National Institute for Health and Care Excellence

Final

Barrett's oesophagus and stage 1 oesophageal adenocarcinoma

[L] Evidence review for non-surgical treatment for T1b oesophageal adenocarcinoma

NICE guideline NG231

Evidence review underpinning recommendation 1.7.1 in the NICE guideline

February 2023

Final

National Institute for Health and Care Excellence

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The recommendations in this guideline represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, professionals are expected to take this guideline fully into account, alongside the individual needs, preferences and values of their patients or service users. The recommendations in this guideline are not mandatory and the guideline does not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

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1.1 Review question

For adults with T1b oesophageal adenocarcinoma, what is the clinical and cost effectiveness of different non-surgical interventions?

1.1.1 Introduction

There remains uncertainty in the management of T1b oesophageal adenocarcinoma. There is a balance between potential under treatment with endoscopic treatment alone or over treatment in the role of surgery in other cases. In particular, the role of definitive chemo-radiotherapy treatment (i.e., the use of the modality as sole treatment) or adjuvant treatment (the use of these treatments in addition to primary endoscopic and surgical therapy) is less well defined. In patients with more advanced but localised adenocarcinoma of the oesophagus, the mainstay of curative treatment has been surgery where there remains a risk after endoscopic treatment/biopsy. Chemotherapy alone in this setting is used to reduce risk of recurrence where the risk of systemic disease is high but is not currently considered to be definitive therapy. Radiotherapy with/without concurrent chemotherapy may be associated with long-term disease control and survival in patients with localised oesophageal adenocarcinoma who are not suitable for surgery. This is not an uncommon scenario as we continue to endoscopically survey older patients with dysplastic Barrett's oesophagus.

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 T1b oesophageal adenocarcinoma Exclusion: Adults with Barrett's oesophagus with any other stages and related neoplasia
Interventions	• Oncological treatment O Radiotherapy O Chemotherapy O Combination therapy • Endoscopic surveillance • Oncological treatment + Endoscopic surveillance
Comparisons	• Oesophagectomy
Outcomes	• Mortality (all-cause mortality & disease specific mortality) • Health related quality of life (any validated score) • Progression of stage 1 adenocarcinoma to higher stages • Severe adverse events from oncological treatment. Such as: O Infection O Thrombosis O Myelosuppression O Cardiac or respiratory complications O Radiation stricture or fistula

	O GI disease effects (diarrhoea, nausea, vomiting) • Adverse events from surgery & endoscopic treatment Minimum follow up period from 1 year but to include longest follow up period
Study design	• RCT • If no RCT data is available, non-randomised studies will be considered if there is an active comparator within the study • Systematic review of RCTs Published NMAs and IPDs will be considered for inclusion.

1.1.3 Methods and process

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

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

1.1.4 Effectiveness evidence

1.1.4.1 Included studies

No relevant clinical studies comparing oncological treatment and/or endoscopic surveillance with oesophagectomy in people with T1b adenocarcinoma were identified.

See also the study selection flow chart in Appendix C.

1.1.4.2 Excluded studies

See the excluded studies list in Appendix E.

1.1.6 Summary of the effectiveness evidence

There was no clinical evidence found.

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 D.

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.

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	
FE21Z: Diagnostic endoscopic upper gastrointestinal tract procedure with biopsy	£554	
SB11Z: Deliver Simple Parenteral Chemotherapy at First Attendance	£284	
SB12Z: Deliver more Complex Parenteral Chemotherapy at First Attendance	£478	
SB13Z: Deliver Complex Chemotherapy, including Prolonged Infusional Treatment, at First Attendance	£406	
SB15Z: Deliver Subsequent Elements of a Chemotherapy Cycle	£341	
SC46Z: Preparation for Simple Radiotherapy with Imaging and Dosimetry, with Technical Support	£541	

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, severe adverse events from oncological treatment (such as infection, thrombosis, myelosuppression, cardiac or respiratory complications, radiation stricture or fistula, GI disease effects) and adverse events from surgery and endoscopic treatment. For purposes of decision making, all outcomes are considered equally important and were therefore rated as critical by the committee. No evidence was identified for any of the outcomes.

1.1.12.2 The quality of the evidence

No clinical evidence comparing oncological treatment and/or endoscopic surveillance with oesophagectomy in people with T1b adenocarcinoma was identified. Studies were commonly excluded due to the population not being people with T1b adenocarcinoma (such as people with squamous cell carcinoma) or due to comparing chemotherapy in combination with oesophagectomy with oesophagectomy alone, which was not the aim of the review.

1.1.12.3 Benefits and harms

Oesophagectomy is one of the main treatments for stage 1 adenocarcinoma, but clinical practice varies as endoscopic treatment is also widely used for specific types of stage 1 adenocarcinoma. Oesophagectomy is not an option for some people with stage 1 adenocarcinoma if they are not fit enough to undergo surgery and this review aimed to assess the effectiveness of alternative treatments such as oncological therapies, endoscopic surveillance, or combined interventions. Although there was no evidence on chemotherapy or radiotherapy for people with T1b adenocarcinoma, following endoscopic resection, the committee were aware of evidence of oncological treatment improving patient outcomes when combined with surgery for higher stages of oesophageal adenocarcinoma. The committee noted the research recommendation made for this population to determine the effectiveness of endoscopic resection with or without adjuvant chemoradiotherapy and oesophagectomy..

. The committee agreed that when people are not fit for oesophagectomy, surveillance or oncological treatments would be appropriate options, and this reflected current practice. They noted that chemotherapy alone is not a definitive treatment and therefore is not likely to be sufficient. Based on their experience, the committee agreed that radiotherapy alone or in combination with chemotherapy, is likely to be effective in people with T1b oesophageal adenocarcinoma who are not operable and should be considered for those who have a high risk of cancer progression based on staging by endoscopic resection (such as these with incomplete resection and/or lymph vascular invasion and/or infiltration in the submucosa deepen than 500 micron). The committee noted that there are cases where radiotherapy should be offered alone, rather than in combination with chemotherapy such as in people with co-morbidities who might be unfit for chemo-radiotherapy.

1.1.12.4 Cost effectiveness and resource use

There were no published clinical or economic evaluations found that compared any intervention to oesophagectomy. In the absence of suitable evidence, the committee instead relied on their clinical expertise. Unit costs for interventions were presented to the committee to aid their decision-making.

Although there was no evidence found, oesophagectomy is the established as the main treatment option in people with stage I T1b adenocarcinoma and high risk of recurrence (see recommendation 1.5.4). However, in people who are unfit for surgery, the committee considered oncological treatments (such as chemoradiotherapy), endoscopic treatment or endoscopic surveillance.

The committee noted that the short-term the cost of chemoradiotherapy is greater than endoscopic surveillance with or without endoscopic treatment, but that it could be less costly in the long-term if less frequent surveillance is required. They noted that the long-term implication of endoscopic surveillance without treatment would likely be a greater burden on patient quality of life and on the NHS resulting from advanced cancer care costs. Given that the risk of cancer remission would be lower with chemoradiotherapy than with endoscopic treatment, they thought that chemoradiotherapy is likely more cost-effective than endoscopic treatment and therefore recommended it be considered as a treatment option.

On consideration, the committee did not think there would be a significant increase in NHS resource use, given this recommendation reflects current practice.

1.1.13 Recommendations supported by this evidence review

This evidence review supports recommendation 1.7.1.

1.1.14 References

1. National Institute for Health and Care Excellence. Developing NICE guidelines: the manual [updated January 2022]. London. National Institute for Health and Care Excellence, 2014. Available from: http://www.nice.org.uk/article/PMG20/chapter/1%20Introduction%20and%20overview

Appendices

Appendix A – Review protocols

Review protocol for non-surgical treatment for T1b oesophageal adenocarcinoma

ID	Field	Content
0.	PROSPERO registration number	CRD42022306864
1.	Review title	Non-surgical treatment for T1b oesophageal adenocarcinoma
2.	Review question	For adults with T1b oesophageal adenocarcinoma, what is the clinical and cost effectiveness of different non-surgical interventions?
3.	Objective	To assess the efficacy and cost effectiveness of non-surgical options, in adults with T1b oesophageal adenocarcinoma who cannot have oesophagectomy
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 will 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	T1b oesophageal adenocarcinoma on endoscopic resection
6.	Population	Inclusion: Adults, 18 years and over, with Barrett's oesophagus and T1b oesophageal adenocarcinoma Exclusion: Adults with Barrett's oesophagus with any other stages and related neoplasia

7.	Intervention	• Oncological treatment
		  ○ Radiotherapy
		  ○ Chemotherapy
		  ○ Combination therapy
		• Endoscopic surveillance

		• Oncological treatment + Endoscopic surveillance
8.	Comparator	• Oesophagectomy
9.	Types of study to be included	• RCT • If no RCT data is available, non-randomised studies will be considered 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 may not be a viable treatment option. This review aims to assess the effectiveness of alternative treatment pathways that that would be more suitable for this population such as curative endoscopic procedures, surveillance or oncological treatments.

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 mortality)
		• Health related quality of life (any validated score)
		• Progression of stage 1 adenocarcinoma to higher stages
		• Severe adverse events from oncological treatment. Such as:
		  ○ Infection
		  ○ Thrombosis
		  ○ Myelosuppression

		○ Cardiac or respiratory complications ○ Radiation stricture or fistula ○ GI disease effects (diarrhoea, nausea, vomiting) • Adverse events from surgery & endoscopic treatment Minimum follow up period from 1 year but to include longest follow up period
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: If serious or very serious heterogeneity (I2>50%) is present, sub-grouping will occur according to the following strategies: T1b (SM1 vs SM2/3) Operable vs inoperable	
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 Mark Perry Melina Vasileiou
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).[1] **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.[1]

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 2: 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.	Adenocarcinoma/
18.	(stage* 1* or stage* I or stage* IA or stage* IB or stage* IC or earl* stage* or T1* or adenocarcinom*).ti,ab.
19.	or/17-18
20.	16 and 19
21.	letter/
22.	editorial/
23.	news/
24.	exp historical article/
25.	Anecdotes as Topic/
26.	comment/
27.	case report/
28.	(letter or comment*).ti.
29.	or/21-28
30.	randomized controlled trial/ or random*.ti,ab.
31.	29 not 30
32.	animals/ not humans/
33.	exp Animals, Laboratory/
34.	exp Animal Experimentation/
35.	exp Models, Animal/
36.	exp Rodentia/
37.	(rat or rats or mouse or mice or rodent*).ti.
38.	or/31-37
39.	20 not 38
40.	limit 39 to English language
41.	Radiotherapy/
42.	Radiation Oncology/
43.	Brachytherapy/
44.	Drug Therapy/
45.	*Drug Therapy, Combination/

46.	exp Fluorouracil/
47.	exp Leucovorin/
48.	exp Paclitaxel/
49.	Cisplatin/
50.	Bevacizumab/
51.	Methotrexate/
52.	Epirubicin/
53.	Irinotecan/
54.	Carboplatin/
55.	Oxaliplatin/
56.	Docetaxel/
57.	*Combined Modality Therapy/
58.	Chemoradiotherapy/
59.	(radiotherap* or chemoradio* or chemoradiation* or radiation* or chemotherap* or hyperthermochemoradiotherap* or brachytherap* or external beam*).ti,ab.
60.	((oncological* or nonsurg* or non surg* or combined or combination) adj2 (therap* or treatment* or approach* or strateg* or manag*)).ti,ab.
61.	(fluorouracil or capecitabine or xeloda or cisplatin or bevacizumab or methotrexate or epirubicin or pharmorubicin or irinotecan or leucovorin or folinic acid or campto or carboplatin or oxaliplatin or eloxatin or docetaxel or taxotere or paclitaxel or taxol or XELOX or FOLFOX or FOLFIRI or XELIRI or 5?FU or FLOT).ti,ab.
62.	*Endoscopy, Gastrointestinal/
63.	Capsule Endoscopy/
64.	Esophagoscopy/
65.	(oesophagoscop* or esophagoscop*).ti,ab.
66.	(videoendoscop* or endomicroscop* or spectroscop* or endocytoscop* or gastroscop*).ti,ab.
67.	(endoscop* adj2 (imag* or diagn* or identif* or surveillanc* or monitor* or observ* or detect*)).ti,ab.
68.	((capsule or transnasal or nasal) adj2 endoscop*).ti,ab.
69.	exp Optical Imaging/
70.	exp Acetic Acid/
71.	Molecular Imaging/
72.	((molecular or autofluorescen* or fluorescen*) adj3 (imag* or endoscop*)).ti,ab.
73.	((magnif* or high resolution or high definition) adj3 endoscop*).ti,ab.
74.	(chromatograph* or chromoendoscop* or chromoscop* or volumetric laser* or acetic acid or methylene blue or indigo carmine or narrow band or white light or blue laser or blue light or flexible spectral imaging colo?r enhancement or optical coherence tomography or optical enhancement).ti,ab.
75.	exp Artificial Intelligence/
76.	(artificial intelligence or (computer adj (assisted or aided)) or ((deep or machine) adj learning) or neural network*).ti,ab.
77.	(wide area transepithelial sampling or WATS3D or WATS 3D).ti,ab.
78.	(endoscop* adj2 brush*).ti,ab.
79.	(HRE or WLE or NBI or BLI or FICE or AFI or OCT or ETMI or AI or CAD).ti,ab.
80.	or/41-79
81.	40 and 80
82.	Meta-Analysis/
83.	Meta-Analysis as Topic/

84.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
85.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
86.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
87.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
88.	(search* adj4 literature).ab.
89.	(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.
90.	cochrane.jw.
91.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
92.	or/82-91
93.	randomized controlled trial.pt.
94.	controlled clinical trial.pt.
95.	randomi#ed.ab.
96.	placebo.ab.
97.	randomly.ab.
98.	clinical trials as topic.sh.
99.	trial.ti.
100.	or/93-99
101.	81 and (92 or 100)

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.	adenocarcinoma/
18.	esophageal adenocarcinoma/
19.	(stage* 1* or stage* I or stage* IA or stage* IB or stage* IC or earl* stage* or T1* or adenocarcinom*).ti,ab.
20.	or/17-19

21.	16 and 20
22.	letter.pt. or letter/
23.	note.pt.
24.	editorial.pt.
25.	case report/ or case study/
26.	(letter or comment*).ti.
27.	(conference abstract or conference paper).pt.
28.	or/22-27
29.	randomized controlled trial/ or random*.ti,ab.
30.	28 not 29
31.	animal/ not human/
32.	nonhuman/
33.	exp Animal Experiment/
34.	exp Experimental Animal/
35.	animal model/
36.	exp Rodent/
37.	(rat or rats or mouse or mice or rodent*).ti.
38.	or/30-37
39.	21 not 38
40.	limit 39 to English language
41.	exp cancer radiotherapy/
42.	radiotherapy/
43.	radiation oncology/
44.	brachytherapy/
45.	exp cancer chemotherapy/
46.	fluorouracil/
47.	folinic acid/
48.	paclitaxel/
49.	cisplatin/
50.	bevacizumab/
51.	methotrexate/
52.	epirubicin/
53.	irinotecan/
54.	carboplatin/
55.	oxaliplatin/
56.	capecitabine/
57.	capecitabine plus oxaliplatin/
58.	docetaxel/
59.	(radiotherap* or chemoradio* or chemoradiation* or radiation* or chemotherap* or hyperthermochemoradiotherap* or brachytherap* or external beam*).ti,ab.
60.	((oncological* or nonsurg* or non surg* or combined or combination) adj2 (therap* or treatment* or approach* or strateg* or manag*)).ti,ab.
61.	(fluorouracil or capecitabine or xeloda or cisplatin or bevacizumab or methotrexate or epirubicin or pharmorubicin or irinotecan or leucovorin or folinic acid or campto or carboplatin or oxaliplatin or eloxatin or docetaxel or taxotere or paclitaxel or taxol or XELOX or FOLFOX or FOLFIRI or XELIRI or 5?FU or FLOT).ti,ab.
62.	*gastrointestinal endoscopy/

63.	*endoscopy/
64.	endocytoscopy/
65.	high resolution endoscopy/
66.	magnifying endoscopy/
67.	narrow band imaging/
68.	videoendoscopy/
69.	white light endoscopy/
70.	capsule endoscopy/
71.	esophagoscopy/
72.	exp fluorescence imaging/
73.	exp acetic acid/
74.	molecular imaging/
75.	chromoendoscopy/
76.	exp artificial intelligence/
77.	(videoendoscop* or endomicroscop* or spectroscop* or endocytoscop* or oesophagoscop* or esophagoscop* or gastroscop* or chromatograph* or chromoendoscop* or chromoscop* or volumetric laser or acetic acid or methylene blue or indigo carmine or narrow band or white light or blue laser or blue light or flexible spectral imaging colo?r enhancement or optical coherence tomography or trimodal or tri modal or optical enhancement).ti,ab.
78.	(endoscop* adj2 (imag* or diagn* or identif* or surveillanc* or monitor* or observ* or detect*)).ti,ab.
79.	((capsule or transnasal or nasal) adj2 endoscop*).ti,ab.
80.	((molecular or autofluorescen* or fluorescen*) adj3 (imag* or endoscop*)).ti,ab.
81.	((magnif* or high resolution or high definition) adj3 endoscop*).ti,ab.
82.	(artificial intelligence or (computer adj (assisted or aided)) or ((deep or machine) adj learning) or neural network*).ti,ab.
83.	(wide area transepithelial sampling or WATS3D or WATS 3D).ti,ab.
84.	(endoscop* adj2 brush*).ti,ab.
85.	(HRE or WLE or NBI or BLI or FICE or AFI or OCT or ETMI or AI or CAD).ti,ab.
86.	or/41-85
87.	40 and 86
88.	random*.ti,ab.
89.	factorial*.ti,ab.
90.	(crossover* or cross over*).ti,ab.
91.	((doubl* or singl*) adj blind*).ti,ab.
92.	(assign* or allocat* or volunteer* or placebo*).ti,ab.
93.	crossover procedure/
94.	single blind procedure/
95.	randomized controlled trial/
96.	double blind procedure/
97.	or/88-96
98.	Systematic Review/
99.	Meta-Analysis/
100.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
101.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
102.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.

103.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
104.	(search* adj4 literature).ab.
105.	(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.
106.	cochrane.jw.
107.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
108.	or/98-107
109.	87 and (97 or 108)

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: [Adenocarcinoma] this term only
#18.	(stage* 1* or stage* I or stage* IA or stage* IB or stage* IC or earl* stage* or T1* or adenocarcinom*):ti,ab
#19.	#17 or #18
#20.	#16 and #19
#21.	MeSH descriptor: [Radiotherapy] this term only
#22.	MeSH descriptor: [Radiation Oncology] this term only
#23.	MeSH descriptor: [Brachytherapy] this term only
#24.	MeSH descriptor: [Drug Therapy] this term only
#25.	MeSH descriptor: [Drug Therapy, Combination] this term only
#26.	MeSH descriptor: [Fluorouracil] explode all trees
#27.	MeSH descriptor: [Leucovorin] explode all trees
#28.	MeSH descriptor: [Paclitaxel] explode all trees
#29.	MeSH descriptor: [Cisplatin] this term only
#30.	MeSH descriptor: [Bevacizumab] this term only
#31.	MeSH descriptor: [Methotrexate] this term only
#32.	MeSH descriptor: [Epirubicin] explode all trees

#33.	MeSH descriptor: [Irinotecan] this term only
#34.	MeSH descriptor: [Carboplatin] this term only
#35.	MeSH descriptor: [Oxaliplatin] this term only
#36.	MeSH descriptor: [Docetaxel] this term only
#37.	MeSH descriptor: [Combined Modality Therapy] this term only
#38.	MeSH descriptor: [Chemoradiotherapy] this term only
#39.	(radiotherap* or chemoradio* or chemoradiation* or radiation* or chemotherap* or hyperthermochemoradiotherap* or brachytherap* or external beam*):ti,ab
#40.	((oncological* or nonsurg* or non surg* or combined or combination) near/2 (therap* or treatment* or approach* or strateg* or manag*)):ti,ab
#41.	(fluorouracil or capecitabine or xeloda or cisplatin or bevacizumab or methotrexate or epirubicin or pharmorubicin or irinotecan or leucovorin or folinic acid or campto or carboplatin or oxaliplatin or eloxatin or docetaxel or taxotere or paclitaxel or taxol or XELOX or FOLFOX or FOLFIRI or XELIRI or 5?FU or FLOT):ti,ab
#42.	MeSH descriptor: [Endoscopy, Gastrointestinal] this term only
#43.	MeSH descriptor: [Capsule Endoscopy] this term only
#44.	MeSH descriptor: [Esophagoscopy] this term only
#45.	(oesophagoscop* or esophagoscop*):ti,ab
#46.	(videoendoscop* or endomicroscop* or spectroscop* or endocytoscop* or gastroscop*):ti,ab
#47.	(endoscop* near/2 (imag* or diagn* or identif* or surveillanc* or monitor* or observ* or detect*)):ti,ab
#48.	((capsule or transnasal or nasal) near/2 endoscop*):ti,ab
#49.	MeSH descriptor: [Optical Imaging] explode all trees
#50.	MeSH descriptor: [Acetic Acid] explode all trees
#51.	MeSH descriptor: [Molecular Imaging] this term only
#52.	((molecular or autofluorescen* or fluorescen*) near/3 (imag* or endoscop*)):ti,ab
#53.	((magnif* or high resolution or high definition) near/3 endoscop*):ti,ab
#54.	(chromatograph* or chromoendoscop* or chromoscop* or volumetric laser* or acetic acid or methylene blue or indigo carmine or narrow band or white light or blue laser or blue light or flexible spectral imaging colo?r enhancement or optical coherence tomography or optical enhancement):ti,ab
#55.	MeSH descriptor: [Artificial Intelligence] explode all trees
#56.	(artificial intelligence or (computer next (assisted or aided)) or ((deep or machine) next learning) or neural network*):ti,ab
#57.	(wide area transepithelial sampling or WATS3D or WATS 3D):ti,ab
#58.	(endoscop* near/2 brush*):ti,ab
#59.	(HRE or WLE or NBI or BLI or FICE or AFI or OCT or ETMI or AI or CAD):ti,ab
#60.	(or #21-#59)
#61.	#20 and #60
#62.	conference:pt or (clinicaltrials or trialsearch):so
#63.	#61 not #62

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:(radiotherap* OR chemoradio* OR chemoradiation* OR radiation* OR chemotherap* OR hyperthermochemoradiotherap* OR brachytherap* OR "external beam*" OR "combination therap*" OR "oncological* therap*" OR "nonsurg* therap*" OR "non surg* therap*" OR "non-surg* therap*" OR "oncological* treatment*" OR "nonsurg* treatment*" OR "non surg* treatment*" OR "non-surg* treatment*" OR "nonsurg* approach*" OR "non surg* approach*" OR "non-surg* approach*" OR fluorouracil OR capecitabine OR xeloda OR cisplatin OR bevacizumab OR methotrexate OR epirubicin OR pharmorubicin OR irinotecan OR leucovorin OR "folinic acid" OR campto OR carboplatin OR oxaliplatin OR eloxatin OR docetaxel OR taxotere OR paclitaxel OR taxol OR XELOX OR FOLFOX OR FOLFIRI OR XELIRI OR 5FU OR "5-FU" OR FLOT OR "endoscop* imag*" OR "endoscop* diagn*" OR "endoscop* identif*" OR "endoscop* surveillanc*" OR "surveillanc* endoscop*" OR "endoscop* monitor*" OR "endoscop* observ*" OR "endoscop* detect*" OR "capsule endoscop*" OR "transnasal endoscop*" OR "nasal endoscop*" OR "magnif* endoscop*" OR "high resolution endoscop*" OR "high definition endoscop*" OR videoendoscop* OR endomicroscop* OR spectroscop* OR endocytoscop* OR oesophagoscop* OR esophagoscop* OR chromatograph* OR chromoendoscop* OR chromoscop* OR "volumetric laser" OR "acetic acid" OR "methylene blue" OR "indigo carmine" OR "narrow band" OR "white light" OR "blue laser" OR "blue light" OR "flexible spectral imaging" OR autofluorescen* OR fluorescen* OR "optical coherence tomography" OR trimodal OR "tri modal" OR "optical enhancement" OR "artificial intelligence" OR "computer assisted" "computer aided" OR "deep learning" OR "machine learning" OR "neural network" OR "wide area transepithelial sampling" OR WATS3D OR "WATS 3D") OR abstract:(radiotherap* OR chemoradio* OR chemoradiation* OR radiation* OR chemotherap* OR hyperthermochemoradiotherap* OR brachytherap* OR "external beam*" OR "combination therap*" OR "oncological* therap*" OR "nonsurg* therap*" OR "non surg* therap*" OR "non-surg* therap*" OR "oncological* treatment*" OR "nonsurg* treatment*" OR "non surg* treatment*" OR "non-surg* treatment*" OR "nonsurg* approach*" OR "non surg* approach*" OR "non-surg* approach*" OR fluorouracil OR capecitabine OR xeloda OR cisplatin OR bevacizumab OR methotrexate OR epirubicin OR pharmorubicin OR irinotecan OR leucovorin OR "folinic acid" OR campto OR carboplatin OR oxaliplatin OR eloxatin OR docetaxel OR taxotere OR paclitaxel OR taxol OR XELOX OR FOLFOX OR FOLFIRI OR XELIRI OR 5FU OR "5-FU" OR FLOT OR "endoscop* imag*" OR "endoscop* diagn*" OR "endoscop* identif*" OR "endoscop* surveillanc*" OR "surveillanc* endoscop*" OR "endoscop* monitor*" OR "endoscop* observ*" OR "endoscop* detect*" OR "capsule endoscop*" OR "transnasal endoscop*" OR "nasal endoscop*" OR "magnif* endoscop*" OR "high resolution endoscop*" OR "high definition endoscop*" OR videoendoscop* OR endomicroscop* OR spectroscop* OR endocytoscop* OR oesophagoscop* OR esophagoscop* OR chromatograph* OR chromoendoscop* OR chromoscop* OR "volumetric laser" OR "acetic acid" OR "methylene blue" OR "indigo carmine" OR "narrow band" OR "white light" OR "blue laser" OR "blue light" OR "flexible spectral imaging" OR autofluorescen* OR fluorescen* OR "optical coherence tomography" OR trimodal OR "tri modal" OR "optical enhancement" OR "artificial intelligence" OR "computer assisted" "computer aided" OR "deep learning" OR "machine learning" OR "neural network" OR "wide area transepithelial sampling" OR WATS3D OR "WATS 3D")

B.2 Health Economics literature search strategy

Health economic evidence was identified by conducting searches using terms for a broad Barrett's Oesophagus population. The following databases were searched: NHS Economic Evaluation Database (NHS EED - this ceased to be updated after 31st March 2015), Health Technology Assessment database (HTA - this ceased to be updated from 31st March 2018) and The International Network of Agencies for Health Technology Assessment (INAHTA).

Searches for recent evidence were run on Medline and Embase from 2014 onwards for health economics, and all years for quality-of-life studies.

Table 3: Database parameters, filters and limits applied

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

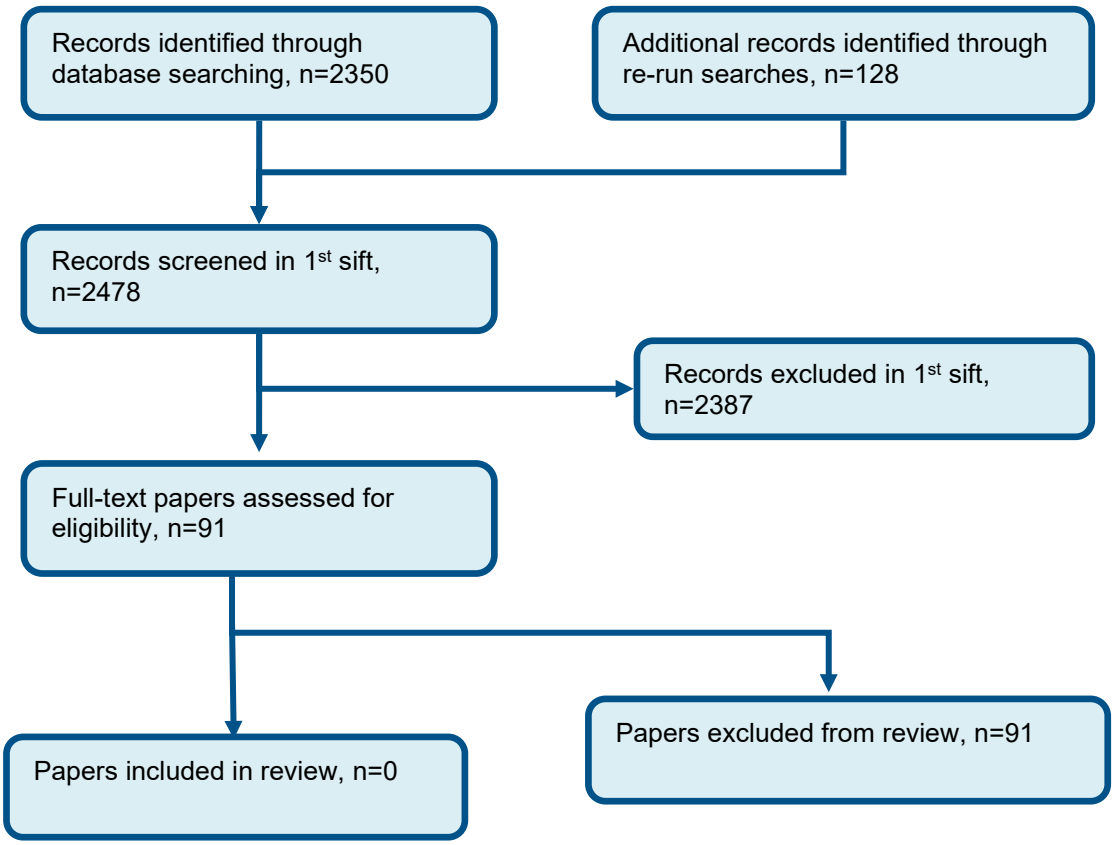
#1.	MeSH DESCRIPTOR Barrett Esophagus EXPLODE ALL TREES
#2.	(barrett*)
#3.	(speciali*) AND (epithel* or oesophag* or esophag* or mucos*)
#4.	(column*) AND (epithel* or oesophag* or esophag* or mucos* or lined or lining or metaplas*)
#5.	#1 OR #2 OR #3 OR #4
#6.	MeSH DESCRIPTOR Precancerous Conditions 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

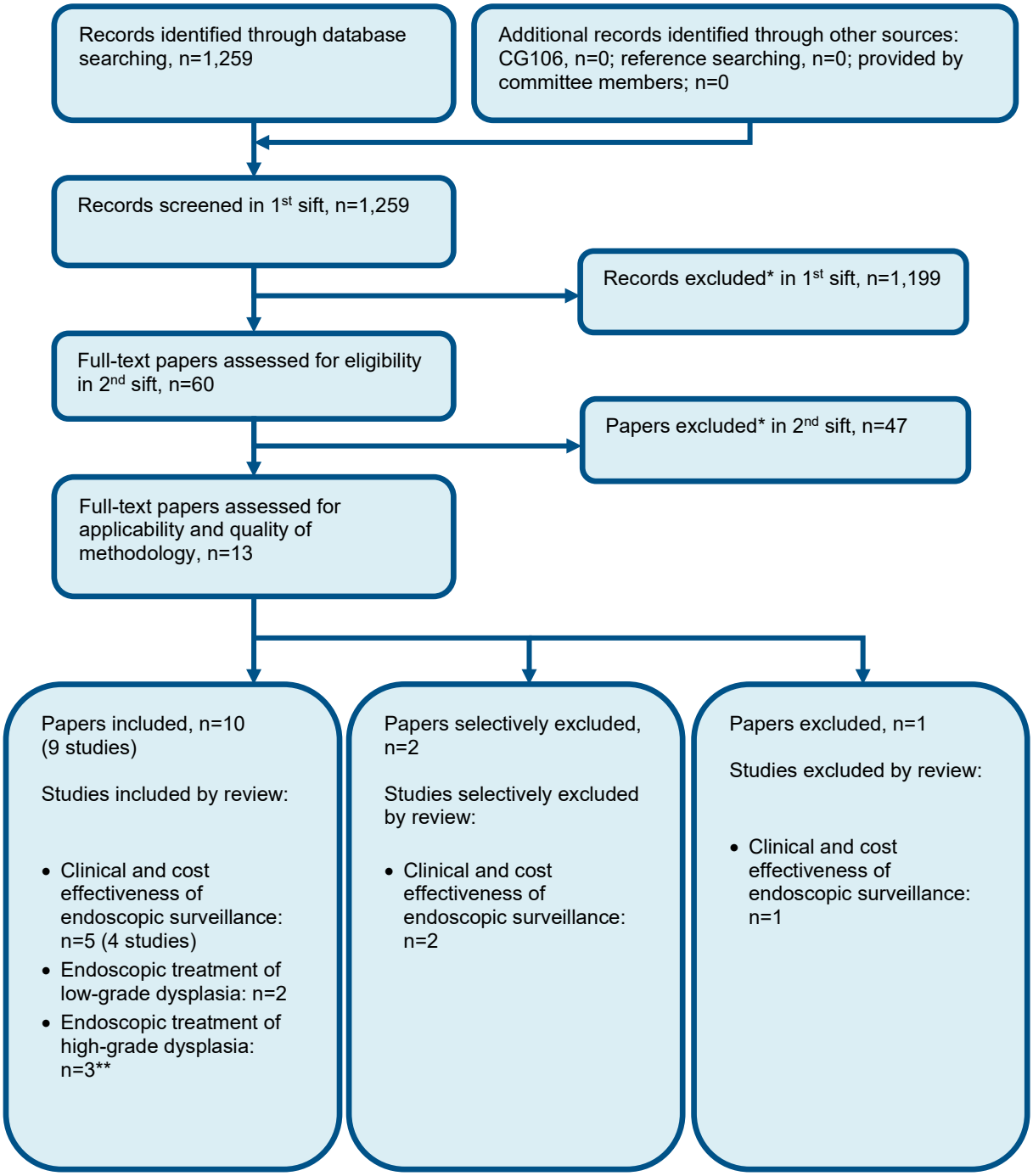
1.	("Barrett Esophagus"[mh]) OR (Barrett*) OR (Esophageal Neoplasms)[mh]

Appendix C – Effectiveness evidence study selection

Figure 1: Flow chart of clinical study selection for the review of non-surgical interventions for stage 1 adenocarcinoma



Appendix D – 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 E – Excluded studies

Clinical studies

Table 4: Studies excluded from the clinical review

Study	Exclusion reason
(2017) The NeoRes trial: questioning the benefit of radiation therapy as part of neoadjuvant therapy for esophageal adenocarcinoma. Journal of thoracic disease 9(10): 3465-3468	- Review article but not a systematic review
Abrams, J. A., Buono, D. L., Strauss, J. et al. (2009) Esophagectomy compared with chemoradiation for early stage esophageal cancer in the elderly. Cancer 115(21): 4924-33	- Population not relevant to this review protocol *Stage 1 and 2, and not restricted to type 1b; no stratification of analysis in paper.*
Ajani, J. A. (1998) Current status of new drugs and multidisciplinary approaches in patients with carcinoma of the esophagus. Chest 113(1suppl): 112S-119S	- Review article but not a systematic review
Anker, C. J., Dragovic, J., Herman, J. M. et al. (2021) Executive Summary of the American Radium Society Appropriate Use Criteria for Operable Esophageal and Gastroesophageal Junction Adenocarcinoma: Systematic Review and Guidelines. International journal of radiation oncology, biology, physics 109(1): 186-200	- Systematic review used as source of primary studies
Ardalan, B., Spector, S. A., Livingstone, A. S. et al. (2007) Neoadjuvant, surgery and adjuvant chemotherapy without radiation for esophageal cancer. Japanese journal of clinical oncology 37(8): 590-6	- Population not relevant to this review protocol *Stage T3N1 population; therefore not in line with protocol population*
Barnett, S. A. and Rizk, N. P. (2010) Randomized Clinical Trials in Esophageal Carcinoma. Surgical Oncology Clinics of North America 19(1): 59-80	- Systematic review used as source of primary studies
Bass, G. A., Furlong, H., O'Sullivan, K. E. et al. (2014) Chemoradiotherapy, with adjuvant surgery for local control, confers a durable survival advantage in adenocarcinoma and squamous cell carcinoma of the oesophagus. European journal of cancer 50(6): 1065-75	- Study does not contain an intervention relevant to this review protocol *Interventions evaluated were chemoradiotherapy and surgery versus surgery alone rather than chemoradiotherapy alone versus surgery alone, as per protocol*

Study	Exclusion reason
Bennett, C, Green, S, DeCaestecker, J et al. (2020) Surgery versus radical endotherapies for early cancer and high-grade dysplasia in Barrett's oesophagus. Cochrane Database of Systematic Reviews	- Comparator in study does not match that specified in this review protocol - 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 - Population not relevant to this review protocol *None of the included studies were adenocarcinoma T1b*
Bosset, J. F., Lorchel, F., Mantion, G. et al. (2005) Radiation and chemoradiation therapy for esophageal adenocarcinoma. Journal of Surgical Oncology 92(3): 239-45	- More recent systematic review included that covers the same topic
Buderi, S. I.; Shackcloth, M.; Page, R. D. (2017) Does neoadjuvant chemoradiotherapy increase survival in patients with resectable oesophageal cancer?. Interactive Cardiovascular & Thoracic Surgery 24(1): 115-120	- Review article but not a systematic review - Study does not contain an intervention relevant to this review protocol *Interventions were chemoradiotherapy plus surgery versus surgery alone, not chemoradiotherapy alone versus surgery alone, as per protocol.*
Carstens, H., Albertsson, M., Friesland, S. et al. (2007) A randomized trial of chemoradiotherapy versus surgery alone in patients with resectable esophageal cancer. Journal of Clinical Oncology 25(18suppl): 4530-4530	- Conference abstract - Population not relevant to this review protocol *stage of cancer unclear*
Coia, L. R. (1994) Chemoradiation: A Superior Alternative for the Primary Management of Esophageal Carcinoma. Seminars in radiation oncology 4(3): 157-164	- Review article but not a systematic review
Collard, J. M. and Giuli, R. (1999) Surgical and multimodal approaches to cancer of the oesophagus: state of the art. Acta Gastro-Enterologica Belgica 62(3): 272-82	- Review article but not a systematic review

Study	Exclusion reason
D'Amico, T. A. (2007) Outcomes after surgery for esophageal cancer. Gastrointestinal cancer research 1(5): 188-96	- Review article but not a systematic review
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	- Population not relevant to this review protocol *High grade dysplasia, not T1b adenocarcinoma*
Delaunoit, T. (2012) Management of esophageal superficial tumors: non take away approaches. Acta Gastroenterologica Belgica 75(1): 5-8	- Study does not contain an intervention relevant to this review protocol *Evaluates endoscopic treatments*
Delcambre, C., Jacob, J. H., Pottier, D. et al. (2001) Localized squamous-cell cancer of the esophagus: retrospective analysis of three treatment schedules. Radiotherapy & Oncology 59(2): 195-201	- Population not relevant to this review protocol *Squamous cell cancer, not adenocarcinoma; Mixed T1a and T1b with no stratification in analysis*
Duan, X. F.; Tang, P.; Yu, Z. T. (2014) Neoadjuvant chemoradiotherapy for resectable esophageal cancer: an in-depth study of randomized controlled trials and literature review. Cancer Biology & Medicine 11(3): 191-201	- Systematic review used as source of primary studies - Study does not contain an intervention relevant to this review protocol *Interventions were chemoradiotherapy plus surgery versus surgery alone, not chemoradiotherapy alone versus surgery alone, as per protocol.*
Duan, X. and Yu, Z. (2017) [Neoadjuvant chemoradiotherapy combined with operation vs. operation alone for resectable esophageal cancer: Meta-analysis on randomized controlled trials]. Zhonghua wei chang wai ke za zhi = Chinese journal of gastrointestinal surgery 20(7): 809-815	- Study not reported in English
Feng, H., Zhao, Y., Jing, T. et al. (2018) Traditional and cumulative meta-analysis: Chemoradiotherapy followed by surgery versus surgery alone for resectable esophageal carcinoma. Molecular & Clinical Oncology 8(2): 342-351	- Study does not contain an intervention relevant to this review protocol *Interventions were chemoradiotherapy plus surgery versus surgery alone, not chemoradiotherapy alone versus surgery alone, as per protocol.*

Study	Exclusion reason
Fietkau, R. (1999) No improvement of prognosis by neoadjuvant chemotherapy alone in operable esophageal carcinoma. Strahlentherapie und Onkologie 175(5): 251-252	- Study not reported in English *In German*
Fiteni, F., Paget-Bailly, S., Messager, M. et al. (2016) Docetaxel, Cisplatin, and 5-Fluorouracil as perioperative chemotherapy compared with surgery alone for resectable gastroesophageal adenocarcinoma. Cancer medicine 5(11): 3085-3093	- Study does not contain an intervention relevant to this review protocol *Interventions were chemoradiotherapy plus surgery versus surgery alone, not chemoradiotherapy alone versus surgery alone, as per protocol.*
Foo, M. L. (1999) Combined modality treatment of esophagus cancer. Cancer Research Therapy and Control 9(3-4): 239-248	- More recent systematic review included that covers the same topic
Gwynne, S., Wijnhoven, B. P., Hulshof, M. et al. (2014) Role of chemoradiotherapy in oesophageal cancer -- adjuvant and neoadjuvant therapy. Clinical Oncology (Royal College of Radiologists) 26(9): 522-32	- Systematic review used as source of primary studies - Study does not contain an intervention relevant to this review protocol *Interventions were chemoradiotherapy plus surgery versus surgery alone, not chemoradiotherapy alone versus surgery alone, as per protocol.*
Hainsworth, J. D., Meluch, A. A., Gray, J. R. et al. (2007) Concurrent chemoradiation followed by esophageal resection vs chemoradiation alone for localized esophageal cancer. Community oncology 4(7): 431-439	- Study does not contain an intervention relevant to this review protocol *Interventions evaluated were chemoradiotherapy and subsequent surgery versus chemoradiation alone rather than surgery alone versus chemoradiotherapy alone, as per protocol* - Population not relevant to this review protocol *Stage not restricted to 1b*
Halliday, B. P., Skipworth, R. J., Wall, L. et al. (2007) Neoadjuvant chemotherapy for carcinoma of the oesophagus and oesophago-gastric junction: a six-year experience. International Seminars in Surgical Oncology 4: 24	- Population not relevant to this review protocol *Stage T3; included 78/167 people with squamous cell carcinoma* - Study does not contain an intervention relevant to this review protocol

Study	Exclusion reason
	Compared neoadjuvant chemotherapy to non-neoadjuvant chemotherapy
Hancock, S. L. (1993) Radiation or surgery for carcinoma of the esophagus: the role of organ-conserving therapy. Frontiers of Radiation Therapy & Oncology 27: 103-17	- More recent systematic review included that covers the same topic
Hejna, M. and Raderer, M. (2005) Neoadjuvant therapy for resectable esophageal cancer. Zeitschrift fur gastroenterologie 43(10): 1141-1147	- Study not reported in English
Hennessy, T. W. T. (1999) Chemoradiotherapy as treatment of choice in oesophageal cancer. European journal of cancer 35(suppl4): 301	- Conference abstract
Iizuka, T. (1995) Multimodal treatment of oesophageal carcinoma. Annales Chirurgiae et Gynaecologiae 84(2): 216-21	- More recent systematic review included that covers the same topic
Jin, H. L., Zhu, H., Ling, T. S. et al. (2009) Neoadjuvant chemoradiotherapy for resectable esophageal carcinoma: a meta-analysis. World journal of gastroenterology 15(47): 5983-91	- Systematic review used as source of primary studies - Study does not contain an intervention relevant to this review protocol *Interventions were chemoradiotherapy plus surgery versus surgery alone, not chemoradiotherapy alone versus surgery alone, as per protocol.*
Klevebro, F.; Ekman, S.; Nilsson, M. (2017) Current trends in multimodality treatment of esophageal and gastroesophageal junction cancer - Review article. Surgical Oncology 26(3): 290-295	- Review article but not a systematic review
Klevebro, F., Lindblad, M., Johansson, J. et al. (2016) Outcome of neoadjuvant therapies for cancer of the oesophagus or gastro-oesophageal junction based on a national data registry. British journal of surgery 103(13): 1864-1873	- Population not relevant to this review protocol *T1-T4 included; vast majority were T2 and T3, and therefore not fitting the protocol population of T1b*
Ku, G. Y. and Ilson, D. H. (2012) Adjuvant therapy in esophagogastric adenocarcinoma:	- Systematic review used as source of primary studies

Study	Exclusion reason
controversies and consensus. Gastrointestinal cancer research 5(3): 85-92	
Law, S. and Wong, J. (2005) Current management of esophageal cancer. Journal of gastrointestinal surgery 9(2): 291-310	- Review article but not a systematic review
Leonard, G. D.; McCaffrey, J. A.; Maher, M. (2003) Optimal therapy for oesophageal cancer. Cancer Treatment Reviews 29(4): 275-82	- Review article but not a systematic review
Lordick, F., Holscher, A. H., Haustermans, K. et al. (2013) Multimodal treatment of esophageal cancer. Langenbecks Archives of Surgery 398(2): 177-87	- Review article but not a systematic review
Lu, D.J., David, J., Anderson, E. et al. (2019) Alternative Strategies to Esophagectomy in the Management of T1b Esophageal Adenocarcinoma. International Journal of Radiation Oncology, Biology, Physics 105(1): e191	- Conference abstract
Lv, J., Cao, X. F., Zhu, B. et al. (2009) Effect of neoadjuvant chemoradiotherapy on prognosis and surgery for esophageal carcinoma. World journal of gastroenterology : WJG 15(39): 4962-8	- Review article but not a systematic review
Ma, H. F., Lv, G. X., Cai, Z. F. et al. (2018) Comparison of the prognosis of neoadjuvant chemoradiotherapy treatment with surgery alone in esophageal carcinoma: A meta-analysis. Oncotargets and therapy 11: 3441-3447	- Study does not contain an intervention relevant to this review protocol *Interventions were chemoradiotherapy plus surgery versus surgery alone, not chemoradiotherapy alone versus surgery alone, as per protocol.*
Malthaner, R. A., Wong, R. K., Rumble, R. B. et al. (2004) Neoadjuvant or adjuvant therapy for resectable esophageal cancer: a systematic review and meta-analysis. BMC medicine 2(nopagination): 35	- Systematic review used as source of primary studies - Study does not contain an intervention relevant to this review protocol *Interventions were chemoradiotherapy plus surgery versus surgery alone, not chemoradiotherapy alone versus surgery alone, as per protocol.*

Study	Exclusion reason
Mariette, C., Piessen, G., Briez, N. et al. (2011) Oesophagogastric junction adenocarcinoma: which therapeutic approach?. Lancet oncology 12(3): 296-305	- Systematic review used as source of primary studies
Max Almond, L. and Barr, H. (2014) Management controversies in Barrett's oesophagus. Journal of gastroenterology 49(2): 195-205	- Review article but not a systematic review
May, K. S.; Yang, G. Y.; Khushalani, N. I. (2011) The role of radiation in the perioperative treatment of esophagogastric cancer. Current Treatment Options in Oncology 12(1): 61-71	- Review article but not a systematic review
Mei, L. X., Mo, J. X., Chen, Y. et al. (2021) Esophagectomy versus definitive chemoradiotherapy as initial treatment for clinical stage I esophageal cancer: a systematic review and meta-analysis. Diseases of the esophagus 27: 27	- 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	- Study does not contain an intervention relevant to this review protocol *Endoscopic treatments*
Minsky, B. D. (1999) Carcinoma of the esophagus. Part 1: Primary therapy. Oncology (Williston Park) 13(9): 1225-32, 1235	- More recent systematic review included that covers the same topic
Miyata, H., Yamasaki, M., Kurokawa, Y. et al. (2011) Multimodal treatment for resectable esophageal cancer. General Thoracic & Cardiovascular Surgery 59(7): 461-6	- Review article but not a systematic review - Study does not contain an intervention relevant to this review protocol *Interventions were chemoradiotherapy plus surgery versus surgery alone, not chemoradiotherapy alone versus surgery alone, as per protocol.*
Mooney, M. M. (2005) Neoadjuvant and adjuvant chemotherapy for esophageal adenocarcinoma. Journal of Surgical Oncology 92(3): 230-8	- Full text paper not available
Morgan, M. A., Lewis, W. G., Casbard, A. et al. (2009) Stage-for-stage comparison of definitive	- Population not relevant to this review protocol

Study	Exclusion reason
chemoradiotherapy, surgery alone and neoadjuvant chemotherapy for oesophageal carcinoma. British journal of surgery 96(11): 1300-7	*Less than 50% with adenocarcinoma in definitive chemoradiation group; Stratified analysis for separate stages 1 to 4, but not one for T1b (also unclear if these are T stages - they may be radiological stages)*
Murakami, M., Kuroda, Y., Nakajima, T. et al. (1999) Comparison between chemoradiation protocol intended for organ preservation and conventional surgery for clinical T1-T2 esophageal carcinoma. International journal of radiation oncology, biology, physics 45(2): 277-84	- Population not relevant to this review protocol *Squamous cell carcinoma; Stages I-II: some stratification of results into stages I and II, but no report of results for stage Ib.*
Nabeya, Y. and Ochiai, T. (2003) [Chemotherapy for esophageal cancer]. Gan to kagaku ryoho. Cancer & chemotherapy 30(12): 1873-1880	- Study not reported in English
Narsule, C. K.; Montgomery, M. M.; Fernando, H. C. (2012) Evidence-Based Review of the Management of Cancers of the Gastroesophageal Junction. Thoracic Surgery Clinics 22(1): 109-121	- Systematic review used as source of primary studies
Naughton, P., Tormey, S., Kelly, A. et al. (2003) Prospective randomised trial comparing multimodal therapy with surgery alone for oesophageal adenocarcinoma: a long-term follow-up. European journal of cancer 1(5): 72	- Conference abstract
Ng, T., Dipetrillo, T., Purviance, J. et al. (2006) Multimodality treatment of esophageal cancer: A review of the current status and future directions. Current Oncology Reports 8(3): 174-182	- Review article but not a systematic review
Noordman, B. J., Wijnhoven, B. P. L., Lagarde, S. M. et al. (2017) Active surveillance in clinically complete responders after neoadjuvant chemoradiotherapy for esophageal or junctional cancer. Diseases of the esophagus 30(12)	- Review article but not a systematic review
Oliver, S. E.; Robertson, C. S.; Logan, R. F. (1992) Oesophageal cancer: a population-based study of survival after treatment. British journal of surgery 79(12): 1321-5	- Population not relevant to this review protocol *Stage of cancer not reported*
Pasquali, S., Yim, G., Vohra, R. S. et al. (2017) Survival After Neoadjuvant and Adjuvant	- Systematic review used as source of primary studies

Study	Exclusion reason
Treatments Compared to Surgery Alone for Resectable Esophageal Carcinoma: A Network Meta-analysis. Annals of surgery 265(3): 481-491	- Study does not contain an intervention relevant to this review protocol *Interventions were chemoradiotherapy plus surgery versus surgery alone, not chemoradiotherapy alone versus surgery alone, as per protocol.*
Piessen G, Messager M, Mirabel X et al. (2013) Is there a role for surgery for patients with a complete clinical response after chemoradiation for esophageal cancer? An intention-to-treat case-control study. Annals of surgery 258(5): 793	- Study does not contain an intervention relevant to this review protocol *CRT + surveillance versus CRT plus surgery - this is not in line with the protocol*
Piraino, A., Vita, M. L., Tessitore, A. et al. (2006) Neoadjuvant therapy for esophageal cancer: Surgical considerations. Rays - International Journal of Radiological Sciences 31(1): 37-45	- More recent systematic review included that covers the same topic
Pöttgen, C. and Stuschke, M. (2012) Radiotherapy versus surgery within multimodality protocols for esophageal cancer--a meta-analysis of the randomized trials. Cancer Treatment Reviews 38(6): 599-604	- Systematic review used as source of primary studies
Raja, S. G.; Salhiyyah, K.; Nagarajan, K. (2007) Does neoadjuvant chemotherapy improve survival in patients with resectable thoracic oesophageal cancer?. Interactive Cardiovascular & Thoracic Surgery 6(5): 661-4	- Systematic review used as source of primary studies - Study does not contain an intervention relevant to this review protocol *Interventions were chemoradiotherapy plus surgery versus surgery alone, not chemoradiotherapy alone versus surgery alone, as per protocol.*
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	- Systematic review used as source of primary studies
Reid, T. D., Davies, I. L., Mason, J. et al. (2012) Stage for stage comparison of recurrence patterns after definitive chemoradiotherapy or surgery for oesophageal carcinoma. Clinical	- Population not relevant to this review protocol *Majority at stage T2 to T4, so not in line with protocol.*

Study	Exclusion reason
Oncology (Royal College of Radiologists) 24(9): 617-24	
Rice, T. W., Lu, M., Ishwaran, H. et al. (2019) Precision Surgical Therapy for Adenocarcinoma of the Esophagus and Esophagogastric Junction. Journal of thoracic oncology	- Study does not contain an intervention relevant to this review protocol *Contains oesophagectomy, but not non-surgical therapy alone.*
Ronellenfitsch, U., Jensen, K., Seide, S. et al. (2019) Disease-free survival as a surrogate for overall survival in neoadjuvant trials of gastroesophageal adenocarcinoma: Pooled analysis of individual patient data from randomised controlled trials. European journal of cancer 123: 101-111	- Systematic review used as source of primary studies - Study does not contain an intervention relevant to this review protocol *Interventions were chemoradiotherapy plus surgery versus surgery alone, not chemoradiotherapy alone versus surgery alone, as per protocol.*
Ronellenfitsch, U., Schwarzbach, M., Hofheinz, R. et al. (2013) Preoperative chemo(radio)therapy versus primary surgery for gastroesophageal adenocarcinoma: systematic review with meta-analysis combining individual patient and aggregate data. European journal of cancer 49(15): 3149-58	- Review article but not a systematic review - Study does not contain an intervention relevant to this review protocol *Interventions evaluated were chemoradiotherapy and surgery versus surgery alone rather than chemoradiotherapy alone versus surgery alone, as per protocol*
Ronellenfitsch, U., Schwarzbach, M., Hofheinz, R. et al. (2017) Predictors of overall and recurrence-free survival after neoadjuvant chemotherapy for gastroesophageal adenocarcinoma: Pooled analysis of individual patient data (IPD) from randomized controlled trials (RCTs). European journal of surgical oncology 43(8): 1550-1558	- Systematic review used as source of primary studies - Study does not contain an intervention relevant to this review protocol *Interventions were chemoradiotherapy plus surgery versus surgery alone, not chemoradiotherapy alone versus surgery alone, as per protocol.*
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 - Study does not contain an intervention relevant to this review protocol *Evaluates endoscopic therapy*

Study	Exclusion reason
Sjoquist, K. M., Burmeister, B. H., Smithers, B. M. et al. (2011) Survival after neoadjuvant chemotherapy or chemoradiotherapy for resectable oesophageal carcinoma: an updated meta-analysis. Lancet oncology 12(7): 681-92	- Systematic review used as source of primary studies - Study does not contain an intervention relevant to this review protocol *Interventions were chemoradiotherapy plus surgery versus surgery alone, not chemoradiotherapy alone versus surgery alone, as per protocol.*
Stahl, M. (2004) Adjuvant chemoradiotherapy in gastric cancer and carcinoma of the oesophago-gastric junction. Onkologie 27(1): 33-6	- Population not relevant to this review protocol *Gastric cancer and carcinoma of the OGJ*
Stuschke, M. and Sauer, R. (1997) Multimodal therapy or surgery alone in adenocarcinoma of the esophagus?. Strahlentherapie und Onkologie 173(9): 486-487	- Study not reported in English *In German*
Sun XD, Yu JM, Fan XL et al. (2006) [Randomized clinical study of surgery versus radiotherapy alone in the treatment of resectable esophageal cancer in the chest]. Zhonghua zhong liu za zhi [Chinese journal of oncology] 28(10): 784-787	- Study not reported in English
Tai, P. and Yu, E. (2014) Esophageal cancer management controversies: Radiation oncology point of view. World Journal of Gastrointestinal Oncology 6(8): 263-74	- Systematic review used as source of primary studies
Taketa T, Xiao L, Sudo K et al. (2013) Propensity-based matching between esophagogastric cancer patients who had surgery and who declined surgery after preoperative chemoradiation. Oncology 85(2): 95-99	- Study does not contain an intervention relevant to this review protocol *Compares chemoradiation to trimodal therapy, rather than chemoradiation to surgery alone, as per protocol.*
Urschel, J. D. and Vasan, H. (2003) A meta-analysis of randomized controlled trials that compared neoadjuvant chemoradiation and surgery to surgery alone for resectable esophageal cancer. American journal of surgery 185(6): 538-43	- Review article but not a systematic review
Urschel, J. D.; Vasan, H.; Blewett, C. J. (2002) A meta-analysis of randomized controlled trials that compared neoadjuvant chemotherapy and	- Systematic review used as source of primary studies

Study	Exclusion reason
surgery to surgery alone for resectable esophageal cancer. American journal of surgery 183(3): 274-9	- Study does not contain an intervention relevant to this review protocol *Interventions evaluated were chemoradiotherapy and surgery versus surgery alone rather than chemoradiotherapy alone versus surgery alone, as per protocol*
van der Wilk BJ, Noordman BJ, Neijenhuis LKA et al. (2021) Active Surveillance Versus Immediate Surgery in Clinically Complete Responders After Neoadjuvant Chemoradiotherapy for Esophageal Cancer: A Multicenter Propensity Matched Study. Annals of surgery 274(6): 1009-1016	- Population not relevant to this review protocol *Population were post neoadjuvant chemoradiotherapy, which is not in line with the protocol*
van der Wilk, B. J., Eyck, B. M., Hofstetter, W. L. et al. (2021) Chemoradiotherapy followed by Active Surveillance Versus Standard Esophagectomy for Esophageal Cancer: A Systematic Review and Individual Patient Data Meta-Analysis. Annals of surgery	- Systematic review used as source of primary studies
Van Der Wilk, B., Eyck, B. M., Wijnhoven, B. P. L. et al. (2021) Chemoradiotherapy followed by active surveillance versus standard surgery for oesophageal cancer: a systematic review and individual patient data meta-analysis. Eur. J. Surg. Oncol. 47(2): e26-None	- Conference abstract *SR with no reference list so not useful for gaining references*
Waddell, T. S. and Cunningham, D. (2011) Chemotherapy: Perioperative therapy improves gastroesophageal cancer survival. Nature Reviews Clinical Oncology 8(8): 450-452	- Review article but not a systematic review
Wang, D. B., Sun, Z. Y., Deng, L. M. et al. (2016) Neoadjuvant chemoradiotherapy improving survival outcomes for esophageal carcinoma: An updated meta-analysis. Chinese Medical Journal 129(24): 2974-2982	- Systematic review used as source of primary studies - Study does not contain an intervention relevant to this review protocol *Interventions were chemoradiotherapy plus surgery versus surgery alone, not chemoradiotherapy alone versus surgery alone, as per protocol.*
Wilson, K. S.; Wilson, A. G.; Dewar, G. J. (2002) Curative treatment for esophageal cancer:	- Population not relevant to this review protocol *Majority with stage T2-3 disease*

Study	Exclusion reason
Vancouver Island Cancer Centre experience from 1993 to 1998. Canadian journal of gastroenterology 16(6): 361-8	
Xiao, X., Hong, H. G., Zeng, X. et al. (2020) The Efficacy of Neoadjuvant Versus Adjuvant Therapy for Resectable Esophageal Cancer Patients: A Systematic Review and Meta-Analysis. World journal of surgery 44(12): 4161-4174	- Systematic review used as source of primary studies - Study does not contain an intervention relevant to this review protocol *Interventions evaluated were chemoradiotherapy and surgery versus surgery alone rather than chemoradiotherapy alone versus surgery alone, as per protocol*
Zacherl, J., Sendler, A., Stein, H. J. et al. (2003) Current status of neoadjuvant therapy for adenocarcinoma of the distal esophagus. World journal of surgery 27(9): 1067-74	- Review article but not a systematic review
Zhang, C. D., Zeng, Y. J., Li, H. W. et al. (2013) Neoadjuvant chemotherapy for nonmetastatic esophago-gastric adenocarcinomas: a systematic review and meta-analysis. Cancer investigation 31(6): 421-31	- Systematic review used as source of primary studies - Study does not contain an intervention relevant to this review protocol *Interventions evaluated were chemoradiotherapy and surgery versus surgery alone rather than chemoradiotherapy alone versus surgery alone, as per protocol*
Zhao, Q., Li, Y., Wang, J. et al. (2015) Concurrent Neoadjuvant Chemoradiotherapy for Siewert II and III Adenocarcinoma at Gastroesophageal Junction. American journal of the medical sciences 349(6): 472-476	- Population not relevant to this review protocol *T3/4 stage; Gastroesophageal junction cancer*
Zheng, B., Zheng, W., Zhu, Y. et al. (2013) Role of adjuvant chemoradiotherapy in treatment of resectable esophageal carcinoma: A meta-analysis. Chinese Medical Journal 126(6): 1178-1182	- Study not reported in English
Zhou, H. Y., Zheng, S. P., Li, A. L. et al. (2020) Clinical evidence for association of neoadjuvant chemotherapy or chemoradiotherapy with efficacy and safety in patients with resectable esophageal carcinoma (NewEC study). EClinicalMedicine 24: 100422	- Systematic review used as source of primary studies - Study does not contain an intervention relevant to this review protocol

Study	Exclusion reason
	Interventions were chemoradiotherapy plus surgery versus surgery alone, not chemoradiotherapy alone versus surgery alone, as per protocol.

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.