ discretion, aiming to achieve complete BE clearance

Comparator	APC, an axial firing APC catheter was used with gas flow of 2 L/minute. A forced 60 W setting was used with ERBE ICC 200 or a pulsed 50 W setting with ERBE Vio (ERBE Electromedizin, GmbH, Tubingen, Germany), depending on equipment available at each site. Ablation was carried out by using a stroking technique, with the tip of a forward-firing APC catheter protruding approximately 1 cm beyond the endoscope, which was withdrawn from distal to proximal, starting at the junction of BE with the longitudinal gastric folds. Up to 60% of the circumference was treated in any 1 session, by using endoscope torque to treat successive radial segments. The same APC settings were used for focal treatment of islands or tongues of BE. Use of a distal endoscopic attachment cap was optional. For both ablation techniques, repeated treatment of the gastroesophageal junction was emphasized during the initial standardization meeting of endoscopists at the start of the trial.
Number of participants	76; 56 completed the trial
Duration of follow-up	12 months

Study arms

ER+RFA (N = 36)

ER+APC (N = 40)

Characteristics

Arm-level characteristics

Characteristic	ER+RFA (N = 36)	ER+APC (N = 40)
% Female Sample size	n = 8 ; % = 22.2	n = 4 ; % = 10
Mean age (SD) Mean (SD)	68.2 (10.2)	71 (8.1)
Maximal BE lenght (cm) Mean (SD)	5.6 (2.3)	6.2 (3.4)
Circumferential BE length Mean (SD)	3.3 (2.8)	4.1 (3.8)
High-grade dysplasia Sample size	n = 29 ; % = 80.6	n = 29 ; % = 72.5

Characteristic	ER+RFA (N = 36)	ER+APC (N = 40)
T1 adenocarcinoma Sample size	n = 7 ; % = 19.4	n = 11 ; % = 27.5

Outcomes

Study timepoints

12 month

Clearance of dysplasia/Barrett's oesophagus

Outcome	ER+RFA, 12 month, N = 34	ER+APC, 12 month, N = 31
Clearance of high-grade dysplasia/cancer No of events	n = 27 ; % = 79.4	n = 26 ; % = 83.9
Clearance of BE on endoscopy No of events	n = 19 ; % = 55.9	n = 15 ; % = 48.4

Adverse events

Outcome	ER+RFA, 12 month, N = 36	ER+APC, 12 month, N = 37
Stricture	n = 3 ; % = 8.3	n = 3 ; % = 8.1

Outcome	ER+RFA, 12 month, N = 36	ER+APC, 12 month, N = 37
No of events		
GI bleeding No of events	n = 1 ; % = 2.8	n = 2 ; % = 5.4

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

Clearanceofdysplasia/Barrett'soesophagus-Clearanceofhigh-gradedysplasia/cancer-NoOfEvents-ER+RFA-ER+APC-t12

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

Clearanceofdysplasia/Barrett'soesophagus-ClearanceofBEonendoscopy-NoOfEvents-ER+RFA-ER+APC-t12

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

Adverseevents-Stricture-NoOfEvents-ER+RFA-ER+APC-t12

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

Adverseevents-GIbleeding-NoOfEvents-ER+RFA-ER+APC-t12

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

Pouw, 2011

Bibliographic Reference	Pouw, R. E.; van Vilsteren, F. G.; Peters, F. P.; Alvarez Herrero, L.; Ten Kate, F. J.; Visser, M.; Schenk, B. E.; Schoon, E. J.; Peters, F. T.; Houben, M.; Bisschops, R.; Weusten, B. L.; Bergman, J. J.; Randomized trial on endoscopic resection-cap versus multiband mucosectomy for piecemeal endoscopic resection of early Barrett's neoplasia; Gastrointestinal Endoscopy; 2011; vol. 74 (no. 1); 35-43

Study details

Study location	Amsterdam, The Netherlands
Study setting	Tertiary-care and community-care centres: Academic Medical Center Amsterdam, St. Antonius Hospital Nieuwegein, Catharina Hospital Eindhoven, or the University Hospitals Leuven.
Study dates	January 2005 until June 2010

Sources of funding	J. Bergman (author) received research support in the form of grants and materials from Olympus Endoscopy and Wilson-Cook. This work was supported by an unrestricted grant from AstraZeneca BV, The Netherlands
Inclusion criteria	patients scheduled for piecemeal ER meet all following criteria: BE with biopsy-proven HGIN and/or early cancer; No suspicion of submucosal invasion, based on the macroscopic appearance and/or endosonography; No signs of lymph node and/or distant metastases on endosonography and CT-scanning of the thorax and abdomen; written informed consent. Indications for piecemeal ER were: (1) monotherapy for removal of early neoplastic lesions (generally for patients with BE >5 cm),1 (2) as part of a stepwise radical endoscopic resection protocol of the whole BE in multiple sessions,9-11 or (3) removal of visible abnormalities before additional ablation therapy
Exclusion criteria	not specified
Recruitment / selection of participants	The first 34 patients were consecutively included and randomized at the Academic Medical Centre and treated by an endoscopist with extensive experience in ER with the use of both techniques (J.B.).7 Fifty patients were included at the University Hospital Leuven, St. Antonius Hospital, or Academic Medical Centre during hands-on training sessions for endoscopists training in ER. These patients were treated by endoscopists with limited experience in performing ER, who participated in a training program for endoscopic detection and treatment of early neoplasia in the upper GI tract.
Intervention(s)	Endoscopic procedures were performed with patients under conscious sedation including midazolam with fentanyl or pethidine. During endoscopy, visible lesions were classified according to the Japanese classification for early gastric cancer: type 0-I being protruding, type 0-IIa elevated, type 0-IIb flat, type 0-IIc depressed, type 0-III excavated.14 In addition, the distance from the incisors, location, and estimated diameter were recorded for each lesion. The area that needed to be resected was delineated by markings made with argon plasma coagulation (APC) (forced coagulation 20 W, gas flow 1.6 L/minute; ERBE Vio System; Erbe Elektromedizin GmbH, Tübingen, Germany). After the delineation, patients were randomized to the ER-cap or MBM technique, and timing of the procedure was started. For the ER-cap technique, an ER kit (Olympus GmbH; Hamburg, Germany) was used, which contains a spraying catheter, an injection needle, a hard, oblique cap (inner Ø 12 mm), and a crescent-shaped snare. The cap was attached to the tip of the endoscope, and the endoscope was reintroduced. First, the lesion was lifted by submucosal injection of diluted adrenaline (1: 100.000 NaCl 0.9%). Then a snare was prelooped in the distal rim of the cap, the mucosa was sucked into the cap, and, by tightening of the snare, a pseudopolyp was created that was resected by using pure coagulation current (ERBE Vio 40 W). After the resection, the snare was disposed of, the specimen was pushed into the stomach, and the

	resection wound was inspected. For all subsequent resections, submucosal lifting was repeated, and a new snare was used. After the last resection, the wound edges were inspected to assess whether all markings used to delineate the target area had been removed. The resection specimens were retrieved from the stomach by using a foreign body retrieval basket (disposable 2.5 mm foreign body Roth net; US endoscopy, Mentor, Ohio). Specimens were pinned down on paraffin (mucosal side up) and preserved in formalin for histological evaluation. Timing of the procedure was stopped when the endoscope was removed, after retrieval of all resection specimens and treatment of any complications.
Population subgroups	not applicable
Comparator	MBM was performed by using the Duette MBM system (Cook Endoscopy, Limerick, Ireland), which consists of a transparent cap with 6 rubber bands (inner Ø 9 mm), releasing wires, a cranking device, and a 7F hexagonal braided polypectomy snare that can be reused for multiple resections because of its shape stability. For MBM, the cranking device and transparent cap were assembled onto the endoscope before the endoscope was reintroduced. The target mucosa was sucked into the cap, and with the release of a rubber band, a pseudopolyp was created. The hexagonal snare was introduced, closed beneath the rubber band, and, by using pure coagulation current (ERBE Vio 40 W), the pseudopolyp was resected. Immediately after the resection, the snare was retracted, the resected specimen was pushed into the stomach, and the resection wound was inspected. Subsequent resections were performed in the same way, allowing a small overlap (10%-25%) between adjacent resections to prevent residual tissue bridges (Fig. 1). In the case of a residual tissue bridge, the bridge was lifted and removed by simple snare resection. If a bridge could not be captured in the snare, additional APC could be used to ablate the residual tissue.
Number of participants	84
Duration of follow-up	not specified

Study arms

ER-cap (N = 42)

MBM (N = 42)

Characteristics

Study-level characteristics

Characteristic	Study (N = 84)
% Female Sample size	n = 20 ; % = 23.81
Mean age (SD) Median (IQR)	70 (63.3 to 76)

Arm-level characteristics

Characteristic	ER-cap (N = 42)	MBM (N = 42)
BE lenght: circumferential (cm) Median (IQR)	4 (0 to 6)	3 (1 to 7)

Characteristic	ER-cap (N = 42)	MBM (N = 42)
BE lenght: maximum (cm) Median (IQR)	6 (3 to 7)	5 (3 to 9)

Outcomes

Study timepoints

48 hour (During the procedure and 0-48 hours later)

Complications of treatment

Outcome	ER-cap, 48 hour, N = 42	MBM, 48 hour, N = 42
Clinically not relevant bleeding No of events	n = 22 ; % = 52	n = 17 ; % = 40
Perforation No of events	n = 3 ; % = 7	n = 1 ; % = 2

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

Complicationsoftreatment-Clinicallynotrelevantbleeding-NoOfEvents-ER-cap-MBM-t48

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)	High
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	Some concerns *(unclear how the outcome was measures; complications were recorded only if considered 'clinically significant')*
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 *(unclear how outcome was measured and difference in level of expertise in participating endoscopists)*
Overall bias and Directness	Overall Directness	Directly applicable

Complicationsoftreatment-Perforation-NoOfEvents-ER-cap-MBM-t48

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)	High
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	Some concerns *(unclear how the outcome was measures; complications were recorded only if considered 'clinically significant')*
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 *(unclear how outcome was measured and difference in level of expertise in participating endoscopists)*
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	
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 specified
Sources of funding	Differenr authors received various sources of funding inluding: AstraZeneca, TAP/Takeda, CSA Medical, Procter & Gamble, Given Imaging and Olympus, Santarus, BÂRRX Medical, Fujinon, Cook, EndoGastric Solutions, Pfizer, Novartis, Merck, and Santarus
Inclusion criteria	Patients who were 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. For patients with high-grade dysplasia, we additionally required negative results on endoscopic ultrasonography for lymphadenopathy and esophageal-wall abnormalities within 12 months before enrollment. Previous endoscopic mucosal resection was permissible 8 weeks or more before study entry if subsequent endoscopy showed non-nodular dysplasia.
Exclusion criteria	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)	All patients underwent upper endoscopy, oesophageal intubation with a study catheter, measurement of the oesophageal inner diameter, and periprocedural assignment to a study group with the use of a computer-generated block-randomization sequence. Among patients in the ablation group, the entire segment of Barrett's oesophagus was ablated. Among those in the control group, the study catheter was removed and the procedure was terminated. Radiofrequency ablation: 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 dysplasia underwent such procedures at 3, 6, 9, and 12 months. Endoscopic biopsies were performed with maximum-capacity or jumbo forceps in four quadrants every 1 cm throughout the original length of Barrett's oesophagus; in addition, directed biopsies were performed at sites with any visible abnormalities. Patients who were assigned to receive radiofrequency ablation were treated with a circumferential ablation device (HALO360, BÂRRX Medical) The ablation catheter incorporated a cylindrical balloon that was inflated, bringing the electrodes into contact with the oesophageal lining. A preset amount of energy was then delivered (12 J and 40 W per square centimeter). For Barrett's oesophagus segments that were more than 3 cm in length, the catheter was repositioned, and the remaining Barrett's oesophagus was ablated in 3-cm increments. The catheter was withdrawn, coagulative debris was cleaned from the ablation zone and electrodes, and the abnormal tissue was again ablated. Patients who received radiofrequency ablation and had residual Barrett's oesophagus at subsequent visits were treated with a focal ablation device (HALO90). Ablation was applied to the residual Barrett's oesophagus twice, followed by removal of coagulum from the treatment area and the electrodes. Two additional treatments were then delivered, totalling four applications per session. All patients received 40 mg of esomeprazole (which was provided by AstraZeneca) twice daily throughout the trial.

Comparator	Sham endoscopic procedure. 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	127; 63 with high-grade dysplasia included in the present review
Duration of follow-up	12 months

Study arms

RFA (N = 42)

Sham (N = 21)

Characteristics

Arm-level characteristics

Characteristic	**RFA (N = 42)**	**Sham (N = 21)**
% Female Sample size	n = 5 ; % = 12	n = 0 ; % = 0
Mean age (SD) Mean (SE)	65.9 (1.4)	67.3 (1.8)

Characteristic	RFA (N = 42)	Sham (N = 21)
Ethnicity White Sample size	n = 39 ; % = 90	n = 21 ; % = 100
Length of Barrett's oesophagus (cm) Mean (SE)	5.3 (0.3)	5.3 (0.5)
Subsquamous intestinal metaplasia Sample size	n = 10 ; % = 24	n = 3 ; % = 14
Multifocal dysplasia No of events	n = 33 ; % = 79	n = 18 ; % = 86
Current use of aspirin or NSAID Sample size	n = 18 ; % = 43	n = 12 ; % = 57

Outcomes

Study timepoints

12 month

Complete eradication of dysplasia

Outcome	RFA, 12 month, N = 38	Sham, 12 month, N = 20
Complete eradication of dysplasia No of events	n = 34 ; % = 90	n = 4 ; % = 20
Complete eradication of intestinal metaplasia No of events	n = 31 ; % = 82	n = 0 ; % = 0

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

Completeeradicationofdysplasia-Completeeradicationofdysplasia-NoOfEvents-RFA-Sham-t12

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High *(baseline differences in subsquamous metaplasia, multifocal dysplasia, current use of aspirin or NSAIDS)*

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)	Some concerns *(difference in use of NSAID or aspirin)*
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 *(due to baseline differences in subsquamous metaplasia, multifocal dysplasia, current use of aspirin or NSAIDS, lack of clarity over how eligible participants were derived)*
Overall bias and Directness	Overall Directness	Directly applicable

Completeeradicationofdysplasia-Completeeradicationofintestinalmetaplasia-NoOfEvents-RFA-Sham-t12

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High *(baseline differences in subsquamous metaplasia, multifocal dysplasia, current use of aspirin or NSAIDS)*
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 NSAID or aspirin)*
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 *(due to baseline differences in subsquamous metaplasia, multifocal dysplasia, current use of aspirin or NSAIDS, lack of clarity over how eligible participants were derived)*
Overall bias and Directness	Overall Directness	Directly applicable

Terheggen, 2017

Bibliographic Reference	Terheggen, G.; Horn, E. M.; Vieth, M.; Gabbert, H.; Enderle, M.; Neugebauer, A.; Schumacher, B.; Neuhaus, H.; A randomised trial of endoscopic submucosal dissection versus endoscopic mucosal resection for early Barrett's neoplasia; Gut; 2017; vol. 66 (no. 5); 783-793

Study details

Study type	Randomised controlled trial (RCT)
Study location	Germany
Study setting	Department of Gastroenterology of the Evangelisches Krankenhaus Düsseldorf.
Study dates	November 2012 to May 2014
Sources of funding	Not commissioned
Inclusion criteria	Male or female patients aged ≥18 years with an American Society of Anesthesiologists (ASA) health status 1–3; BO with endoscopically visible single neoplastic superficial lesion of type 0–Is, 0–IIa, 0–IIc or their combinations according to an update on the Paris classification of superficial neoplastic lesions in the digestive tract24 while biopsies of the remaining BO did not show any neoplastic changes; Limitation of the horizontal extent to a diameter of ≤3 cm in the longitudinal direction or less than half of the oesophageal circumference in the lateral direction; No endoscopic suspicion of massive infiltration into the submucosal layer and no additional neoplastic lesions according to endoscopic appearance; evaluation of BO biopsy specimens by two independent histopathologists within 2 months before inclusion of the patient with diagnosis of HGIN or EAC of the focal lesion and non-neoplastic intestinal metaplasia of mapping biopsies (four-quadrant/every 1–2 cm) of the remaining BO segment. The histological criteria, classification and assessment of the grade of differentiation were in accordance with the WHO classification.
Exclusion criteria	pregnancy; coagulopathy (international normalised ratio >2.0, platelets <70×100/L); previous endoscopic or surgical treatment of BO neoplasia; neoplastic lesions that do not meet the inclusion criteria, particularly flat lesions (type 0–IIb) and additional areas of HGIN or AC.
Recruitment / selection of participants	Patients referred to the Department of Gastroenterology of the Evangelisches Krankenhaus Düsseldorf for endoscopic treatment of BO with high-grade intraepithelial neoplasia (HGIN) or early adenocarcinoma (EAC). Eligible patients were enrolled provided that they signed an informed consent after detailed information about the study details.

Intervention(s)	ESD: A transparent distance cap was mounted to the tip of the endoscope to facilitate positioning of accessories and compression of bleeding sites. An indigocarmine-stained isotonic saline solution (2 mL in 250 mL) with diluted epinephrine (1:250 000) was used for submucosal injection. The water-jet surgical system (ERBEJet 2, Erbe Elektromedizin GmbH) was used for ESD in combination with the HybridKnife instrument (T-type or I-type, Erbe Elektromedizin GmbH), which allows a combination of a high-pressure water-jet and electrosurgical interventions. The preselected effect setting of the water-jet was set to 30 bar according to results of previous experimental animal and clinical trials. The effect could be changed at the discretion of the operator. The aim of injection was to obtain an appropriate elevation of the lesion for a safe circumferential incision of the mucosa and dissection of the submucosa. There was no limitation for the volume of injections during the procedure. The modular VIO generator (VIO 300D, V2.1.4, Erbe Elektromedizin GmbH) was used as radiofrequency surgical system. The VIO mode ENDO CUT Q 2-3-3 was selected for circumferential cutting at the periphery of the coagulation markers and the mode Dry Cut E3, 80W for submucosal dissection. The FORCED COAG mode E2, 60W was used for coagulation of visible vessels or bleedings not being stopped by the herein used cutting-mode Dry Cut. Coagulation forceps (Olympus FD-1U-1, Olympus Europe, Hamburg, Germany) at the setting SOFT COAG E5, 80W were only used for bleedings not amenable to coagulation with the HybridKnife. All diathermic settings could be changed at the discretion of the operator. The aim was to resect the targeted lesion including all coagulation markers as a single piece. Patients were hospitalised for at least 48 h after ESD because of the potential risk of delayed complications. Only liquid diet was allowed during the first 24 h in asymptomatic patients followed by semi-solid diet during hospitalisation. Clinical investigation and determination of the blood cell count and the serum level of C-reactive protein was done after 24 or 48 h. Proton pump inhibitors (PPI) was orally administered in double standard during the study period.
Comparator	EMR: An oblique hard EMR cap, a wide-opening and a distal rim (diameter 16 mm; MAJ-295-297; Olympus), was mounted to the tip of the endoscope. An indigocarmine-stained isotonic saline solution (1.0 mL in 120 mL) with diluted epinephrine (1:250 000) was used for submucosal injection. Injection of fluid was manually performed by use of a 23-gauche injection needle to obtain an appropriate bulging of the lesion. A crescent-shaped snare (SD-7P-1; Olympus Europe) was used for resection in conjunction with the VIO mode ENDO CUT Q 2-3-3. The aim was to resect the lesion including all coagulation markers as a single piece; we started with removal of the central part of a lesion with the first resection to provide an appropriate specimen of the most tumorous part for histology. Additional resections were then performed at the periphery in case of any remaining parts showing coagulation marks with the aim to minimise the number of specimen. For this piecemeal approach, submucosal mechanical injection was repeated if an appropriate bulging of the lesion was no longer visible. The cap was positioned at a distance to the previously resected area, which allowed appropriate suction of the tissue into the cap, without leaving bridges between the resection areas. Each resected specimen was separately removed.

	Coagulation forceps (Olympus FD-1U-1, Olympus Europe) at the setting SOFT COAG E5, 80W were used for coagulation of visible vessels or bleeding sites. Proton pump inhibitors (PPI) was orally administered in double standard during the study period.
Number of participants	40
Duration of follow-up	mean (SD) follow-up was 22.6 (7.8) months for the ESD and 23.6 (5) months for the EMR group.

Study arms

ESD (N = 20)

EMR (N = 20)

Characteristics

Arm-level characteristics

Characteristic	ESD (N = 20)	EMR (N = 20)
Mean age (SD) Mean (SD)	64 (12)	65 (11)

Characteristic	ESD (N = 20)	EMR (N = 20)
Histology before treatment: HGIN Sample size	n = 5 ; % = 25	n = 4 ; % = 20
Histology before treatment: adenocarcinoma Sample size	n = 15 ; % = 75	n = 16 ; % = 80

Outcomes

Study timepoints

30 day

Complete resection of the targeted area

Outcome	ESD, 30 day, N = 17	EMR, 30 day, N = 17
Complete resection of high-grade intraepithelial neoplasia or oesophageal adenocarcinoma No of events	n = 10 ; % = 58.8	n = 2 ; % = 11.8
Curative resection resection of the targeted neoplastic area; histologically complete resection of HGIN/ mucosal EAC or EAC with low risk superficial submucosal invasion No of events	n = 9 ; % = 52.9	n = 2 ; % = 11.8

Complete single piece (en bloc) resection of the targeted lesion plus histological confirmation of horizontal and vertical free margins (R0) for both EAC and HGIN

Adverse events

Outcome	ESD, 30 day, N = 20	EMR, 30 day, N = 20
Perforation Intraprocedural adverse event No of events	n = 2 ; % = 10	n = 0 ; % = 0
Mediastinitis Post-procedural adverse event No of events	n = 1 ; % = 5	n = 0 ; % = 0
Temporary chest discomfort Post-procedural adverse event No of events	n = 3 ; % = 15	n = 2 ; % = 10
Severe adverse events that caused prolongation of hospitalisation and/or its management required additional therapeutic interventions No of events	n = 2 ; % = 10	n = 0 ; % = 0
30-day mortality No of events	n = 0 ; % = 0	n = 0 ; % = 0

Complete remission of neoplasia >30 day follow-up

Outcome	ESD, 30 day, N = 16	EMR, 30 day, N = 17
Complete remission of neoplasia after initial resection No of events	n = 15 ; % = 93.8	n = 16 ; % = 94.2
Complete remission of intestinal neoplasia No of events	n = 6 ; % = 37.5	n = 10 ; % = 58.8
Recurrence of neoplasia No of events	n = 1 ; % = 6.3	n = 0 ; % = 0

Need for treatment

Outcome	ESD, 30 day, N = 20	EMR, 30 day, N = 20
Patients referred to elective surgery No of events	n = 4 ; % = 20	n = 3 ; % = 15

>30 day follow-up

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

Completeresectionofthetargetedarea-Completeresectionofhigh-gradeintraepithelialneoplasiaoroesophagealadenocarcinoma-NoOfEvents-ESD-EMR-t30

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

Completeresectionofthetargetedarea-Curativeresection-NoOfEvents-ESD-EMR-t30

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

Adverseevents-Perforation-NoOfEvents-ESD-EMR-t30

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

Adverseevents-Mediastinitis-NoOfEvents-ESD-EMR-t30

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

Section	Question	Answer
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

Adverseevents-Temporarychestdiscomfort-NoOfEvents-ESD-EMR-t30

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

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Adverseevents-Severeadverseevent-NoOfEvents-ESD-EMR-t30

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

Adverseevents-30-daymortality-NoOfEvents-ESD-EMR-t30

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

Completeremissionofneoplasia>30dayfollow-up-CompleteremissionofneoplasiaafterinitialresectionNoOfEvents-ESD-EMR-t30

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

Completeremissionofneoplasia>30dayfollow-up-CompleteremissionofintestinalneoplasiaNoOfEvents-ESD-EMR-t30

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

Completeremissionofneoplasia>30dayfollow-up-Recurrenceofneoplasia-NoOfEvents-ESD-EMR-t30

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

Needfortreatment-Patientsreferredtoelectivesurgery-NoOfEvents-ESD-EMR-t30

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

van Vilsteren, 2011

Bibliographic Reference	van Vilsteren, F. G.; Pouw, R. E.; Seewald, S.; Alvarez Herrero, L.; Sondermeijer, C. M.; Visser, M.; Ten Kate, F. J.; Yu Kim Teng, K. C.; Soehendra, N.; Rosch, T.; Weusten, B. L.; Bergman, J. J.; Stepwise radical endoscopic resection versus radiofrequency ablation for Barrett's oesophagus with high-grade dysplasia or early cancer: a multicentre randomised trial; Gut; 2011; vol. 60 (no. 6); 765-73

Study details

Study type	Randomised controlled trial (RCT)
Study location	The Netherlands, Germany
Study setting	Academic Medical Center (Amsterdam, The Netherlands), Sint Antonius Hospital (Nieuwegein, The Netherlands) or the University Medical Center Hamburg-Eppendorf (Hamburg, Germany)
Study dates	April 2006 to April 2008
Sources of funding	BARRX Medical, Sunnyvale, CA, USA
Inclusion criteria	(1) age between 18 and 85 years; (2) BO length #5 cm; (3) HGD and/or EC in BO in specimens obtained at two separate endoscopies; (4) no signs of deep submucosal invasion, regional lymph node involvement or distant metastases on endoscopic ultrasonography (EUS) and CTof thorax and abdomen (in the case of EC); (5) no prior endoscopic treatment of BO other than a single prior ER for staging; (6) in the case of a prior diagnostic ER, specimens with a negative deep resection margin, no deep submucosal invasion ($T1sm2), no lymphatic/vascular invasive growth and no poorly or undifferentiated cancer (G3eG4); and (7) written informed consent.
Exclusion criteria	Not specified
Recruitment / selection of participants	Patients meeting inclusion criteria at the study centres; recruitment method not specified
Intervention(s)	Endoscopic-resection: ER-cap technique and the multiband mucosectomy (MBM) technique were used. Additionally, the use of the ‘simple snare’ technique was allowed. SRER: In SRER, the Barrett’s segment was removed in consecutive sessions at 6e8 week intervals, with a maximum of four sessions, inclusive of the baseline ER (where applicable). In the initial SRER session, piecemeal ER of 50% of the circumference of the entire Barrett’s segment was performed, inclusive of the visible abnormality if not yet removed in a diagnostic ER session.26 For short segment BO (length of circumferential BO (C) #1, maximal BO length (M) #3), SRER in a single session was allowed. In cases where small bridges of residual BO were left in situ between ER wounds, these were preferably removed with additional ER, but argon plasma coagulation (APC) of tissue bridges during SRER was also allowed (60e80 W for Erbe ICC200; 30e40 W for Erbe Vio; APC-probe 2200A, Erbe Elektromedizin, Tübingen, Germany). If visible Barrett’s mucosa was present after the maximum allowable SRER sessions, patients underwent escape treatment

	with RFA. Escape treatment with APC or hot biopsy forceps for areas of residual BO (<5 mm) was allowed to avoid an additional ER or RFA, or when ER was not possible.
Comparator	Endoscopic-resection: ER-cap technique and the multiband mucosectomy (MBM) technique were used. Additionally, the use of the 'simple snare' technique was allowed. RFA: Patients randomised to RFA underwent focal ER of visible abnormalities followed by RFA after 6e8 weeks, when the residual BO contained at the utmost HGD upon biopsy. RFA was performed using the HALO system (BÂRRX Medical, Sunnyvale, California, USA) as previously described.9 19 Primary circumferential ablation was performed using the HALO360 balloon catheter, with a double RFA delivery (12 J/cm2 , 40 W/ cm2) and a cleaning step in between two ablation passes to remove coagulum from the ablation zone and electrode surface. At subsequent RFA sessions, the HALO90 device was used for focal ablation of residual Barrett's tongues and islands <2 cm in length, and to ablate the squamocolumnar junction ('Z-line') circumferentially at the gastric folds. The HALO90 catheter consists of a small electrode that is fixed to the tip of the endoscope. Focal RFA was delivered twice to each area (15 J/cm2 , 40 W/cm2), followed by a cleaning step and a second ablation pass, again delivering RFA twice.17 RFA was repeated every 2e3 months until complete endoscopic eradication of BO was acieved. In cases where BO persisted after four RFA sessions (#2 HALO360 procedures), escape ER was performed using the MBM technique. For minute islands of unsuspicious BO (<5 mm), hot biopsy forceps treatment was allowed when this avoided an additional RFA session or escape ER.
Number of participants	47
Duration of follow-up	Median (IQR) follow-up from initial treatment 24 (18-29) months; from final treatment sessions 18 (11-23) months

Study arms

ER+SRER (N = 25)
Stepwise radical endoscopic resection (SRER) after endoscopic resection (ER)

ER+RFA (N = 22)
Radiofrequency ablation (RFA) after Focal endoscopic resection (ER)

Characteristics

Arm-level characteristics

Characteristic	ER+SRER (N = 25)	ER+RFA (N = 22)
% Female Sample size	n = 4 ; % = 16	n = 3 ; % = 13.6
Mean age (SD) Median (IQR)	68 (45 to 88)	69 (55 to 73)
Visible lesions prior to treatment No of events	n = 17 ; % = 68	n = 18 ; % = 82
Worst diagnosis histology of biopsies or ER specimens: HGD Sample size	n = 12 ; % = 48	n = 7 ; % = 31.8
Worst diagnosis histology of biopsies or ER specimens: early cancer Sample size	n = 13 ; % = 52	n = 15 ; % = 68.2

Outcomes

Study timepoints

- 2 year (Median (IQR) follow-up from initial treatment 24 (18-29) months; from final treatment sessions 18 (11-23) months)

Complete histological response; recurrence; complications

Outcome	ER+SRER, 2 year, N = 25	ER+RFA, 2 year, N = 22
Complete histological response for neoplasia CR-neoplasia No of events	n = 25 ; % = 100	n = 21 ; % = 96
Complete histological response for intestinal metaplasia CR-IM Sample size	n = 23 ; % = 92	n = 21 ; % = 96
Recurrence Recurrence of early cancer requiring ER No of events	n = 1 ; % = 4	n = 0 ; % = 0
Severe complications 1 perforation, 5 stenoses No of events	n = 6	n = 0
Moderate complications 1 early bleeding, 17 stenoses; 1 late bleeding, 3 stenoses No of events	n = 18	n = 4

Outcome	ER+SRER, 2 year, N = 25	ER+RFA, 2 year, N = 22
Mild complications 5 acute bleedings; 2 acute bleedings, 1 acute non-transmural laceration) No of events	n = 5	n = 3

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

Completehistologicalresponse;recurrence;complications-Completehistologicalresponseforneoplasia-NoOfEvents-ER+SRER-ER+RFA-t2

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)	High *(some had ER before while others had it after randomisation)*
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	Some concerns *(some had ER before while others had it after randomisation; potential selection bias as limited details on recruitment are provides)*
Overall bias and Directness	Overall Directness	Directly applicable

Observational studies

Li, 2016

Bibliographic Reference	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.; 2016

Study details

Trial name / registration number	US RFA Patient registry
Study type	Retrospective cohort study
Study location	Multicentre study at 148 institutions in the United States (113 community based, 35 academic affiliated).

Study setting	Community based and academic institutions; data were analysed at the University of North Carolina Centre for Gastrointestinal Biology and Disease
Study dates	July 2007 to July 2011
Sources of funding	Covidien, Inc
Inclusion criteria	Patients undergoing treatment of BE with RFA using the HALO Ablation Systems (GI Solutions, Sunnyvale, CA, a subsidiary of Covidien); Patients were eligible for inclusion in the registry if: (i) they had endoscopic evidence of columnar metaplasia in the tubular esophagus with accompanying biopsies demonstrating intestinal metaplasia (IM), and (ii) they were candidates for RFA for BE. Histology was classified using standardized grading, including non-dysplastic BE (NDBE), indefinite for dysplasia (IND), low-grade dysplasia (LGD), high-grade dysplasia (HGD), intramucosal carcinoma (IMC), and invasive adenocarcinoma. Those patients who had previously received one or more treatments prior to enrollment had collection of retrospective data, with subsequent prospective collection of data for ensuing visits. Patients who had not yet undergone treatment were prospectively enrolled. For purposes of this analysis, all eligible registry patients with confirmed HGD or IMC were included.
Exclusion criteria	Not specified
Recruitment / selection of participants	Patients meeting inclusion criteria were enrolled in the registry from July 2007 to July 2011.
Intervention(s)	The trial standardized protocol suggested medical therapy with twice-daily proton pump inhibitors (PPIs) to minimize any baseline inflammatory changes of the esophageal mucosa and to decrease acid reflux prior to and throughout RFA treatment, unless the patient had documented history of antireflux surgery. The endoscopic resection device used to resect visible lesions varied by institution. RFA was recommended at 2 months after all visible lesions underwent successful EMR. At the initial visit, patients were treated with one of two ablation devices: the HALO360 Circumferential Ablation System or the HALO90 Focal Ablation System. The decision regarding device was based on the burden of disease (Barrett's segments of >3 cm being generally best treated with the circumferential catheter), as well as operator preference. Recommended treatment protocols were based on previously published data. Following the initial RFA treatment, repeat endoscopy at 2–3 month intervals was recommended, with additional circumferential or focal RFA treatment for any visible residual BE. If no visible BE was observed, four-quadrant biopsies every cm were recommended throughout the length of the pretreatment BE. If these biopsies demonstrated no BE on pathologic review, the patients entered endoscopic surveillance. Initial surveillance was recommended at 3 months for patients with HGD or 6 months for patients with NDBE, IND, or LGD. If follow-up biopsies revealed IM or dysplasia, recurrent treatment with RFA was recommended

Population subgroups	High-grade dysplasia Intramucosal carcinoma
Comparator	RFA alone, not preceded by EMR
Number of participants	1263
Duration of follow-up	Mean (SD) follow-up time: 2.86 (1.53) years for EMR+RFA, 2.76 (1.66) years for RFA alone
Indirectness	

Study arms

EMR+RFA (N = 406)

RFA (N = 857)

Characteristics

Study-level characteristics

Characteristic	**Study (N = 1263)**
% Female Sample size	n = 178 ; % = 14

Characteristic	Study (N = 1263)
High-grade dysplasia Sample size	n = 1054 ; % = 83
Intramucosal cancer Sample size	n = 209 ; % = 17
Mean age (SD) Mean (SD)	66.59 (10.34)
Ethnicity Caucasian Sample size	n = 1190 ; % = 94

Arm-level characteristics

Characteristic	EMR+RFA (N = 406)	RFA (N = 857)
Lenght of BE segment (cm) Mean (SD)	4.6 (3.6)	5.4 (3.6)
Pre-treatment fundoplication (n (%)) Sample size	n = 15 ; % = 3.7	n = 31 ; % = 3.6
High-grade dysplasia Sample size	n = 252 ; % = 62	n = 802 ; % = 94

Characteristic	EMR+RFA (N = 406)	RFA (N = 857)
Intramucosal carcinoma Sample size	n = 154 ; % = 38	n = 55 ; % = 6
Taking twice daily PPI (n (%)) Sample size	n = 299 ; % = 74	n = 693 ; % = 81

Outcomes

Study timepoints

2 year (Mean (SD) follow-up time: 2.86 (1.53) years for EMR+RFA, 2.76 (1.66) years for RFA alone)

Safety outcomes

Outcome	EMR+RFA, 2 year, N = 406	RFA, 2 year, N = 857
Mortality (treatment-related) No of events	n = 0 ; % = 0	n = 0 ; % = 0
Complications (any) some experience more than one complication No of events	n = 34 ; % = 8.4	n = 62 ; % = 7.2
High-grade dysplasia	n = 26 ; % = 10.3	n = 60 ; % = 7.5

Outcome	EMR+RFA, 2 year, N = 406	RFA, 2 year, N = 857
No of events		
Intramucosal carcinoma No of events	n = 8 ; % = 5.2	n = 2 ; % = 3.6
Stricture (n (%)) No of events	n = 29 ; % = 7.1	n = 52 ; % = 6.1
High-grade dysplasia No of events	n = 21 ; % = 8.3	n = 50 ; % = 6.2
Intramucosal carcinoma No of events	n = 8 ; % = 5.2	n = 2 ; % = 3.6
Bleeding (n (%)) No of events	n = 3 ; % = 0.7	n = 8 ; % = 0.9
High-grade dysplasia No of events	n = 3 ; % = 1.2	n = 8 ; % = 1
Intramucosal carcinoma No of events	n = 0 ; % = 0	n = 0 ; % = 0
Hospitalisation (n (%)) No of events	n = 7 ; % = 1.7	n = 11 ; % = 1.3
High-grade dysplasia No of events	n = 7 ; % = 2.8	n = 11 ; % = 1.4

Outcome	EMR+RFA, 2 year, N = 406	RFA, 2 year, N = 857
Intramucosal carcinoma No of events	n = 0 ; % = 0	n = 0 ; % = 0

Efficacy outcomes

Outcome	EMR+RFA, 2 year, N = 331	RFA, 2 year, N = 663
Progression to invasive adenocarcinoma (n (%)) No of events	n = 5 ; % = 1.5	n = 24 ; % = 3.6
High-grade dysplasia No of events	n = 2 ; % = 1	n = 23 ; % = 3.7
Intramucosal carcinoma No of events	n = 3 ; % = 2.4	n = 1 ; % = 2.9
RFA sessions required (n (%)) Mean (SD)	3 (1.9)	3.5 (2.1)

Progression to invasive adenocarcinoma - Polarity - Lower values are better

Durability outcome

Outcome	EMR+RFA, 2 year, N = 277	RFA, 2 year, N = 554
Recurrence of intestinal metaplasia (n (%)) No of events	n = 57 ; % = 21	n = 108 ; % = 19

Recurrence of intestinal metaplasia - Polarity - Lower values are better

Complete regression of dysplasia- High-grade dysplasia population

Outcome	EMR+RFA, 2 year, N = 204	RFA, 2 year, N = 628
Complete eradication of dysplasia No of events	n = 192 ; % = 94	n = 574 ; % = 92
Complete eradication of intestinal metaplasia No of events	n = 173 ; % = 85	n = 521 ; % = 83

Complete regression - Intramucosal carcinoma population

Outcome	EMR+RFA, 2 year, N = 127	RFA, 2 year, N = 35
Complete eradication of dysplasia No of events	n = 120 ; % = 95	n = 35 ; % = 100
Complete eradication of intestinal metaplasia No of events	n = 104 ; % = 82	n = 33 ; % = 94

Critical appraisal - ROBINS-I checklist

Safetyoutcomes-Mortality(treatment-related)-NoOfEvents-EMR+RFA-RFA-t2

Section	Question	Answer
1. Bias due to confounding	Risk of bias judgement for confounding	Moderate *(due to certain baseline differences)*

Section	Question	Answer
2. Bias in selection of participants into the study	Risk of bias judgement for selection of participants into the study	High (due to study not being a randomised study)
3. Bias in classification of interventions	Risk of bias judgement for classification of interventions	Moderate
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	High
Overall bias	Directness	Directly applicable

Safetyoutcomes-Complications(any)-NoOfEvents-EMR+RFA-RFA-t2

Section	Question	Answer
1. Bias due to confounding	Risk of bias judgement for confounding	Moderate *(due to certain baseline differences)*
2. Bias in selection of participants into the study	Risk of bias judgement for selection of participants into the study	High (due to study not being a randomised study)
3. Bias in classification of interventions	Risk of bias judgement for classification of interventions	Moderate

Section	Question	Answer
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	High
Overall bias	Directness	Directly applicable

Safetyoutcomes-Complications(any)-High-gradedysplasia-NoOfEvents-EMR+RFA-RFA-t2

Section	Question	Answer
1. Bias due to confounding	Risk of bias judgement for confounding	Moderate *(due to certain baseline differences)*
2. Bias in selection of participants into the study	Risk of bias judgement for selection of participants into the study	High (due to study not being a randomised study)
3. Bias in classification of interventions	Risk of bias judgement for classification of interventions	Moderate
4. Bias due to deviations from intended interventions	Risk of bias judgement for deviations from intended interventions	Low

Section	Question	Answer
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	High
Overall bias	Directness	Directly applicable

Safetyoutcomes-Complications(any)-Intramucosalcarcinoma-NoOfEvents-EMR+RFA-RFA-t2

Section	Question	Answer
1. Bias due to confounding	Risk of bias judgement for confounding	Moderate *(due to certain baseline differences)*
2. Bias in selection of participants into the study	Risk of bias judgement for selection of participants into the study	High (due to study not being a randomised study)
3. Bias in classification of interventions	Risk of bias judgement for classification of interventions	Moderate
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

Section	Question	Answer
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	High
Overall bias	Directness	Directly applicable

Safetyoutcomes-Stricture-NoOfEvents-EMR+RFA-RFA-t2

Section	Question	Answer
1. Bias due to confounding	Risk of bias judgement for confounding	Moderate *(due to certain baseline differences)*
2. Bias in selection of participants into the study	Risk of bias judgement for selection of participants into the study	High (due to study not being a randomised study)
3. Bias in classification of interventions	Risk of bias judgement for classification of interventions	Moderate
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	High
Overall bias	Directness	Directly applicable

Safetyoutcomes-Bleeding-NoOfEvents-EMR+RFA-RFA-t2

Section	Question	Answer
1. Bias due to confounding	Risk of bias judgement for confounding	Moderate *(due to certain baseline differences)*
2. Bias in selection of participants into the study	Risk of bias judgement for selection of participants into the study	Low
3. Bias in classification of interventions	Risk of bias judgement for classification of interventions	High (due to study not being a randomised study)
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	High
Overall bias	Directness	Directly applicable

Safetyoutcomes-Hospitalisation-NoOfEvents-EMR+RFA-RFA-t2

Section	Question	Answer
1. Bias due to confounding	Risk of bias judgement for confounding	Moderate *(due to certain baseline differences)*
2. Bias in selection of participants into the study	Risk of bias judgement for selection of participants into the study	Low
3. Bias in classification of interventions	Risk of bias judgement for classification of interventions	High (due to study not being a randomised study)
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	High
Overall bias	Directness	Directly applicable

Efficacyoutcomes-RFAsessionsrequired-MeanSD-EMR+RFA-RFA-t2

Section	Question	Answer
1. Bias due to confounding	Risk of bias judgement for confounding	Moderate *(due to certain baseline differences)*
2. Bias in selection of participants into the study	Risk of bias judgement for selection of participants into the study	Low
3. Bias in classification of interventions	Risk of bias judgement for classification of interventions	High (due to study not being a randomised study)
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	High
Overall bias	Directness	Directly applicable

Efficacyoutcomes-Progressiontoinvasiveadenocarcinoma-NoOfEvents-EMR+RFA-RFA-t2

Section	Question	Answer
1. Bias due to confounding	Risk of bias judgement for confounding	Moderate *(due to certain baseline differences)*

Section	Question	Answer
2. Bias in selection of participants into the study	Risk of bias judgement for selection of participants into the study	Low
3. Bias in classification of interventions	Risk of bias judgement for classification of interventions	High (due to study not being a randomised study)
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	High
Overall bias	Directness	Directly applicable

Durabilityoutcome-Recurrenceofintestinalmetaplasia-NoOfEvents-EMR+RFA-RFA-t2

Section	Question	Answer
1. Bias due to confounding	Risk of bias judgement for confounding	Moderate *(due to certain baseline differences)*
2. Bias in selection of participants into the study	Risk of bias judgement for selection of participants into the study	Low

Section	Question	Answer
3. Bias in classification of interventions	Risk of bias judgement for classification of interventions	High (due to study not being a randomised study)
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	High
Overall bias	Directness	Directly applicable

Completeregression-Intramucosalcarcinomapopulation-Completeeradicationofintestinalmetaplasia-NoOfEvents-EMR+RFA-RFA-t2

Section	Question	Answer
1. Bias due to confounding	Risk of bias judgement for confounding	Moderate *(due to certain baseline differences)*
2. Bias in selection of participants into the study	Risk of bias judgement for selection of participants into the study	Low
3. Bias in classification of interventions	Risk of bias judgement for classification of interventions	High (due to study not being a randomised study)

Section	Question	Answer
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	High
Overall bias	Directness	Directly applicable

Completeregression-Intramucosalcarcinomapopulation-CompleteeradicationofdysplasiaNoOfEvents-EMR+RFA-RFA-t2

Section	Question	Answer
1. Bias due to confounding	Risk of bias judgement for confounding	Moderate *(due to certain baseline differences)*
2. Bias in selection of participants into the study	Risk of bias judgement for selection of participants into the study	Low
3. Bias in classification of interventions	Risk of bias judgement for classification of interventions	High (due to study not being a randomised study)
4. Bias due to deviations from intended interventions	Risk of bias judgement for deviations from intended interventions	Low

Section	Question	Answer
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	High
Overall bias	Directness	Directly applicable

Completeregressionofdysplasia-High-gradedysplasiapopulation-Completeeradicationofintestinalmetaplasia-NoOfEvents-EMR+RFA-RFA-t2

Section	Question	Answer
1. Bias due to confounding	Risk of bias judgement for confounding	Moderate *(due to certain baseline differences)*
2. Bias in selection of participants into the study	Risk of bias judgement for selection of participants into the study	Low
3. Bias in classification of interventions	Risk of bias judgement for classification of interventions	High (due to study not being a randomised study)
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

Section	Question	Answer
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	High
Overall bias	Directness	Directly applicable

Completeregressionofdysplasia-High-gradedysplasiapopulation-Completeeradicationofdysplasia-NoOfEvents-EMR+RFA-RFA-t2

Section	Question	Answer
1. Bias due to confounding	Risk of bias judgement for confounding	Moderate *(due to certain baseline differences)*
2. Bias in selection of participants into the study	Risk of bias judgement for selection of participants into the study	Low
3. Bias in classification of interventions	Risk of bias judgement for classification of interventions	High (due to study not being a randomised study)
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

Section	Question	Answer
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	High
Overall bias	Directness	Directly applicable

Thota, 2018

Bibliographic Reference	Thota PN; Arora Z; Dumot JA; Falk G; Benjamin T; Goldblum J; Jang S; Lopez R; Vargo JJ; Cryotherapy and Radiofrequency Ablation for Eradication of Barrett's Esophagus with Dysplasia or Intramucosal Cancer.; Digestive diseases and sciences; 2018; vol. 63 (no. 5)

Study details

Study type	Retrospective cohort study
Study location	USA
Study setting	Cleveland clinic
Study dates	2006 to 2011
Sources of funding	Not specified
Inclusion criteria	Patients who had undergone endoscopic therapy for dysplastic BE or Intramucosal cancer from 2006 to 2011; who had undergone either RFA or cryotherapy with at least one surveillance endoscopy after treatment.
Exclusion criteria	Patients who underwent endoscopic mucosal resection (EMR) only, or who were still actively undergoing treatment at the time of the study.

Recruitment / selection of participants	Patients who had undergone endoscopic therapy for dysplastic BE or Intramucosal cancer from 2006 to 2011 at the Cleveland clinic, meeting inclusion criteria.
Intervention(s)	Initial RFA was performed with the Halo 360 (Medtronics, Minneapolis, Minnesota, USA) if the BE segment length was ≥ 3 cm. The procedure involved measuring the diameter of esophagus at different levels using a sizing balloon. *N*-acetyl cysteine was applied to clear mucus. Then, the appropriate sized RFA balloon was passed over guide wire. RFA energy was applied at 12 J/cm2 every 3-cm intervals with slight overlap under endoscopic guidance. The white coagulated tissue was scraped with a friction-fit cap mounted on the endoscope. Then second series of ablation was similarly completed. Follow-up treatments were performed with Halo-90 device. Energy was applied twice, then coagulated tissue was scraped off, and the whole sequence was repeated. All patients were brought back every 2–3 months for repeat treatments until endoscopic and histological eradication of BE or until the treatment was stopped due to progression or other clinical reasons based on patient and clinician preference. Once endoscopically visible BE was eliminated, four quadrant biopsies were obtained at every 1-cm interval along the original length of Barrett's segment to confirm histological eradication.
Comparator	Cryotherapy involved passage of a cryospray catheter passed through the biopsy channel of endoscope which delivered liquid nitrogen at − 196 °C and decompression tube with side holes for active venting of the stomach and esophagus (Generation 2 device, CSA Medical, Baltimore, MD). A hemi-circumferential 2–3 cm area was considered a treatment site. Initially, each site was frozen for two to three cycles of 20 s each with at least 45 s between freezes to allow tissue thawing. Of note, carbon dioxide-based cryotherapy was not used in this study. All patients were brought back every 2–3 months for repeat treatments until endoscopic and histological eradication of BE or until the treatment was stopped due to progression or other clinical reasons based on patient and clinician preference. Once endoscopically visible BE was eliminated, four quadrant biopsies were obtained at every 1-cm interval along the original length of Barrett's segment to confirm histological eradication. Cryotherapy was used in instances when RFA was not feasible due to uneven surface (nodular BE segment, *n* = 16) or proximal esophageal strictures precluding passage of RFA catheter (*n* = 2) and in an IMC in proximal esophagus when EMR could not be done. It was also used in patients with bleeding diathesis (cirrhosis, *n* = 7, thrombocytopenia in one patient) or on blood thinners (Coumadin, *n* = 8, clopidogrel, *n* = 11, aspirin, *n* = 36). It was used as salvage therapy when patients failed other ablative therapies such as RFA (*n* = 7), failed photodynamic therapy (*n* = 1), failed APC (*n* = 1). Finally,

	cryotherapy was performed in 20 patients due to their preference and in 5 patients with severe chronic obstructive pulmonary disease and IMC as they were high risk for esophagectomy.
Number of participants	154
Duration of follow-up	Follow-up data from 2006 to 2011; Following the completion of treatment, patients came back for surveillance endoscopy and biopsies every 3–6 months for a year and then yearly thereafter.
Indirectness	Population indirectness: 23/154 participants had low-grade dysplasia at baseline

Study arms

RFA (N = 73)

Cryotherapy (N = 81)

Characteristics

Arm-level characteristics

Characteristic	**RFA (N = 73)**	**Cryotherapy (N = 81)**
% Female Sample size	n = 7 ; % = 9.6	n = 16 ; % = 19.8
Mean age (SD) Mean (SD)	66.4 (9.5)	65 (80.2)

Characteristic	RFA (N = 73)	Cryotherapy (N = 81)
Ethnicity Caucasia Sample size	n = 66 ; % = 94.3	n = 66 ; % = 97.1
Current alcohol use Sample size	n = 39 ; % = 54.9	n = 25 ; % = 31.6
Use of aspirin Sample size	n = 33 ; % = 45.2	n = 37 ; % = 45.7
Use of NSAIDS Sample size	n = 8 ; % = 11	n = 6 ; % = 7.4
Use of statins Sample size	n = 40 ; % = 54.8	n = 43 ; % = 53.1
PPI use Sample size	n = 72 ; % = 98.6	n = 81 ; % = 100
History of fundoplication Sample size	n = 3 ; % = 4.1	n = 2 ; % = 2.5
Baseline biopsy: low-grade dysplasia Sample size	n = 13 ; % = 17.8	n = 11 ; % = 13.6
Baseline biopsy: high-grade dysplasia Sample size	n = 50 ; % = 68.5	n = 49 ; % = 60.5

Characteristic	RFA (N = 73)	Cryotherapy (N = 81)
Baseline biopsy: intramucosal cancer Sample size	n = 10 ; % = 13.7	n = 21 ; % = 25.9

Outcomes

Study timepoints

- 2 year (Median (range) follow up in months; RFA: 25.1 [13.0, 38.5] Cryotherapy: 31.8 [12.6, 50.7])

Complete eradication of metaplasia/ dysplasia

Outcome	RFA, 2 year, N = 72	Cryotherapy, 2 year, N = 80
Complete eradication of metaplasia No of events	n = 48 ; % = 66.7	n = 33 ; % = 41
Complete eradication of dysplasia No of events	n = 63 ; % = 87.5	n = 63 ; % = 78.8
Mortality No of events	n = 1 ; % = 1.4	n = 8 ; % = 10
Mortality due to cancer No of events	n = 1 ; % = 1.4	n = 4 ; % = 5

Recurrence of disease (if eradication)

Outcome	RFA, 2 year, N = 63	Cryotherapy, 2 year, N = 63
Recurrence of disease No of events	n = 7 ; % = 11.1	n = 9 ; % = 14.3

Critical appraisal - ROBINS-I checklist

Completeeradicationofmetaplasia/dysplasia-Completeeradicationofmetaplasia-NoOfEvents-RFA-Cryotherapy-t2

Section	Question	Answer
1. Bias due to confounding	Risk of bias judgement for confounding	Serious *(Difference in proportion of patients with baseline biopsy of cancer between groups; patients were not randomised and each therapy was given for different reasons which could be confounding)*
2. Bias in selection of participants into the study	Risk of bias judgement for selection of participants into the study	Low
3. Bias in classification of interventions	Risk of bias judgement for classification of interventions	Serious *(each intervention was given for different reasons which could be confounding)*
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

Section	Question	Answer
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
Overall bias	Directness	Indirectly Applicable *(due to inclusion of people with low-grade dysplasia)*

Completeeradicationofmetaplasia/dysplasia-Completeeradicationofdysplasia-NoOfEvents-RFA-Cryotherapy-t2

Section	Question	Answer
1. Bias due to confounding	Risk of bias judgement for confounding	Serious *(Difference in proportion of patients with baseline biopsy of cancer between groups; patients were not randomised and each therapy was given for different reasons which could be confounding)*
2. Bias in selection of participants into the study	Risk of bias judgement for selection of participants into the study	Low
3. Bias in classification of interventions	Risk of bias judgement for classification of interventions	Serious *(each intervention was given for different reasons which could be confounding)*
4. Bias due to deviations from intended interventions	Risk of bias judgement for deviations from intended interventions	Low

Section	Question	Answer
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
Overall bias	Directness	Indirectly Applicable *(due to inclusion of people with low-grade dysplasia)*

Completeeradicationofmetaplasia/dysplasia-Mortality-NoOfEvents-RFA-Cryotherapy-t2

Section	Question	Answer
1. Bias due to confounding	Risk of bias judgement for confounding	Serious *(Difference in proportion of patients with baseline biopsy of cancer between groups; patients were not randomised and each therapy was given for different reasons which could be confounding)*
2. Bias in selection of participants into the study	Risk of bias judgement for selection of participants into the study	Low
3. Bias in classification of interventions	Risk of bias judgement for classification of interventions	Serious *(each intervention was given for different reasons which could be confounding)*

Section	Question	Answer
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
Overall bias	Directness	Indirectly Applicable *(due to inclusion of people with low-grade dysplasia)*

Completeeradicationofmetaplasia/dysplasia-Mortalityduetocancer-NoOfEvents-RFA-Cryotherapy-t2

Section	Question	Answer
1. Bias due to confounding	Risk of bias judgement for confounding	Serious *(Difference in proportion of patients with baseline biopsy of cancer between groups; patients were not randomised and each therapy was given for different reasons which could be confounding)*
2. Bias in selection of participants into the study	Risk of bias judgement for selection of participants into the study	Low

Section	Question	Answer
3. Bias in classification of interventions	Risk of bias judgement for classification of interventions	Serious *(each intervention was given for different reasons which could be confounding)*
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
Overall bias	Directness	Indirectly Applicable *(due to inclusion of people with low-grade dysplasia)*

Recurrenceofdisease(iferadication)-Recurrenceofdisease-NoOfEvents-RFA-Cryotherapy-t2

Section	Question	Answer
1. Bias due to confounding	Risk of bias judgement for confounding	Serious *(Difference in proportion of patients with baseline biopsy of cancer between groups; patients were not randomised and each therapy was given for different reasons which could be confounding)*

Section	Question	Answer
2. Bias in selection of participants into the study	Risk of bias judgement for selection of participants into the study	Low
3. Bias in classification of interventions	Risk of bias judgement for classification of interventions	Serious *(each intervention was given for different reasons which could be confounding)*
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
Overall bias	Directness	Indirectly Applicable *(due to inclusion of people with low-grade dysplasia)*

Appendix E – Forest plots

EMR+RFA vs RFA alone for high-grade dysplasia/ intramucosal carcinoma

Figure 2: Mortality in people with high-grade dysplasia/ intramucosal carcinoma

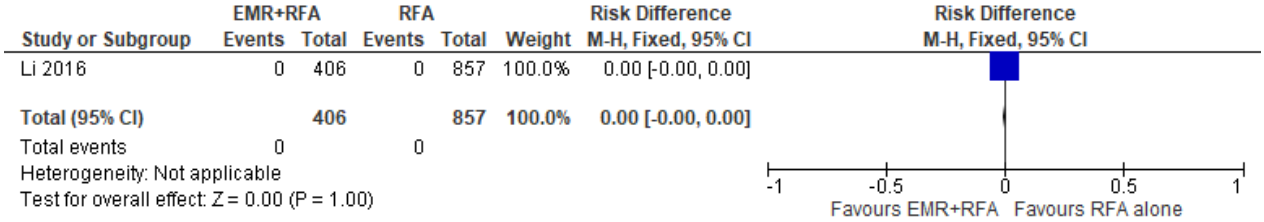


Figure 3: Recurrence of intestinal metaplasia

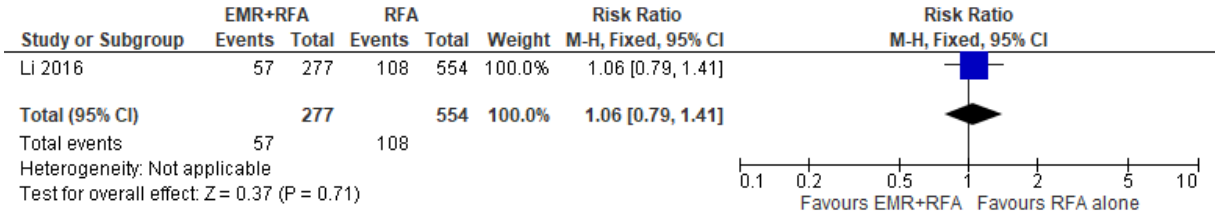
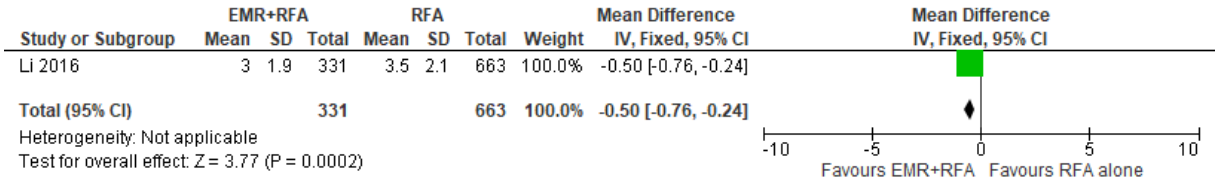


Figure 4: Number of RFA sessions required



EMR+RFA vs RFA alone for high-grade dysplasia

Figure 5: Complete eradication of dysplasia in people with high-grade dysplasia

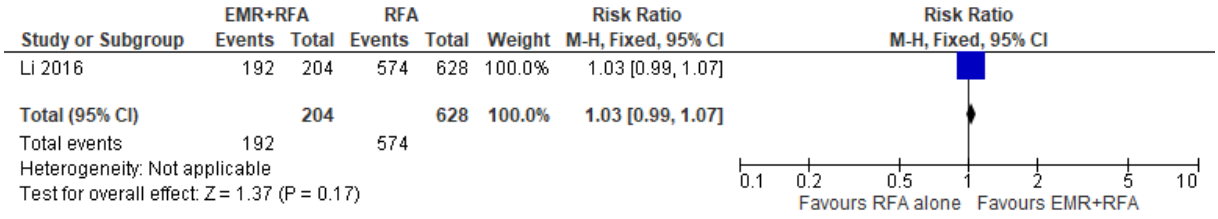


Figure 6: Complete eradication of intestinal metaplasia in people with high-grade dysplasia

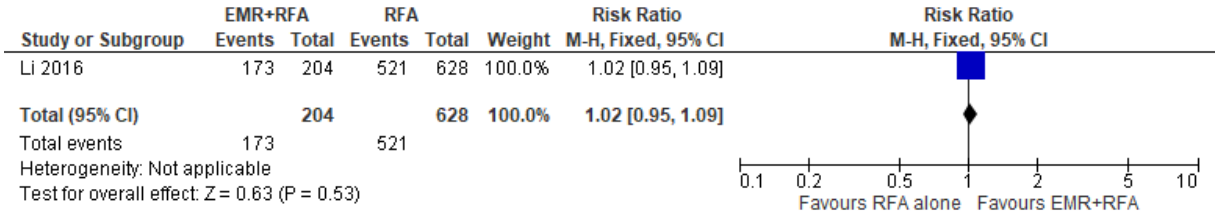


Figure 7: Complications (any) in people with high-grade dysplasia

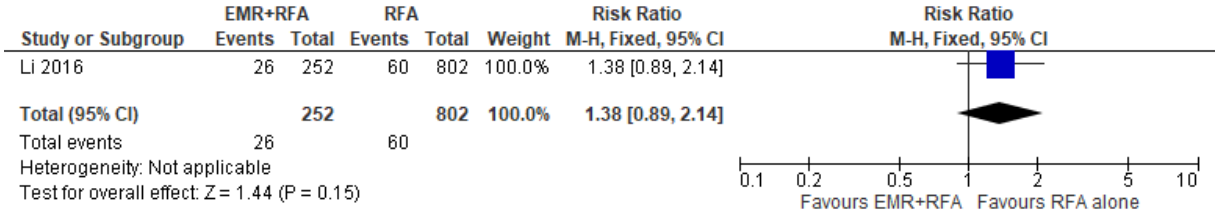


Figure 8: Stricture in people with high-grade dysplasia

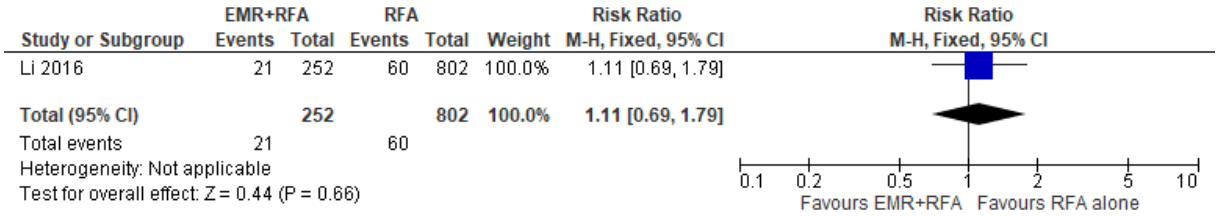


Figure 9: Bleeding in people with high-grade dysplasia

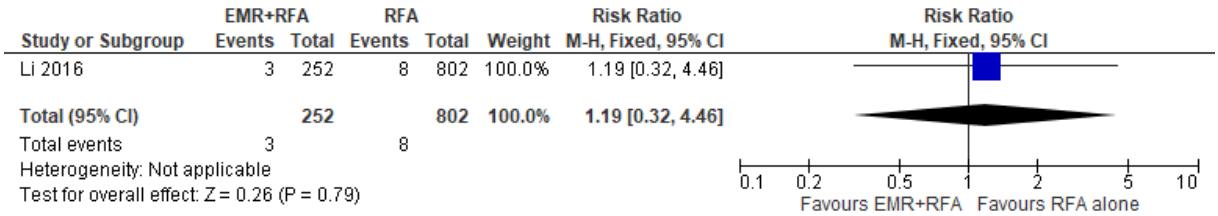


Figure 10: Hospitalisation in people with high-grade dysplasia

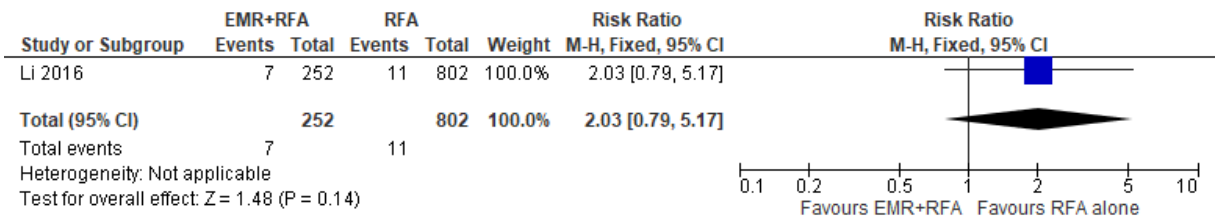


Figure 11: Complete eradication of dysplasia in people with intramucosal carcinoma

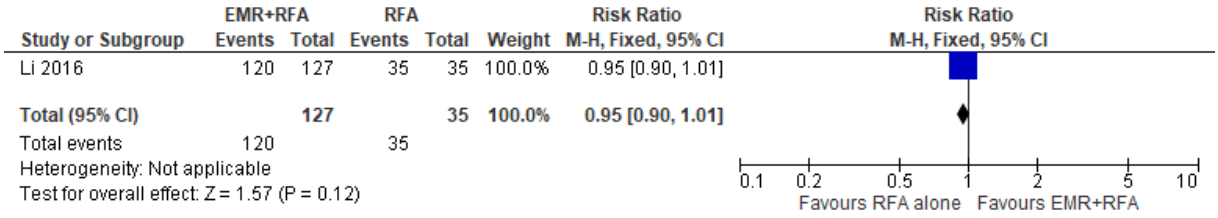


Figure 12: Complete eradication of intestinal metaplasia in people with intramucosal carcinoma

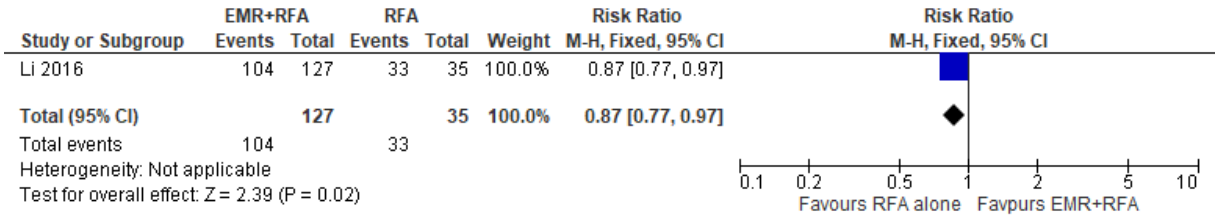


Figure 13: Complications (any) in people with intramucosal carcinoma

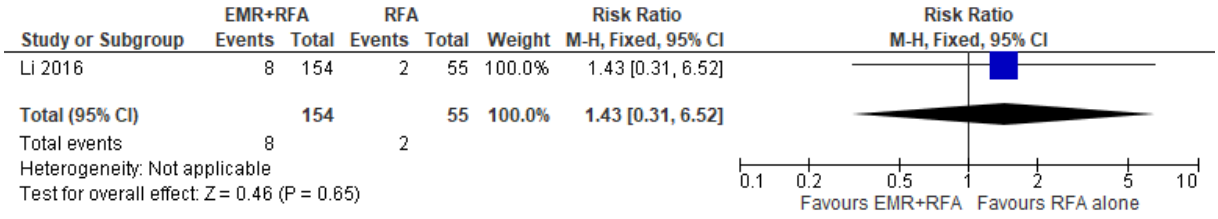


Figure 14: Stricture in people with intramucosal carcinoma

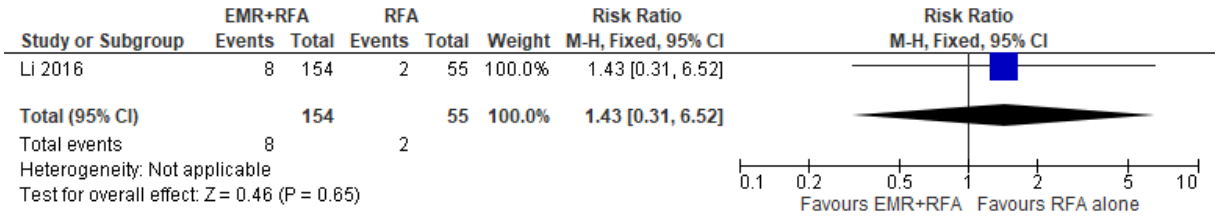


Figure 15: Bleeding in people with intramucosal carcinoma

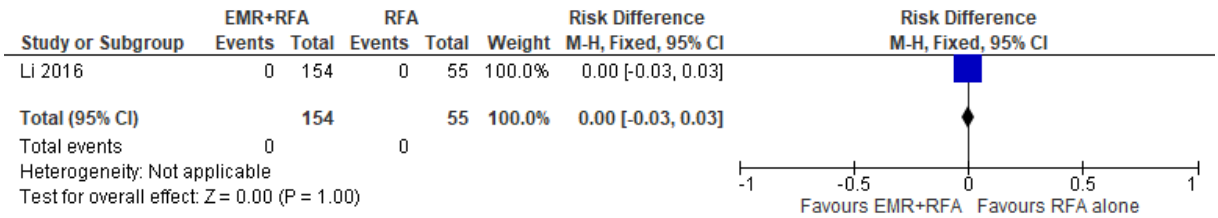
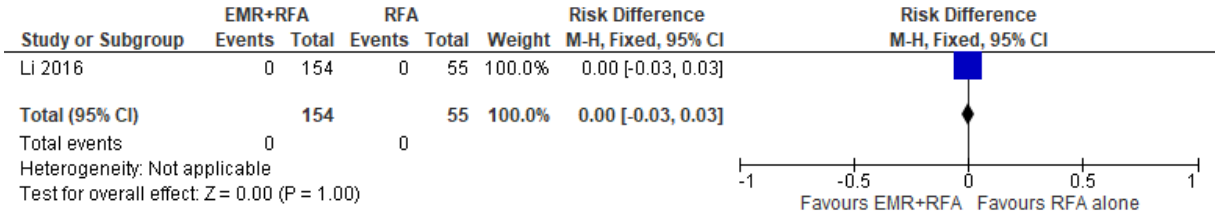
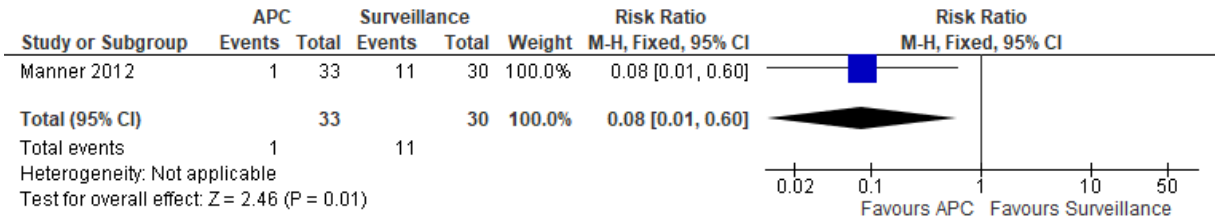


Figure 16: Hospitalisation in people with intramucosal carcinoma



E.2 APC versus surveillance in people with high-grade neoplasia or mucosal cancer (RCT data)

Figure 17: Recurrence of neoplasia



E.3 ER+APC versus ER+RFA in people with high-grade dysplasia/T1a cancer (RCT data)

Figure 18: Clearance of high-grade dysplasia/cancer at 12 months

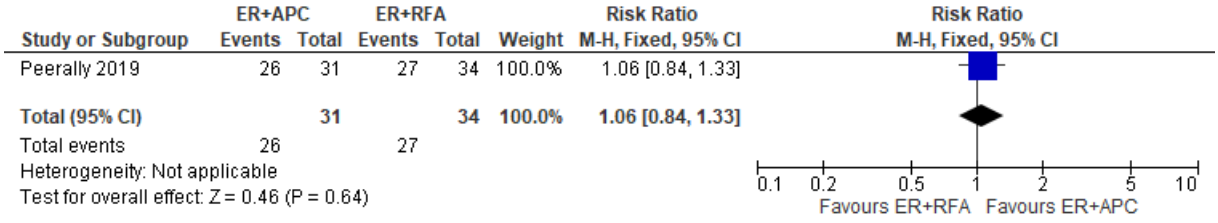


Figure 19: Clearance of BE on endoscopy at 12 months

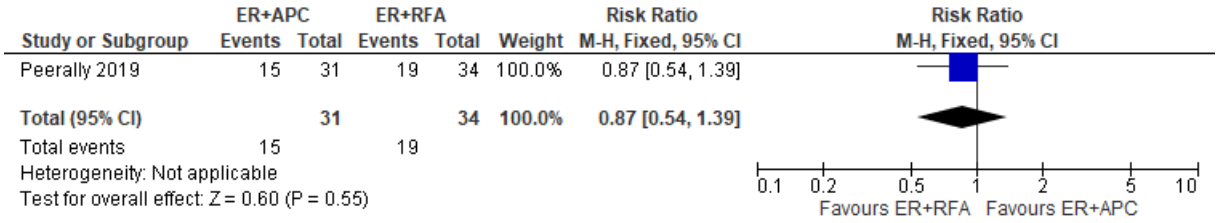
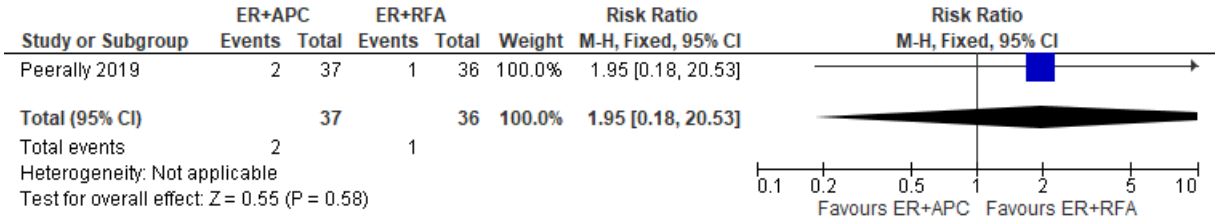


Figure 20: Stricture at 12 months

Figure 21: GI bleeding at 12 months



E.4 ER-cap versus MBM in people with high-grade dysplasia/ early cancer

Figure 22: Clinically not relevant bleeding during the procedure or 0-48 hours later

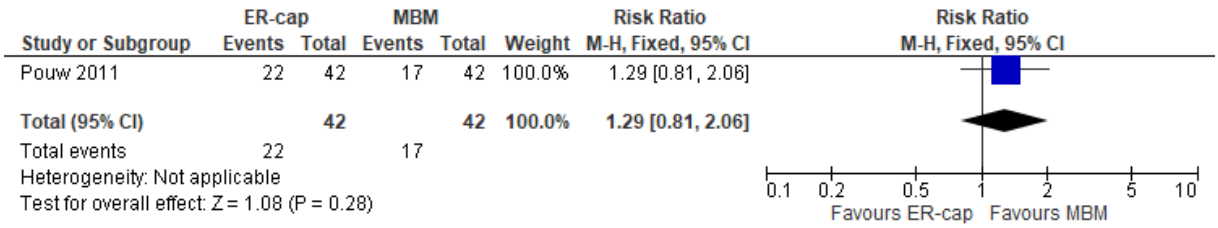
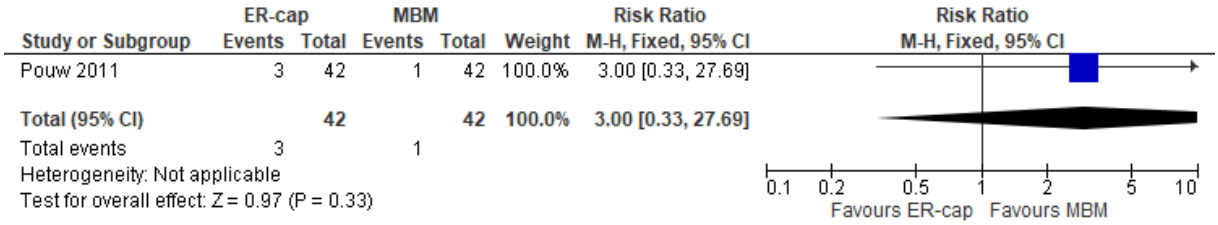


Figure 23: Perforation during the procedure or 0-48 hours later



E.5 RFA vs sham endoscopic procedure in people with high-grade dysplasia

Figure 24: Complete eradication of dysplasia at 12 months

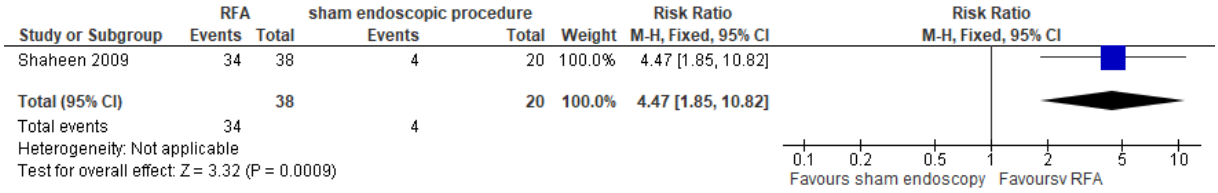
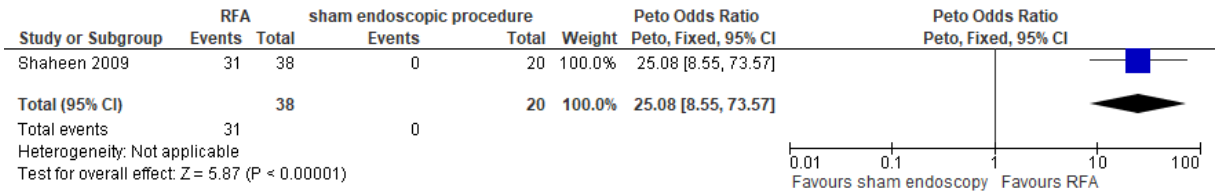


Figure 25: Complete eradication of intestinal metaplasia at 12 months



E.6 ESD versus EMR in people with high-grade intraepithelial neoplasia/ early adenocarcinoma

Figure 26: Complete resection of high-grade intraepithelial neoplasia or oesophageal adenocarcinoma

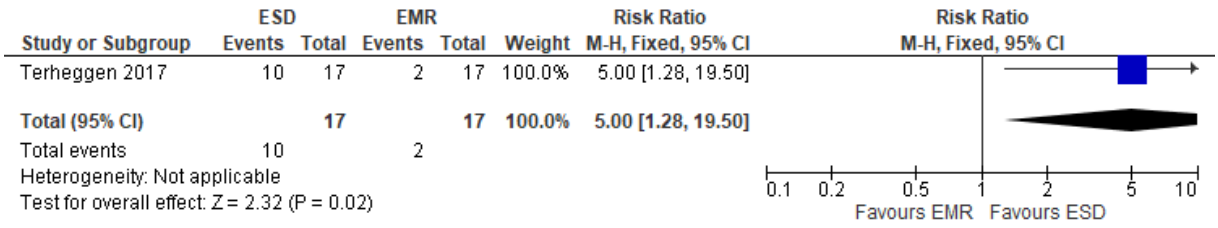


Figure 27: Curative resection

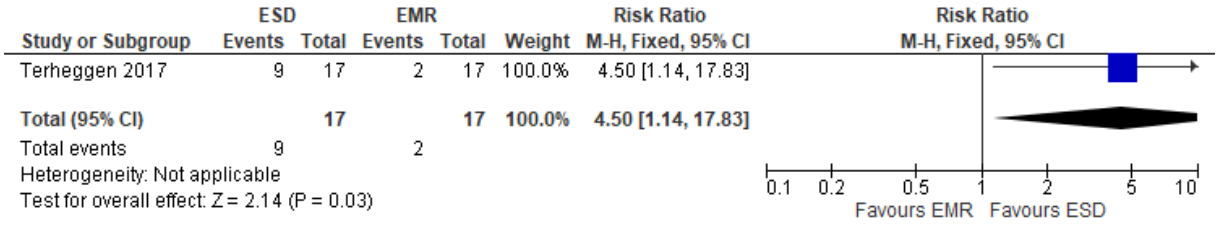


Figure 28: Complete remission of neoplasia after initial resection

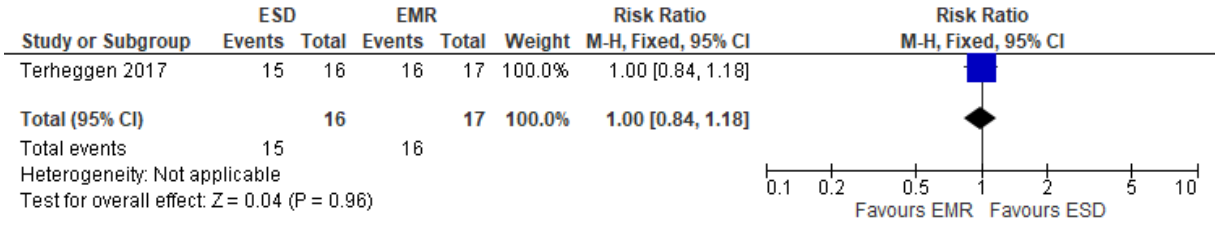


Figure 29: Complete remission of intestinal neoplasia

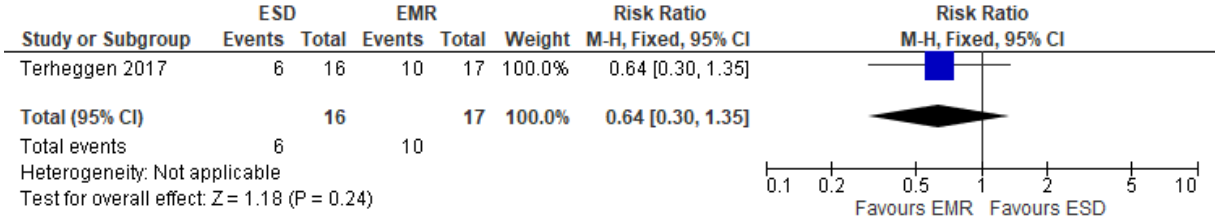


Figure 30: Recurrence of neoplasia

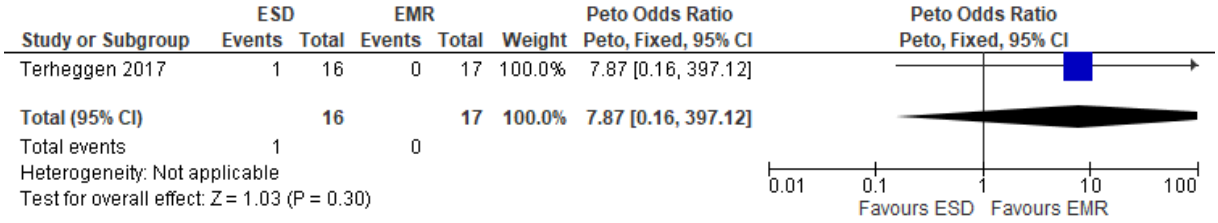


Figure 31: Patients referred for elective surgery

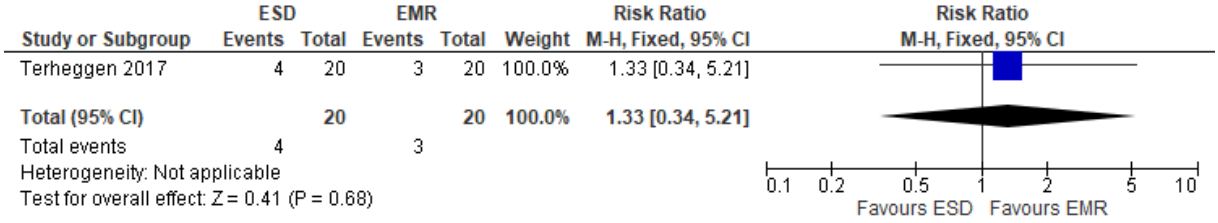


Figure 32: Perforation

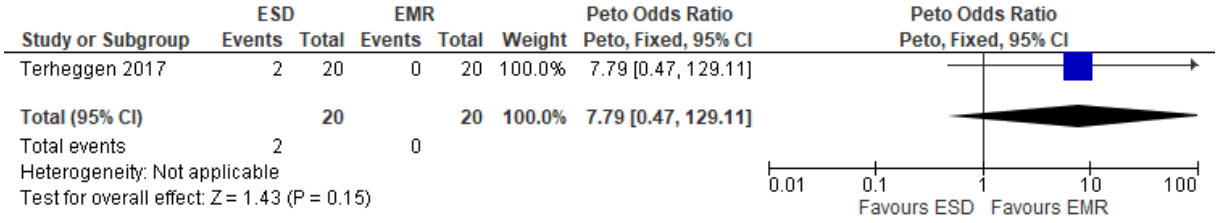


Figure 33: Mediastinitis

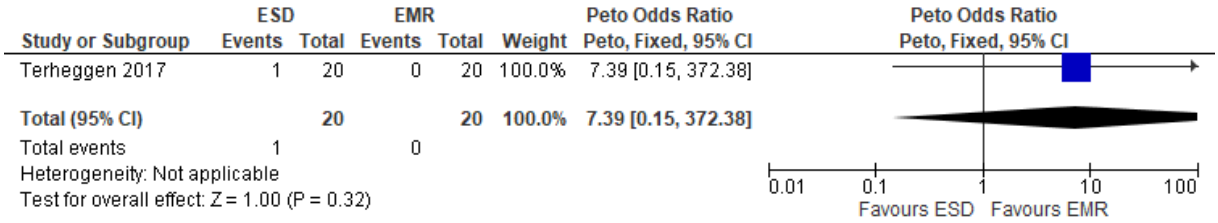


Figure 34: Temporary chest discomfort

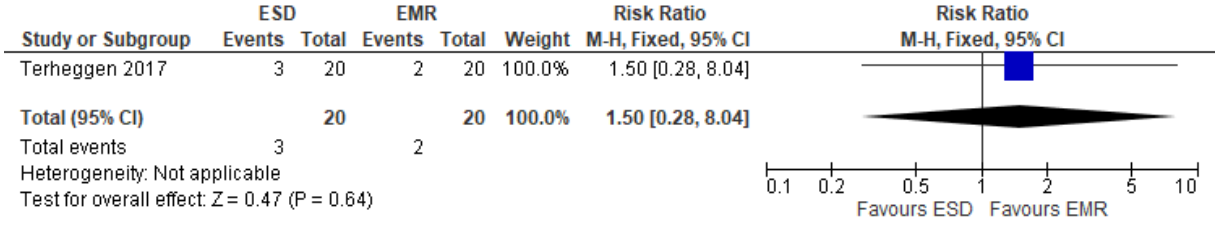


Figure 35: Severe adverse events

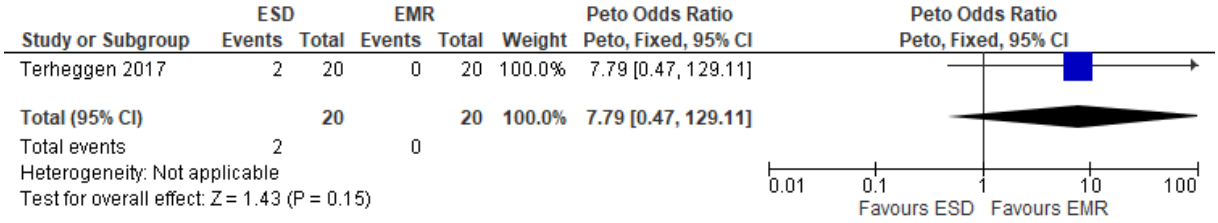
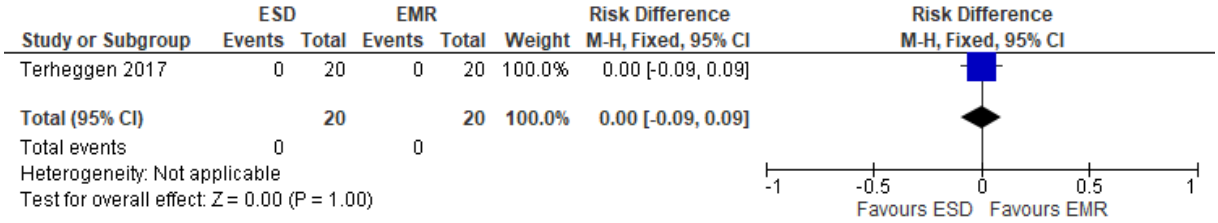


Figure 36: 30-day mortality



E.7 RFA versus cryotherapy in people with dysplasia/ intramucosal cancer

Figure 37: Mortality (all-cause)

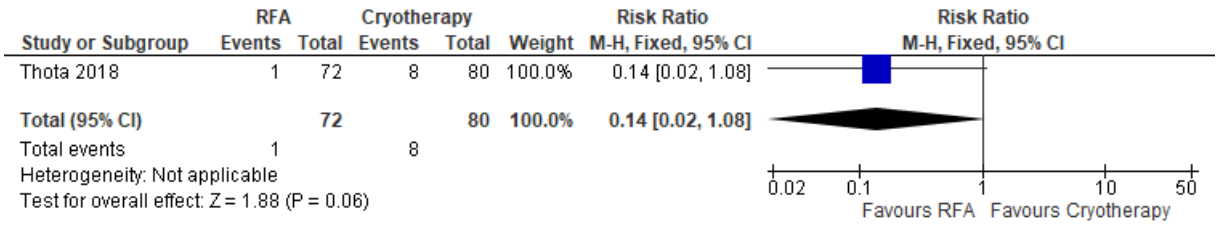


Figure 38: Mortality (due to cancer)

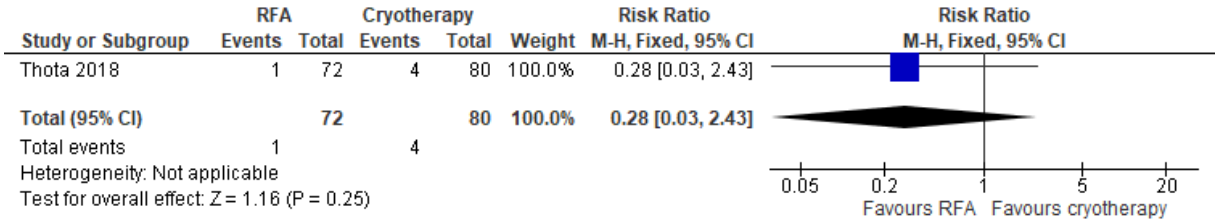

RFA
Cryotherapy
Risk Ratio
Risk Ratio
Study or Subgroup
Events
Total
Events
Total
Weight
M-H, Fixed, 95% CI
M-H, Fixed, 95% CI
Thota 2018
1
72
4
80
100.0%
0.28 [0.03, 2.43]
Total (95% CI)
72
80
100.0%
0.28 [0.03, 2.43]
Total events
1
4
Heterogeneity: Not applicable
Test for overall effect: Z = 1.16 (P = 0.25)
0.05
0.2
1
5
20
Favours RFA
Favours cryotherapy

Figure 39: Complete eradication of metaplasia

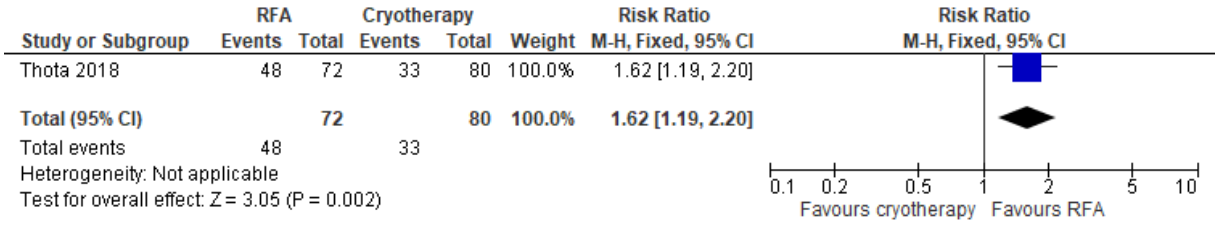


Figure 40: Complete eradication of dysplasia

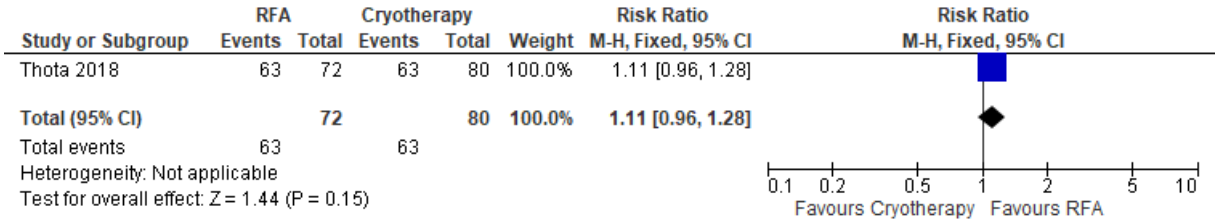
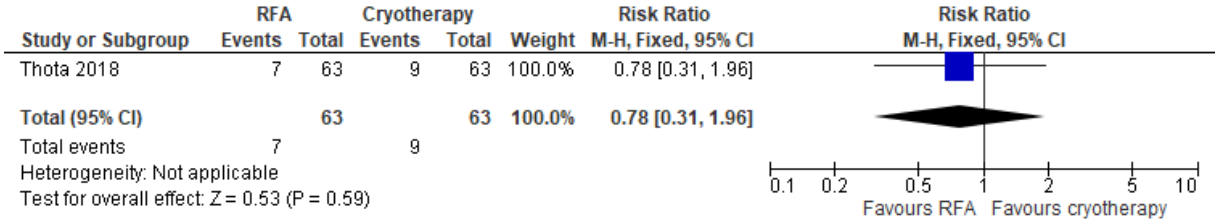


Figure 41: Recurrence of disease



E.8 ER-cap + SRER versus ER-cap + RFA in people with high-grade dysplasia/early cancer

Figure 42: Complete histological response for neoplasia

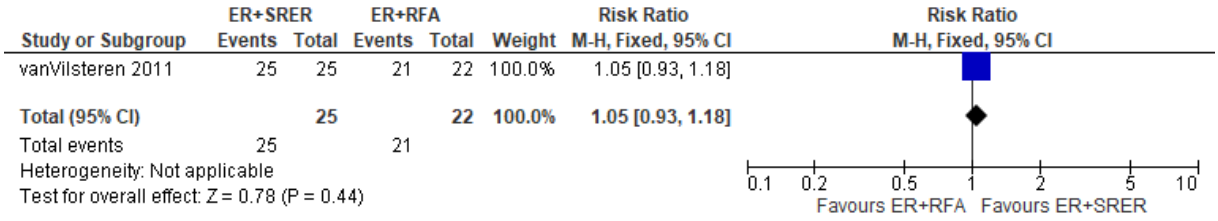


Figure 43: Complete histological response for intestinal metaplasia

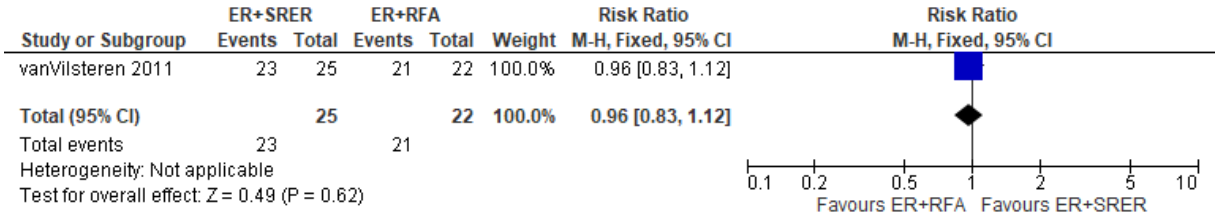


Figure 44: Recurrence

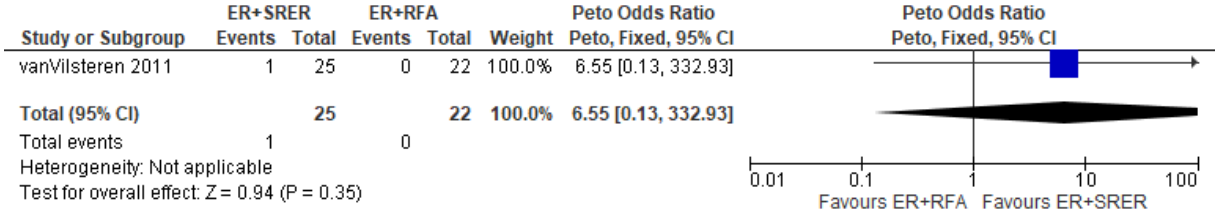


Figure 45: Severe complications (perforation, stenoses)

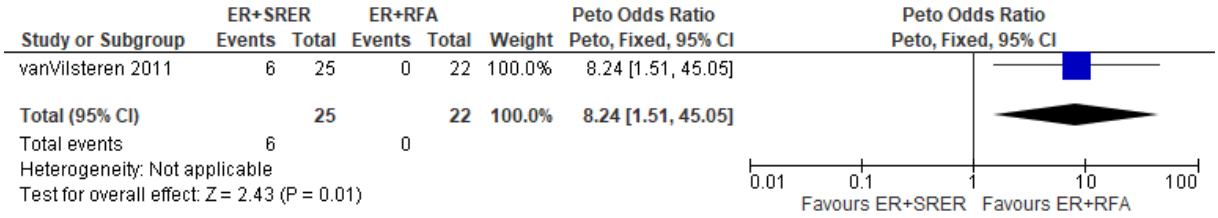


Figure 46: Moderate complications (early bleeding, stenoses, late bleeding)

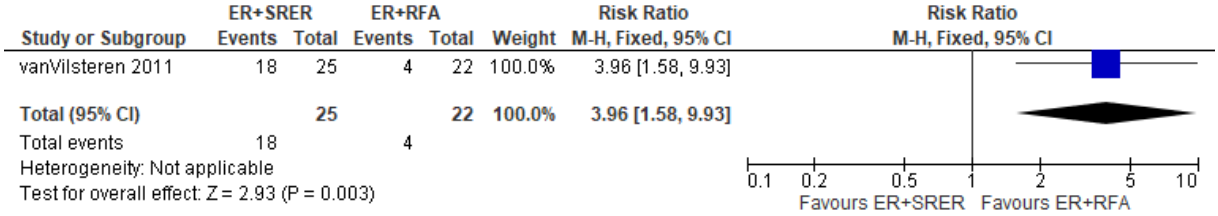
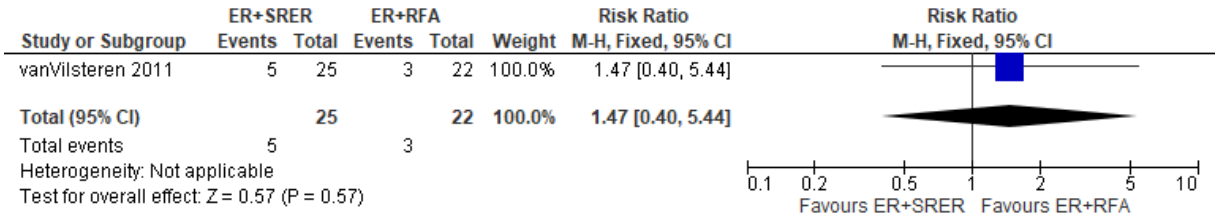


Figure 47: Mild complications (acute bleeding, acute non-transmural laceration)



Appendix F – GRADE tables

Table 19: Clinical evidence profile: EMR + RFA versus RFA alone in people with high-grade dysplasia/intramucosal carcinoma

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	EMR+RFA	RFA alone	Relative (95% CI)	Absolute (95% CI)		
Mortality (treatment-related)												
1	observational studies	serious [a]	not serious	not serious	not serious	none	0/406 (0.0%)	0/857 (0.0%)	not estimable	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	⨁◯◯◯ Very low	CRITICAL
Recurrence of intestinal metaplasia												
1	observational studies	serious [a]	not serious	not serious	serious [b]	none	57/277 (20.6%)	108/554 (19.5%)	**RR 1.06** (0.79 to 1.41)	**12 more per 1,000** (from 41 fewer to 80 more)	⨁◯◯◯ Very low	CRITICAL
Number of RFA sessions required												
1	observational studies	serious [a]	not serious	not serious	not serious	none	331	663	-	MD **0.5 lower** (0.76 lower to 0.24 lower)	⨁◯◯◯ Very low	CRITICAL

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

b. 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; for continuous outcomes: 0.5*SD of the control group

Table 20: Clinical evidence profile: EMR + RFA versus RFA alone in people with high-grade dysplasia

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	EMR+RFA	RFA alone	Relative (95% CI)	Absolute (95% CI)		
Complete eradication of dysplasia in people with HGD												
1	observational studies	serious [a]	not serious	not serious	not serious	none	192/204 (94.1%)	574/628 (91.4%)	**RR 1.03** (0.99 to 1.07)	**27 more per 1,000** (from 9 fewer to 64 more)	⨁◯◯◯ Very low	CRITICAL
Complete eradication of intestinal metaplasia in people with HGD												
1	observational studies	serious [a]	not serious	not serious	not serious	none	173/204 (84.8%)	521/628 (83.0%)	**RR 1.02** (0.95 to 1.09)	**17 more per 1,000** (from 41 fewer to 75 more)	⨁◯◯◯ Very low	CRITICAL
Complications (any) in people with HGD												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	EMR+RFA	RFA alone	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious [a]	not serious	not serious	serious[b]	none	26/252 (10.3%)	60/802 (7.5%)	**RR 1.38** (0.89 to 2.14)	**28 more per 1,000** (from 8 fewer to 85 more)	⨁◯◯◯ Very low	CRITICAL
Stricture in people with HGD												
1	observational studies	serious [a]	not serious	not serious	very serious[b]	none	21/252 (8.3%)	60/802 (7.5%)	**RR 1.11** (0.69 to 1.79)	**8 more per 1,000** (from 23 fewer to 59 more)	⨁◯◯◯ Very low	CRITICAL
Bleeding in people with HGD												
1	observational studies	serious [a]	not serious	not serious	very serious[b]	none	3/252 (1.2%)	8/802 (1.0%)	**RR 1.19** (0.32 to 4.46)	**2 more per 1,000** (from 7 fewer to 35 more)	⨁◯◯◯ Very low	CRITICAL
Hospitalisation in people with HGD												
1	observational studies	serious [a]	not serious	not serious	very serious[b]	none	7/252 (2.8%)	11/802 (1.4%)	**RR 2.03** (0.79 to 5.17)	**14 more per 1,000** (from 3 fewer to 57 more)	⨁◯◯◯ Very low	CRITICAL

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

b. 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

Table 21: Clinical evidence profile: EMR + RFA versus RFA alone in people with intramucosal carcinoma

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	EMR+RFA	RFA alone	Relative (95% CI)	Absolute (95% CI)		
Complete eradication of dysplasia in people with intramucosal carcinoma												
1	observational studies	serious [a]	not serious	not serious	not serious	none	120/127 (94.5%)	35/35 (100.0%)	**RR 0.95** (0.90 to 1.01)	**50 fewer per 1,000** (from 100 fewer to 10 more)	⨁◯◯◯ Very low	CRITICAL
Complete eradication of intestinal metaplasia in people with intramucosal carcinoma												
1	observational studies	serious [a]	not serious	not serious	serious[b]	none	104/127 (81.9%)	33/35 (94.3%)	**RR 0.87** (0.77 to 0.97)	**123 fewer per 1,000** (from 217 fewer to 28 fewer)	⨁◯◯◯ Very low	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	EMR+RFA	RFA alone	Relative (95% CI)	Absolute (95% CI)		
Complications (any) in people with intramucosal carcinoma												
1	observational studies	serious [a]	not serious	not serious	very serious[b]	none	8/154 (5.2%)	2/55 (3.6%)	**RR 1.43** (0.31 to 6.52)	**16 more per 1,000** (from 25 fewer to 201 more)	⨁◯◯◯ Very low	CRITICAL
Stricture in people with intramucosal carcinoma												
1	observational studies	serious [a]	not serious	not serious	very serious[b]	none	8/154 (5.2%)	2/55 (3.6%)	**RR 1.43** (0.31 to 6.52)	**16 more per 1,000** (from 25 fewer to 201 more)	⨁◯◯◯ Very low	CRITICAL
Bleeding in people with intramucosal carcinoma												
1	observational studies	serious [a]	not serious	not serious	not serious	none	0/154 (0.0%)	0/55 (0.0%)	not estimable	**0 fewer per 1,000** (from 30 fewer to 30 more)	⨁◯◯◯ Very low	CRITICAL
Hospitalisation in people with intramucosal carcinoma												
1	observational studies	serious [a]	not serious	not serious	not serious	none	0/154 (0.0%)	0/55 (0.0%)	not estimable	**0 fewer per 1,000** (from 30 fewer to 30 more)	⨁◯◯◯ Very low	CRITICAL

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

b. 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

Table 22: Clinical evidence profile: APC versus surveillance in people with high-grade neoplasia or mucosal cancer (RCT data)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	APC	Surveillance	Relative (95% CI)	Absolute (95% CI)		
Recurrence of neoplasia (follow-up: mean 24 months)												
1	randomised trials	not serious	not serious	not serious	not serious	none	1/33 (3.0%)	11/30 (36.7%)	**RR 0.08** (0.01 to 0.60)	**337 fewer per 1,000** (from 363 fewer to 147 fewer)	⨁⨁⨁⨁ High	CRITICAL

Table 23: Clinical evidence profile: ER+APC versus ER+RFA in people with high-grade dysplasia/T1a cancer

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ER+APC	ER+RFA	Relative (95% CI)	Absolute (95% CI)		
Clearance of high-grade dysplasia/cancer (follow-up: 12 months)												
1	randomised trials	not serious	not serious	not serious	serious[a]	none	26/31 (83.9%)	27/34 (79.4%)	**RR 1.06** (0.84 to 1.33)	**48 more per 1,000** (from 127 fewer to 262 more)	⨁⨁⨁◯ Moderate	CRITICAL
Clearance of BE on endoscopy (follow-up: 12 months)												
1	randomised trials	not serious	not serious	not serious	very serious[a]	none	15/31 (48.4%)	19/34 (55.9%)	**RR 0.87** (0.54 to 1.39)	**73 fewer per 1,000** (from 257 fewer to 218 more)	⨁⨁◯◯ Low	CRITICAL
Stricture (follow-up: 12 months)												
1	randomised trials	not serious	not serious	not serious	very serious[a]	none	3/37 (8.1%)	3/36 (8.3%)	**RR 0.97** (0.21 to 4.51)	**3 fewer per 1,000** (from 66 fewer to 293 more)	⨁⨁◯◯ Low	CRITICAL
GI bleeding (follow-up: 12 months)												
1	randomised trials	not serious	not serious	not serious	very serious[a]	none	2/37 (5.4%)	1/36 (2.8%)	**RR 1.95** (0.18 to 20.53)	**26 more per 1,000** (from 23 fewer to 543 more)	⨁⨁◯◯ Low	CRITICAL

a. 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

Table 24: Clinical evidence profile: ER-cap versus MBM in people with high-grade dysplasia/ early cancer

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ER-cap	MBM	Relative (95% CI)	Absolute (95% CI)		
Clinically not relevant bleeding												
1	randomised trials	serious[a]	not serious	not serious	serious[b]	none	22/42 (52.4%)	17/42 (40.5%)	**RR 1.29** (0.81 to 2.06)	**117 more per 1,000** (from 77 fewer to 429 more)	⨁⨁◯◯ Low	CRITICAL
Perforation												
1	randomised trials	serious[a]	not serious	not serious	very serious[b]	none	3/42 (7.1%)	1/42 (2.4%)	**RR 3.00** (0.33 to 27.69)	**48 more per 1,000** (from 16 fewer to 635 more)	⨁◯◯◯ Very low	CRITICAL

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

b. 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

Table 25: Clinical evidence profile: RFA vs sham endoscopic procedure in people with high-grade dysplasia

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RFA	sham endoscopic procedure	Relative (95% CI)	Absolute (95% CI)		
Complete eradication of dysplasia												
1	randomised trials	serious[a]	not serious	not serious	not serious	none	34/38 (89.5%)	4/20 (20.0%)	**RR 4.47** (1.85 to 10.82)	**694 more per 1,000** (from 170 more to 1,000 more)	⨁⨁⨁◯ Moderate	CRITICAL
Complete eradication of intestinal metaplasia												
1	randomised trials	serious[a]	not serious	not serious	serious[b]	none	31/38 (81.6%)	0/20 (0.0%)	**risk difference 0.82** (0.68 to 0.96)	**820 more per 1,000** (from 680 more to 960 more)	⨁⨁◯◯ Low	CRITICAL

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

b. 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

Table 26: Clinical evidence profile: ESD versus EMR in people with high-grade intraepithelial neoplasia/ early adenocarcinoma

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ESD	EMR	Relative (95% CI)	Absolute (95% CI)		
Complete resection of high-grade intraepithelial neoplasia or oesophageal adenocarcinoma												
1	randomised trials	not serious	not serious	not serious	not serious	none	10/17 (58.8%)	2/17 (11.8%)	**RR 5.00** (1.28 to 19.50)	**471 more per 1,000** (from 33 more to 1,000 more)	⨁⨁⨁⨁ High	CRITICAL
Curative resection												
1	randomised trials	not serious	not serious	not serious	serious[a]	none	9/17 (52.9%)	2/17 (11.8%)	**RR 4.50** (1.14 to 17.83)	**412 more per 1,000** (from 16 more to 1,000 more)	⨁⨁⨁◯ Moderate	CRITICAL
Complete remission of neoplasia after initial resection												
1	randomised trials	not serious	not serious	not serious	not serious	none	15/16 (93.8%)	16/17 (94.1%)	**RR 1.00** (0.84 to 1.18)	**0 fewer per 1,000** (from 151 fewer to 169 more)	⨁⨁⨁⨁ High	CRITICAL
Complete remission of intestinal neoplasia												
1	randomised trials	not serious	not serious	not serious	very serious[a]	none	6/16 (37.5%)	10/17 (58.8%)	**RR 0.64** (0.30 to 1.35)	**212 fewer per 1,000** (from 412 fewer to 206 more)	⨁⨁◯◯ Low	CRITICAL
Recurrence of neoplasia												
1	randomised trials	not serious	not serious	not serious	serious[a]	none	1/16 (6.3%)	0/17 (0.0%)	**Risk difference 0.06** (-0.09 to 0.22)	**60 more per 1,000** (from 90 fewer to 220 more)	⨁⨁⨁◯ Moderate	CRITICAL
Patients referred for elective surgery												
1	randomised trials	not serious	not serious	not serious	very serious[a]	none	4/20 (20.0%)	3/20 (15.0%)	**RR 1.33** (0.34 to 5.21)	**50 more per 1,000** (from 99 fewer to 632 more)	⨁⨁◯◯ Low	CRITICAL
Perforation												
1	randomised trials	not serious	not serious	not serious	serious[a]	none	2/20 (10.0%)	0/20 (0.0%)	**Risk difference 0.10** (-0.05 to 0.25)	**100 more per 1,000** (from 50 fewer to 250 more)	⨁⨁⨁◯ Moderate	CRITICAL
Mediastinitis												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ESD	EMR	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	not serious	not serious	not serious	serious[a]	none	1/20 (5.0%)	0/20 (0.0%)	**Risk difference 0.05** (-0.08 to 0.18)	**50 more per 1,000** (from 80 fewer to 180 more)	⨁⨁⨁◯ Moderate	CRITICAL

Temporary chest discomfort

1	randomised trials	not serious	not serious	not serious	very serious[a]	none	3/20 (15.0%)	2/20 (10.0%)	**RR 1.50** (0.28 to 8.04)	**50 more per 1,000** (from 72 fewer to 704 more)	⨁⨁◯◯ Low	CRITICAL

Severe adverse events

1	randomised trials	not serious	not serious	not serious	serious[a]	none	2/20 (10.0%)	0/20 (0.0%)	**Risk difference 0.10** (-0.05 to 0.25)	**100 more per 1,000** (from 50 fewer to 250 more)	⨁⨁⨁◯ Moderate	CRITICAL

30-day mortality

1	randomised trials	not serious	not serious	not serious	not serious	none	0/20 (0.0%)	0/20 (0.0%)	not estimable	**0 fewer per 1,000** (from 90 fewer to 90 more)	⨁⨁⨁⨁ High	CRITICAL

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

Table 27: Clinical evidence profile: RFA versus cryotherapy in people with dysplasia/ intramucosal cancer

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RFA	cryotherapy	Relative (95% CI)	Absolute (95% CI)		

Mortality (all cause) (follow-up: 2 years)

1	observational studies	serious[a]	not serious	serious[b]	serious[c]	none	1/72 (1.4%)	8/80 (10.0%)	**RR 0.14** (0.02 to 1.08)	**86 fewer per 1,000** (from 98 fewer to 8 more)	⨁◯◯◯ Very low	CRITICAL

Complete eradication of metaplasia (follow-up: 2 years)

1	observational studies	serious[a]	not serious	serious[b]	serious[c]	none	48/72 (66.7%)	33/80 (41.3%)	**RR 1.62** (1.19 to 2.20)	**256 more per 1,000** (from 78 more to 495 more)	⨁◯◯◯ Very low	CRITICAL

Mortality (due to cancer) (follow-up: 2 years)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RFA	cryotherapy	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious [a]	not serious	serious[b]	very serious[c]	none	1/72 (1.4%)	4/80 (5.0%)	**RR 0.28** (0.03 to 2.43)	**36 fewer per 1,000** (from 49 fewer to 72 more)	⨁◯◯◯ Very low	CRITICAL
Complete eradication of dysplasia (follow-up: 2 years)												
1	observational studies	serious [a]	not serious	serious[b]	serious[c]	none	63/72 (87.5%)	63/80 (78.8%)	**RR 1.11** (0.96 to 1.28)	**87 more per 1,000** (from 32 fewer to 221 more)	⨁◯◯◯ Very low	CRITICAL
Recurrence of disease (follow-up: 2 years)												
1	observational studies	serious [a]	not serious	serious[b]	very serious[c]	none	7/63 (11.1%)	9/63 (14.3%)	**RR 0.78** (0.31 to 1.96)	**31 fewer per 1,000** (from 99 fewer to 137 more)	⨁◯◯◯ Very low	CRITICAL

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
b. Downgraded by 1 increment because the evidence included an indirect population: people with low-grade dysplasia
c. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs; for dichotomous outcomes default MIDs: 0.8 and 1.25

Table 28: Clinical evidence profile: ER-cap + SRER versus ER-cap + RFA in people with high-grade dysplasia/early cancer

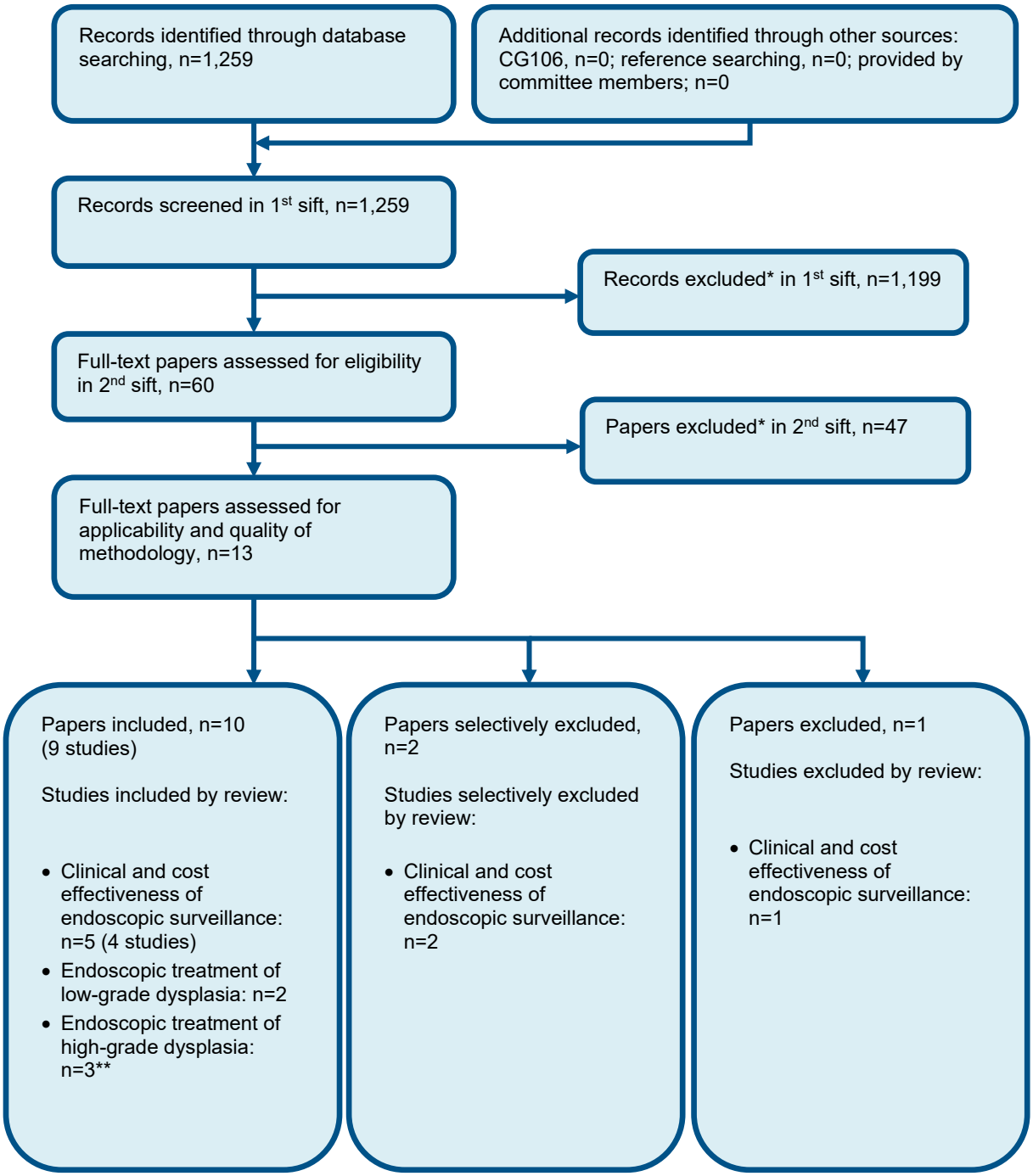
Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ER+SRER	ER+RFA	Relative (95% CI)	Absolute (95% CI)		
Complete histological response for neoplasia												
1	randomised trials	serious [a]	not serious	not serious	not serious	none	25/25 (100.0%)	21/22 (95.5%)	**RR 1.05** (0.93 to 1.18)	**48 more per 1,000** (from 67 fewer to 172 more)	⨁⨁⨁◯ Moderate	CRITICAL
Complete histological response for intestinal metaplasia												
1	randomised trials	serious [a]	not serious	not serious	not serious	none	23/25 (92.0%)	21/22 (95.5%)	**RR 0.96** (0.83 to 1.12)	**38 fewer per 1,000** (from 162 fewer to 115 more)	⨁⨁⨁◯ Moderate	CRITICAL
Recurrence												
1	randomised trials	serious [a]	not serious	not serious	serious[b]	none	1/25 (4.0%)	0/22 (0.0%)	**Risk difference 0.04** (-0.07 to 0.15)	**40 more per 1,000** (from 70 fewer to 150 more)	⨁⨁◯◯ Low	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ER+SRER	ER+RFA	Relative (95% CI)	Absolute (95% CI)		
Severe complications (perforation, stenoses)												
1	randomised trials	serious [a]	not serious	not serious	very serious[b]	none	6/25 (24.0%)	0/22 (0.0%)	**Risk difference 0.24** (0.06 to 0.42)	**240 more per 1,000** (from 60 more to 420 more)	⨁◯◯◯ Very low	CRITICAL
Moderate complications (early bleeding, stenoses, late bleeding)												
1	randomised trials	serious [a]	not serious	not serious	not serious	none	18/25 (72.0%)	4/22 (18.2%)	**RR 3.96** (1.58 to 9.93)	**538 more per 1,000** (from 105 more to 1,000 more)	⨁⨁⨁◯ Moderate	CRITICAL
Mild complciations (acute bleeding, acute non-transmural laceration)												
1	randomised trials	serious [a]	not serious	not serious	very serious[b]	none	5/25 (20.0%)	3/22 (13.6%)	**RR 1.47** (0.40 to 5.44)	**64 more per 1,000** (from 82 fewer to 605 more)	⨁◯◯◯ Very low	CRITICAL

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

b. 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

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	Boger 2010[1]			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: Cost-utility analysis (health outcome: QALYs) **Study design:** Probabilistic Markov model **Approach to analysis:** The natural history of BO was simulated in a cohort of patients undergoing one of two treatment options, after which patients could either be cured, experience adverse events or see the return of Barrett's. Failure of oesophagectomy led to terminal cancer. **Perspective:** UK NHS **Time horizon:** 25 years (lifetime)	**Population:** People with HGD in BO **Cohort settings:** Start age: 64 Male: 100% **Intervention 1:** oesophagectomy **Intervention 2:** RFA followed by endoscopic surveillance* with oesophagectomy for HGD recurrence or persistence *For neo-squamous oesophagus patients post-RFA, annual surveillance for 5 years. Patients with BO after RFA were surveilled for 5 years, and if they had not progressed to HGD, surveillance continued on a 2-yearly basis.	**Total costs (mean per patient):** Intervention 1: £8,555 Intervention 2: £6,653 Incremental (2−1): -£1,902 (95% CI: NR; p=NR) **Currency & cost year:** 2009/10 UK pounds **Cost components incorporated:** surveillance, RFA, oesophagectomy, complications from oesophagectomy and dilatation, outpatient follow-up, palliation of untreatable adenocarcinoma	**QALYs (mean per patient):** Intervention 1: 13.8 Intervention 2: 14.2 Incremental (2−1): 0.4 (95% CI: NR; p=NR)	**ICER (Intervention 2 versus Intervention 1):** Intervention 2 dominates (pa) 95% CI:NR Probability Intervention 2 cost effective (£20k/£30K threshold): 85%/83% **Analysis of uncertainty:** Various one-way sensitivity analyses were conducted, after which RFA remained cost effective oesophagectomy at a threshold of £20k.

Discounting: Costs: 3.5%; Outcomes: 3.5%				
Data sources				
Health outcomes: Transition probabilities resulting from oesophagectomy and RFA were taken from various literature sources. **Quality-of-life weights:** Health state utilities were taken from literature and do not appear to be taken from EQ-5D valuations. Utilities derived from the standard gamble technique were preferred as it avoids ratings scales biases. Where health state utilities were unknown, they were estimated by consensus amongst the authors relative to known scores, **Cost sources:** Most costs were taken from NHS Reference costs 2009/10. The cost of RFA was supplied by a pharmaceutical company.				
Comments				
Source of funding: None. **Limitations:** Sources for costs are dated and not likely reflective of current NHS costs. QALYs were not captured using the EQ-5D scale. Model does not include the natural history of Barrett's oesophagus, therefore progression of Barrett's recurrence post-treatment is not adequately captured. **Other:**				
Overall applicability:[c] Partially applicable **Overall quality:**[d] Potentially serious limitations				

Abbreviations: 95% CI= 95% confidence interval; BO= Barrett's oesophagus; CUA= cost–utility analysis; EQ-5D= Euroqol 5 dimensions; HGD= high-grade dysplasia; ICER= incremental cost-effectiveness ratio; NR= not reported; pa= probabilistic analysis; QALYs= quality-adjusted life years; RFA= radiofrequency ablation
(a) Directly applicable / Partially applicable / Not applicable
(b) Minor limitations / Potentially serious limitations / Very serious limitations

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. Costs and health outcomes were captured. Model cycles were 1 year in length. **Perspective:** Spanish NHS **Time horizon:** 15 years **Discounting:** Costs: 3%; Outcomes: 3%	**Population:** People with HGD in BO **Cohort settings:** Start age: 65 Male: NR **Intervention 1:** oesophagectomy **Intervention 2:** RFA (RFA)	**Total costs (mean per patient):** Intervention 1: £39,969 Intervention 2: £27,787 Incremental (2−1): -£12,182 (95% CI: NR; p=NR) **Currency & cost year:** 2016 Euros, (presented here as 2016 UK pounds[(a)]) **Cost components incorporated:** drug costs, procedure costs, follow-up costs, treatment complication costs	**QALYs (mean per patient):** Intervention 1: 8.22 Intervention 2: 9.45 Incremental (2−1): 1.23 (95% CI: NR; p=NR)	**ICER (Intervention 2 versus Intervention 1):** Intervention 2 dominates (pa) 95% CI:NR Probability Intervention 2 dominates intervention 1: 100% **Analysis of uncertainty:** Various one-way sensitivity analyses were conducted, for example changing the time horizon between 5-25 years, the age between 55-75 years, the discount rate between 0-5%, transitions probabilities by 25% either way, among others. In all scenarios, RFA-EMR dominates oesophagectomy.

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.[7, 15] Transition probabilities between health states were taken from Hur 2012 and Imadomi 2009.[6, 7] **Quality-of-life weights:** Utilities were used to represent QALYs on a scale of 1, representing perfect health, and 0, representing death., **Cost sources:** Resource use data was based on a panel of three clinical experts. Unit costs were taken from 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 were not discounted in line with the NICE guideline. However, it should be noted that results did not change when the discount was varied during sensitivity analysis. QALYS were not captured using the EQ-5D measure. Resource use associated with treatment was based on expert clinical opinion. Study was funded by a pharmaceutical company. **Other:** Probabilistic analysis was based on 1,000 iterations only as 100% of cases reported that RFA-EMR dominated oesophagectomy. It was assumed that patients would not undergo secondary RFA, 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; NHS= national health service; NR= not reported; pa= probabilistic analysis; QALYs= quality-adjusted life years; RFA= radiofrequency ablation;
(c) Converted using 2016 purchasing power parities[12]
(d) Directly applicable / Partially applicable / Not applicable
(e) Minor limitations / Potentially serious limitations / Very serious limitations

Study	Filby 2017[3]			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: Cost-utility analysis (health outcome: QALYs) **Study design:** Probabilistic decision analytic model (Markov model) **Approach to analysis:** **Perspective:** UK NHS **Time horizon:** Lifetime **Discounting:** Costs: 3.5%; Outcomes: 3.5%	**Population:** People with HGD in BO **Cohort settings:** Start age: NR Male: NR **Intervention 1:** endoscopic surveillance* until oesophageal cancer developed **Intervention 2:** Endoscopic eradication therapy of BO neoplasia *For NDBO, one surveillance session every 3–5 years was assumed, two sessions per year for LGD and three sessions per year for HGD.	**Total costs (mean per patient):** Intervention 1: £9,524 Intervention 2: £10,769 Incremental (2−1): £1,246 (95% CI: NR; p=NR) **Currency & cost year:** UK pounds (cost year unclear) **Cost components incorporated:** surveillance, oesophagectomy, RFA, EMR, treatment for perforation and stricture, endoscopy and biopsy, PPIs and H2 receptor antagonists following surgery	**QALYs (mean per patient):** Intervention 1: 9.062 Intervention 2: 10.041 Incremental (2−1): 0.979 (95% CI: NR; p=NR)	**ICER (Intervention 2 versus Intervention 1):** £1,272 per QALY gained (pa) 95% CI:NR Probability Intervention 2 cost effective (£20k/£30K threshold): 65%/67% **Analysis of uncertainty:** Univariate analysis identified two areas likely to change the direction of results: 3. Proportion of patients having residual dysplasia following RFA. For the intervention to cross the £20k threshold, treatment efficacy would have to fall below 20% (base case efficacy: 92.6%). 4. HGD multiplier: In the model, when there are fewer people with HGD, there are more people with NDBO, LGD and OAC. For the ICER to cross over £20k, there would have to be less than half the proportion of patients staying in the HGD health state each year.
Data sources				
Health outcomes: Natural history of Barrett's taken from Inadomi 2009. Treatment effectiveness was based on the results from Shaheen 2011. Key outcomes were the complete ablation of dysplasia and presence of residual dysplasia. **Quality-of-life weights:** The reference cited for utilities is incorrect, but they appear to be taken from various literature including the NICE CG106 model. Here, a utility score of 1 (representing perfect health) was applied to				

no BO, which is unrealistic. Therefore, the average age-related population utility for the UK was applied instead. **Cost sources:** References for costs are cited but these appear to be incorrect.
Comments
Source of funding: Medtronic **Limitations:** Sources for costs are unclear as well as which year they relate to. Sources for QALYs used in the model are unclear. Analysis was funded by a pharmaceutical company. **Other:**
Overall applicability:[c] Partially applicable **Overall quality:**[d] Potentially serious limitations

Abbreviations: 95% CI= 95% confidence interval; BO= Barrett's oesophagus; CUA= cost–utility analysis; EMR= endoscopic mucosal resection; EQ-5D= Euroqol 5 dimensions; H2= histamine 2; HGD= high-grade dysplasia; ICER= incremental cost-effectiveness ratio; LGD= low-grade dysplasia; NDBO= non-dysplastic Barrett's oesophagus; NR= not reported; OAC= oesophageal adenocarcinoma; pa= probabilistic analysis; PPI= proton pump inhibitor; QALYs= quality-adjusted life years; RFA= radiofrequency ablation

(a) Directly applicable / Partially applicable / Not applicable

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

Study	NICE Barrett's oesophagus: ablative therapy clinical guideline 2010 (CG106)			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: Cost-utility analysis (health outcome: QALYs) **Study design:** Probabilistic decision analytic model (Markov model) **Approach to analysis:** Natural history of Barrett's oesophagus over a lifetime including NBO, BO, LGD, HGD, asymptomatic cancer and symptomatic cancer. **Perspective:** UK NHS **Time horizon:** Lifetime **Discounting:** Costs: 3.5%; Outcomes: 3.5%	**Population:** People aged 60 years with HGD **Cohort settings:** Start age: 60 Male: NR **Intervention 1:** no surveillance **Intervention 2:** Surveillance every three months for the first year, then every 6 months in second year, then annually in years 3-5, then every 5 years thereafter. **Intervention 3:** Surgery **Intervention 4:** Endoscopic mucosal resection plus surveillance **Intervention 5:** Radiofrequency ablation plus surveillance **Intervention 6:** Endoscopic mucosal resection plus radiofrequency ablation plus surveillance **Intervention 7:** Endoscopic mucosal resection plus argon plasma coagulation plus surveillance	**Total costs (mean per patient):** Intervention 1: £7,249 Intervention 2: £22,741 Intervention 3: £15,855 Intervention 4: £20,993 Intervention 5: £24,740 Intervention 6: £23,136 Intervention 7: £23,924 **Currency & cost year:** 2007/08 UK pounds **Cost components incorporated:** surgery for HGD, asymptomatic and symptomatic cancer, complications, treatment for perforation and stricture, endoscopy and biopsy, endoscopic mucosal resection, ablation, PPIs, untreatable cancer	**QALYs (mean per patient):** Intervention 1: 8.44 Intervention 2: 8.50 Intervention 3: 9.25 Intervention 4: 8.98 Intervention 5: 9.15 Intervention 6: 9.44 Intervention 7: 9.33	**ICER (2 versus 1):** £283,009 per QALY gained (pa) **ICER (3 versus 1):** £10,612 per QALY gained (pa) **ICER (4 versus 1):** £25,662 per QALY gained (pa) **ICER (5 versus 1):** £24,823 per QALY gained (pa) **ICER (6 versus 1):** £15,916 per QALY gained (pa) **ICER (7 versus 1):** £18,745 per QALY gained (pa) 95% CI:NR Probability of each intervention being cost effective versus intervention 1(£20K/30K threshold) **Int.** / **£20k** / **£30k** 2 / 11% / 17% 3 / 58% / 62% 4 / 36% / 44% 5 / 39% / 53% 6 / 55% / 70% 7 / 45% / 60% **Analysis of uncertainty:** The probability of each intervention being the optimal

				choice at 20K/30K thresholds was reported. Surgery was the most cost-effective intervention in both instances.
Data sources				
Health outcomes: Natural history of Barrett's taken from Garside 2006.[4] Treatment effectiveness was based on the results of the guideline clinical review. Key outcomes were the complete ablation of dysplasia (in both NBO and BO) and the complete ablation of Barrett's. **Quality-of-life weights:** Utilities were taken various literature sources and were calculated using techniques such as the time trade-off, standard gamble and the visual analogue scale. These were then used as weights on the UK population norm for EQ-5D. **Cost sources:** Costs were taken from the NHS Reference Costs 2007/08 and the British National Formulary 58.				
Comments				
Source of funding: National Institute for Health and Clinical Excellence. **Limitations:** Source of natural history data for Barrett's progression is dated. Sources for costs are dated and not likely reflective of current NHS costs. QALYs were not captured using the EQ-5D scale. **Other:** It was assumed in the model that HGD and intramucosal cancer can be merged into one state. There was no drop-out from surveillance in the model. The study authors advise against making data comparisons and ranking treatments due to the poor quality of data informing the modelling.				
Overall applicability:(c) Partially applicable **Overall quality:**(d) Potentially serious limitations				

Abbreviations: 95% CI= 95% confidence interval; BO= Barrett's oesophagus; CUA= cost–utility analysis; EQ-5D= Euroqol 5 dimensions; HGD= high-grade dysplasia; ICER= incremental cost-effectiveness ratio; NBO= non-Barrett's oesophagus; NR= not reported; pa= probabilistic analysis; PPI= proton pump inhibitor; QALYs= quality-adjusted life years
(c) Directly applicable / Partially applicable / Not applicable
Minor limitations / Potentially serious limitations / Very serious limitation

Appendix I – Excluded studies

Clinical studies

Table 29: Studies excluded from the clinical review

Study	Reason for exclusion
(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 *Includes large proportion with low-grade dysplasia and results cannot be separated for the different level of dysplasia populations*
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 *includes large proportion with low-grade dysplasia*
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 *Large proportion with low-grade dysplasia and results are not reported separately for different populations*
Anonymous (2006) Erratum: Photodynamic therapy with porfimer sodium for ablation of high-grade dysplsia in Barrett's esophagus: International, partially blinded, randomized phase III trial (Gastrointestinal Endoscopy (October 2005) 62 (488-498)). Gastrointestinal Endoscopy 63(2): 359	- Full text paper not available
Barr, H. (2008) Surgical efficiency or eradication sufficiency. American Journal of Gastroenterology 103(6): 1346-8	- Review article but not a systematic review
Bergman, J. J. G. H. M. (2005) Endoscopic treatment of high-grade intraepithelial neoplasia and early cancer in Barrett oesophagus. Best Practice and Research: Clinical Gastroenterology 19(6): 889-907	- Review article but not a systematic review
Bustamante, F. A., Hourneaux, D. E. Moura E. G., Bernardo, W. et al. (2016) SURGERY VERSUS ENDOSCOPIC THERAPIES FOR	- Systematic review used as source of primary studies

Study	Reason for exclusion
EARLY CANCER AND HIGH-GRADE DYSPLASIA IN THE ESOPHAGUS: a systematic review. Arquivos de Gastroenterologia 53(1): 10-9	
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	- Systematic review used as source of primary studies
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	- Comparator in study does not match that specified in this review protocol *study reports a relevant outcome of recurrence but compares recurrence incidence according to baseline dysplasia status (low-grade vs high-grade dysplasia) rather than in response to the treatment received.*
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 Journal of Gastrointestinal Endoscopy 11(3): 239-248	- Systematic review used as source of primary studies
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	- Systematic review used as source of primary studies *Cochrane review that was set to include carcinoma not limited to Barrett's oesophagus, including squamous cell carcinoma. The review had no included studies but included a meta-analysis of 5 excluded studies that were independently assessed for inclusion in the present review. None met the review protocol as they included interventions not included in the protocol of the current 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
Haidry, R. J., Butt, M. A., Dunn, J. M. et al. (2015) Improvement over time in outcomes for	- Study does not contain an intervention relevant to this review protocol

Study	Reason for exclusion
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	*non-randomised study with no comparison group*
Hu, W., Yu, J., Yao, N. et al. (2022) Efficacy and Safety of Four Different Endoscopic Treatments for Early Esophageal Cancer: a Network Meta-analysis. Journal of Gastrointestinal Surgery 22: 22	- Systematic review used as source of primary studies
Huh, C. W., Ma, D. W., Kim, B. W. et al. (2021) Endoscopic Submucosal Dissection versus Surgery for Undifferentiated-Type Early Gastric Cancer: A Systematic Review and Meta-Analysis. Clinical Endoscopy 54(2): 202-210	- Systematic review used as source of primary studies
Phoa, K. N., Pouw, R. E., Van Vilsteren, F. G. I. et al. (2013) Remission of Barrett's esophagus with early neoplasia 5 years after radiofrequency ablation with endoscopic resection: A Netherlands cohort study. Gastroenterology 145(1): 96-104	- Comparator in study does not match that specified in this review protocol *non-randomised study with no comparison group*
Seewald, S., Akaraviputh, T., Seitz, U. et al. (2003) Circumferential EMR and complete removal of Barrett's epithelium: a new approach to management of Barrett's esophagus containing high-grade intraepithelial neoplasia and intramucosal carcinoma. Gastrointestinal Endoscopy 57(7): 854-859	- Comparator in study does not match that specified in this review protocol *non-randomised study with no comparison group*
Seewald, S., Ang, T. L., Pouw, R. E. et al. (2018) Management of Early-Stage Adenocarcinoma of the Esophagus: Endoscopic Mucosal Resection and Endoscopic Submucosal Dissection. Digestive Diseases & Sciences 63(8): 2146-2154	- Review article but not a systematic review
Sgourakis, G.; Gockel, I.; Lang, H. (2013) Endoscopic and surgical resection of T1a/T1b esophageal neoplasms: a systematic review. World Journal of Gastroenterology 19(9): 1424-37	- Systematic review used as source of primary studies
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 high and low grade dysplasia and results cannot be distinguished for any outcomes*

Study	Reason for exclusion
van Munster, S. N., Overwater, A., Haidry, R. et al. (2018) Focal cryoballoon versus radiofrequency ablation of dysplastic Barrett's esophagus: impact on treatment response and postprocedural pain. Gastrointestinal Endoscopy 88(5): 795-803.e2	- Population not relevant to this review protocol [Mixed population of low-grade and high-grade dysplasia/ oesophageal adenocarcinoma; outcomes not reported in an extractable format that can be meta-analysed (only reported as median (IQR)]
Van Munster, S., Nieuwenhuis, E., Weusten, B. L. A. M. et al. (2021) Long-term outcomes after endoscopic treatment for Barrett's neoplasia with radiofrequency ablation +/- endoscopic resection: Results from the national Dutch database in a 10-year period. Gut.	- Comparator in study does not match that specified in this review protocol [non-comparative study; does not compare different interventions; mixed population of low-grade dysplasia, high-grade dysplasia]
Wani, Sachin; Heif, Muhannad; Fukami, Norio (2012) Tu1591 Efficacy of Endoscopic Spray Cryotherapy With Endoscopic Mucosal Resection (EMR) or Submucosal Dissection (ESD) in Patients With Barrett's Esophagus (BE) Related Neoplasia. Gastrointestinal Endoscopy 75(4supplement): ab457	- Conference abstract
Wu, J., Pan, Y. M., Wang, T. T. et al. (2014) Endotherapy versus surgery for early neoplasia in Barrett's esophagus: a meta-analysis. Gastrointestinal Endoscopy 79(2): 233-241.e2	- Systematic review used as source of primary studies
Xie, M. and Smith, M. S. (2021) ID: 3524127 LIQUID NITROGEN SPRAY CRYOTHERAPY IS EFFECTIVE AND SAFE WHEN USE IN THE MANAGEMENT OF EARLY ESOPHAGEAL ADENOCARCINOMA: SYSTEMIC REVIEW AND META-ANALYSIS. Gastrointest. Endosc. 93(6): AB305-None	- Conference abstract
Yoshida, M., Takizawa, K., Nonaka, S. et al. (2020) Conventional versus traction-assisted endoscopic submucosal dissection for large esophageal cancers: a multicenter, randomized controlled trial (with video). Gastrointestinal Endoscopy 91(1): 55-65.e2	- Population not relevant to this review protocol *mixed population with squamous cell carcinoma and basal cell carcinoma*

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.

Appendix J – Research recommendations

Endoscopic treatment

For adults with Barrett's oesophagus with dysplasia or stage 1 oesophageal adenocarcinoma, what is the effectiveness of different endoscopic ablation techniques alone or in combination with endoscopic resection?

Why this is important

People with Barrett's oesophagus with dysplasia are at high risk of progression to cancer. Previous research has shown that this risk can be as high as 10-20% per year. People who have received endoscopic resection for stage I adenocarcinoma in Barrett's oesophagus are also at high risk of developing a new Barrett's adenocarcinoma from another area of their Barrett's oesophagus. Previous research has shown that this risk can be as high as 30% at 5 years.

It is therefore important to ablate any Barrett's mucosa to reduce this risk. There are a number of different endoscopic techniques that can be used for this including radio-frequency ablation, argon plasma coagulation and cryotherapy. These ablation techniques have different effectiveness and cost and may require a different number of treatment sessions. There is no research data on the comparative clinical and cost effectiveness of the different availabletechniques.

Rationale for research recommendation

Importance to 'patients' or the population	The different ablation techniques may have different efficacies with fewer treatment sessions and endoscopies for patients.
Relevance to NICE guidance	A recommendation was made to offer endoscopic ablation to people with Barrett's oesophagus with dysplasia and in those that have received successful endoscopic resection of stage I adenocarcinoma, but it was not possible to give specific guidance on which modality should be used. Further research might produce more specific recommendations on the most clinically and cost-effective modality to use in different groups of patients.
Relevance to the NHS	Potentially reducing the cost of ablation therapy for Barrett's oesophagus
National priorities	N/A
Current evidence base	There are no comparative data on different ablation techniques In Barrett's oesophagus
Equality considerations	None

Modified PICO table

Population	People with Barrett's oesophagus with dysplasia or with stage 1 oesophageal adenocarcinoma following endoscopic resection
Intervention	Head to head comparison of radio-frequency ablation and argon plasma coagulation and/or cryotherapy
Comparator	See intervention

Outcome	Quality of life, rate of remission from Barrett's and neoplasia, type of treatment required if cancer progression occurs , stage of cancer, grade of dysplasia, complications from treatment, number of treatment sessions required, cost of therapies
Study design	Randomised controlled trial
Timeframe	1 year following treatment, with possibility to capture longer term data
Additional information	None