National Institute for Health and Care Excellence

Final

Barrett's oesophagus and stage 1 oesophageal adenocarcinoma

[K] Evidence review for oesophagectomy versus endoscopic treatment

NICE guideline NG231

Evidence review underpinning recommendations 1.6.1 to 1.6.3 and 1.6.5 and research recommendations in the NICE guideline

February 2023

Final

National Institute for Health and Care Excellence

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Contents

1 Oesophagectomy versus endoscopic treatment

1.1 Review question

For adults with stage 1 oesophageal adenocarcinoma, what is the clinical and cost effectiveness of oesophagectomy?

1.1.1 Introduction

Endoscopic resection (ER) has become increasingly used as treatment for early stage oesophageal cancers. The risk of lymph node invasion is regarded as low and ranges from from 0 to 6 % for tumours confined to the epithelium and laminar propria, but up to 50% in those invading the submucosa.

The low risk of lymph node metastasis in T1a disease make ER the treatment of choice, as oesophagectomy is associated with substantial mortality and morbidity and may compromise long-term quality of life. However, the optimum treatment for T1b disease is still not known.

1.1.2 Summary of the protocol

For full details see the review protocol in Appendix A.

Table 1: PICO characteristics of review question

Population	Inclusion: Adults, 18 years and over, with Barrett's oesophagus and stage 1 oesophageal adenocarcinoma Exclusion: Adults with Barrett's oesophagus with any other stages and related neoplasia
Intervention	• Oesophagectomy
Comparison	• Endoscopic treatment
Outcomes	• Mortality (all-cause mortality, disease specific and treatment related) • Health related quality of life (any validated scores) • Progression of stage 1 adenocarcinoma to higher stages • Complications of surgery (e.g. perforation, stricture, pneumonia, anastomotic leak, weight loss, sepsis) • Adverse events (e.g. stricture, chronic ill health, chronic pain) • Length of hospital stay • Regression of Barrett's oesophagus • Recurrence of Barrett's oesophagus and Barrett's related neoplasia • Repeat intervention • (need for) Conversion from endoscopic to surgery Time points: beyond 1 year of follow up (minimum) up to longest follow up period
Study design	RCTs, or observational if no RCTs

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

We initially searched for RCTs, comparing oesophagectomy to endoscopic treatment, but no RCTs were found. We therefore searched for observational studies, and six eligible observational studies were found that are included in the review.[1, 3-7] These are summarised in Table 2 below, and evidence from these studies is summarised in the clinical evidence summaries below (Table 3 to Table 4).

The main limitation of the studies was the high risk of bias inherent in their observational design. Rigorous statistical adjustment was used by one study [5] and this has been judged to have partially reduced the risk of selection bias. The remaining studies failed to adjust for any potential confounding and are therefore at critical risk of selection bias. The results from these five studies should thus be interpreted with caution.

Analysis was performed in two strata (as defined pre-hoc in the protocol): studies with patients at stage T1a, and studies with a mixed T1a/T1b population. For each stratum, there were no outcomes with serious or very serious heterogeneity, and so no further subgrouping (see protocol in Appendix A) was necessary.

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

See the excluded studies list in Appendix H.

1.1.5 Summary of studies included in the effectiveness evidence

Table 2: Summary of studies included in the evidence review

Study (n)	Intervention	Comparator	Inclusion/exclusion criteria	Stage	Grade of differentiation	LVI	R0/R1	Submucosal grades
Li, 2017[1] N=23	oesophagectomy was performed by Ivor-Lewis or transhiatal technique	Endoscopic mucosal resection (EMR)	Inclusion: Patients with intramucosal carcinoma and Barrett's oesophagus from a single-centre pathology specimen database; undergoing EMR or oesophagectomy; Adenocarcinoma Exclusion: Patients with invasive disease not amenable to endoscopic treatment (deeper than T1sm1 or node positive) were excluded	All T1a or T1b. T1a 92% in Sx group and 91% in endo group. Taken as T1a overall	Mostly well differentiated (67% Sx, 82% endo)	none	No data	Only 2 submucosal cases: both sm1.
Pacifico, 2003 [3] N=88	Oesophagectomy – no details were provided.	EMR followed by photodynamic therapy (PDT) about 1 month later	Inclusion: All patients with Barretts Oesophagus and adenocarcinoma. The stage of adenocarcinoma was determined by EUS and histology of the EMR specimen if surgery was not performed and by histopathologic staging following esophagectomy. Patients who were considered to have mucosal disease by EUS and/or found to be	62/64 T1 in Sx group, and 24/24 T1 in endo group. Taken as 'mixed' T1 as no sub-grouping for T1a and T1b.	No data	No data	No data	No data

Study (n)	Intervention	Comparator	Inclusion/exclusion criteria	Stage	Grade of differentiation	LVI	R0/R1	Submucosal grades
			surgical stage 0 or 1 were included in the study. Exclusion: Patients with lymph node metastasis					
Pech, 2011[4] N=	Trannsthoracic oesophageal resection. En-bloc oesophagectomy after open or laparoscopic gastric mobilisation	EMR. After endoscopic resection, following later follow up and remission of neoplasia, patients underwent ablation of the remaining nondysplastic epithelium using argon plasma coagulation	Inclusion: Patients with mucosal Barretts adenocarcinoma treated with surgery or endoscopy. Exclusion: Patients with ypT1 after neoadjuvant chemoradiation	All T1a	Most graded 1 or 2: 36/38 Sx group, 72/74 endo group	No lymph or vascular invasion	No data	Not applicable
Prasad, 2009 [5] N=178	Oesophagectomy was via the transthoracic or the transhiatal route.	The initial technique was a variceal ligation method in which a Bard Six-Shooter and suction was used to retract the lesion of interest and had a band placed over it	Inclusion: Patients were either referred for endoscopic treatment of mucosal EAC to the Barrett's oesophagus Unit by physicians or were under surveillance for HGD in the BE Unit. All patients seen in the BE Unit for endoscopic therapy had either received consultation with thoracic surgeons at the Mayo Clinic or at their	All T1a	No data	4 in Sx group had metastatic lymphadenopathy; none in endo gp	No data	Not applicable

Study (n)	Intervention	Comparator	Inclusion/exclusion criteria	Stage	Grade of differentiation	LVI	R0/R1	Submucosal grades
		to create a pseudopolyp, which was then resected. Beginning in April 2000, EMR was performed. PDT was administered at a lter date after the achievement of histologic remission.	local hospitals. Patients referred for esophagectomy were usually referred directly by their physicians or were elected to undergo surgery after initial evaluation at the BE Unit. Barrett's oesophagus and mucosal OAC Exclusion: Submucosal carcinoma					
Schmidt, 2016[6] N=85	Oesophagectomy - surgical patients underwent transthoracic oesophageal resections in 94 % and transhiatal resections in 6 %.	Endoscopic treatments - in patients undergoing endoscopic therapy, all visible neoplastic lesions were treated with EMR. Residual Barrett's oesophagus mucosa was subsequently treated with ablative techniques or radical mucosectomy	Inclusion: All Barrett's patients presenting with clinically T1a OAC; undergone oesophageal resection or endoscopic treatment of Barrett's oesophagus Exclusion: Patients with high-grade dysplasia, submucosal invasion (T1b EAC), and those undergoing neoadjuvant therapy.	T1a	No data	4 with nodal mets in Sx group; 1 with pT2N1 in endo group.	R1: 48% in Sx group and 14% in endo group	Not applicable

Study (n)	Intervention	Comparator	Inclusion/exclusion criteria	Stage	Grade of differentiation	LVI	R0/R1	Submucosal grades
		depending on the length of the Barrett's oesophagus. Photodynamic therapy was utilized to 2006 with radiofrequency ablation subsequently being the most common ablative therapy. APC was selectively applied.						
Zehetner, 2011[7] N=66 (in review analysis, at stage T1a)	Oesophagectomy was performed as a transthoracic en bloc, transhiatal, minimally invasive, or vagus-sparing resection. Reconstruction in all cases was with a tubularized gastric pull-up.	EMR. Occasionally, argon plasma coagulation was used to touch up small areas, typically at the time of endoscopic resection of a lesion. In some patients immediately after endoscopic resection of a nodule, the surrounding	Inclusion: All patients with high-grade dysplasia or intramucosal adenocarcinoma treated endoscopically or by an esophagectomy Exclusion: Patients with tumors invasive into the submucosa were excluded, but lymphovascular invasion or poor differentiation in an intramucosal lesion did not deter endoscopic therapy	In overall paper there were 21% in Sx group at stage T0 and 55% in endo group at stage T0. However, it was possible to extract data separately for T1a stage by analysis of the text. Therefore, only T1a patients were included in the analyses for this review.	No data	1 lymph node met in Sx group	R0: 100%	Not applicable

Study (n)	Intervention	Comparator	Inclusion/exclusion criteria	Stage	Grade of differentiation	LVI	R0/R1	Submucosal grades
		Barrett's mucosa was ablated with the Halo 90 device. Ablation was not performed over areas just resected.						

LVI: lymph/vascular invasion

See Appendix D for full evidence tables

1.1.6 Summary of the effectiveness evidence

Table 3: Clinical evidence summary: oesophagectomy vs endoscopic treatment for stage T1a

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with endoscopy	Absolute risk difference (oesophagectomy minus endoscopy) (95% CI)
All cause mortality	381 (4 studies) 2-5 years	VERY LOW[1,2]	RR 1.02 (0.58, 1.80)	33/237 (13.9%)	3 more per 1,000 (from 58 fewer to 111 more)
All cause mortality (adjusted HR)	178 (1 study) 2 years	VERY LOW[1,2]	HR 0.65 (0.27, 1.56)	-	-
Mortality from OAC (adjusted HR)	178 (1 study) 2 years	MODERATE[1]	HR 0.38 (0.25, 0.58)	-	-
5 year survival	85 (1 study) 3.5 years	LOW[1]	86% survival vs 69% survival	-	-
Any recurrence	400 (4 studies) 2-5 years	VERY LOW[1,2]	RR 0.26 (0.08 to 0.85)	22/255 (8.6%)	64 fewer per 1,000 (from 79 fewer to 13 fewer)
Metastatic recurrence	85 (1 study) 3.5 years	VERY LOW[1,2]	RR 0.73 (0.05 to 11.36)	1/36 (2.8%)	8 fewer per 1,000 (from 26 fewer to 288 more)
Progression to metachronous neoplasia	180 (2 studies) 2-5 years	LOW[1]	Peto OR 0.09 (0.02 to 0.45)	7/94 (7.4%)	67 fewer per 1,000 (from 73 fewer to 40 fewer)
Major or serious complications	400 (4 studies) 2-5 years	LOW[1]	RR 4.05 (2.41 to 6.80)	20/255 (7.8%)	239 more per 1,000 (from 111 more to 455 more)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with endoscopy	Absolute risk difference (oesophagectomy minus endoscopy) (95% CI)
Need to switch treatment	286 (3 studies) 2-3.5 years	LOW[1]	Peto OR 0.18 (0.05 to 0.69)	11/179 (6.1%)	50 fewer per 1,000 (from 58 fewer to 18 fewer)
Length of hospital stay (days)	2 (1 study) 3 years	LOW[1]	Median (IQR) 15 (10-22) vs 0 (0-0)	-	-

[1] Downgraded by one increment if moderate risk of bias and downgraded by two increments if serious or critical risk of bias
[2] Downgraded by one increment if the 95% CIs crossed one of the default MIDs (0.8 or 1.25) and downgraded by two increments if the 95% CIs crossed both of the default MIDs (0.8 and 1.25).

Table 4: Clinical evidence summary: oesophagectomy vs endoscopic treatment for mixed stage T1a/T1b

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with endoscopy	Absolute risk difference (oesophagectomy minus endoscopy) (95% CI)
All cause mortality	88 (1 study) 1 year	VERY LOW[1,2]	RR 0.37 (0.06 to 2.51)	2/24 (8.3%)	53 fewer per 1,000 (from 78 fewer to 126 more)
Mortality from OAC	88 (1 study) 1 year	VERY LOW[1,2]	Not estimable	0/24 (0.0%)	0 fewer per 1,000 (from 60 fewer to 60 more)
Recurrence of OAC in first follow-up biopsy	88 (1 study) 1 year	LOW[1]	Peto OR 0.02 (0.00 to 0.21)	4/24 (16.7%)	-
Major or serious complications	88 (1 study) 1 year	VERY LOW[1,2]	RR 2.91 (1.15 to 7.36)	4/24 (16.7%)	318 more per 1,000 (from 25 more to 1,000 more)
Need to switch treatment	88 (1 study) 1 year	VERY LOW[1,2]	Peto OR 0.03 (0.00 to 2.08)	1/24 (4.2%)	-

[1] Downgraded by one increment if moderate risk of bias and downgraded by two increments if serious or critical risk of bias
[2] Downgraded by one increment if the 95% CIs crossed one of the default MIDs (0.8 or 1.25) and downgraded by two increments if the 95% CIs crossed both of the default MIDs (0.8 and 1.25).

See Appendix F for full GRADE tables

1.1.7 Economic evidence

1.1.7.1 Included studies

No health economic studies were included.

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

There was no economic evidence found.

1.1.9 Economic model

This area was given medium priority for new cost-effectiveness analysis. Therefore, it was not prioritised for original modelling as there were higher priority review questions.

1.1.10 Unit costs

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

Resource	Unit costs	Source
FF05Z: Intermediate Upper Gastrointestinal Tract Procedures, 19 years and over	£302	NHS reference costs 2019/20{NHS England, #1132}
FF04A-D: Major, Oesophageal, Stomach or Duodenum Procedures, 19 years and over, with CC Scores 0-7+	£5,394	
FF02A-C: Complex, Oesophageal, Stomach or Duodenum Procedures, 19 years and over, with CC Score 0-4+	£8,454	
FF01A-C: Very Complex, Oesophageal, Stomach or Duodenum Procedures, 19 years and over, with CC Score 0-6+	£13,553	
FE20Z: Therapeutic Endoscopic Upper Gastrointestinal Tract Procedures, 19 years and over	£993	

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, health related quality of life, progression of stage 1 adenocarcinoma to higher stages, complications of surgery, adverse events, length of stay, regression of Barrett's oesophagus, recurrence of Barrett's oesophagus and Barrett's related neoplasia, repeat intervention and need for conversion from one treatment to another. For purposes of decision-making all outcomes were equally regarded as being of critical importance. No evidence was identified for the outcomes of health related quality of life, progression of stage 1 adenocarcinoma to higher stages, regression of Barrett's oesophagus, and need for conversion from one treatment to another.

1.1.12.2 The quality of the evidence

Most of the evidence for the outcomes was graded as low or very low. One reason for this was serious or critical risk of bias in the majority of evidence. Serious or critical risk of bias resulted from selection bias in studies due to their observational design. Although one study used a form of statistical adjustment to reduce potential bias (baseline variables including age, gender, length of BE segment, age adjusted Charlson comorbidity index score and propensity score, were analysed as factors affecting overall survival using Cox proportional hazards modelling), this will not have reduced selection bias to the levels expected in randomised studies. In the other five studies there were no attempts to reduce confounding, leading to critical risk of bias. Another important factor explaining the low or very low grading of evidence was the serious or very serious imprecision in the majority of the effect estimates.

1.1.12.3 Benefits and harms

The committee discussed how the evidence was difficult to evaluate given the lack of adjustment for selection bias in 5 out of the 6 observational studies. The single adjusted study by Prasad only adjusted for the outcomes of all-cause mortality and mortality related to oesophageal adenocarcinoma. This study showed no clear effect for all-cause mortality, but did demonstrate a very clear benefit for oesophagectomy in terms of mortality related to oesophageal adenocarcinoma. However, the committee noted the study's limitations

because of the age of that study, and that an older technique had been used for many of the patients in the endoscopy therapy arm. The study had been carried out in 2007, and the committee agreed that because this was before the formalisation of quality standards in endoscopic treatment in 2010 this may have underestimated endoscopic treatment benefits. Therefore, the adjusted evidence was not considered as reliable as it might otherwise have been by the committee.

For the remaining studies, none of which were adjusted, the direction of potential bias was debated. It was initially thought that endoscopic therapies might be allocated to patients with a worse prognosis, such as those with more comorbidities, because this form of treatment might be expected to be better tolerated and cause less harmful complications than oesophagectomy. However, it was also suggested that oesophagectomy might tend to be allocated to patients with a worse prognosis, because such patients might require the more radical treatment. Interestingly, the study by Prasad showed reduced mortality in the oesophagectomy group relative to the endoscopy group when adjustments were made for confounding, but these effects disappeared when such adjustments were not made, and the effect estimate moved over the null line. This suggested an underlying bias favouring endoscopy, and therefore supported the latter premise. Nevertheless, the committee agreed that the direction of bias was difficult to discern and that the evidence from most of the unadjusted studies was therefore difficult to interpret. However, there was general agreement that the results tallied with clinical experience and confirmed the committee's belief that for T1a adenocarcinoma, endoscopic treatments were not inferior to oesophagectomy in terms of efficacy and superior in terms of complications. In addition, it was agreed that endoscopic treatment had the advantage that it could be attempted first, and then, if unsuccessful, surgery could be used as a second option. The committee therefore agreed that for patients with T1a oesophageal adenocarcinoma, endoscopic resection should be considered as the first line treatment followed by endoscopic ablation of any residual Barrett's unless there were special clinical reasons to do otherwise. An example was given of the special case of multifocality (two or more cancerous lesions present), where oesophagectomy may be more useful. The committee confirmed endoscopic resection as the first line option reflected current practice and was more likely to lead to a better quality of life post-treatment because of preserved anatomy.

A reason discussed for considering oesophagectomy as first line treatment for stage T1a patients was patient preference. The committee agreed there is variation in the attitudes of patients towards both forms of therapy because some patients are more 'cancer averse', whilst others are more 'complications averse'. In the more 'cancer averse' patients there might be a tendency to select the more definitive surgical option, whilst in the more 'complications averse' patients there might be a desire to opt for the endoscopic choice. For this reason, the committee agreed that there should be a prior discussion between patient and clinician, where the advantages and disadvantages of both approaches are discussed, and where the suitability of either for each patient is evaluated.

The committee agreed that the lack of quality of life data in the literature was a major drawback in the evidence base and drew upon their own experience. Although endoscopy was thought to lead to better quality of life post-treatment because of preserved anatomy and lower incidence of complications, there was also the belief that the greater need for ongoing surveillance could lead to anxiety about recurrence, which might reduce quality of life.

The lack of evidence for T1b patients was a concern for the committee, who agreed that this patient group was where the greatest uncertainty lay. For this population, the committee agreed that a research recommendation would be useful to compare endoscopic resection with adjuvant chemoradiotherapy and oesophagectomy for people with T1b oesophageal adenocarcinoma.

In the absence of any evidence the committee decided to make a consensus recommendation based on their clinical experience that oesophagectomy rather than

endoscopic resection should be offered to people with T1b oesophageal adenocarcinoma at high risk of cancer progression such as those with incomplete endoscopic resection, or presence of lymph vascular invation or deep submucosal invasion (more than 500 micron) on endoscopic resection specimen. The committee noted that in cases of incomplete endoscopic resection, there is a high risk of local recurrence and in cases with deep submucosal invasion (more than 5000 micron) there is a high risk of lymph node metastasis, thus oesophagectomy would be more appropriate for people with T1b at high-risk of pregression. . They decided not to make a recommendation for people with T1b at low risk of cancer progression as it was less clear which treatment option would be best but made a research recommendation to examine the effectiveness of endoscopic resection with or without adjuvant chemotherapy and oesophagectomy for adults with T1b oesophageal adenocarcinoma.

1.1.12.4 Cost effectiveness and resource use

There were no published economic evaluations found. In the absence of suitable clinical evidence, cost-effectiveness modelling was not feasible.

The committee's decision to recommend offering:

- endoscopic resection followed by ablation of residual Barrett's oesophagus as first line treatment to people with stage I T1a adenocarcinoma
- oesophagectomy to people with stage I T1b adenocarcinoma who have a high risk of recurrence and are fit for surgery

reflects current practice in people with Barrett's oesophagus and is therefore unlikely to have a substantial impact on resource.

For people with stage I T1a adenocarcinoma, the committee thought endoscopic treatment with endoscopic resection followed by ablation is likely to be more cost effective than oesophagectomy because it is a less costly procedure with a lower risk of serious adverse events.

For people with stage I T1b adenocarcinoma the committee were uncertain about which treatment strategy is the most cost effective so they made a research recommendation to assess the clinical and cost effectiveness of endoscopic resection, with or without adjuvant chemo-radiotherapy and oesophagectomy.

For people with stage I T1b adenocarcinoma and high risk of recurrence the committee thought that oesophagectomy is likely to be more cost effective than endoscopic treatment, since it can more effectively deal with the high risk of recurrence.

1.1.13 Recommendations supported by this evidence review

This evidence review supports recommendations 1.6.1, 1.6.2, 1.6.3, , 1.6.5 and the research recommendation on oesophagectomy.

1.1.14 References

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Appendices

Appendix A – Review protocols

Review protocol for oesophagectomy vs endoscopic treatment

ID	Field	Content
0.	PROSPERO registration number	CRD42021272037
1.	Review title	Oesophagectomy vs endoscopic treatment
2.	Review question	For adults with stage 1 adenocarcinoma, what is the clinical and cost effectiveness of oesophagectomy?
3.	Objective	To assess the efficacy and cost effectiveness of oesophagectomy, 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 • Epistemonikus Searches will be restricted by: • English language studies • Human studies

		• Letters and comments are excluded Other searches: • Inclusion lists of systematic reviews will be checked by the reviewers The searches may be re-run 6 weeks before the final committee meeting and further studies retrieved for inclusion if relevant. The full search strategies will be published in the final review. Medline search strategy to be quality assured using the PRESS evidence-based checklist (see methods chapter for full details).
5.	Condition or domain being studied	Stage 1 oesophageal adenocarcinoma
6.	Population	Inclusion: Adults, 18 years and over, with Barrett's oesophagus and stage 1 oesophageal adenocarcinoma Exclusion: Adults with Barrett's oesophagus with any other stages and related neoplasia
7.	Intervention	• Oesophagectomy
8.	Comparator	• Endoscopic treatment

9.	Types of study to be included	• RCT • If no RCT data is available, non-randomised studies will be considered only if there is an active comparator within the study • Systematic review 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	In adults with stage 1 adenocarcinoma, oesophagectomy is used as a treatment option. This review aims to assess the effectiveness of this procedure from a clinical and cost effectiveness view compared endoscopic treatment for stage 1 adenocarcinoma
12.	Primary outcomes (critical outcomes)	All outcomes are considered equally important for decision making and therefore have all been rated as critical: • Mortality (all-cause mortality, disease specific and treatment related) • Health related quality of life (any validated scores) • Progression of stage 1 adenocarcinoma to higher stages • Complications of surgery (e.g. perforation, stricture, pneumonia, anastomotic leak, weight loss, sepsis) • Adverse events (e.g. stricture, chronic ill health, chronic pain) • Length of hospital stay • Regression of Barrett's Oesophagus

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

15.	Risk of bias (quality) assessment	Risk of bias will be assessed using the appropriate checklist as described in Developing NICE guidelines: the manual. For Intervention reviews the following checklist will be used according to study design being assessed: Systematic reviews: Risk of Bias in Systematic Reviews (ROBIS) Randomised Controlled Trial: Cochrane RoB (2.0) Nonrandomised study, including cohort studies: Cochrane ROBINS-I Case control study: CASP case control checklist
16.	Strategy for data synthesis	Where available, outcome data from new studies will be meta-analysed. 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: T1a T1b Subgroups that will be investigated if heterogeneity is present: Type of endoscopic surgery Histopathological risk factors (lymph vascular invasion, grade of differentiation, incomplete resection or R1) 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: Amy Crisp Gill Ritchie Lina Gulhane Muksitur Rahman Stephen Deed Vimal Bedia
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.

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	

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). [2] **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.

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.[2]

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 5: 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.	Esophagectomy/
38.	(esophagectom* or oesophagectom*).ti,ab.
39.	(esophagogastrectom* or oesophagogastrectom*).ti,ab.
40.	((esophag* or oesophag*) adj3 (resect* or dissect* or shorten* or surg* or operat* or reconstruct* or remov*)).ti,ab.
41.	(surg* adj2 (resect* or dissect* or shorten*)).ti,ab.
42.	(transhiatal or trans hiatal or transthoracic or trans thoracic).ti,ab.
43.	(Merendino* or McKeown* or Ivor Lewis*).ti,ab.
44.	or/37-43
45.	36 and 44

46.	Meta-Analysis/
47.	Meta-Analysis as Topic/
48.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
49.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
50.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
51.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
52.	(search* adj4 literature).ab.
53.	(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.
54.	cochrane.jw.
55.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
56.	or/46-55
57.	randomized controlled trial.pt.
58.	controlled clinical trial.pt.
59.	randomi#ed.ab.
60.	placebo.ab.
61.	randomly.ab.
62.	clinical trials as topic.sh.
63.	trial.ti.
64.	or/57-63
65.	Epidemiologic studies/
66.	Observational study/
67.	exp Cohort studies/
68.	(cohort adj (study or studies or analys* or data)).ti,ab.
69.	((follow up or observational or uncontrolled or non randomi#ed or epidemiologic*) adj (study or studies or data)).ti,ab.
70.	((longitudinal or retrospective or prospective) and (study or studies or review or analys* or cohort* or data)).ti,ab.
71.	Controlled Before-After Studies/
72.	Historically Controlled Study/
73.	Interrupted Time Series Analysis/
74.	(before adj2 after adj2 (study or studies or data)).ti,ab.
75.	exp case control study/
76.	case control*.ti,ab.
77.	Cross-sectional studies/
78.	(cross sectional and (study or studies or review or analys* or cohort* or data)).ti,ab.
79.	or/65-78
80.	45 and (56 or 64)

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.	esophagus resection/
37.	(esophagectom* or oesophagectom*).ti,ab.
38.	(esophagogastrectom* or oesophagogastrectom*).ti,ab.
39.	((esophag* or oesophag*) adj3 (resect* or dissect* or shorten* or surg* or operat* or reconstruct* or remov*)).ti,ab.
40.	(surg* adj2 (resect* or dissect* or shorten*)).ti,ab.
41.	(transhiatal or trans hiatal or transthoracic or trans thoracic).ti,ab.
42.	(Merendino* or McKeown* or Ivor Lewis*).ti,ab.
43.	or/36-42
44.	35 and 43
45.	random*.ti,ab.
46.	factorial*.ti,ab.
47.	(crossover* or cross over*).ti,ab.
48.	((doubl* or singl*) adj blind*).ti,ab.

49.	(assign* or allocat* or volunteer* or placebo*).ti,ab.
50.	crossover procedure/
51.	single blind procedure/
52.	randomized controlled trial/
53.	double blind procedure/
54.	or/45-53
55.	Systematic Review/
56.	Meta-Analysis/
57.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
58.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
59.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
60.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
61.	(search* adj4 literature).ab.
62.	(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.
63.	cochrane.jw.
64.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
65.	or/55-64
66.	Clinical study/
67.	Observational study/
68.	Family study/
69.	Longitudinal study/
70.	Retrospective study/
71.	Prospective study/
72.	Cohort analysis/
73.	Follow-up/
74.	cohort*.ti,ab.
75.	73 and 74
76.	(cohort adj (study or studies or analys* or data)).ti,ab.
77.	((follow up or observational or uncontrolled or non randomi#ed or epidemiologic*) adj (study or studies or data)).ti,ab.
78.	((longitudinal or retrospective or prospective) and (study or studies or review or analys* or cohort* or data)).ti,ab.
79.	(before adj2 after adj2 (study or studies or data)).ti,ab.
80.	exp case control study/
81.	case control*.ti,ab.
82.	cross-sectional study/
83.	(cross sectional and (study or studies or review or analys* or cohort* or data)).ti,ab.
84.	or/66-72,75-83
85.	44 and (54 or 65)

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: [Esophagectomy] explode all trees
#18.	(esophagectom* or oesophagectom*):ti,ab
#19.	(esophagogastrectom* or oesophagogastrectom*):ti,ab
#20.	((esophag* or oesophag*) near/3 (resect* or dissect* or shorten* or surg* or operat* or reconstruct* or remov*)):ti,ab
#21.	(surg* near/2 (resect* or dissect* or shorten*)):ti,ab
#22.	(transhiatal or trans hiatal or transthoracic or trans thoracic):ti,ab
#23.	(Merendino* or McKeown* or Ivor Lewis*):ti,ab
#24.	(or #17-#23)
#25.	#16 and #24
#26.	conference:pt or (clinicaltrials or trialsearch):so
#27.	#25 not #26

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:(esophagectom* OR oesophagectom* OR esophagogastrectom* OR oesophagogastrectom* OR "esophag* resect*" OR "oesophag* resect*" OR "esophag* dissect*" OR "oesophag* dissect*" OR "esophag* shorten*" OR "oesophag* shorten*" OR "surg* resect*" OR "resect* surg*" OR transhiatal OR "trans hiatal" OR transthoracic OR "trans thoracic" OR lymphadenectom* OR Merendino* OR McKeown* OR "Ivor Lewis*") OR abstract:(esophagectom* OR oesophagectom* OR esophagogastrectom* OR oesophagogastrectom* OR "esophag* resect*" OR "oesophag* resect*" OR "esophag* dissect*" OR "oesophag* dissect*" OR "esophag* shorten*" OR "oesophag* shorten*" OR "surg* resect*" OR "resect* surg*" OR transhiatal OR "trans hiatal" OR transthoracic OR "trans thoracic" OR lymphadenectom* OR Merendino* OR McKeown* OR "Ivor Lewis*")

B.1 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 6: Database parameters, filters and limits applied

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

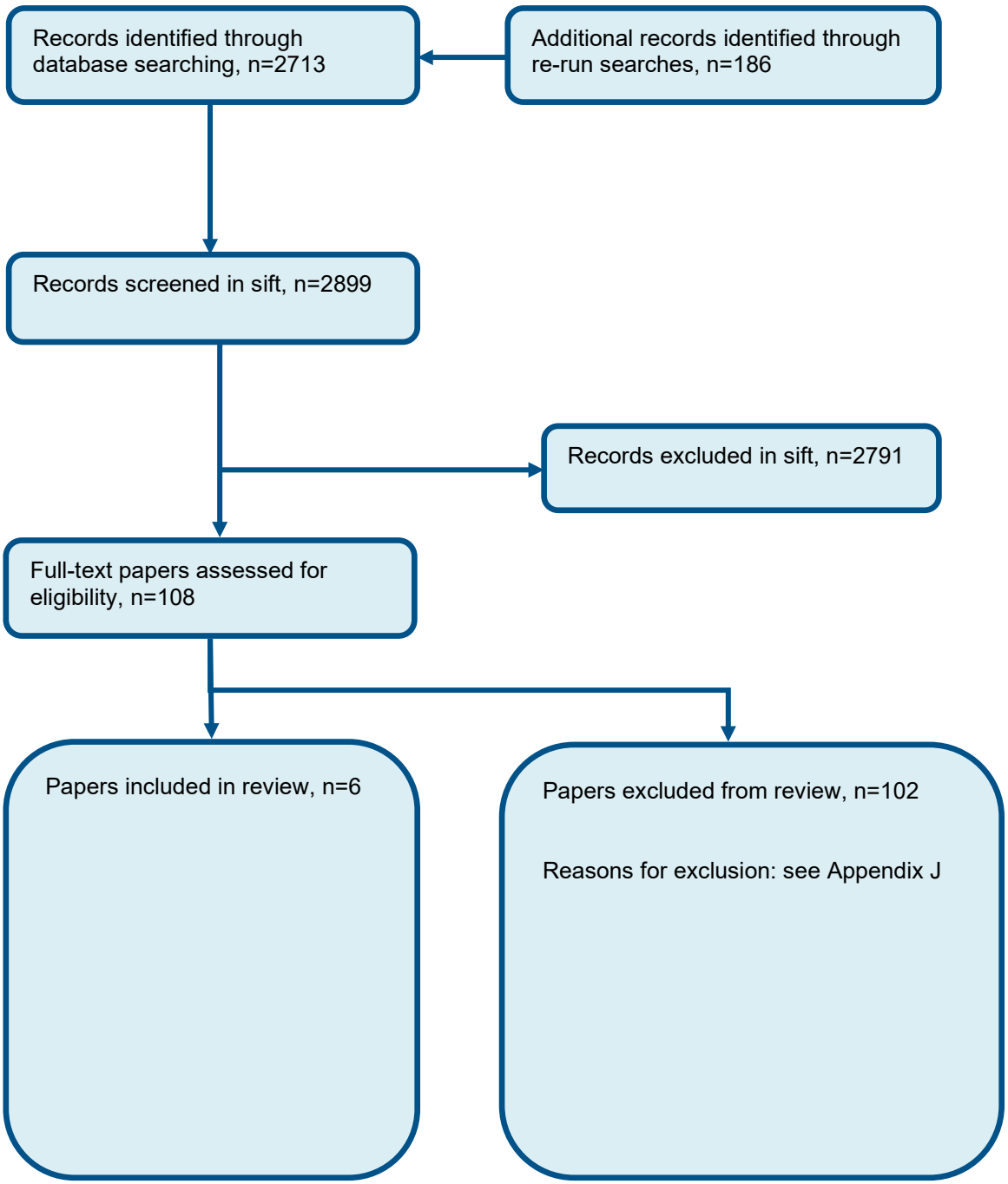
#1.	MeSH DESCRIPTOR Barrett Esophagus EXPLODE ALL TREES
#2.	(barrett*)
#3.	(speciali*) AND (epithel* or oesophag* or esophag* or mucos*)
#4.	(column*) AND (epithel* or oesophag* or esophag* or mucos* or lined or lining or metaplas*)
#5.	#1 OR #2 OR #3 OR #4
#6.	MeSH DESCRIPTOR Precancerous Conditions 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 surveillance versus no surveillance



Appendix D – Effectiveness evidence

Li, 2017

Bibliographic Reference	Li, C.; Yamashita, D. T.; Hawel, J. D.; Bethune, D.; Henteleff, H.; Ellsmere, J.; Endoscopic mucosal resection versus esophagectomy for intramucosal adenocarcinoma in the setting of barrett's esophagus; Surg Endosc; 2017; vol. 31 (no. 10); 4211-4216

Study details

Secondary publication of another included study- see primary study for details	NA
Other publications associated with this study included in review	NA
Trial name / registration number	NA
Study location	Canada
Study setting	Secondary care

Study dates	2005-2103
Sources of funding	No funding reported
Inclusion criteria	Patients with intramucosal carcinoma and Barrett's oesophagus from a single-centre pathology specimen database; undergoing EMR or oesophagectomy
Exclusion criteria	Patients with invasive disease not amenable to endoscopic treatment (deeper than T1sm1 or node positive) were excluded
Recruitment / selection of participants	Retrospective perusal of hospital database
Intervention(s)	Prior to 2009, oesophagectomy was performed by one of two surgeons either by Ivor-Lewis or transhiatal technique. Operative and postoperative care was at the discretion of the treating surgeon. Post-operatively, patients were not kept intubated and were not routinely transferred to the intensive care unit, but were rather kept in a specialized step-down area. Nasogastric tubes were removed on post-operative day 2 and diet advanced thereafter. Chest tubes were removed on postoperative day 3–4 for patients undergoing a transthoracic approach. Patients were then followed with a control visit 6 weeks after surgery and upper endoscopy at 3, 6 months, and then yearly if asymptomatic.
Comparator	All patients with a diagnosis of intramucosal carcinoma on biopsy were evaluated for endoscopic mucosal resection as a preferred approach after 2009 at the research hospital. Nodular lesions were identified using a combination of location of prior biopsy sites, mucosal and vascular pattern abnormalities, and narrow band imaging. EMR was performed using the Duette multi-band mucosectomy device. A capfitted endoscope was used to aspirate and band the selected mucosal area followed by a snare resection supplemented with electrocautery. This technique was used to resect nodular lesions either as a single specimen or in a piecemeal fashion to achieve complete gross resection. Patients were subsequently followed every 3 months with repeat endoscopies and repeat EMR treatment if persistence of nodularity or dysplasia. Once visually and pathologically clear, patients were followed at 3, 6 months, then surveyed yearly with four-quadrant and random biopsies.
Number of participants	23
Duration of follow-up	3.5 in oesophagectomy group and 2.7 in EMR group

Indirectness	None
Additional comments	No adjustments were made for potential confounding. Definite Barrett's population. OAC T1a and 1b only. T1a: 92% Sx, 91% endo; T1b: 8% Sx, 9% endo. Mostly well differentiated: 67%,82% LVI: 0,0 R0/R1: no data Sm1: 1,1 sm2: 0,0 sm3: 0,0

Study arms

Oesophagectomy (N = 12)
Esophagectomy was performed by one of two surgeons either by Ivor-Lewis or transhiatal technique. Operative and postoperative care was at the discretion of the treating surgeon. Post-operatively, patients were not kept intubated and were not routinely transferred to the intensive care unit, but were rather kept in a specialized step-down area. Nasogastric tubes were removed on post-operative day 2 and diet advanced thereafter. Chest tubes were removed on postoperative day 3–4 for patients undergoing a transthoracic approach. Patients were then followed with a control visit 6 weeks after surgery and upper endoscopy at 3, 6 months, and then yearly if asymptomatic.

Endoscopic mucosal resection (N = 11)
All patients with a diagnosis of intramucosal carcinoma on biopsy were evaluated for endoscopic mucosal resection as a preferred approach. Nodular lesions were identified using a combination of location of prior biopsy sites, mucosal and vascular pattern abnormalities, and narrow band imaging. EMR was performed using the Duette multi-band mucosectomy device. A capfitted endoscope was used to aspirate and band the selected mucosal area followed by a snare resection supplemented with electrocautery. This technique was used to resect nodular lesions either as a single specimen or in a piecemeal fashion to achieve complete gross resection. Patients were subsequently followed every 3 months with repeat endoscopies and repeat EMR treatment if persistence of nodularity or dysplasia. Once visually and pathologically clear, patients were followed at 3, 6 months, then surveyed yearly with four-quadrant and random biopsies.

Characteristics

Arm-level characteristics

Characteristic	Oesophagectomy (N = 12)	Endoscopic mucosal resection (N = 11)
Age Mean (SD)	64.8 (8.8)	65.3 (12)

Characteristic	Oesophagectomy (N = 12)	Endoscopic mucosal resection (N = 11)
Male gender No of events	n = 10 ; % = 83	n = 7 ; % = 64
Batrrett's length > 3cm No of events	n = 3 ; % = 25	n = 1 ; % = 9
Tumour depth: T1m1 or T1m2 No of events	n = 6 ; % = 50	n = 6 ; % = 55
Tumour grade: 'well differentiated' No of events	n = 8 ; % = 67	n = 9 ; % = 82

Outcomes

Oesophagectomy versus endoscopy

Outcome	Oesophagectomy, , N = 12	Endoscopic mucosal resection, , N = 11
Mortality No of events	n = 1 ; % = 8.33	n = 1 ; % = 9.09
Recurrence No of events	n = 1 ; % = 8.88	n = 1 ; % = 9.09
Need to move to other treatment No of events	n = 0 ; % = 0	n = 1 ; % = 9.09

Outcome	Oesophagectomy, , N = 12	Endoscopic mucosal resection, , N = 11
Post operative minor complications No of events	n = 7 ; % = 58.33	n = 0 ; % = 0
Major complications requiring reintervention or ICU stay No of events	n = 2 ; % = 16.7	n = 1 ; % = 9.09
Length of stay Median (IQR)	15 (10 to 22)	0 (0 to 0)

Pacifico, 2003

Bibliographic Reference	Pacifico, R. J.; Wang, K. K.; Wongkeesong, L. M.; Buttar, N. S.; Lutzke, L. S.; Combined endoscopic mucosal resection and photodynamic therapy versus esophagectomy for management of early adenocarcinoma in Barrett's esophagus; Clinical Gastroenterology & Hepatology; 2003; vol. 1 (no. 4); 252-7

Study details

Secondary publication of another included study- see primary study for details	NA

Other publications associated with this study included in review	NA
Trial name / registration number	NA
Study location	USA
Study setting	Secondary care
Study dates	1996-2001
Sources of funding	National Institutes of Health grants CA85992-01 and R01CA097048-01.
Inclusion criteria	All patients who presented to the Mayo Clinic between January 1996 and November 2001 with Barretts Oesophagus for further evaluation and treatment were eligible for this study. The stage of adenocarcinoma was determined by EUS and histology of the EMR specimen if surgery was not performed and by histopathologic staging following esophagectomy. Patients who were considered to have mucosal disease by EUS and/or found to be surgical stage 0 or 1 were included in the study.
Exclusion criteria	Patients with lymph node metastasis
Recruitment / selection of participants	Review of the case notes of all eligible patients.
Intervention(s)	Oesophagectomy – no details were provided.
Comparator	EMR followed by PDT about 1 month later. EMR. To allow for a safer resection, an average of 10 –15 mL of dilute epinephrine (1:20,000 to 1:100,000 solution) was initially injected in the submucosa underneath the lesion that was considered amenable to EMR. Between January 1996 and March 2000, mucosal resections were performed using the

	endoscopic variceal ligation method. With this technique, suction was applied over the lesion of interest into the cap and a band placed to create a pseudopolyp. The pseudopolyp was then resected with a standard snare and retrieved. Placement of the band was initially considered to improve haemostasis. Beginning in April 2000, mucosal resections were performed using a commercially available disposable EMR kit because this technique necessitated only one oesophageal intubation. With this method, a forward resecting cap was placed at the end of the endoscope. The distal end of the cap has a small ledge where a crescent snare can be placed around the circumference of the cap. The mucosal abnormality is suctioned into the cap, resected with the snare, and retrieved within the cap. Both EMR techniques were performed by a single experienced endoscopist, and the resected specimens were assessed by experienced gastrointestinal pathologists with an interest in Barrett's oesophagus. The specimens were assessed for histology, size, and depth of tumour penetration and margins for completeness of tumour resection. PDT. PDT was performed a mean of 4.2 ± 0.3 weeks after EMR to allow for healing of the mucosectomy site. The photosensitizers used were either purified hematoporphyrin derivative (4 mg/kg) or porfimer sodium at an equivalent dose of 2 mg/kg. Both photosensitizers were administered intravenously 48 hours before endoscopy and photoradiation. Photoradiation was performed using a 2.5- or 5.0-cm cylindrical diffusing fiber that is passed through the accessory channel of the endoscope and placed in the center of the oesophageal lumen. The fiber was coupled to a laser producing 630-nm light with an adjusted power output of 400 mW/cm fiber. A total light dose of 300 J/cm fiber was applied, with an estimated energy density of 32 J/cm2 at the Barrett's mucosa. Barrett's segments longer than 5 cm were treated with minimal overlapping areas. The maximal length of Barrett's epithelium treated in one session was 7.5 cm to prevent excessive pain after therapy. Indicator: patients offered EMR/PDT if patient not believed to be a suitable candidate for surgery of if patient refused surgery.
Number of participants	88
Duration of follow-up	19 months for oesophagectomy group and 12 months for endoscopy group

Indirectness	None
Additional comments	No adjustments for confounding. Confounding highly likely as the EMR/PDT given to those for whom surgery was not indicated or to those who refused surgery. Definite Barrett's population. OAC. Almost all T1: 62/64, 24/24 T1. LVI: no data Differentiation: no data R0/R1: no data sm1,2,3: no data

Study arms

Oesophagectomy (N = 64)

EMR/PDT (N = 24)

Characteristics

Study-level characteristics

Characteristic	Study (N = 88)
% Female No of events	n = 9 ; % = 10.22

Arm-level characteristics

Characteristic	Oesophagectomy (N = 64)	EMR/PDT (N = 24)
age (yrs) Mean (SD)	67 (8)	68 (9.8)
Barretts length (cm) Mean (SD)	6.5 (4)	5.6 (3.9)

Characteristic	Oesophagectomy (N = 64)	EMR/PDT (N = 24)
OAC grade 1 (EUS criteria) No of events	n = 62 ; % = 96.88	n = 24 ; % = 100
Cardiac comorboidities No of events	n = 20 ; % = 31	n = 10 ; % = 42
Pulmonary comorbidities No of events	n = 12 ; % = 19	n = 10 ; % = 42

Outcomes

Oesophagectomy v EMR/PDT

Outcome	Oesophagectomy, , N = 64	EMR/PDT, , N = 24
Serious complications (photosensitivity, strictures, anastomotic leaks, wound infection, dumping syndrome, empyema, blood transfusions, AF, aspiration, chylothorax) No of events	n = 31 ; % = 48.4	n = 4 ; % = 16.7
All cause mortality No of events	n = 2 ; % = 3.1	n = 2 ; % = 8.3
OAC mortality No of events	n = 0 ; % = 0	n = 0 ; % = 0

Outcome	Oesophagectomy, , N = 64	EMR/PDT, , N = 24
conversion to surgery No of events	n = 0 ; % = 0	n = 1 ; % = 4.1
Recurrence of OAC in first follow up biopsy No of events	n = 0 ; % = 0	n = 4 ; % = 16.7

Pech, 2011

Bibliographic Reference	Pech, O; Holscher, A. H.; Bollschweiler, E; Manner, H; Leers, J; Ell, C; Comparison between endoscopic and surgical resection of mucosal esophageal adenocarcinoma in Barrett's esophagus at two high-volume centers; Annals of surgery; 2011; vol. 254 (no. 1); 67-72

Study details

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

Trial name / registration number	NA
Study location	Germany
Study setting	Department of general, visceral and cancer surgery in a university hospital
Study dates	1996-2009
Sources of funding	None reported
Inclusion criteria	Patients with mucosal Barretts cancer treated with surgery or endoscopy.
Exclusion criteria	Patients with ypT1 after neoadjuvant chemoradiation
Recruitment / selection of participants	Restrospective perusal of hospital records
Intervention(s)	Trannsthoracic oesophageal resection. En-bloc oesophagectomy after open or laparoscopic gastric mobilisation. a 2-filed lymphadenectomy of mediastinal and abdominal lymph nodes via an abdomino right transthoracic approach was performed. Radical lymphadenectomy was applied because preoperative differentiation between mucosal or submucosal carcinoma or detection of lymph node metastasis is difficult.
Comparator	Before endoscopic treatment all patients underwent HR WLE and methylene blue staining or acetic acid staining and/or virtual chromoendoscopy. In addition, all patients underwent CT of the chest and upper abdomen and endoscopic US. After endoscopic resection, following later follow up and remission of neoplasia, patients underwent ablation of the remaining nondysplastic epithelium using argon plasma coagulation at a power of 90-99W (argon beamer) or 50W (APC2). These 76 patients were matched to the intervention group patients from a pool of 967 patients.

	Indicators for treatments: 2 different hospitals used for the 2 different treatments so likely to be a case of the prevalent approach used in each centre rather than being decided by patient-centred indicators.
Number of participants	114
Duration of follow-up	5 years
Indirectness	None
Additional comments	1:2 Matching was based on age, gender, tumour infiltration depth, tumour differentiation grade and duration of follow up. Survival analysis was conducted with adjustment for confounding using a cox regression analysis, but this was not used for the analyses included in this review (only applied to an analysis evaluating the effects of gender, age, depth of tumour and CCI grade on survival, and treatment was not included). Definite Barrett's. OAC. All T1a. LVI: uN0/pN0: 38,76; uN1/pN1: 0,0; no lymphatic invasion Differentiation grade 1or 2: 36/38, 72/74 R0/R1: no data

Study arms

Oesophagectomy (N = 38)
Trannsthoracic oesophageal resection. En-bloc oesophagectomy after open or laparoscopic gastric mobilisation. a 2-filed lymphadenectomy of mediastinal and abdominal lymph nodes via an abdomino right transthoracic approach was performed. Radical lymphadenectomy was applied because preoperative differentiation between mucosal or submucosal carcinoma or detection of lymph node metastasis is difficult.

Endoscopy (N = 76)
Before endoscopic treatment all patients underwent HR WLE and methylene blue staining or acetic acid staining and/or virtual chromoendoscopy. In addition, all patients underwent CT of the cehst and upper abdomen and endoscopic US. After endoscopic resection, following later follow up and remission of neoplasia, patients underwent ablation of the remaining nondysplastic epiithelium using argon plasma coagulation at a power of 90-99W (argon beamer) or 50W (APC2). These 76 patients were matched to the intervention group patients from a pool of 967 patients.

Characteristics

Arm-level characteristics

Characteristic	Oesophagectomy (N = 38)	Endoscopy (N = 76)
Age Median (IQR)	62.76 (3 to 72)	62.25 (7 to *empty data*)
Charlson comorbidity index Grade 0-1 No of events	n = 25 ; % = 66	n = 55 ; % = 72
T1m1	n = 19 ; % = 50	n = 40 ; % = 52.6

Characteristic	Oesophagectomy (N = 38)	Endoscopy (N = 76)
No of events		
T1m2 No of events	n = 4 ; % = 10.52	n = 14 ; % = 18.42
T1m3 No of events	n = 15 ; % = 39.5	n = 22 ; % = 28.9
Differentaition G3 No of events	n = 2 ; % = 5.26	n = 2 ; % = 1.56
Male No of events	n = 37 ; % = 97.37	n = 73 ; % = 96.05
Minor complications No of events	n = 0 ; % = 0	n = 13 ; % = 17

Outcomes

Study timepoints

- 5 year

Oesophagectomy vs endoscopy

Outcome	Oesophagectomy, 5 year, N = 38	Endoscopy, 5 year, N = 76
Overall mortality No of events	n = 4 ; % = 10.53	n = 8 ; % = 10.53
Major complications No of events	n = 12 ; % = 32	n = 0 ; % = 0
Recurrence No of events	n = 0 ; % = 0	n = 1 ; % = 1.32
Metachronous neoplasia No of events	n = 0 ; % = 0	n = 4 ; % = 5.26

Prasad, 2009

Bibliographic Reference	Prasad, G. A.; Wu, T. T.; Wigle, D. A.; Buttar, N. S.; Wongkeesong, L. M.; Dunagan, K. T.; Lutzke, L. S.; Borkenhagen, L. S.; Wang, K. K.; Endoscopic and surgical treatment of mucosal (T1a) esophageal adenocarcinoma in Barrett's esophagus; Gastroenterology; 2009; vol. 137 (no. 3); 815-23

Study details

Secondary publication of another included	NA

study- see primary study for details	
Other publications associated with this study included in review	NA
Trial name / registration number	NA
Study type	Retrospective cohort study
Study location	USA
Study setting	Secondary care
Study dates	1998-2007
Sources of funding	Supported by NIH grants: R01CA111603-01A1 (KKW), R01CA097048 (KKW), R21CA122426-01 (KKW), R03CA135991-01 (GAP) and the Shirley and Miles Fiterman Digestive Disease Center
Inclusion criteria	Patients were either referred for endoscopic treatment of mucosal EAC to the Barrett's oesophagus Unit by physicians or were under surveillance for HGD in the BE Unit. All patients seen in the BE Unit for endoscopic therapy had either received consultation with thoracic surgeons at the Mayo Clinic or at their local hospitals. Patients referred for esophagectomy were usually referred directly by their physicians or were elected to undergo surgery after initial evaluation at the BE Unit. Barrett's oesophagus and mucosal OAC
Exclusion criteria	Submucosal carcinoma
Recruitment / selection of participants	Retrospective perusal of databases

Intervention(s)	Oesophagectomy was performed by experienced thoracic surgeons using either the transthoracic or the transhiatal route.
Comparator	Endoscopy: the initial technique was a variceal ligation method in which a Bard Six-Shooter and suction was used to retract the lesion of interest and had a band placed over it to create a pseudopolyp, which was then resected. Beginning in April 2000, EMR was performed using a commercially available EMR cap. Lesions were lifted using submucosal injection with 4–10cc of 1:200000 strength saline epinephrine solution. Mucosal resection was performed by suctioning the lesion into the cap after positioning of a crescent snare. The snare was then closed with application of cautery current (energy setting of 16 watts blend 2 using a Meditron unit) removing the tissue. Since 2004, EMR was also performed using the Duette multiband mucosectomy device using previously described techniques14. Submucosal injection was used in the same manner as described above, as well as the same energy settings with resection being performed using a hexagonal snare which is part of the kit. Patients with smaller lesions likely to be removed by a single resection typically underwent EMR using the Olympus EMR cap while those with larger lesions underwent EMR using the Duette device (which allows multiple resections in a single intubation) in an effort to obtain clean margins. Ablative therapy: PDT was administered as previously described15 after the achievement of histologic remission (defined as the absence of carcinoma on histology from 2 consecutive surveillance endoscopies). In brief, porfimer sodium at a dose of 2mg/kg, was administered intravenously 48 hours before photoradiation. Photoradiation was performed using a bare cylindrical diffusing fiber. The cylindrical diffusing fibers were either 2.5 or 5.0 cm long fibers . The cylindrical diffusing fiber was passed through the accessory channel of the endoscope and placed in the center of the oesophageal lumen. The light was delivered from a laser (Lambda Plus [Coherent, Palo Alto, CA] or Diomed producing 630 nm light with an adjusted power output of 400mW/cm fiber delivering a total energy of 200J/cm fiber energy to the mucosa. PDT was performed more frequently following resection of carcinoma and achieving remission during the initial phase of the study (1998–2003). Patients who had mucosal carcinoma diagnosed on mucosal biopsy specimens alone without visible lesions were also more likely to receive PDT. During the latter phase of the study this was performed selectively given the lack of consensus on whether ablation following initial remission definitively reduces risk of metachronous neoplasia.
Number of participants	178
Duration of follow-up	2 years in oesophagectomy group and up to 10 years in endoscopic group
Indirectness	None

Additional comments	Baseline variables (age, gender, length of BE segment, age adjusted Charlson comorbidity index score and propensity score) were analysed as factors affecting overall survival using Cox proportional hazards modelling. (Propensity score is the predicted probability of being in the PDT group based on age, gender, length of BE, and the age-adjusted Charlson comorbidity index. The propensity score was obtained using logistic regression. Estimates of hazard rates (HRs) and 95% confidence intervals (CIs) were determined. Definite Barrett's. OAC. All T1a. LVI: 4 in Sx group had metastatic lymphadenopathy; none in endo gp. R0/R1: no data differentiation; no data sm1,2,3: not applicable as all T1a.

Study arms

Oesophagectomy (N = 46)
Oesophagectomy was performed by experienced thoracic surgeons using either the transthoracic or the transhiatal route.

Endoscopy (N = 132)
The initial technique was a variceal ligation method in which a Bard Six-Shooter and suction was used to retract the lesion of interest and had a band placed over it to create a pseudopolyp, which was then resected. Beginning in April 2000, EMR was performed using a commercially available EMR cap. Lesions were lifted using submucosal injection with 4–10cc of 1:200000 strength saline

epinephrine solution. Mucosal resection was performed by suctioning the lesion into the cap after positioning of a crescent snare. The snare was then closed with application of cautery current (energy setting of 16 watts blend 2 using a Meditron unit) removing the tissue. Since 2004, EMR was also performed using the Duette multiband mucosectomy device using previously described techniques14. Submucosal injection was used in the same manner as described above, as well as the same energy settings with resection being performed using a hexagonal snare which is part of the kit. Patients with smaller lesions likely to be removed by a single resection typically underwent EMR using the Olympus EMR cap while those with larger lesions underwent EMR using the Duette device (which allows multiple resections in a single intubation) in an effort to obtain clean margins. Ablative therapy: PDT was administered as previously described15 after the achievement of histologic remission (defined as the absence of carcinoma on histology from 2 consecutive surveillance endoscopies). In brief, porfimer sodium at a dose of 2mg/kg, was administered intravenously 48 hours before photoradiation. Photoradiation was performed using a bare cylindrical diffusing fiber. The cylindrical diffusing fibers were either 2.5 or 5.0 cm long fibers . The cylindrical diffusing fiber was passed through the accessory channel of the endoscope and placed in the center of the esophageal lumen. The light was delivered from a laser (Lambda Plus [Coherent, Palo Alto, CA] or Diomed producing 630 nm light with an adjusted power output of 400mW/cm fiber delivering a total energy of 200J/cm fiber energy to the mucosa. PDT was performed more frequently following resection of carcinoma and achieving remission during the initial phase of the study (1998–2003). Patients who had mucosal carcinoma diagnosed on mucosal biopsy specimens alone without visible lesions were also more likely to receive PDT. During the latter phase of the study this was performed selectively given the lack of consensus on whether ablation following initial remission definitively reduces risk of metachronous neoplasia.

Characteristics

Arm-level characteristics

Characteristic	**Oesophagectomy (N = 46)**	**Endoscopy (N = 132)**
age (yrs) Mean (SD)	67.7 (9.5)	71.2 (11.03)
Male No of events	n = 43 ; % = 94	n = 111 ; % = 84

Characteristic	Oesophagectomy (N = 46)	Endoscopy (N = 132)
BO length Mean (SD)	7.3 (5.22)	5.5 (4.14)
Cardiac disease No of events	n = 26 ; % = 56.5	n = 38 ; % = 28.8
Pulmonary disease No of events	n = 6 ; % = 13.04	n = 17 ; % = 12.88
Diabetes mellitus No of events	n = 14 ; % = 30.43	n = 20 ; % = 15.15
prior malignancy No of events	n = 16 ; % = 34.78	n = 24 ; % = 18.18
Age-adjusted Charleson comorbidity index Median (IQR)	0 (0 to 4)	4 (0 to 5)

Outcomes

Study timepoints

- 2 year

oesophagectomy versus endoscopy

Outcome	Oesophagectomy, 2 year, N = 46	Endoscopy, 2 year, N = 132
All cause mortality No of events	n = 9 ; % = 19.56	n = 23 ; % = 17.42
Incidence rate of mortality Custom value	3.7 / 100 person years	4.9 / 100 person years
Recurrence of OAC No of events	n = 1 ; % = 2.17	n = 16 ; % = 12.12
Incidence rate of recurrence of OAC Custom value	0.56 /100 person years	5.5 / 100 person years
Post treatment complications No of events	n = 17 ; % = 36.9	n = 18 ; % = 13
Transfer to other group treatment No of events	n = 0 ; % = 0	n = 8 ; % = 6.06

Oesophagectomy versus endoscopy

Outcome	Oesophagectomy vs Endoscopy, 2 year, N2 = 132, N1 = 46
All cause mortality adjusted for propensity score Hazard ratio/95% CI	0.65 (0.27 to 1.56)

Outcome	Oesophagectomy vs Endoscopy, 2 year, N2 = 132, N1 = 46
Mortality due to OAC adjusted for propensity score Hazard ratio/95% CI	0.38 (0.25 to 0.59)

Schmidt, 2016

Bibliographic Reference	Schmidt, H. M.; Mohiuddin, K.; Bodnar, A. M.; El Lakis, M.; Kaplan, S.; Irani, S.; Gan, I.; Ross, A.; Low, D. E.; Multidisciplinary treatment of T1a adenocarcinoma in Barrett's esophagus: contemporary comparison of endoscopic and surgical treatment in physiologically fit patients; Surg Endosc; 2016; vol. 30 (no. 8); 3391-401

Study details

Secondary publication of another included study- see primary study for details	NA

Other publications associated with this study included in review	NA
Trial name / registration number	NA
Study type	Retrospective cohort study
Study location	USA
Study setting	Review of 2 prospective databases from a large medical centre in Seattle
Study dates	2000-2012
Sources of funding	No funding reported
Inclusion criteria	All patients presenting with clinically T1a EAC; undergone oesophageal resection or endoscopic treatment of Barrett's oesophagus
Exclusion criteria	Patients with high-grade dysplasia, submucosal invasion (T1b EAC), and those undergoing neoadjuvant therapy were excluded from the analysis
Recruitment / selection of participants	Retrospective inspection of databases
Intervention(s)	Oesophagectomy - surgical patients underwent transthoracic oesophageal resections in 94 % and transhiatal resections in 6 %. All patients were managed according to a standardized multidisciplinary care pathway after oesophageal resection.
Comparator	Endoscopic treatments - in patients undergoing endoscopic therapy, all visible neoplastic lesions were treated with endoscopic mucosal resection. EMR was performed utilizing either the Duette TM Multiband mucosectomy device or the cap mucosectomy kit. Residual Barrett's oesophagus mucosa was subsequently treated with ablative techniques or radical

	mucosectomy depending on the length of the Barrett's oesophagus segment. Photodynamic therapy was utilized to 2006 with radiofrequency ablation subsequently being the most common ablative therapy. APC was selectively applied. All patients were treated with twice a day PPI during and after ET. Endoscopically treated patients were routinely followed according to an institutional Barrett's oesophagus treatment algorithm. In endoscopically treated patients, 4-quadrant biopsies according to the Seattle protocol were obtained at every 3 months for the first year, biannually in the following year and subsequently annually. Patients found to have residual neoplastic tissue or metachronous lesions underwent repeat EMR.
Number of participants	85
Duration of follow-up	mean 42.6 months
Indirectness	none
Additional comments	Binary logistic regression analysis was performed for treatment modality as dependent variable, including age, Charlson comorbidity score, endoscopic findings, and pathology. Factors affecting overall survival were analysed using the Cox proportional hazards modelling. This was not relevant, however, to the outcomes in this review. Definite Barrett's. OAC. All T1a R1: 48%, 14% LVI: 4 with nodal mets in Sx group; 1 with pT2N1 in endo group. Differentiation: no data

	sm1,2,3: not applicable as all mucosal

Study arms

Oesophagectomy (N = 49)
Surgical patients underwent transthoracic oesophageal resections in 94 % and transhiatal resections in 6 %. All patients were managed according to a standardized multidisciplinary care pathway after oesophageal resection.

Endoscopic treatment (N = 36)
In patients undergoing endoscopic therapy, all visible neoplastic lesions were treated with endoscopic mucosal resection. EMR was performed utilizing either the Duette TM Multiband mucosectomy device or the cap mucosectomy kit. Residual Barrett's oesophagus mucosa was subsequently treated with ablative techniques or radical mucosectomy depending on the length of the Barrett's oesophagus segment. Photodynamic therapy was utilized to 2006 with radiofrequency ablation subsequently being the most common ablative therapy. APC was selectively applied. All patients were treated with twice a day PPI during and after ET. Endoscopically treated patients were routinely followed according to an institutional Barrett's oesophagus treatment algorithm. In endoscopically treated patients, 4-quadrant biopsies according to the Seattle protocol were obtained at every 3 months for the first year, biannually in the following year and subsequently annually. Patients found to have residual neoplastic tissue or metachronous lesions underwent repeat EMR.

Characteristics

Arm-level characteristics

Characteristic	Oesophagectomy (N = 49)	Endoscopic treatment (N = 36)
Age (years) Mean (SD)	64.9 (9.6)	67.6 (11.3)
Male No of events	n = 42 ; % = 86	n = 28 ; % = 78
median length if BO (cm) Median (IQR)	4.5 (2 to 8)	4 (1 to 7.25)
Mass lesion (more than or equal to 1cm) No of events	n = 17 ; % = 35	n = 4 ; % = 11

Outcomes

Study timepoints

- 3 year

Oesophagectomy vs endoscopic treatments

Outcome	Oesophagectomy, 3 year, N = 49	Endoscopic treatment, 3 year, N = 36
Adverse events No of events	n = 25 ; % = 51.02	n = 14 ; % = 38.89
Major adverse events No of events	n = 5 ; % = 10.2	n = 1 ; % = 2.78
Recurrence No of events	n = 1 ; % = 2.04	n = 4 ; % = 11.11
complete eradication No of events	n = 49 ; % = 100	n = 33 ; % = 91.67
5 year survival Custom value	86%	69%
Conversion to alternative treatment No of events	n = 0 ; % = 0	n = 2 ; % = 5.55
metastatic recurrence No of events	n = 1 ; % = 2	n = 1 ; % = 3
minor adverse events No of events	n = 20 ; % = 40.2	n = 13 ; % = 36.1

Zehetner, 2011

Bibliographic Reference	Zehetner, J.; DeMeester, S. R.; Hagen, J. A.; Ayazi, S.; Augustin, F.; Lipham, J. C.; DeMeester, T. R.; Endoscopic resection and ablation versus esophagectomy for high-grade dysplasia and intramucosal adenocarcinoma; J Thorac Cardiovasc Surg; 2011; vol. 141 (no. 1); 39-47

Study details

Secondary publication of another included study- see primary study for details	NA
Other publications associated with this study included in review	NA
Trial name / registration number	NA
Study type	Retrospective cohort study
Study location	USA
Study setting	Single centre - secondary care

Study dates	2001-2010
Sources of funding	No funding
Inclusion criteria	All patients with high-grade dysplasia or intramucosal adenocarcinoma treated endoscopically or by an esophagectomy
Exclusion criteria	Patients with tumors invasive into the submucosa were excluded, but lymphovascular invasion or poor differentiation in an intramucosal lesion did not deter endoscopic therapy
Recruitment / selection of participants	Retrospective inspection of patient databases
Intervention(s)	Oesophagectomy was performed as a transthoracic en bloc, transhiatal, minimally invasive, or vagus-sparing resection. Reconstruction in all cases was with a tubularized gastric pull-up. Patients were followed up clinically by the operating surgeon after the esophagectomy for any evidence of recurrence, with selective use of CT or PET scans
Comparator	All endoscopic resections were performed as an outpatient procedure in the operating room under general anaesthesia by thoracic/foregut surgeons. Visible lesions were excised with endoscopic resection, and the depth of invasion was pathologically determined in the fixed specimen. Endoscopic resection was performed by the Inoue cap technique with either the straight 13.9-mm or the soft, oblique 18-mm Olympus cap after dilute epinephrine in saline was injected into the submucosa to lift the lesion.8 Multiple resections were performed at a single setting, but never circumferential or exceeding 3 cm in height at one site. Ablation was usually performed with either the Halo 360 or the Halo 90 radiofrequency catheters at the recommended energy setting (12 J/cm2). Occasionally, argon plasma coagulation was used to touch up small areas, typically at the time of endoscopic resection of a lesion. In some patients immediately after endoscopic resection of a nodule, the surrounding Barrett's mucosa was ablated with the Halo 90 device. Ablation was not performed over areas just resected.
Number of participants	101
Duration of follow-up	17-34 months
Indirectness	Serious - proportion not T1 stage

Additional comments	No adjustments made for confounding

Study arms

Oesophagectomy (N = 61)
Esophagectomy was performed as a transthoracic en bloc, transhiatal, minimally invasive, or vagus-sparing resection. Reconstruction in all cases was with a tubularized gastric pull-up. Patients were followed up clinically by the operating surgeon after the esophagectomy for any evidence of recurrence, with selective use of CT or PET scans

Endoscopic treatment (N = 40)
All endoscopic resections were performed as an outpatient procedure in the operating room under general anaesthesia by thoracic/foregut surgeons. Visible lesions were excised with endoscopic resection, and the depth of invasion was pathologically determined in the fixed specimen. Endoscopic resection was performed by the Inoue cap technique with either the straight 13.9-mm or the soft, oblique 18-mm Olympus cap after dilute epinephrine in saline was injected into the submucosa to lift the lesion.8 Multiple resections were performed at a single setting, but never circumferential or exceeding 3 cm in height at one site. Ablation was usually performed with either the Halo 360 or the Halo 90 radiofrequency catheters at the recommended energy setting (12 J/cm2). Occasionally, argon plasma coagulation was used to touch up small areas, typically at the time of endoscopic resection of a lesion. In some patients immediately after endoscopic resection of a nodule, the surrounding Barrett's mucosa was ablated with the Halo 90 device. Ablation was not performed over areas just resected.

Characteristics

Arm-level characteristics

Characteristic	Oesophagectomy (N = 61)	Endoscopic treatment (N = 40)
age (yrs) Median (IQR)	68 (58 to 75)	66 (58 to 76)
Male No of events	n = 49 ; % = 80.3	n = 33 ; % = 82.5
Intramucosal cancer No of events	n = 48 ; % = 79	n = 18 ; % = 45
HGD No of events	n = 13 ; % = 21	n = 22 ; % = 55
Comorbid conditions No of events	n = 50 ; % = 82	n = 32 ; % = 80
R1 No of events	n = 0 ; % = 0	n = 0 ; % = 0
lymph node mets No of events	n = 1 ; % = 1.6	n = 0 ; % = 0

Outcomes

Study timepoints

- 2 year

Oesophagectomy vs endoscopic treatments

Outcome	Oesophagectomy, 2 year, N = 48	Endoscopic treatment, 2 year, N = 18
Mortality No of events	n = 1 ; % = 2.1	n = 1 ; % = 5.6
Progression (to metachronous cancer) No of events	n = 0 ; % = 0	n = 3 ; % = 16.67

The above outcomes are confined to those with intramucosal cancer

Oesophagectomy vs endoscopic treatments

Outcome	Oesophagectomy, 2 year, N = 61	Endoscopic treatment, 2 year, N = 40
Complications No of events	n = 37 ; % = 61	n = 0 ; % = 0

All patients

Appendix E – Forest plots

Oesophagectomy versus endoscopy stage T1a

Figure 2: All cause mortality

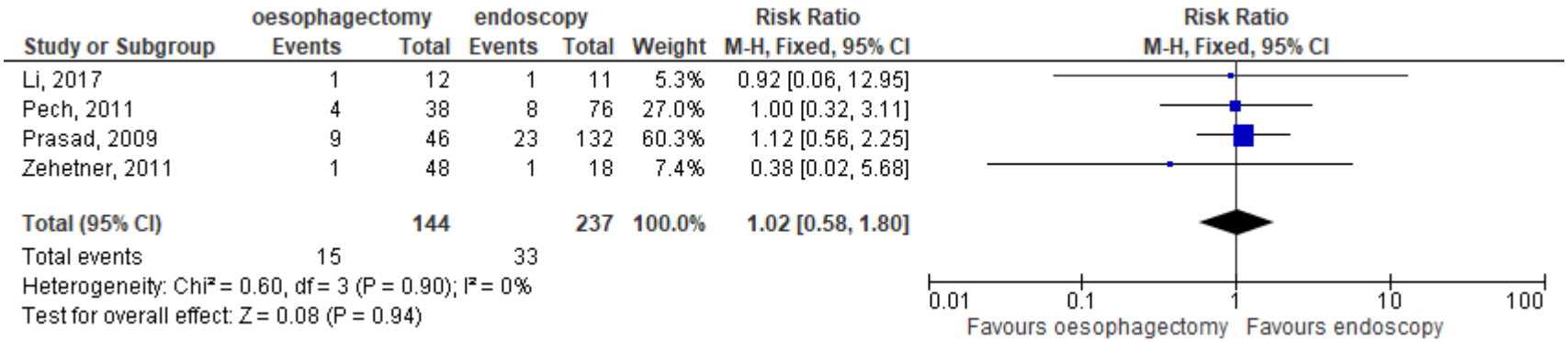


Figure 3: All cause mortality (adjusted HR)

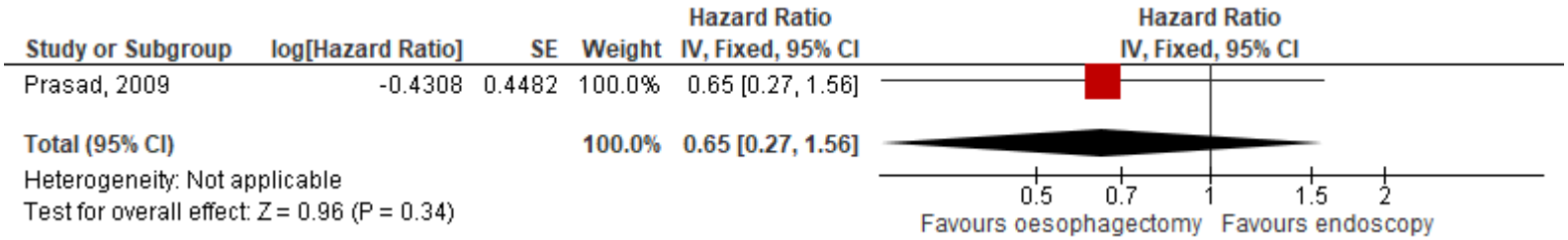


Figure 4: Mortality from OAC (adjusted HR)

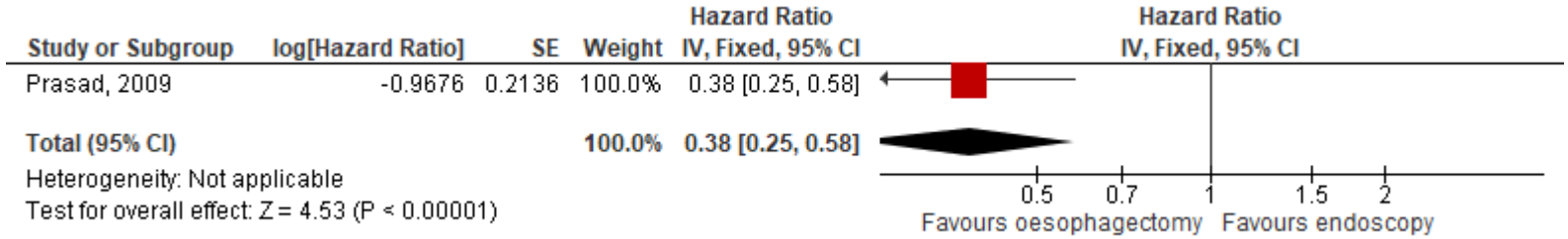


Figure 5: All recurrence

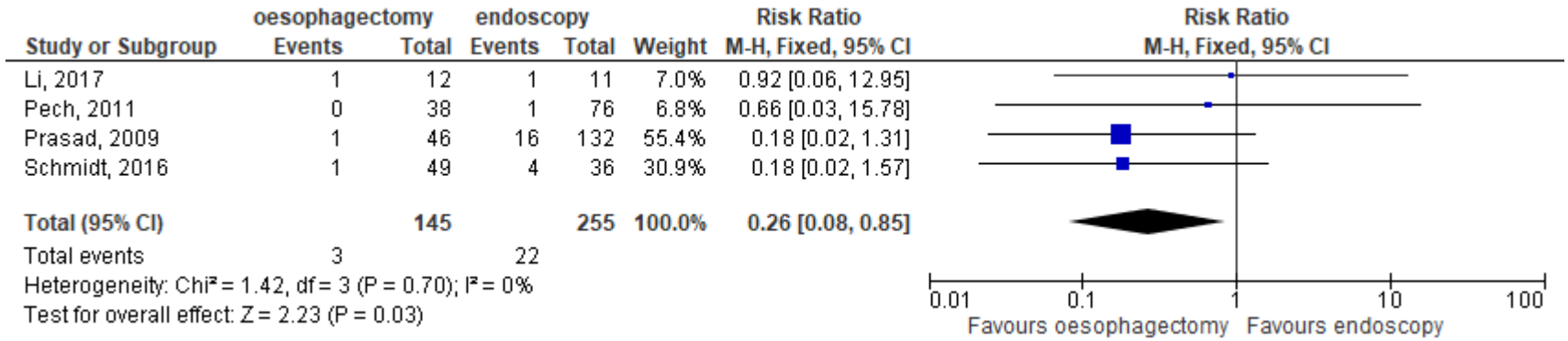


Figure 6: metastatic recurrence

Study or Subgroup	oesophagectomy Events	Total	endoscopy Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Schmidt, 2016	1	49	1	36	100.0%	0.73 [0.05, 11.36]
Total (95% CI)		**49**		**36**	**100.0%**	**0.73 [0.05, 11.36]**
Total events	1		1			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.22 (P = 0.83)

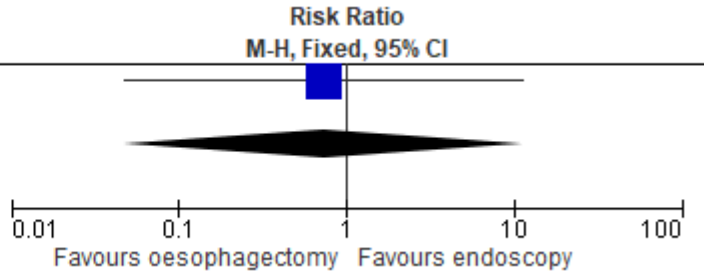


Figure 7: Progression to metachronous neoplasia

Study or Subgroup	oesophagectomy Events	Total	endoscopy Events	Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Pech, 2011	0	38	4	76	60.0%	0.21 [0.03, 1.76]
Zehetner, 2011	0	48	3	18	40.0%	0.02 [0.00, 0.30]
Total (95% CI)		**86**		**94**	**100.0%**	**0.09 [0.02, 0.45]**
Total events	0		7			

Heterogeneity: Chi² = 1.74, df = 1 (P = 0.19); I² = 43%
Test for overall effect: Z = 2.93 (P = 0.003)

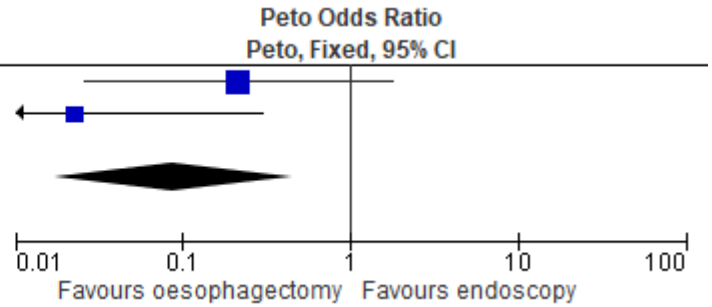


Figure 8: Major or serious complications

Study or Subgroup	oesophagectomy Events	Total	endoscopy Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Li, 2017	2	12	1	11	8.8%	1.83 [0.19, 17.51]
Pech, 2011	12	38	0	76	2.8%	49.36 [3.00, 811.96]
Prasad, 2009	17	46	18	132	78.6%	2.71 [1.53, 4.80]
Schmidt, 2016	5	49	1	36	9.7%	3.67 [0.45, 30.10]
Total (95% CI)		**145**		**255**	**100.0%**	**4.05 [2.41, 6.80]**
Total events	36		20			

Heterogeneity: Chi² = 5.45, df = 3 (P = 0.14); I² = 45%
Test for overall effect: Z = 5.30 (P < 0.00001)

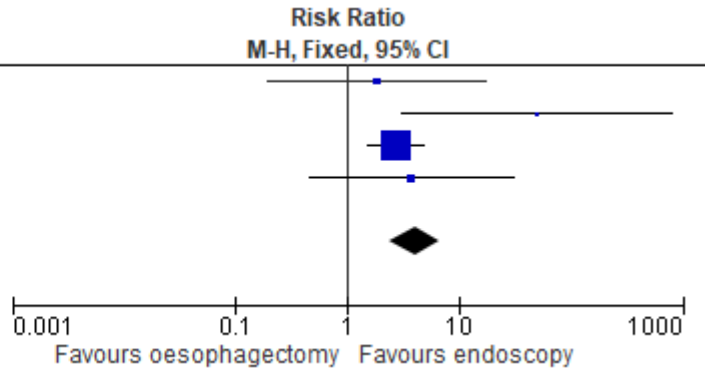
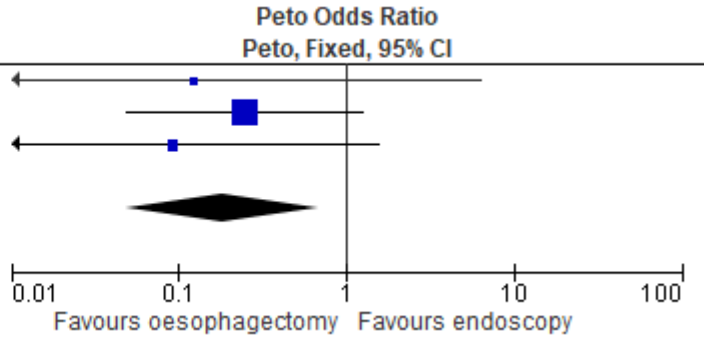


Figure 9: Need to switch treatment

Study or Subgroup	oesophagectomy Events	Total	endoscopy Events	Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Li, 2017	0	12	1	11	11.3%	0.12 [0.00, 6.25]
Prasad, 2009	0	46	8	132	66.8%	0.25 [0.05, 1.24]
Schmidt, 2016	0	49	2	36	21.9%	0.09 [0.01, 1.54]
Total (95% CI)		**107**		**179**	**100.0%**	**0.18 [0.05, 0.69]**
Total events	0		11			

Heterogeneity: Chi² = 0.40, df = 2 (P = 0.82); I² = 0%
Test for overall effect: Z = 2.52 (P = 0.01)



Oesophagectomy vs endoscopy stage mixed stage T1a/T1b

Figure 10: All cause mortality

Study or Subgroup	oesophagectomy Events	Total	endoscopy Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Pacifico, 2003	2	64	2	24	100.0%	0.38 [0.06, 2.51]
Total (95% CI)		**64**		**24**	**100.0%**	**0.37 [0.06, 2.51]**
Total events	2		2			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.01 (P = 0.31)

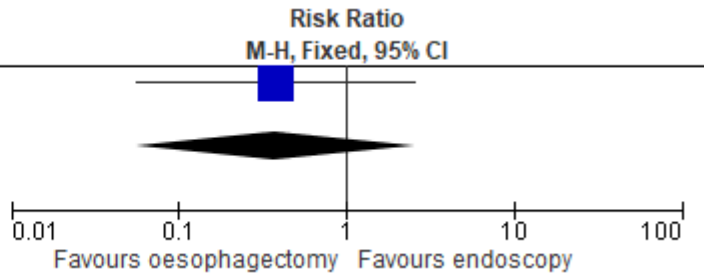


Figure 11: OAC-related mortality

Study or Subgroup	oesophagectomy Events	Total	endoscopy Events	Total	Weight	Risk Difference M-H, Fixed, 95% CI
Pacifico, 2003	0	64	0	24	100.0%	0.00 [-0.06, 0.06]
Total (95% CI)		**64**		**24**	**100.0%**	**0.00 [-0.06, 0.06]**
Total events	0		0			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.00 (P = 1.00)

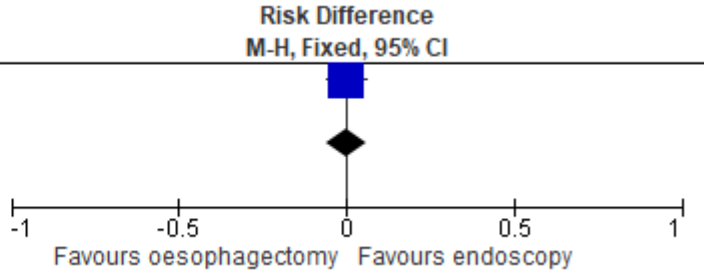


Figure 12: Recurrence of OAC in first follow up biopsy

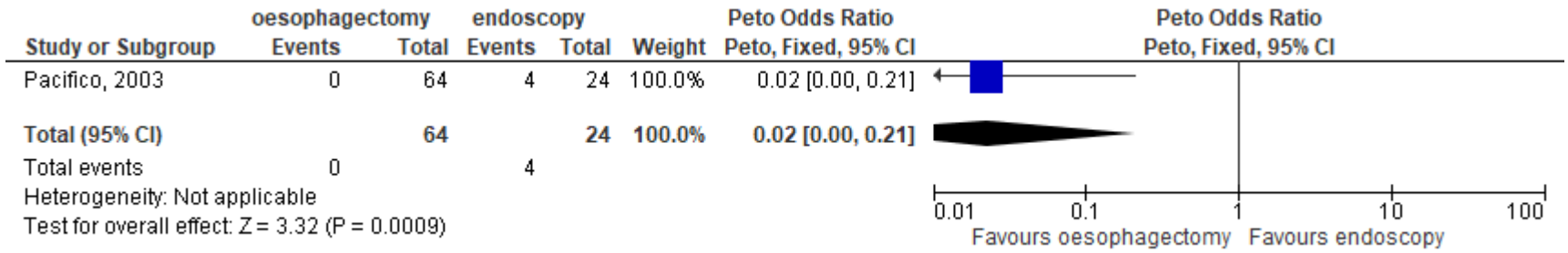


Figure 13: Major or serious complications

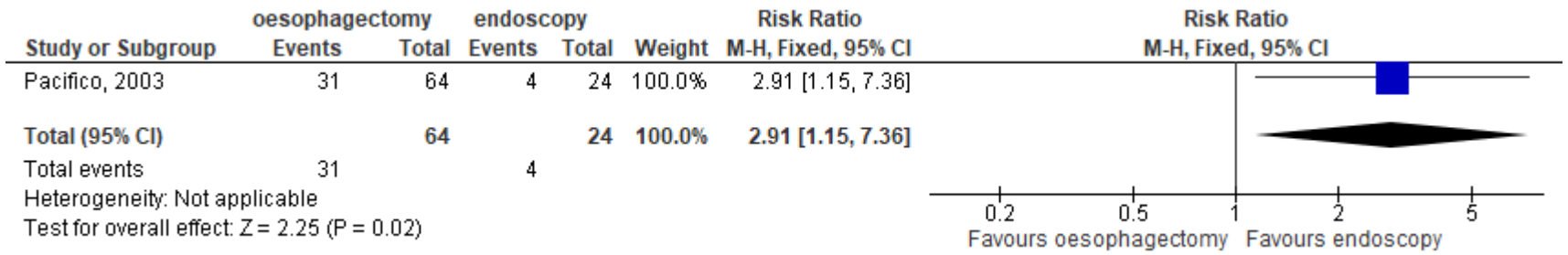
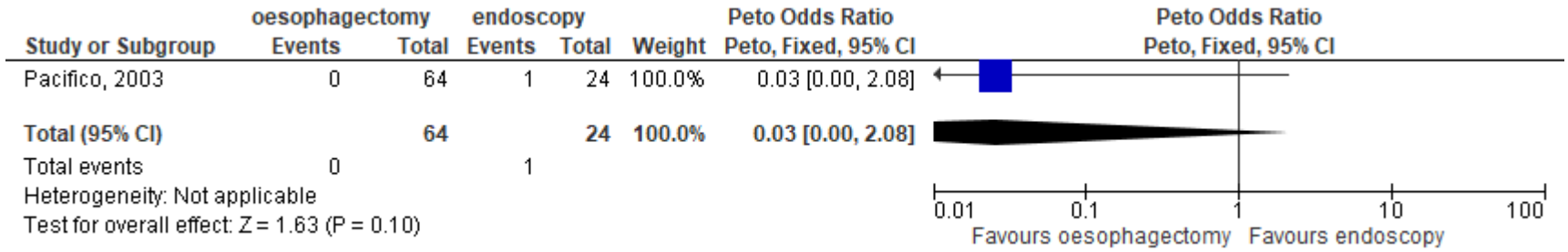


Figure 14: Need to switch treatment



Appendix F – GRADE tables

Table 7: Clinical evidence profile: oesophagectomy v endoscopic treatment T1a

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	oesophagectomy	Endoscopic treatment	Relative (95% CI)	Absolute		
All cause mortality at 2-5 years												
4	Observational studies	Critical risk of bias[1]	no serious inconsistency	No serious indirectness	Very serious imprecision[2]	none	15/144 (10.4%)	33/237 (13.9%)	RR 1.02 (0.58 to 1.80)	3 more per 1,000 (from 58 fewer to 111 more)	VERY LOW	CRITICAL
All cause mortality at 2 years (adjusted HR)												
1	Observational studies	Serious risk of bias[1]	NA	No serious indirectness	Very serious imprecision[2]	none	46	132	HR 0.65 (0.27 to 1.56)	-	VERY LOW	CRITICAL
OAC-related mortality at 2 years (adjusted HR)												
1	Observational studies	Serious risk of bias[1]	NA	No serious indirectness	No serious imprecision	none	46	132	HR 0.38 (0.25 to 0.58)	-	MOD	CRITICAL
5 year survival												
1	Observational studies	Critical risk of bias[1]	NA	No serious indirectness	Not measurable	none	86% survival	69% survival	-	-	LOW	CRITICAL
All recurrence at 2-5 years												
4	Observational studies	Critical risk of bias[1]	no serious inconsistency	No serious indirectness	Serious imprecision[2]	none	3/145 (2.1%)	22/255 (8.6%)	RR 0.26 (0.08 to 0.85)	64 fewer per 1,000 (from 79	VERY LOW	CRITICAL

										fewer to 13 fewer)		
Metastatic recurrence at 3.5 years												
1	Observational studies	Critical risk of bias[1]	NA	No serious indirectness	Very serious imprecision[2]	none	1/49 (2.0%)	1/36 (2.8%)	RR 0.73 (0.05 to 11.36)	8 fewer per 1,000 (from 26 fewer to 288 more)	VERY LOW	CRITICAL
Progression to metachronous neoplasia at 2-5 years												
2	Observational studies	Critical risk of bias[1]	no serious inconsistency	No serious indirectness	No serious imprecision[2]	none	0/86 (0.0%)	7/94 (7.4%)	OR 0.09 (0.02 to 0.45)	67 fewer per 1,000 (from 73 fewer to 40 fewer)	LOW	CRITICAL
Major or serious complications at 2-5 years												
4	Observational studies	Critical risk of bias[1]	no serious inconsistency	No serious indirectness	No serious imprecision[2]	none	36/145 (24.8%)	20/255 (7.8%)	RR 4.05 (2.41 to 6.80)	239 more per 1,000 (from 111 more to 455 more)	LOW	CRITICAL
Need to switch treatment at 2-3.5 years												
3	Observational studies	Critical risk of bias[1]	no serious inconsistency	No serious indirectness	No serious imprecision[2]	none	0/107 (0.0%)	11/179 (6.1%)	OR 0.18 (0.05 to 0.69)	50 fewer per 1,000 (from 58 fewer to 18 fewer)	LOW	CRITICAL
Length of hospital stay (days)												
1	Observational studies	Critical risk of bias[1]	no serious inconsistency	No serious indirectness	Not measurable	none	15(10-22)	0(0-0)	-	-	LOW	CRITICAL

[1] Downgraded by one increment if moderate risk of bias and downgraded by two increments if serious or critical risk of bias

[2] Downgraded by one increment if the 95% CIs crossed one of the default MIDs (0.8 or 1.25) and downgraded by two increments if the 95% CIs crossed both of the default MIDs (0.8 and 1.25).

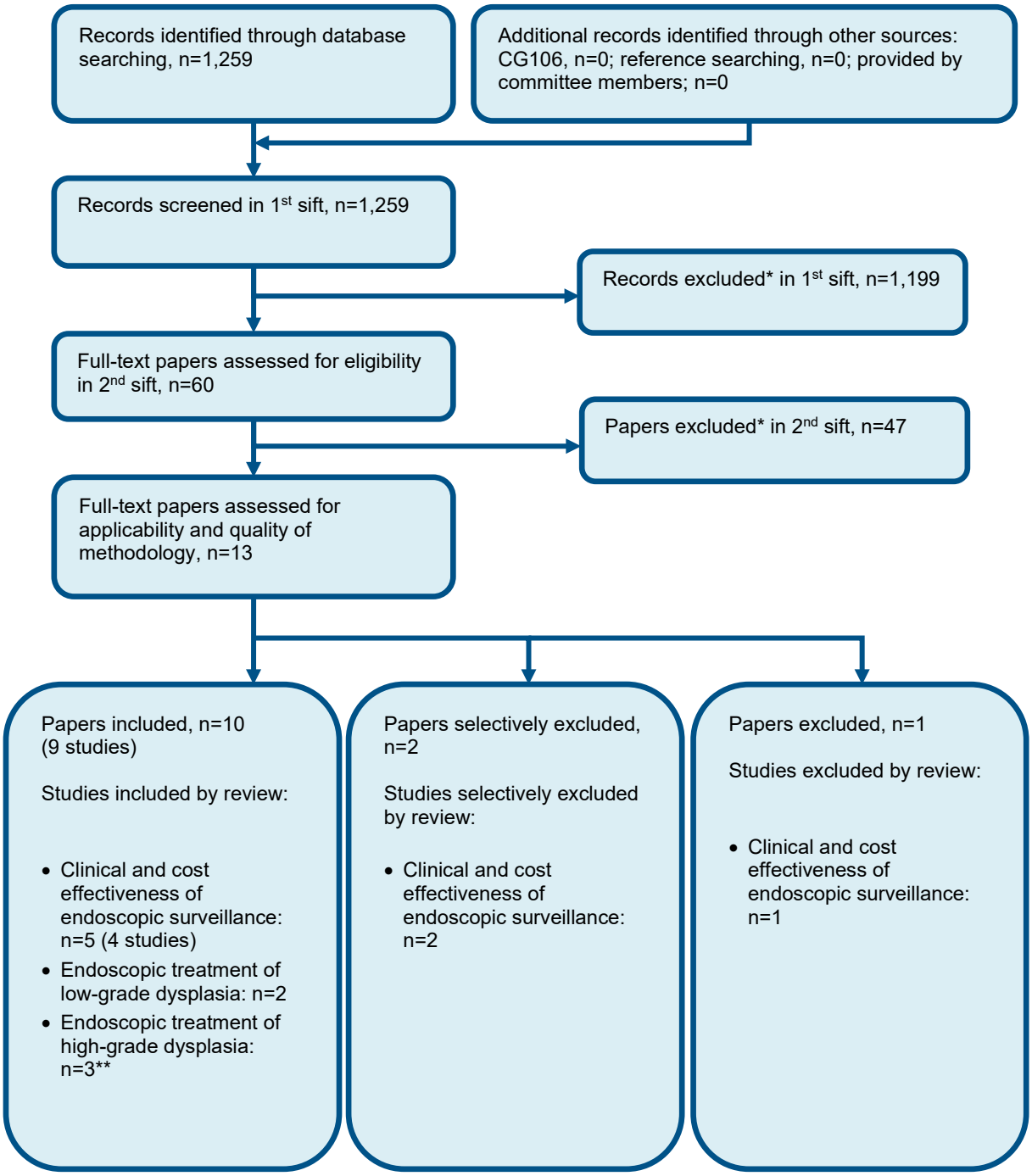
Table 8: Clinical evidence profile: oesophagectomy v endoscopic treatment at mixed stage T1a/T1b

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	oesophagectomy	Endoscopic treatment	Relative (95% CI)	Absolute		
All cause mortality at 1 year												
1	Observational studies	Critical risk of bias[1]	NA	No serious indirectness	Very serious imprecision[2]	none	2/64 (3.1%)	2/24 (8.3%)	RR 0.37 (0.06 to 2.51)	53 fewer per 1,000 (from 78 fewer to 126 more)	VERY LOW	CRITICAL
OAC-related mortality at 1 year												
1	Observational studies	Critical risk of bias[1]	NA	No serious indirectness	Very serious imprecision[2]	none	0/64 (0.0%)	0/24 (0.0%)	not estimable	0 fewer per 1,000 (from 60 fewer to 60 more)	VERY LOW	CRITICAL
Recurrence of OAC in first follow-up biopsy at 1 year												
1	Observational studies	Critical risk of bias[1]	NA	No serious indirectness	No serious imprecision[2]	none	0/64 (0.0%)	4/24 (16.7%)	OR 0.02 (0.00 to 0.21)	-	LOW	CRITICAL
Major or serious complications at 1 year												
1	Observational studies	Critical risk of bias[1]	NA	No serious indirectness	Serious imprecision[2]	none	31/64 (48.4%)	4/24 (16.7%)	RR 2.91 (1.15 to 7.36)	318 more per 1,000 (from 25	VERY LOW	CRITICAL

										more to 1,000 more)		
Need to switch treatment at 1 year												
1	Observational studies	Critical risk of bias[1]	NA	No serious indirectness	Very serious imprecision[2]	none	0/64 (0.0%)	1/24 (4.2%)	OR 0.03 (0.00 to 2.08)	-	VERY LOW	CRITICAL

[1] Downgraded by one increment if moderate risk of bias and downgraded by two increments if serious or critical risk of bias
[2] Downgraded by one increment if the 95% CIs crossed one of the default MIDs (0.8 or 1.25) and downgraded by two increments if the 95% CIs crossed both of the default MIDs (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 – Excluded studies

Clinical studies

Table 9: Studies excluded from the clinical review

Study	Code [Reason]
Anand, O.; Wani, S.; Sharma, P. (2008) Gastroesophageal reflux disease and Barrett's esophagus. Endoscopy 40(2): 126-130	- Review article but not a systematic review
Anonymous (2010) 3rd International Gastrointestinal Consensus Symposium (IGICS): Present Situation and Future Prospects on Endoscopic Diagnosis and Treatment in Asia. Digestion. Conference: 3rd International Gastrointestinal Consensus Symposium 81(3)	- Conference abstract
Barr, H. (2008) Surgical efficiency or eradication sufficiency. American Journal of Gastroenterology 103(6): 1346-8	- Review article but not a systematic review
Barr, H., Stone, N., Ding, D. C. et al. (2008) Current practice in management of high-grade dysplasia in Barrett's oesophagus: the real problem. Photodiagnosis & Photodynamic Therapy 5(1): 38-41	- Review article but not a systematic review
Beger, H. G.; Schwarz, A.; Bergmann, U. (2003) Progress in gastrointestinal tract surgery: the impact of gastrointestinal endoscopy. Surgical Endoscopy 17(2): 342-50	- Review article but not a systematic review
Bennett, C., Green, S., Decaestecker, J. et al. (2012) Surgery versus radical endotherapies for early cancer and high-grade dysplasia in Barrett's oesophagus. Cochrane Database Syst Rev 11: cd007334	- Systematic review used as source of primary studies
Best, Lmj; Mughal, M; Gurusamy, Ks (2016) Non-surgical versus surgical treatment for oesophageal cancer. Cochrane Database of Systematic Reviews	- Systematic review used as source of primary studies
Blom, D. (2003) Surgical management of esophageal malignancy. Current Gastroenterology Reports 5(3): 192-7	- Review article but not a systematic review
Bulsiewicz, W. J. and Shaheen, N. J. (2011) The role of radiofrequency ablation in the management of Barrett's esophagus. Gastrointestinal Endoscopy Clinics of North America 21(1): 95-109	- 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 EARLY CANCER AND HIGH-GRADE DYSPLASIA IN THE ESOPHAGUS: a systematic review. Arquivos de Gastroenterologia 53(1): 10-9	- Systematic review used as source of primary studies

Study	Code [Reason]
Caygill, C. P. J. and Gatenby, P. A. C. (2014) Randomised controlled trial: Radiofrequency ablation of Barrett's oesophagus with confirmed low-grade dysplasia reduces risk of development of high-grade dysplasia and adenocarcinoma. Evidence-Based Medicine 19(5): 185	- Study does not contain an intervention relevant to this review protocol
Chai, N., Du, C., Gao, Y. et al. (2018) Comparison between submucosal tunneling endoscopic resection and video-assisted thoracoscopic enucleation for esophageal submucosal tumors originating from the muscularis propria layer: a randomized controlled trial. Surgical endoscopy 32(7): 3364-3372	- Study does not contain an intervention relevant to this review protocol VATE, although surgical, is not oesophagectomy.
Comay, D., Blackhouse, G., Goeree, R. et al. (2007) Photodynamic therapy for Barrett's esophagus with high-grade dysplasia: A cost-effectiveness analysis. Canadian Journal of Gastroenterology 21(4): 217-222	- Study design not relevant to this review protocol cost effectiveness analysis
Cordice, J. W. (1990) Carcinoma of the esophagus seen in a 12-year period at queens hospital center. Journal of the National Medical Association 82(4): 273-280	- Comparator in study does not match that specified in this review protocol
Das, A.; Singh, V.; Fleischer, D. E.; Sharma, V. K.; A comparison of endoscopic treatment and surgery in early esophageal cancer: an analysis of surveillance epidemiology and end results data; Am J Gastroenterol; 2008; vol. 103 (no. 6); 1340-5	Not specifically defined as a Barrett's population.; Only 63% were at stage T1 in endoscopic treatment group. Oesophagectomy arm included gastrectomy
Deb, S. J.; Shen, K. R.; Deschamps, C. (2012) An analysis of esophagectomy and other techniques in the management of high-grade dysplasia of Barrett's esophagus. Diseases of the Esophagus 25(4): 356-66	- Review article but not a systematic review
Dumot, J. A., Vargo, J. J., 2nd, Falk, G. W. et al. (2009) An open-label, prospective trial of cryospray ablation for Barrett's esophagus high-grade dysplasia and early esophageal cancer in high-risk patients. Gastrointestinal Endoscopy 70(4): 635-44	- Study design not relevant to this review protocol Single arm study
Dunbar, K. B. (2013) Endoscopic eradication therapy for mucosal neoplasia in Barrett's esophagus. Current Opinion in Gastroenterology 29(4): 446-53	- Review article but not a systematic review
Eisen, G. (2005) Is there now an acceptable alternative to esophagectomy for patients with high-grade dysplasia in Barrett's esophagus?. Evidence-based gastroenterology 6(4): 102-103	- Population not relevant to this review protocol - Review article but not a systematic review Review of a study which was also not relevant due to the intervention not including oesophagectomy
Fayter, D., Corbett, M., Heirs, M. et al. (2010) A systematic review of photodynamic therapy in the treatment of precancerous skin conditions, Barrett's oesophagus and cancers of the biliary	- Systematic review used as source of primary studies

Study	Code [Reason]
tract, brain, head and neck, lung, oesophagus and skin. Health Technology Assessment 14(37): 3-129	
Ferguson, M. K. and Naunheim, K. S. (1997) Resection for Barrett's mucosa with high-grade dysplasia: implications for prophylactic photodynamic therapy. Journal of Thoracic & Cardiovascular Surgery 114(5): 824-9	- Comparator in study does not match that specified in this review protocol
Fujita, H.; Sueyoshi, S.; Yamana, H.; Shinozaki, K.; Toh, U.; Tanaka, Y.; Mine, T.; Kubota, M.; Shirouzu, K.; Toyonaga, A.; Harada, H.; Ban, S.; Watanabe, M.; Toda, Y.; Tabuchi, E.; Hayabuchi, N.; Inutsuka, H.; Optimum treatment strategy for superficial esophageal cancer: endoscopic mucosal resection versus radical esophagectomy; World J Surg; 2001; vol. 25 (no. 4); 424-31	Not specifically defined as a Barrett's population.; Not oesophageal adenocarcinoma – this study comprised a sample with squamous cell carcinoma.
Gockel, I. and Hoffmeister, A. (2018) Endoscopic or Surgical Resection for Gastro-Esophageal Cancer. Deutsches Arzteblatt International 115(3132): 513-519	- Systematic review used as source of primary studies
Gong, E. J., Kim, D. H., Ahn, J. Y. et al. (2017) Comparison of long-term outcomes of endoscopic submucosal dissection and surgery for esophagogastric junction adenocarcinoma. Gastric Cancer 20(suppl1): 84-91	- Population not relevant to this review protocol Patients had oesophogastric junction adenocarcinoma - Study does not contain an intervention relevant to this review protocol Patients treated by surgery underwent an open or laparoscopic total gastrectomy with lymph node dissection, with or without esophagectomy. This does not comply with the protocol intervention definition.
Gong, L.; Yue, J.; Duan, X.; Jiang, H.; Zhang, H.; Zhang, X.; Yu, Z.; Comparison of the therapeutic effects of endoscopic submucosal dissection and minimally invasive esophagectomy for T1 stage esophageal carcinoma; Thorac Cancer; 2019; vol. 10 (no. 11); 2161-2167	Not specifically defined as a Barrett's population.; Not oesophageal adenocarcinoma – this study comprised a sample with squamous cell carcinoma.
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	- Systematic review used as source of primary studies
Hamade, N. and Sharma, P. (2017) Ablation Therapy for Barrett's Esophagus: New Rules for Changing Times. Current Gastroenterology Reports 19(10): 48	- Review article but not a systematic review
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	- Population not relevant to this review protocol
Hur, C.; Nishioka, N. S.; Gazelle, G. S. (2003) Cost-effectiveness of photodynamic therapy for	- Study design not relevant to this review protocol

Study	Code [Reason]
treatment of Barrett's esophagus with high grade dysplasia. Digestive Diseases and Sciences 48(7): 1273-1283	Cost effectiveness analysis
Jin, X. F.; Gai, W.; Chai, T. H.; Li, L.; Guo, J. Q.; Comparison of Endoscopic Resection and Minimally Invasive Esophagectomy in Patients With Early Esophageal Cancer; J Clin Gastroenterol; 2017; vol. 51 (no. 3); 223-227	Not specifically defined as a Barrett's population.; Not predomoinantly oesophageal adenocarcinoma – this study largely comprised a sample with squamous cell carcinoma.
Jung, H. K.; Tae, C. H.; Lee, H. A.; Lee, H.; Don Choi, K.; Park, J. C.; Kwon, J. G.; Choi, Y. J.; Hong, S. J.; Sung, J.; Chung, W. C.; Kim, K. B.; Kim, S. Y.; Song, K. H.; Park, K. S.; Jeon, S. W.; Kim, B. W.; Ryu, H. S.; Lee, O. J.; Baik, G. H.; Kim, Y. S.; Jung, H. Y.; Korean College of, Helicobacter; Upper Gastrointestinal, Research; Treatment pattern and overall survival in esophageal cancer during a 13-year period: A nationwide cohort study of 6,354 Korean patients; PLoS ONE [Electronic Resource]; 2020; vol. 15 (no. 4); e0231456	Not specifically defined as a Barrett's population.; Not predomoinantly oesophageal adenocarcinoma – this study largely comprised a sample with squamous cell carcinoma.
Kallam, A.; Alsop, B. R.; Sharma, P. (2015) Limitations of endoscopic ablation in Barrett's esophagus. Expert Review of Gastroenterology and Hepatology 9(4): 487-496	- Review article but not a systematic review
Kim, H. J., Chung, H., Shin, S. K. et al. (2018) Comparison of long-term clinical outcomes between endoscopic and surgical resection for early-stage adenocarcinoma of the esophagogastric junction. Surg Endosc 32(8): 3540-3547	- Population not relevant to this review protocol Oesophogogastric junction adenocarcinoma - Study does not contain an intervention relevant to this review protocol All patients received total gastrectomy with lymph node dissection; this does not accord with the protocol intervention definition of oesophagectomy.
Kim, J. S.; Kim, B. W.; Shin, I. S. (2014) Efficacy and safety of endoscopic submucosal dissection for superficial squamous esophageal neoplasia: a meta-analysis. Digestive Diseases & Sciences 59(8): 1862-9	- Systematic review used as source of primary studies
Kitagawa, Y., Takeuchi, H., Saikawa, Y. et al. (2007) Surgical treatment of esophageal cancer: benefit and limitation of endoscopic surgery. American Journal of Surgery 194(4suppl): S158-S161	- Review article but not a systematic review
Knabe, M.; May, A.; Ell, C. (2015) Endoscopic Therapy of Early Carcinoma of the Oesophagus. Viszeralmedizin 31(5): 320-5	- Systematic review used as source of primary studies
Knabe, M.; May, A.; Ell, C. (2016) Endoscopic resection for patients with mucosal adenocarcinoma of the esophagus. Minerva Gastroenterologica e Dietologica 62(4): 281-295	- Review article but not a systematic review
Labenz, J., Koop, H., Tannapfel, A. et al. (2015) The epidemiology, diagnosis, and treatment of Barrett's carcinoma. Deutsches Arzteblatt International 112(13): 224-33; quiz 234	- Review article but not a systematic review

Study	Code [Reason]
Lee, H. D.; Chung, H.; Kwak, Y.; Choi, J.; Lee, A.; Kim, J. L.; Cho, S. J.; Kim, S. G.; Endoscopic Submucosal Dissection Versus Surgery for Superficial Esophageal Squamous Cell Carcinoma: A Propensity Score-Matched Survival Analysis; Clin Transl Gastroenterol; 2020; vol. 11 (no. 7); e00193	Not specifically defined as a Barrett's population.; Not predomoinantly oesophageal adenocarcinoma – this study largely comprised a sample with squamous cell carcinoma.
Leung, W. D. and Chennat, J. (2011) Comparison of endoscopic and surgical resection of intramucosal carcinoma in Barrett's esophagus. Expert Rev Gastroenterol Hepatol 5(5): 575-8	- Review article but not a systematic review Review of another study
Li, P., Ma, B., Gong, S. et al. (2020) Endoscopic submucosal tunnel dissection for superficial esophageal neoplastic lesions: a meta-analysis. Surgical Endoscopy 34(3): 1214-1223	- Systematic review used as source of primary studies
Marino, K. A.; Sullivan, J. L.; Weksler, B.; Esophagectomy versus endoscopic resection for patients with early-stage esophageal adenocarcinoma: A National Cancer Database propensity-matched study; J Thorac Cardiovasc Surg; 2018; vol. 155 (no. 5); 2211-2218.e1	Not specifically defined as a Barrett's population..
Max Almond, L. and Barr, H. (2014) Management controversies in Barrett's oesophagus. Journal of Gastroenterology 49(2): 195-205	- Systematic review used as source of primary studies
McCann, P., Stafinski, T., Wong, C. et al. (2011) The safety and effectiveness of endoscopic and non-endoscopic approaches to the management of early esophageal cancer: a systematic review. Cancer Treatment Reviews 37(1): 11-62	- Systematic review used as source of primary studies
Menon, D., Stafinski, T., Wu, H. et al. (2010) Endoscopic treatments for Barrett's esophagus: a systematic review of safety and effectiveness compared to esophagectomy. BMC Gastroenterology 10: 111	- Systematic review used as source of primary studies
Merkow, R. P.; Bilimoria, K. Y.; Keswani, R. N.; Chung, J.; Sherman, K. L.; Knab, L. M.; Posner, M. C.; Bentrem, D. J.; Treatment trends, risk of lymph node metastasis, and outcomes for localized esophageal cancer; J Natl Cancer Inst; 2014; vol. 106 (no. 7)	Not specifically defined as a Barrett's population.
Min, Y. W.; Lee, H.; Song, B. G.; Min, B. H.; Kim, H. K.; Choi, Y. S.; Lee, J. H.; Hwang, N. Y.; Carriere, K. C.; Rhee, P. L.; Kim, J. J.; Zo, J. I.; Shim, Y. M.; Comparison of endoscopic submucosal dissection and surgery for superficial esophageal squamous cell carcinoma: a propensity score-matched analysis; Gastrointest Endosc; 2018; vol. 88 (no. 4); 624-633	Not specifically defined as a Barrett's population.; Not oesophageal adenocarcinoma – this study comprised a sample with squamous cell carcinoma.
Nealis, T. B.; Washington, K.; Keswani, R. N. (2011) Endoscopic therapy of esophageal premalignancy and early malignancy. J Natl Compr Canc Netw 9(8): 890-9	- Review article but not a systematic review

Study	Code [Reason]
Ngamruengphong, S.; Wolfsen, H. C.; Wallace, M. B.; Survival of patients with superficial esophageal adenocarcinoma after endoscopic treatment vs surgery; Clin Gastroenterol Hepatol; 2013; vol. 11 (no. 11); 1424-1429.e2; quiz e81	Not specifically defined as a Barrett's population.
Nguyen, N. T., Roberts, P., Follette, D. M. et al. (2003) Thoracoscopic and laparoscopic esophagectomy for benign and malignant disease: lessons learned from 46 consecutive procedures. J Am Coll Surg 197(6): 902-13	- Study design not relevant to this review protocol Single arm study
Nishizawa, T. and Suzuki, H. (2020) Long-term outcomes of endoscopic submucosal dissection for superficial esophageal squamous cell carcinoma. Cancers 12(10): 1-11	- Systematic review used as source of primary studies
Osugi, H., Takemura, M., Higashino, M. et al. (2002) Video-assisted thoracoscopic esophagectomy and radical lymph node dissection for esophageal cancer. A series of 75 cases. Surg Endosc 16(11): 1588-93	- Study does not contain an intervention relevant to this review protocol
Park, S. J., Ahn, J. Y., Jung, H. Y. et al. (2015) Endoscopic Resection for Synchronous Esophageal Squamous Cell Carcinoma and Gastric Adenocarcinoma in Early Stage Is a Possible Alternative to Surgery. Gut and liver 9(1): 59-65	- Data not reported in an extractable format or a format that can be analysed The data were analysed for a mixed population including gastric cancer. The two groups relevant to this review were not provided as defined in the protocol, with some people having additional treatments that would critically bias results.
Pech, O., Bollschweiler, E., Manner, H. et al. (2011) DUPLICATE DO NOT USE Comparison between endoscopic and surgical resection of mucosal esophageal adenocarcinoma in Barrett's esophagus at two high-volume centers. Ann Surg 254(1): 67-72	- Duplicate reference
Pech, O., May, A., Gossner, L. et al. (2003) Barrett's esophagus: endoscopic resection. Gastrointestinal Endoscopy Clinics of North America 13(3): 505-12	- Review article but not a systematic review
Pech, O., May, A., Gunter, E. et al. (2006) The impact of endoscopic ultrasound and computed tomography on the TNM staging of early cancer in Barrett's esophagus. American Journal of Gastroenterology 101(10): 2223-2229	- Study does not contain an intervention relevant to this review protocol
Pech, O., May, A., Manner, H. et al. (2014) Long-term efficacy and safety of endoscopic resection for patients with mucosal adenocarcinoma of the esophagus. Gastroenterology 146(3): 652-660.e1	- Study design not relevant to this review protocol Single arm study
Pech, O., May, A., Rabenstein, T. et al. (2007) Endoscopic resection of early oesophageal cancer. Gut 56(11): 1625-34	- Review article but not a systematic review
Peng, W., Tan, S., Ren, Y. et al. (2020) Efficacy and safety of endoscopic submucosal tunnel dissection for superficial esophageal neoplastic	- Systematic review used as source of primary studies

Study	Code [Reason]
lesions: a systematic review and meta-analysis. Journal Of Cardiothoracic Surgery 15(1): 33	
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	- Study design not relevant to this review protocol Single arm study
Pouw, R. E., Wirths, K., Eisendrath, P. et al. (2010) Efficacy of radiofrequency ablation combined with endoscopic resection for barrett's esophagus with early neoplasia. Clin Gastroenterol Hepatol 8(1): 23-9	- Study design not relevant to this review protocol Single arm study
Prasad, G. A., Wang, K. K., Buttar, N. S. et al. (2007) Long-term survival following endoscopic and surgical treatment of high-grade dysplasia in Barrett's esophagus. Gastroenterology 132(4): 1226-33	- Population not relevant to this review protocol Population were people with high grade dysplasia - only 4% had malignancy at baseline
Qin, J.; Peng, Y.; Chen, W.; Ma, H.; Zheng, Y.; Li, Y.; Wang, J.; Comparative study of esophagectomy, endoscopic therapy, and radiotherapy for cT1N0M0 esophageal cancer in elderly patients: A SEER database analysis; Thorac Cancer; 2019; vol. 10 (no. 7); 1511-1520	Not specifically defined as a Barrett's population.
Ramay, F. H., Vareedayah, A. A., Visrodia, K. et al. (2019) What Constitutes Optimal Management of T1N0 Esophageal Adenocarcinoma?. Annals of Surgical Oncology 26(3): 714-731	- Review article but not a systematic review
Reed, M. F., Tolis, G., Jr., Edil, B. H. et al. (2005) Surgical treatment of esophageal high-grade dysplasia. Ann Thorac Surg 79(4): 1110-5; discussion 1110	- Population not relevant to this review protocol Only 10/49 had T1 stage in oesophagectomy group and unclearly reported in endoscopy group.
Rees, J. R., Lao-Sirieix, P., Wong, A. et al. (2010) Treatment for Barrett's oesophagus. Cochrane Database of Systematic Reviews: cd004060	- Population not relevant to this review protocol
Rosmolen, W. D.; Boer, K. R.; de Leeuw, R. J.; Gamel, C. J.; van Berge Henegouwen, M. I.; Bergman, J. J.; Sprangers, M. A.; Quality of life and fear of cancer recurrence after endoscopic and surgical treatment for early neoplasia in Barrett's esophagus; Endoscopy; 2010; vol. 42 (no. 7); 525-31	Only 44% of endoscopic treatment group were at stage T1. 74% of oesophagectomy group were at stage T1.
Sanchez, A., Reza, M., Blasco, J. A. et al. (2010) Effectiveness, safety, and cost-effectiveness of photodynamic therapy in Barrett's esophagus: a systematic review. Diseases of the Esophagus 23(8): 633-40	- Systematic review used as source of primary studies
Sayana, H.; Wani, S.; Sharma, P. (2007) Esophageal adenocarcinoma and Barrett's esophagus. Minerva Gastroenterologica e Dietologica 53(2): 157-169	- Review article but not a systematic review
Schembre, D. B., Huang, J. L., Lin, O. S. et al. (2008) Treatment of Barrett's esophagus with	- Study design not relevant to this review protocol

Study	Code [Reason]
early neoplasia: a comparison of endoscopic therapy and esophagectomy. Gastrointest Endosc 67(4): 595-601	Sample with early neoplasia and no cancer at baseline
Schembre, D.; Arai, A.; Levy, S.; Farrell-Ross, M.; Low, D.; Quality of life after esophagectomy and endoscopic therapy for Barrett's esophagus with dysplasia; Dis Esophagus; 2010; vol. 23 (no. 6); 458-64	Only 21.3% od ensocopic treatment group were at stage T1. 53.12% of oesophagectomy group at stage T1.
Schlottmann, F.; Patti, M. G.; Shaheen, N. J. (2017) Endoscopic Treatment of High-Grade Dysplasia and Early Esophageal Cancer. World Journal of Surgery 41(7): 1705-1711	- 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
Shaheen, N. J., Sharma, P., Overholt, B. F. et al. (2009) Radiofrequency ablation in Barrett's esophagus with dysplasia. N Engl J Med 360(22): 2277-88	- Population not relevant to this review protocol
Shimizu, Y., Kato, M., Yamamoto, J. et al. (2004) EMR combined with chemoradiotherapy: a novel treatment for superficial esophageal squamous-cell carcinoma. Gastrointestinal endoscopy 59(2): 199-204	- Comparator in study does not match that specified in this review protocol EMR combined with chemoradiotherapy
Shimizu, Y.; Tsukagoshi, H.; Fujita, M.; Hosokawa, M.; Kato, M.; Asaka, M.; Long-term outcome after endoscopic mucosal resection in patients with esophageal squamous cell carcinoma invading the muscularis mucosae or deeper; Gastrointestinal Endoscopy; 2002; vol. 56 (no. 3); 387-90	Not specifically defined as a Barrett's population; Not oesophageal adenocarcinoma – this study comprised a sample with squamous cell carcinoma.
Singh, S. and Sharma, P. (2009) How effective is endoscopic therapy in the treatment of patients with early esophageal cancer?. Nature Clinical Practice Gastroenterology & Hepatology 6(2): 70-1	- Review article but not a systematic review
Subramaniam, S., Chedgy, F., Longcroft-Wheaton, G. et al. (2017) Complex early Barrett's neoplasia at 3 Western centers: European Barrett's Endoscopic Submucosal Dissection Trial (E-BEST). Gastrointestinal Endoscopy 86(4): 608-618	- Study design not relevant to this review protocol Single arm study
Subramanian, C. R. and Triadafilopoulos, G. (2015) Endoscopic treatments for dysplastic Barrett's esophagus: resection, ablation, what else?. World Journal of Surgery 39(3): 597-605	- Review article but not a systematic review
Sun, F., Yuan, P., Chen, T. et al. (2014) Efficacy and complication of endoscopic submucosal dissection for superficial esophageal carcinoma:	- Systematic review used as source of primary studies

Study	Code [Reason]
a systematic review and meta-analysis. Journal Of Cardiothoracic Surgery 9: 78	
Swisher, S. G., Pisters, P. W., Komaki, R. et al. (2000) Gastroesophageal junction adenocarcinoma. Current Treatment Options in Oncology 1(5): 387-98	- Population not relevant to this review protocol
Tan, L., Feng, J., Zhao, Q. et al. (2017) Preoperative endoscopic titanium clip placement facilitates intraoperative localization of early-stage esophageal cancer or severe dysplasia. World journal of surgical oncology 15(1): 145	- Study does not contain an intervention relevant to this review protocol
Takeuchi, M.; Suda, K.; Hamamoto, Y.; Kato, M.; Mayanagi, S.; Yoshida, K.; Fukuda, K.; Nakamura, R.; Wada, N.; Kawakubo, H.; Takeuchi, H.; Yahagi, N.; Kitagawa, Y.; Technical feasibility and oncologic safety of diagnostic endoscopic resection for superficial esophageal cancer; Gastrointest Endosc; 2018; vol. 88 (no. 3); 456-465	Not specifically defined as a Barrett's population. Not predominantly oesophageal adenocarcinoma (<10%) – this study mainly comprised a sample with squamous cell carcinoma.
Thomas, T., Richards, C. J., de Caestecker, J. S. et al. (2005) High-grade dysplasia in Barrett's oesophagus: natural history and review of clinical practice. Aliment Pharmacol Ther 21(6): 747-55	- Population not relevant to this review protocol Only a subset of 9 in study had OAC. Of the 3 having endoscopy it was not reported what grade of OAC they were. One was having palliative endoscopic treatment suggesting it was beyond T! but no information was available for the other two studies.
Tian, J., Prasad, G. A., Lutzke, L. S. et al. (2011) Outcomes of T1b esophageal adenocarcinoma patients. Gastrointest Endosc 74(6): 1201-6	- Comparator in study does not match that specified in this review protocol Comparator group were those not having esophagectomies. Only 15/29 had endoscopic therapies only as treatment, 5 had endoscopy combined with CRT and 9 had only CRT or nothing. As results were not sub-grouped for endoscopy alone this study has had to be excluded.
Tokar, J. L.; Haluszka, O.; Weinberg, D. S. (2007) Endoscopic therapy of dysplasia and early-stage cancers of the esophagus. Seminars in Radiation Oncology 17(1): 10-21	- Review article but not a systematic review
Tomizawa, Y., Konda, V. J. A., Coronel, E. et al. (2018) Efficacy, Durability, and Safety of Complete Endoscopic Mucosal Resection of Barrett Esophagus: A Systematic Review and Meta-Analysis. Journal of Clinical Gastroenterology 52(3): 210-216	- Systematic review used as source of primary studies
van Lanschot, J. J.; Gonzalez Gonzalez, D.; Richel, D. J. (2001) Surgery, radiotherapy, and chemotherapy for esophageal carcinoma. Current Opinion in Gastroenterology 17(4): 400-5	- Review article but not a systematic review
Walker, S. J.; Selvasekar, C. R.; Birbeck, N. (2002) Mucosal ablation in Barrett's esophagus. Diseases of the Esophagus 15(1): 22-9	- Review article but not a systematic review
Wang, K. K., Tian, J. M., Gorospe, E. et al. (2012) Medical and endoscopic management of	- Population not relevant to this review protocol

Study	Code [Reason]
high-grade dysplasia in Barrett's esophagus. Diseases of the Esophagus 25(4): 349-55	
Wani, S.; Drahos, J.; Cook, M. B.; Rastogi, A.; Bansal, A.; Yen, R.; Sharma, P.; Das, A.; Comparison of endoscopic therapies and surgical resection in patients with early esophageal cancer: a population-based study; Gastrointest Endosc; 2014; vol. 79 (no. 2); 224-232.e1	Not specifically defined as a Barrett's population. Stage T0 for 33% in endo group.
Watson, T. J. (2008) Endoscopic resection for Barrett's esophagus with high-grade dysplasia or early esophageal adenocarcinoma. Seminars in Thoracic & Cardiovascular Surgery 20(4): 310-9	- Review article but not a systematic review
Wong Kee Song, L. M. and Wang, K. K. (2003) Optical detection and eradication of dysplastic Barrett's esophagus. Technology in Cancer Research and Treatment 2(4): 289-302	- Review article but not a systematic review
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
Yachimski, P., Nishioka, N. S., Richards, E. et al. (2008) Treatment of Barrett's esophagus with high-grade dysplasia or cancer: predictors of surgical versus endoscopic therapy. Clin Gastroenterol Hepatol 6(11): 1206-11	- Population not relevant to this review protocol Unclear how many were T1 stage as data for HGD/IMC were mixed. In endoscopy group 88% were HGD/IMC and 8% T1b but unclear how many were HGD. However clear that in oesophagectomy group 54% were T2 or greater, so there cannot have been more than 46% at T1 in that group. - Study design not relevant to this review protocol Outcomes not applicable to this review - the outcome was allocation to therapy.
Yang, Z. Q., Lu, H. X., Zhang, J. H. et al. (2016) Comparative study on long-term survival results between minimally invasive surgery and traditional resection for esophageal squamous cell carcinoma. European review for medical and pharmacological sciences 20(16): 3368-3372	- Comparator in study does not match that specified in this review protocol
Yeh, J. H., Huang, R. Y., Lee, C. T. et al. (2020) Long-term outcomes of endoscopic submucosal dissection and comparison to surgery for superficial esophageal squamous cancer: a systematic review and meta-analysis. Therapeutic Advances in Gastroenterology 13: 1756284820964316	- Systematic review used as source of primary studies
Yuan, B.; Liu, L.; Huang, H.; Li, D.; Shen, Y.; Wu, B.; Liu, J.; Yang, M.; Wang, Z.; Lu, H.; Liu, Y.; Liao, L.; Wang, F.; Comparison of the short-term and long-term outcomes of surgical treatment versus endoscopic treatment for early esophageal squamous cell neoplasia larger than 2 cm: a retrospective study; Surg Endosc; 2019; vol. 33 (no. 7); 2304-2312	Squamous cell carcinoma. Only 36.2% at T1 stage in endoscopic treatment group. 57.55 at T1 stage in oesophagectomy group.

Study	Code [Reason]
Zeng, Y.; Liang, W.; Liu, J.; He, J.; Endoscopic Treatment Versus Esophagectomy for Early-Stage Esophageal Cancer: a Population-Based Study Using Propensity Score Matching; J Gastrointest Surg; 2017; vol. 21 (no. 12); 1977-1983	Not specifically defined as a Barrett's population.
Zhang, Y.; Ding, H.; Chen, T.; Zhang, X.; Chen, W. F.; Li, Q.; Yao, L.; Korrapati, P.; Jin, X. J.; Zhang, Y. X.; Xu, M. D.; Zhou, P. H.; Outcomes of Endoscopic Submucosal Dissection vs Esophagectomy for T1 Esophageal Squamous Cell Carcinoma in a Real-World Cohort; Clin Gastroenterol Hepatol; 2019; vol. 17 (no. 1); 73-81.e3	Not specifically defined as a Barrett's population.; Not oesophageal adenocarcinoma – this study comprised a sample with squamous cell carcinoma
Zheng, H., Kang, N., Huang, Y. et al. (2021) Endoscopic resection versus esophagectomy for early esophageal cancer: A meta-analysis. Translational Cancer Research 10(6): 2653-2662	- Systematic review used as source of primary studies

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 I – Research recommendation

Oesophagectomy

What is the clinical and cost-effectiveness of endoscopic resection with or without adjuvant chemoradiotherapy and oesophagectomy for adults with T1b oesophageal adenocarcinoma?

Why this is important

Endoscopic resection (ER) has become increasingly used as treatment for early stage oesophageal cancers. The low risk of lymph node metastasis in T1a disease make ER the treatment of choice, as oesophagectomy is associated with substantial mortality and morbidity and may compromise long-term quality of life. However, the optimum treatment for patients with T1b disease is not understood. It is important that further research is carried out to determine whether ER (with or without oncological adjuncts such as chemo(radio)therapy) and oesophagectomy are oncologically equivalent and further the importance and impact on quality of life of each of the treatment modalities.

Rationale for research recommendation

Importance to 'patients' or the population	The optimal treatment for patients with T1b oesophageal adenocarcinoma is currently unknown. Oesophagectomy confers the advantage of removing the cancer and the adjacent Barrett's oesophagus, as well as the surrounding lymph nodes. However, it carries a higher risk of acute complications and long-term morbidity of surgery. Endoscopic resection preserves the anatomy of the oesophagus and its function but does not provide any treatment to lymph node metastasis. It can be combined with adjuvant oncological treatments, such as radiotherapy or chemo-radiation. Further, the cost implications of each treatment as well as quality of life is poorly understood based on the current evidence base.
Relevance to NICE guidance	Good quality research would provide evidence allowing NICE to make recommendations on the optimal treatment for people with T1b adenocarcinoma in terms of clinical outcomes including mortality, regression of Barrett's oesophagus, recurrence of neoplasia, quality of life and cost.
Relevance to the NHS	Establishing the clinical and cost-effectiveness of treatments may lead to cost saving if the need for surgery is reduced.
National priorities	N/A
Current evidence base	The use of endoscopic resection has been recognised as the standard of care for treatment for cT1a (intramucosal) oesophageal. However, in patients with T1b disease there is a known risk of lymph node metastases of up to 50% in

	cancers with deep invasion of the submucosa and/or lymph vascular involvement. Surgery potentially has a high chance of cure, by clearing the cancer and any undiagnosed, associated lymph node involvement as part of a lymphadenectomy, and also improves staging. However, surgery may impact on long-term quality of life. Current evidence for the optimum modality of treatment for T1b disease is limited to small institutional cohort studies.
Equality considerations	The recommendation is unlikely to impact on equality issues.