National Institute for Health and Care Excellence

Final

Barrett's oesophagus and stage 1 oesophageal adenocarcinoma

[G] Evidence review for endoscopic and radiological staging techniques

NICE guideline NG231

Evidence review underpinning recommendations 1.4.1 to 1.4.4 in the NICE guideline

February 2023

Final

National Institute for Health and Care Excellence

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1. Contents

1. Diagnostic accuracy of endoscopic and radiological staging techniques

1.1. Review question

For adults with suspected stage 1 adenocarcinoma, what is the diagnostic accuracy of different endoscopic and radiological staging techniques?

1.1.1. Introduction

Staging of suspected stage 1 oesophageal adenocarcinoma is an important step in the management pathway which allows doctors and patients to decide upon the best treatment option. Although the risk of lymph node metastases in stage 1 tumours is low, that risk increases as the tumour invades the submucosa (T1b). Endoscopic resection facilitates gold-standard pathological tumour staging. Radiological staging (cross-sectional imaging and endoscopic ultrasound) can be used for both tumour and nodal staging. This evidence review evaluates the diagnostic accuracy of endoscopic and radiological staging in stage 1 oesophageal adenocarcinoma.

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	Adults, 18 years and over, with suspected stage 1 adenocarcinoma including those with high grade dysplasia only on biopsies Exclusion: Adults with non-dysplastic Barrett's oesophagus, low grade dysplasia and those with suspected stages higher than stage 1 adenocarcinoma
Target condition	Barrett's Oesophagus with stage 1 adenocarcinoma
Index tests	Endoscopic staging techniques: • high resolution endoscopy with biopsies • Chromoendoscopy (e.g. narrow band imaging) Radiological staging techniques • EUS (endoscopic ultrasound, including mini probes) • CT • CT PET
Reference standard	Comparison to final clinical staging (non- imaging) endoscopic resection or surgical resection
Outcomes	Tumour or Node or Metastasis staging (or all) • Sensitivity • Specificity • Data to calculate 2x2 tables to calculate sensitivity and specificity (number of true positives, true negatives, false positives and false negatives)
Study design	Observational studies: • Cross-sectional studies • Prospective / Retrospective diagnostic cohort studies • Systematic Reviews of observational studies Any study containing a diagnostic accuracy data or analysis

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. Diagnostic evidence

1.1.4.1. Included studies

Five studies were included in the review.[1, 3-6] These are summarised in Table 2 below. Evidence from these studies is summarised in the clinical evidence summary below in Table 3.

Three studies looked at the diagnostic accuracy of the EUS, looking at slightly different outcomes (stages of cancer) and including different populations (in terms of cancer stage and high-grade dysplasia). Thus, findings from these studies have not been meta-analysed but have been reported separately. One retrospective cohort study looked at the diagnostic accuracy of EUS for detecting T1a (vs T1b, T2-4) staging, and N staging compared with histopathology in people with oesophageal cancer. One further retrospective study looked at the diagnostic accuracy of EUS for detecting T1b (vs Tcis/T1a,T2,T3) in people with high-grade dysplasia or intramucosal carcinoma. One study looked at the diagnostic accuracy of the EUS for detecting T1b (vs T0, T1a) and N staging in people with high-grade dysplasia or intramucosal carcinoma.

One prospective cohort study looked at the diagnostic accuracy of mini-probe EUS and CT for T(T1a vs T1b) and N staging compared with histology based on endoscopic or surgical resection.

One prospective randomised cross-over study looked at the diagnostic accuracy of High frequency mini-probes (HFPs) and conventional radial endoscopic ultrasonography (crEUS) for T (T1a vs T1b) and N staging compared with histology based on endoscopic or surgical resection.

The committee set clinical decision thresholds as sensitivity/specificity =0.9 and 0.8 above which a test would be recommended and 0.6 and 0.5 below which a test is of no clinical use. Sensitivity was prioritised for decision making as the committee agreed not missing the detection of cancer or metastasis was the most important factor to consider and under-staging can have adverse consequences for patients.

No relevant diagnostic test accuracy studies of endoscopic staging techniques were identified.

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

1.1.4.2. Excluded studies

See the excluded studies list in Appendix G.

1.1.5. Summary of studies included in the diagnostic evidence

Table 2: Summary of studies included in the evidence review

Study	Population	Target condition	Index test	Reference standard	Comments
Cen 2008[1]	Oesophageal cancer patients (N=87; n=81 with adenocar-cinoma, n=6 squamous cell carcinoma) Median age: 65 years USA	T1 staging (T1a vs T1b, T2-4) Metastasis/N staging (N0 vs N1)	EUS	Histopathologic assessment of resected specimens	Retrospective study Indirectness: N=22 had cancer above stage 1 but it is not clear if this was suspected from baseline. N=6 had squamous cell carcinoma
Pech 2006 [4]	Patients with confirmed 'early' cancer in Barrett's oesophagus (n=100) Median age (range): 64 (58-72) years The T category was assessed using high frequency probes (HFPs) in 66/100 patients who had elevated and/or depressed lesions. EUS with HFPs was not carried out on endoscopically unequivocal mucosal neoplasia (type IIb lesions in the Paris classification) Germany	T (T1m vs T1sm) and N staging Staging using the Paris classification T1m assumed to correspond to T1a T1sm assumed to correspond to T1b	(Miniprobe) EUS (upper gastrointestinal endoscopy) CT (of the chest and upper abdomen, and abdominal ultrasonography)	Histology (based on endoscopic resection or surgical specimens)	Patients in whom carcinoma could not be confirmed by experienced gastroenterological pathologists were excluded Includes people with T2 (n=4) and T3(n=3) histology; data for EUS calculated including those with T1m and T1sm staging based on EUS and Histology (n=55), excluding T2 and T3 2x2 table for N staging and T staging for CT could not be calculated from the paper.
Pech 2010 [3]	Patients with suspected 'early' cancer in Barrett's oesophagus,	T staging (mucosal and submucosal Barrett's	High frequency mini-probes (HFPs)	Histology (based on endoscopic resection or	Prospective randomised cross-over study

Study	Population	Target condition	Index test	Reference standard	Comments
	referred for endoscopic treatment for Barrett's cancer (n=43) Median age (range): 66 (58-73) Germany	cancer i.e. T1m vs T1sm) N staging (N1, N0)	Conventional radial endoscopic ultrasonography (crEUS)	surgical specimens)	Includes people with macroscopic tumour type: I-III; with histological stage T1m1-4 and T1sm1-3 2x2 table only calculated for N staging
Scotiniotis 2001[5]	Patients with Barrett's oesophagus and high-grade dysplasia or intramucosal carcinoma based on endoscopy, endoscopic biopsies, and CT. N=22 Mean age (SD) 64 (8.7) years USA	T staging (T1b vs Tcis/T1a, T2, T3)	EUS	Surgical/pathologic evaluation	Retrospective study Indirectness: n=4 had cancer at stages T2 and T3 N staging results not included in the present review as 3/5 people classified as positive of lymph node metastasis by the EUS had stage beyond T1 (T2/3) and therefore the majority of people for which sensitivity results were based did not meet the review protocol.
Thomas 2010[6]	Patients with histologically proven high-grade intraepithelial neoplasia or intramucosal carcinoma (n=50) Median age (range): 69 (60-79) years UK	T staging (; T1sm vs T0 and T1m) N staging (N1 vs N0)	EUS	Histology	Retrospective study Pre-EUS histology based on 1 to 2 esophagogastruodenoscopies and 2 to 36 mucosal biopsies (median 12): n=31 (62%) high-grade dysplasia, n=10 (38%) intramucosal carcinoma

See Appendix D for full evidence tables

1.1.6. Summary of the diagnostic evidence

The assessment of the evidence quality was conducted with emphasis on sensitivity as the committee agreed not missing the detection of cancer or metastasis was the most important factor to consider and under-staging can have detrimental consequences. The committee set clinical decision thresholds as sensitivity/specificity =0.9 and 0.8 above which a test would be recommended and 0.6 and 0.5 below which a test is of no clinical use.

Table 3: Clinical evidence summary: diagnostic test accuracy for radiological staging techniques

Studies	N	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect size (95%CI)	Quality
CT to detect T1 tumours in people with 'early' cancer in Barrett's oesophagus							
1 prospective cohort study	66	Serious[1]	Not serious	Serious[2]	Cannot be assessed[3]	Sensitivity=1.00	VERY LOW
		Serious[1]	Not serious	Serious[2]	Cannot be assessed[3]	Specificity=0.00	VERY LOW
Mini-probe EUS to detect T1a vs T1b ('T1m vs T1sm') in people with 'early' cancer in Barrett's oesophagus							
1 prospective cohort study	55	Serious[1]	Not serious	Serious[2]	Serious[4]	Sensitivity= 0.89 (0.75 -0.96)	VERY LOW
		Serious[1]	Not serious	Serious[2]	Serious[4]	Specificity= 0.27 (0.06 -0.61)	VERY LOW
CT to detect N staging in people with 'early' cancer in Barrett's oesophagus							
1 prospective cohort study	66	Serious[1]	Not serious	Serious[2]	Cannot be assessed[3]	Sensitivity= 0.38	VERY LOW
		Serious[1]	Not serious	Serious[2]	Cannot be assessed[3]	Specificity=1.00	VERY LOW
Mini-probe EUS to detect N staging in people with 'early' cancer in Barrett's oesophagus							
1 prospective cohort study	66	Serious[1]	Not serious	Serious[2]	Cannot be assessed[3]	Sensitivity= 0.75	VERY LOW
		Serious[1]	Not serious	Serious[2]	Cannot be assessed[3]	Specificity= 0.97	VERY LOW
HFPs for T1a ('pT1m') in people with suspected 'early' cancer in Barrett's oesophagus							
1 prospective randomised cross-over study	36	Serious[1]	Not serious	Serious[2]	Serious[4]	Sensitivity= 0.70 (0.46 -0.87)	VERY LOW
	36	Serious[1]	Not serious	Serious[2]	Very serious[4]	Specificity= 0.69 (0.41- 0.88)	VERY LOW
HFPs for T1b ('pT1sm') in people with suspected 'early' cancer in Barrett's oesophagus							
1 prospective randomised cross-over study	36	Serious[1]	Not serious	Serious[2]	Serious[4]	Sensitivity= 0.69 (0.41 -0.88)	VERY LOW
		Serious[1]	Not serious	Serious[2]	Serious[4]	Specificity= 0.75 (0.50 -0.90)	VERY LOW
crEUS for T1a ('pT1m') in people with suspected 'early' cancer in Barrett's oesophagus							
1 prospective randomised cross-over study	25	Serious[1]	Not serious	Serious[2]	Very serious[4]	Sensitivity= 0.73 (0.39 -0.93)	VERY LOW
		Serious[1]	Not serious	Serious[2]	Very serious[4]	Specificity= 0.78 (0.49- 0.94)	VERY LOW

Studies	N	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect size (95%CI)	Quality
crEUS for T1b ('pT1sm') in people with suspected 'early' cancer in Barrett's oesophagus							
1 prospective randomised cross-over study	25	Serious[1]	Not serious	Serious[2]	Serious[4]	Sensitivity= 0.64 (0.36- 0.86)	VERY LOW
		Serious[1]	Not serious	Serious[2]	Very serious[4]	Specificity= 0.73 (0.39- 0.93)	VERY LOW
crEUS for N1 status in people with suspected 'early' cancer in Barrett's oesophagus							
1 prospective randomised cross-over study	16	Serious[1]	Not serious	Serious[2]	Very serious[4]	Sensitivity= 1.00 (0.29- 1.00)	VERY LOW
		Serious[1]	Not serious	Serious[2]	Serious[4]	Specificity= 0.92 (0.64- 1.00)	VERY LOW
EUS for T1a (vs T1b, T2-4) in people with oesophageal cancer							
1 retrospective cohort study	87	Serious[1]	Not serious	Very serious[2]	Serious[4]	Sensitivity= 0.67 (0.50- 0.80)	VERY LOW
		Serious[1]	Not serious	Very serious[2]	Serious[4]	Specificity= 0.93 (0.82- 0.99)	VERY LOW
EUS for N1 (vs N0) in people with oesophageal cancer							
1 retrospective cohort study	87	Serious[1]	Not serious	Very serious[2]	Serious[4]	Sensitivity= 0.38 (0.18- 0.62)	VERY LOW
		Serious[1]	Not serious	Very serious[2]	Not serious	Specificity= 0.94 (0.85- 0.98)	VERY LOW
EUS for T1b (vs T0, T1a) in people with high-grade intraepithelial neoplasia or intramucosal carcinoma							
1 retrospective series	46	Very serious[1]	Not serious	Not serious	Serious[4]	Sensitivity= 0.56 (0.31- 0.78)	VERY LOW
		Very serious[1]	Not serious	Not serious	Serious[4]	Specificity: 0.93 (0.76- 0.99)	VERY LOW
EUS for N1 status in people with high-grade intraepithelial neoplasia or intramucosal carcinoma							
1 retrospective series	29	Very serious[1]	Not serious	Not serious	Very serious[4]	Sensitivity= 0.50 (0.01- 0.99)	VERY LOW
		Very serious[1]	Not serious	Not serious	Serious[4]	Specificity= 0.96 (0.81- 1.00)	VERY LOW
EUS for T1b (Tcis/T1a, T2, T3) in people with high-grade dysplasia or intramucosal carcinoma							
1 retrospective cohort study	22	Serious[1]	Not serious	Serious[2]	Serious[4]	Sensitivity: 1.00 (0.48- 1.00)	VERY LOW
		Serious[1]	Not serious	Serious[2]	Serious[4]	Specificity: 0.94 (0.71- 1.00)	VERY LOW

[1] *Risk of bias was assessed using the QUADAS-2 checklist. The evidence was downgraded by 1 increment if the studies were rated at serious risk of bias and downgraded by 2 increments if the studies were rated at very serious risk of bias.*

[2] *Evidence was downgraded by 1 increment due to serious concerns over population indirectness or by 2 increments due to very serious concerns over population indirectness.*

[3] *Where the study does not report confidence intervals or the data to calculate 2x2 tables imprecision cannot be assessed. Where this is the case evidence quality was downgraded by 1 increment.*

[4] *Imprecision was assessed based on inspection of the confidence intervals. For sensitivity, two clinical decision thresholds were determined at the value above which a test would be recommended (90%), and a second below which a test would be considered of no clinical use (60%). For specificity, two clinical decision thresholds were determined*

at the value above which a test would be recommended (80%), and a second below which a test would be considered of no clinical use (50%). The evidence was downgraded by 1 increment when the range of the confidence interval around the point estimate crossed one threshold and downgraded by 2 increments when the range covered two thresholds.

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 F.

1.1.8. Summary of included economic evidence

There was no economic evidence found.

1.1.9. Economic model

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

1.1.10. Unit costs

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

Table 4: Unit costs for PET-CT and endoscopy without biopsy

Resource	Unit costs	Source
Positron Emission Tomography with Computed Tomography (PET-CT) of One Area, 19 years and over (RM01A)	£666	NHS Reference Costs 2019/20
Diagnostic Endoscopic Upper Gastrointestinal Tract Procedures, 19 years and over (FE22Z)	£500	
Therapeutic Endoscopic Upper Gastrointestinal Tract Procedures, 19 years and over (FE220)	£746	
Computerised tomography (RD20A, RD21A, RD22Z-RD27Z)	£92*	
Ultrasound scan (RD40Z-RD46Z)	£46*	

*Weighted average unit cost

2. Clinical and cost effectiveness of endoscopic and radiological staging techniques

2.1. Review question

2.1.1. For adults with suspected stage 1 carcinoma, what is the clinical and cost effectiveness of different endoscopic and radiological staging techniques?

2.1.2. Summary of the protocol

For full details see the review protocol in Appendix H.

Table 5: PICO characteristics of review question

Population	Inclusion: Adults, 18 years and over, with suspected stage 1 adenocarcinoma including those with high grade dysplasia only on biopsies Exclusion: Adults with non-dysplastic Barrett's oesophagus, low grade dysplasia and those with suspected stages higher than stage 1 adenocarcinoma
Interventions	Endoscopic staging techniques: • high resolution endoscopy with biopsies • Chromoendoscopy (e.g., narrow band imaging) Radiological staging techniques: • EUS (endoscopic ultrasound including mini probes) • CT • CT PET
Comparisons	• Within group (e.g., endoscopic staging technique vs. endoscopic staging technique) • Each other (e.g., endoscopic staging technique vs. radiological staging technique
Outcomes	• Health-related quality of life • Progression to higher stage of cancer • Mortality • Adverse events (staging perforation, bleeding, pain, allergic reaction to contrast and complications of oesophagectomy)
Study design	• RCT • Systematic Reviews Published NMAs and IPDs will be considered for inclusion.

2.1.3. 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.

2.1.4. Effectiveness evidence

2.1.4.1. Included studies

No relevant clinical studies comparing endoscopic or radiological staging techniques were identified.

See also the study selection flow chart in Appendix J.

2.1.4.2. Excluded studies

See the excluded studies list in Appendix L.

2.1.5. Economic evidence

2.1.5.1. Included studies

No health economic studies were included.

2.1.5.2. 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 K.

2.1.6. Summary of included economic evidence

There was no economic evidence found.

2.1.7. Economic model

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

2.1.8. Unit costs

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

Table 6: Unit costs for PET-CT and endoscopy without biopsy

Resource	Unit costs	Source
Positron Emission Tomography with Computed Tomography (PET-CT) of One Area, 19 years and over (RM01A)	£666	NHS Reference Costs 2019/20
Diagnostic Endoscopic Upper Gastrointestinal Tract Procedures, 19 years and over (FE22Z)	£500	
Therapeutic Endoscopic Upper Gastrointestinal Tract Procedures, 19 years and over (FE220)	£746	
Computerised tomography (RD20A, RD21A, RD22Z-RD27Z)	£92*	
Ultrasound scan (RD40Z-RD46Z)	£46*	

*Weighted average unit cost

2.1.9. The committee's discussion and interpretation of the evidence

2.1.9.1. The outcomes that matter most

Diagnostic review

The committee considered the diagnostic measures of sensitivity and specificity of the staging techniques. Sensitivity was prioritised for decision making as the committee agreed not missing the detection of cancer or metastasis was the most important factor to consider and under-staging can have adverse consequences for patients.

Clinical decision thresholds were set by the committee as sensitivity of 0.9 and specificity of 0.8 above which a test would be recommended, and sensitivity of 0.6 and specificity of 0.5 below which a test is of no clinical use. The committee agreed that the default values of 0.9 and 0.8 that are widely used for decision making across clinical guidelines were also applicable to people with Barrett's oesophagus.

Diagnostic RCT review/ Intervention review

The committee considered the outcomes of health-related quality of life, progression to higher stage of cancer, mortality, adverse events (including staging perforation, bleeding, pain, allergic reaction to contrast and complications of oesophagectomy). For purposes of decision making, all outcomes were considered equally important and were therefore rated as critical by the committee. No evidence was identified for any of the outcomes.

2.1.9.2. The quality of the evidence

Diagnostic review

Clinical evidence for the diagnostic accuracy of radiological staging techniques was available from 5 studies. One prospective cohort study on the diagnostic accuracy of mini-probe endoscopic ultrasound (EUS) and CT for T (T1a vs T1b) and N staging. One prospective randomised cross-over study for the diagnostic accuracy of high frequency mini-probe (HFPs) and conventional radial endoscopic ultrasonography (crEUS) for T (T1a vs T1b) and N staging.

Three further studies looked at the diagnostic accuracy of the EUS, for differentiating between different stages of cancer in slightly different populations. Hence, findings from studies on the EUS were not meta-analysed and were reviewed separately. One retrospective cohort study looked at the diagnostic accuracy of EUS for detecting T1a (vs T1b, T2-4) staging, and N staging in people with oesophageal cancer. One further retrospective study looked at the diagnostic accuracy of EUS for detecting T1b (vs Tcis/T1a, T2, T3) in people with high-grade dysplasia or intramucosal carcinoma. One study looked at the diagnostic accuracy of the EUS for detecting T1b (vs T0, T1a) and N staging in people with high-grade dysplasia or intramucosal carcinoma.

Evidence for both sensitivity and specificity across the different techniques and studies was of very low quality, downgraded due to concerns over risk of bias. This was often due to lack of sufficient detail on participant exclusion, and due to lack of clarity on the interpretation of the index test results without knowledge of the reference standard results. Evidence was further downgraded for population indirectness (due to the studies including people with confirmed 'early' carcinoma and being unclear if a stage higher than 1 was suspected, or due to the inclusion of a small number of people with stage higher than 1) and imprecision in the effect estimates.

No clinical evidence was identified on the diagnostic accuracy of endoscopic staging techniques.

Intervention review/ Diagnostic RCT

No relevant clinical evidence was identified. Studies were commonly excluded because they were done in a population that did not match the review protocol, such as people with oesophageal cancer higher than stage 1, people with non-dysplastic Barrett's oesophagus, squamous cell carcinoma or cancer not related to Barrett's oesophagus, or because no outcomes meeting the review protocol were reported.

2.1.9.3. Benefits and harms

The committee agreed based on their clinical experience that the diagnostic accuracy of CT is very low for detecting stage 1 oesophageal adenocarcinoma because of the resolution of the technique, due to the small size of T1 oesophageal adenocarcinoma. Evidence showed CT had a high specificity (1.00) but a very low sensitivity (0.38) for N staging. The committee noted the evidence illustrating the poor diagnostic value of CT as a staging technique was in line with their experience and reflected the reason why CT should not be used before endoscopic resection for suspected T1 oesophageal adenocarcinoma. The committee noted implementation of the recommendation to not use CT may bring a change in clinical practice across centres where CT is currently being performed before endoscopic resection.

Evidence for the accuracy of mini-probe EUS in detecting T1a s T1b tumours showed a high sensitivity (0.89) almost reaching the clinical threshold of 0.9, but a low specificity (0.27) that did not reach the threshold of 0.8. The committee noted mini-probe EUS performed well in detecting T1a but not T1b tumours. The diagnostic accuracy of the mini-probe EUS for N staging was higher with a sensitivity of 0.75 and a specificity 0.97 that exceeded the clinical threshold.

The diagnostic accuracy of the crEUS for distinguishing T1a (vs T1b) tumours and T1b (vs T1a) in people with early cancer was moderately high with both measures of sensitivity and specificity ranging between 0.64-0.78, but not high enough to reach the agreed thresholds for decision making. However, the diagnostic accuracy for detecting N1 status was very high with sensitivity (1.00) and specificity (0.92) both exceeding clinical thresholds set for decision making. EUS had a similar sensitivity (0.67) for distinguishing T1a vs T1b, T2-T4. It was noted that this evidence was partially indirect due to inclusion of a small number of people with cancer stage higher than 1. For distinguishing T1b from T0, T1a, in people with high-grade dysplasia or cancer, EUS had a sensitivity of 0.56 that was in line with evidence from

populations not including high-grade dysplasia and did not reach the decision-making threshold.

For distinguishing T1b from Tcis, T1a, T2 or T3, EUS has a sensitivity of 1.00 and a very high specificity of 0.94. The committee confirmed based on their clinical experience that EUS can be useful in people with suspected T1b based on endoscopic appearances but noted that the current result was based on only 5 cases with T1b, there was imprecision in the effect estimate and the population was partially indirect due to the inclusion of a small number of people with T2 and T3 in the analysis. The committee noted that in current practice, EUS is routinely used for suspected T1b tumours or higher but considering the current evidence base, agreed not to make any recommendation for EUS in T staging people with suspected T1b. There was consensus that EUS should also not be used before resection for staging T1a oesophageal adenocarcinoma, as the risk of lymph node metastasis is negligible.

Based on the evidence and their clinical experience they emphasised that EUS is not reliable in differentiating T1a with T1b tumours but may be useful to detect lymph node metastasis in patients with confirmed T1b tumours based on histological examination of endoscopic resection specimens and people with suspected T1b tumours based on endoscopic appearances. They agreed EUS should be considered in these populations as they have a high risk of lymph node metastasis, emphasising that the risk would be indicated by the endoscopic resection, and may benefit from additional oncological treatment such as radiotherapy alone or in combination with chemotherapy. Based on their clinical experience the committee also noted that PET, CT and the EUS can all over-stage tumours, but EUS is likely to provide pathological confirmation for the presence of lymph nodes.

Evidence indicated the diagnostic accuracy of HFPs to detect T1a and T1b tumours to be relatively high with sensitivity 0.70 and 0.69 and specificity 0.69 and 0.75 respectively, but not meeting clinical thresholds for decision making. The committee noted the diagnostic accuracy of HFPs and the crEUS are shown to be similar, indicating HFPs do not have any additional benefit to crEUS. This was not in line with their experience as they would expect the accuracy of HFPs to be higher, but as the evidence came from one small study, they could not be confident in the results reported.

In absence of evidence on endoscopic staging techniques, the committee used their clinical experience to make consensus recommendations. They agreed that endoscopic resection is the most accurate staging technique and in current practice is the accepted gold standard. It is also recommended by the British Society of Gastroenterology guidelines on Barrett's oesophagus. They agreed that endoscopic resection should be offered to people with suspected stage 1 oesophageal adenocarcinoma.

2.1.9.4. Cost effectiveness and resource use

Accurate staging is important for determining prognosis and planning appropriate treatment in people with suspected stage 1 oesophageal adenocarcinoma. Imaging techniques and endoscopic resection can both be utilised for this purpose. Imaging tests are less invasive than endoscopic procedures. Average procedure costs were presented to the committee.

No economic evaluations were identified for this review question.

The committee discussed the clinical evidence and agreed that endoscopic resection should be offered for staging in suspected cases of stage 1 oesophageal adenocarcinoma since the evidence suggested that it is more accurate than the alternatives.

While EUS and CT were both cheaper, the committee concurred, based on the evidence and their clinical experience that the resolution on a CT scan is not clear enough to detect stage 1 adenocarcinoma while EUS does not differentiate between T1a and T1b tumours. The committee therefore considered their use to be an unnecessary use of NHS resources and

they recommended to not offer CT for staging suspected T1 adenocarcinoma or EUS for staging of suspected T1a oesophageal adenocarcinoma prior to endoscopic resection staging.

Finally, for people with suspected or confirmed T1b oesophageal adenocarcinoma, they agreed that EUS should be considered since it could confirm the presence of pathological lymph nodes. The evidence suggested that there is no indication for a CT to be performed in this situation.

In the absence of any evidence, the committee refrained from making any recommendations for PET-CT.

These recommendations are in line with current practice and are therefore unlikely to have a substantial impact on NHS resources.

2.1.10. Recommendations supported by this evidence review

This evidence review supports recommendations 1.4.1 to 1.4.4.

2.1.11. References

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Appendices

Appendix A – Review protocols

A.1 Review protocol for diagnostic accuracy of endoscopic and radiological staging techniques

ID	Field	Content
0.	PROSPERO registration number	CRD42022308179
1.	Review title	Diagnostic accuracy of endoscopic and radiological staging techniques
2.	Review question	For adults with suspected stage 1 carcinoma, what is the diagnostic accuracy of different endoscopic and radiological staging techniques?
3.	Objective	To determine how different techniques for staging (endoscopic and radiological) affects the accuracy of the investigations for suspected stage 1 carcinoma
4.	Searches	The following databases (from inception) will be searched: • Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews (CDSR) • Embase • MEDLINE • Epistemonikus Searches will be restricted by: • English language studies • Human studies • Letters and comments are excluded

		Other searches: • Inclusion lists of systematic reviews will be checked by the reviewers The searches may be re-run 6 weeks before the final committee meeting and further studies retrieved for inclusion if relevant. The full search strategies will be published in the final review. Medline search strategy to be quality assured using the PRESS evidence-based checklist (see methods chapter for full details).
5.	Condition or domain being studied	Barrett's Oesophagus with suspected stage 1 adenocarcinoma
6.	Population	Inclusion: Adults, 18 years and over, with suspected stage 1 adenocarcinoma including those with high grade dysplasia only on biopsies Exclusion: Adults with non-dysplastic Barrett's oesophagus, low grade dysplasia and those with suspected stages higher than stage 1 adenocarcinoma
7.	Test	• endoscopic staging techniques ○ high resolution endoscopy with biopsies

		○ Chromoendoscopy (e.g. narrow band imaging) • radiological staging techniques ○ EUS (endoscopic ultrasound, including mini probes) ○ CT ○ CT PET
8.	Reference standard	• Comparison to final clinical staging (non- imaging) endoscopic resection or surgical resection
9.	Types of study to be included	Observational studies: • Cross-sectional studies • Prospective / Retrospective diagnostic cohort studies • Systematic Reviews of observational studies • Any study containing a diagnostic accuracy data or analysis
10.	Other exclusion criteria	Studies that do not report sensitivity and specificity, or insufficient data to derive these values. 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 people with suspected stage 1 adenocarcinoma, different endoscopic and radiological techniques are used for staging. This review aims to determine the diagnostic accuracy of those different staging techniques
12.	Primary outcomes (critical outcomes)	All outcomes are considered equally important for decision making and therefore have all been rated as critical: Tumour or Node or Metastasis staging (or all)

		• Sensitivity • Specificity • Data to calculate 2x2 tables to calculate sensitivity and specificity (number of true positives, true negatives, false positives and false negatives)
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 quality assessment will be assessed using QUADAS-2 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: Individual radiological techniques vs gold standard EUS techniques (standard EUS OR miniprobe vs gold standard) Endoscopic techniques (electronic chromoendoscopy OR dye endoscopy vs gold standard) Subgrouping:

		If serious or very serious heterogeneity (I2>50%) is present, sub-grouping will occur according to the following strategies: electronic chromoendoscopy			
18.	Type and method of review	☐	Intervention		
		☒	Diagnostic		
		☐	Prognostic		
		☐	Qualitative		
		☐	Epidemiologic		
		☐	Service Delivery		
		☐	Other (please specify)		
19.	Language	English			
20.	Country	England			
21.	Anticipated or actual start date				
22.	Anticipated completion date				
23.	Stage of review at time of this submission	Review stage		Started	Completed
		Preliminary searches		☐	☐
		Piloting of the study selection process		☐	☐
		Formal screening of search results		☐	☐

		against eligibility criteria		
		Data extraction	☐	☐
		Risk of bias (quality) assessment	☐	☐
		Data analysis	☐	☐
24.	Named contact	5a. Named contact National Guideline Centre 5b Named contact e-mail @nice.org.uk 5e Organisational affiliation of the review National Institute for Health and Care Excellence (NICE) and National Guideline Centre		
25.	Review team members	From the National Guideline Centre: Norma O Flynn Gill Ritchie Amy Crisp Lina Gulhane Stephen Deed Vimal Bedia Muksitur Rahman Mark Perry		

		Melina Vasileiou Maheen Qureshi
26.	Funding sources/sponsor	This systematic review is being completed by the National Guideline Centre which receives funding from NICE.
27.	Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.
28.	Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website.
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	

A.2 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 7: Database parameters, filters and limits applied

Database	Dates searched	Search filter used
Medline (OVID)	1946 – 28 April 2022	Randomised controlled trials Systematic review studies Observational studies Diagnostic tests studies Exclusions (animal studies, letters, comments, editorials, case studies/reports) English language
Embase (OVID)	1974 – 28 April 2022	Randomised controlled trials Systematic review studies Observational studies Diagnostic tests 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 28 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.	Neoplasm Staging/
38.	((neoplasm* or cancer* or tumour* or tumor* or tnm*) adj2 (staging* or stage* or restage* or restaging* or understage* or understaging* or overstage* or overstaging* or classif*)).ti,ab,kf.
39.	Endoscopy, Gastrointestinal/ or Esophagoscopy/ or Gastroscopy/ or Proctoscopy/
40.	(endoscop* or esophagoscop* or esophagogastroduodenoscop* or esophagograph* or colonoscop* or proctoscop* or gastroscop* or spectroscop*).ti,ab,kf.

41.	Colouring agents/ or Chromogenic Compounds/ or Fluorescent dyes/ or *Indigo Carmine/
42.	(chromoscop* or chromoendoscop* or high resolution colonoscop* or dye spray* or indigo carmine or acetic acid or narrow band imag*).ti,ab,kf.
43.	Ultrasonography/
44.	Elasticity Imaging Techniques/
45.	Endosonography/
46.	Microscopy, Acoustic/
47.	Ultrasonography, Doppler/ or Ultrasonography, Doppler, Duplex/ or Ultrasonography, Doppler, Pulsed/
48.	(ultrasonograph* or ultrasound* or ultra sound* or sonograph* or sonogram* or echograph* or echotomograph* or elastography* or elastosonograph* or sonoelastograph* or doppler or endosonograph* or acoustic microscop* or mini probe* or miniprobe* or ultrasonic biomicroscop*).ti,ab,kf.
49.	Tomography/
50.	exp Tomography, Emission-Computed/
51.	exp Tomography, X-Ray/
52.	tomograph*.ti,ab,kf.
53.	tomodensitometry.ti,ab,kf.
54.	exp Positron-Emission Tomography/
55.	exp Diffusion Magnetic Resonance Imaging/
56.	(Diffusion weighted or DWI).ti,ab,kf.
57.	(CT or MDCT or CAT or PET or PETCT or SPECT).ti,ab,kf.
58.	((radioisotop* or isotop* or gamma camera) adj3 (scan* or imag*)).ti,ab,kf.
59.	or/37-58
60.	36 and 59
61.	randomized controlled trial.pt.
62.	controlled clinical trial.pt.
63.	randomi#ed.ab.
64.	placebo.ab.
65.	randomly.ab.
66.	clinical trials as topic.sh.
67.	trial.ti.
68.	or/61-67
69.	Meta-Analysis/
70.	Meta-Analysis as Topic/
71.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
72.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
73.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
74.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
75.	(search* adj4 literature).ab.
76.	(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.
77.	cochrane.jw.
78.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
79.	or/69-78

80.	exp "sensitivity and specificity"/
81.	(sensitivity or specificity).ti,ab.
82.	((pre test or pretest or post test) adj probability).ti,ab.
83.	(predictive value* or PPV or NPV).ti,ab.
84.	likelihood ratio*.ti,ab.
85.	likelihood function/
86.	((area under adj4 curve) or AUC).ti,ab.
87.	(receive* operat* characteristic* or receive* operat* curve* or ROC curve*).ti,ab.
88.	gold standard.ab.
89.	exp Diagnostic errors/
90.	(false positiv* or false negativ*).ti,ab.
91.	Diagnosis, Differential/
92.	(diagnos* adj3 (performance* or accurac* or utilit* or value* or efficien* or effectiveness or precision or validat* or validity or differential or error*)).ti,ab.
93.	or/80-92
94.	Epidemiologic studies/
95.	Observational study/
96.	exp Cohort studies/
97.	(cohort adj (study or studies or analys* or data)).ti,ab.
98.	((follow up or observational or uncontrolled or non randomi#ed or epidemiologic*) adj (study or studies or data)).ti,ab.
99.	((longitudinal or retrospective or prospective) and (study or studies or review or analys* or cohort* or data)).ti,ab.
100.	Controlled Before-After Studies/
101.	Historically Controlled Study/
102.	Interrupted Time Series Analysis/
103.	(before adj2 after adj2 (study or studies or data)).ti,ab.
104.	exp case control study/
105.	case control*.ti,ab.
106.	Cross-sectional studies/
107.	(cross sectional and (study or studies or review or analys* or cohort* or data)).ti,ab.
108.	or/94-107
109.	60 and (68 or 79 or 93 or 108)

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.	*cancer staging/
37.	((neoplasm* or cancer* or tumour* or tumor* or tnm*) adj2 (staging* or stage* or restage* or restaging* or understage* or understaging* or overstage* or overstaging* or classif*)).ti,ab,kf.
38.	esophagogastroduodenoscopy/ or esophagography/ or esophagoscopy/
39.	(endoscop* or esophagoscop* or esophagogastroduodenoscop* or esophagograph* or colonoscop* or proctoscop* or gastroscop* or spectroscop*).ti,ab,kf.
40.	*Colouring agent/ or *chromoendoscopy/ or *Indigo Carmine/ or *high resolution endoscopy/ or *magnifying endoscopy/
41.	(chromoscop* or chromoendoscop* or high resolution colonoscop* or dye spray* or indigo carmine or acetic acid or narrow band imag*).ti,ab,kf.
42.	*Endoscopic ultrasonography/ or *Echography/
43.	*Elastograph/ or *Elastography/
44.	*Endoscopic ultrasonography/
45.	Microscopy, Acoustic/
46.	*Doppler Ultrasonography/ or *duplex Doppler ultrasonography/ or *pulsed Doppler ultrasonography/
47.	(ultrasonograph* or ultrasound* or ultra sound* or sonograph* or sonogram* or echograph* or echotomograph* or elastography* or elastosonograph* or sonoelastograph* or doppler or endosonograph* or acoustic microscop* or mini probe* or miniprobe* or ultrasonic biomicroscop*).ti,ab,kf.
48.	*tomography/

49.	exp *computer assisted tomography/ or exp *emission tomography/
50.	exp *whole body tomography/ or exp *x-ray tomography/
51.	tomograph*.ti,ab,kf.
52.	tomodensitometry.ti,ab,kf.
53.	*positron emission tomography/ or *computer assisted emission tomography/ or *positron emission tomography-computed tomography/ or *whole body pet/
54.	*diffusion weighted imaging/
55.	(Diffusion weighted or DWI).ti,ab,kf.
56.	(CT or MDCT or CAT or PET or PETCT or SPECT).ti,ab,kf.
57.	((radioisotop* or isotop* or gamma camera) adj3 (scan* or imag*)).ti,ab,kf.
58.	or/36-57
59.	35 and 58
60.	random*.ti,ab.
61.	factorial*.ti,ab.
62.	(crossover* or cross over*).ti,ab.
63.	((doubl* or singl*) adj blind*).ti,ab.
64.	(assign* or allocat* or volunteer* or placebo*).ti,ab.
65.	crossover procedure/
66.	single blind procedure/
67.	randomized controlled trial/
68.	double blind procedure/
69.	or/60-68
70.	systematic review/
71.	Meta-Analysis/
72.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
73.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
74.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
75.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
76.	(search* adj4 literature).ab.
77.	(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.
78.	cochrane.jw.
79.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
80.	or/70-79
81.	exp "sensitivity and specificity"/
82.	(sensitivity or specificity).ti,ab.
83.	((pre test or pretest or post test) adj probability).ti,ab.
84.	(predictive value* or PPV or NPV).ti,ab.
85.	likelihood ratio*.ti,ab.
86.	((area under adj4 curve) or AUC).ti,ab.
87.	(receive* operat* characteristic* or receive* operat* curve* or ROC curve*).ti,ab.
88.	diagnostic accuracy/
89.	diagnostic test accuracy study/
90.	gold standard.ab.
91.	exp diagnostic error/

92.	(false positiv* or false negativ*).ti,ab.
93.	differential diagnosis/
94.	(diagnos* adj3 (performance* or accurac* or utilit* or value* or efficien* or effectiveness or precision or validat* or validity or differential or error*)).ti,ab.
95.	or/81-94
96.	Clinical study/
97.	Observational study/
98.	Family study/
99.	Longitudinal study/
100.	Retrospective study/
101.	Prospective study/
102.	Cohort analysis/
103.	Follow-up/
104.	cohort*.ti,ab.
105.	103 and 104
106.	(cohort adj (study or studies or analys* or data)).ti,ab.
107.	((follow up or observational or uncontrolled or non randomi#ed or epidemiologic*) adj (study or studies or data)).ti,ab.
108.	((longitudinal or retrospective or prospective) and (study or studies or review or analys* or cohort* or data)).ti,ab.
109.	(before adj2 after adj2 (study or studies or data)).ti,ab.
110.	exp case control study/
111.	case control*.ti,ab.
112.	cross-sectional study/
113.	(cross sectional and (study or studies or review or analys* or cohort* or data)).ti,ab.
114.	or/96-102,105-113
115.	59 and (69 or 80 or 95 or 114)

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: [Neoplasm Staging] explode all trees
#18.	((neoplasm* or cancer* or tumour* or tumor* or tnm*) near/2 (staging* or stage* or restage* or restaging* or understage* or understaging* or overstage* or overstaging* or classif*)):ti,ab
#19.	MeSH descriptor: [Endoscopy, Gastrointestinal] this term only
#20.	MeSH descriptor: [Esophagoscopy] this term only
#21.	MeSH descriptor: [Gastroscopy] this term only
#22.	MeSH descriptor: [Proctoscopy] this term only
#23.	(endoscop* or esophagoscop* or esophagogastroduodenoscop* or esophagograph* or colonoscop* or proctoscop* or gastroscop* or spectroscop*):ti,ab
#24.	MeSH descriptor: [Coloring Agents] this term only
#25.	MeSH descriptor: [Chromogenic Compounds] this term only
#26.	MeSH descriptor: [Fluorescent Dyes] this term only
#27.	MeSH descriptor: [Indigo Carmine] this term only
#28.	(chromoscop* or chromoendoscop* or high resolution colonoscop* or dye spray* or indigo carmine or acetic acid or narrow band imag*):ti,ab
#29.	MeSH descriptor: [Ultrasonography] this term only
#30.	MeSH descriptor: [Elasticity Imaging Techniques] this term only
#31.	MeSH descriptor: [Endosonography] this term only
#32.	MeSH descriptor: [Microscopy, Acoustic] this term only
#33.	MeSH descriptor: [Ultrasonography, Doppler] this term only
#34.	MeSH descriptor: [Ultrasonography, Doppler, Duplex] this term only
#35.	MeSH descriptor: [Ultrasonography, Doppler, Pulsed] this term only
#36.	(ultrasonograph* or ultrasound* or ultra sound* or sonograph* or sonogram* or echograph* or echotomograph* or elastography* or elastosonograph* or sonoelastograph* or doppler or endosonograph* or acoustic microscop* or mini probe* or miniprobe* or ultrasonic biomicroscop*):ti,ab
#37.	MeSH descriptor: [Tomography] this term only
#38.	MeSH descriptor: [Tomography, Emission-Computed] explode all trees
#39.	MeSH descriptor: [Tomography, X-Ray] explode all trees
#40.	tomograph*:ti,ab
#41.	tomodensitometry:ti,ab
#42.	MeSH descriptor: [Positron-Emission Tomography] explode all trees
#43.	MeSH descriptor: [Diffusion Magnetic Resonance Imaging] explode all trees
#44.	(Diffusion weighted or DWI):ti,ab
#45.	(CT or MDCT or CAT or PET or PETCT or SPECT):ti,ab
#46.	((radioisotop* or isotop* or gamma camera) near/3 (scan* or imag*)):ti,ab
#47.	(or #17-#46)
#48.	#16 and #47
#49.	conference:pt or (clinicaltrials or trialsearch):so
#50.	#48 not #49

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:("neoplasm* classif*" OR "neoplasm* staging*" OR "cancer* classif*" OR "cancer* staging*" OR "tumour* classif*" OR "tumour* staging*" OR "tumor* classif*" OR "tumor* staging*" OR "classif* staging*" OR cancer* OR "tnm* classif*" OR "tnm* staging*" OR endoscop* OR esophagoscop* OR esophagogastroduodenoscop* OR esophagograph* OR colonoscop* OR proctoscop* OR gastroscop* OR spectroscop* OR chromoscop* OR chromoendoscop* OR "high resolution colonoscop*" OR "dye spray*" OR "indigo carmine" OR "acetic acid" OR "narrow band imag*" OR ultrasonograph* OR ultrasound* OR "ultra sound*" OR sonograph* OR sonogram* OR echograph* OR echotomograph* OR elastography* OR elastosonograph* OR sonoelastograph* OR doppler OR endosonograph* OR "acoustic microscop*" OR "mini probe*" OR "miniprobe*" OR "ultrasonic biomicroscop*" OR tomograph* OR tomodensitometry OR "Diffusion Magnetic Resonance Imaging" OR "Diffusion weighted") OR abstract:("neoplasm* classif*" OR "neoplasm* staging*" OR "cancer* classif*" OR "cancer* staging*" OR "tumour* classif*" OR "tumour* staging*" OR "tumor* classif*" OR "tumor* staging*" OR "classif* staging*" OR cancer* OR "tnm* classif*" OR "tnm* staging*" OR endoscop* OR esophagoscop* OR esophagogastroduodenoscop* OR esophagograph* OR colonoscop* OR proctoscop* OR gastroscop* OR spectroscop* OR chromoscop* OR chromoendoscop* OR "high resolution colonoscop*" OR "dye spray*" OR "indigo carmine" OR "acetic acid" OR "narrow band imag*" OR ultrasonograph* OR ultrasound* OR "ultra sound*" OR sonograph* OR sonogram* OR echograph* OR echotomograph* OR elastography* OR elastosonograph* OR sonoelastograph* OR doppler OR endosonograph* OR "acoustic microscop*" OR "mini probe*" OR "miniprobe*" OR "ultrasonic biomicroscop*" OR tomograph* OR tomodensitometry OR "Diffusion Magnetic Resonance Imaging" OR "Diffusion weighted")

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 8: 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

Database	Dates searched	Search filters and limits applied
	Quality of Life 1974 – 29 April 2022	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

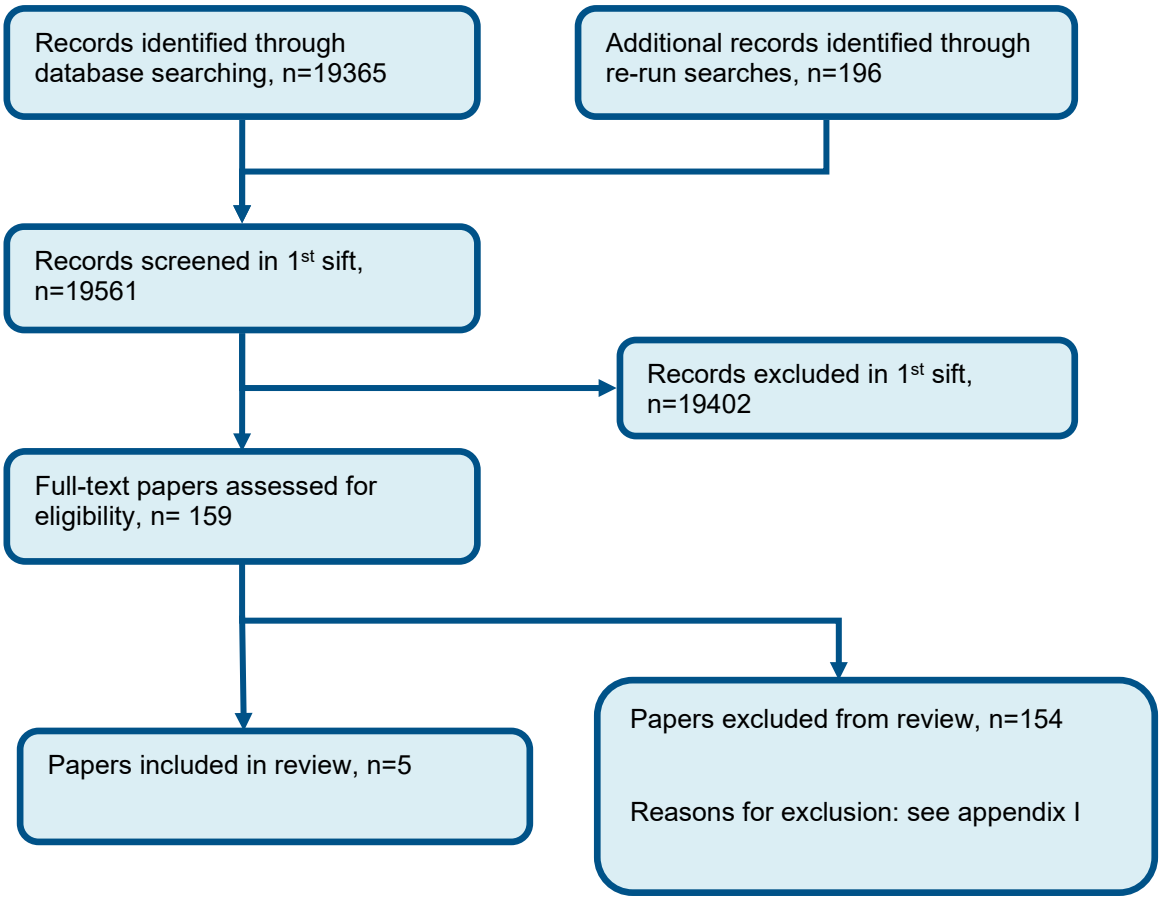
#1.	MeSH DESCRIPTOR Barrett Esophagus EXPLODE ALL TREES
#2.	(barrett*)
#3.	(speciali*) AND (epithel* or oesophag* or esophag* or mucos*)
#4.	(column*) AND (epithel* or oesophag* or esophag* or mucos* or lined or lining or metaplas*)
#5.	#1 OR #2 OR #3 OR #4
#6.	MeSH DESCRIPTOR Precancerous Conditions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

Figure 1: Flow chart of clinical study selection for the review of diagnostic accuracy of endoscopic and radiological staging techniques



Appendix D –Diagnostic evidence

Reference	**Cen 2008[1]**
Study type	Retrospective study
Study methodology	Data source: All patients who had pre-treatment staging with EUS and underwent oesophagectomy as primary therapy for oesophageal cancer between 1999 and 2006, from the Thoracic and Cardiovascular Surgery Oesophageal database at the University of Texas M.D. Anderson Cancer Centre (MDACC) Recruitment: consecutive
Number of patients	n = 87 (n=81 had adenocarcinoma; n=6 had squamous cell carcinoma)
Patient characteristics	Age, median: 65 years Gender (male to female ratio): 69/18 Ethnicity: not specified Setting: Thoracic and Cardiovascular Surgery Oesophageal database at the University of Texas M.D. Anderson Cancer Centre (MDACC) Country: USA Inclusion criteria: Patients with a diagnosis of carcinoma of the oesophagus or the gastroesophageal junction; EUS preoperative staging, primary esophagectomy, and with availability of a postoperative pathology specimen for reanalyses. Exclusion criteria: pre-operative chemotherapy or radiation therapy or the presence of distant metastatic disease Other characteristics: Pathologic T classification: T1a= 42; T1b=23; T2=8; T3=12; T4=2
Target condition(s)	T staging (T1 cancer) and lymph node metastasis

Reference	**Cen 2008[1]**				
Index test(s) and reference standard	Index test: EUS EUS examination was performedusing a radial scanning endoscope (Olympus GF-UM130, GF-UM160; Olympus America, Melville, NYor Pentax EG-3830U, EG-3630UR; Pentax, Tokyo,Japan), a linear array endoscope (Olympus/AlokaGF-UC-130, GF-UC-160P; Aloka Medical Device,Tokyo, Japan or Pentax FG32UA, FG36UX; PentaxPrecision Instruments, Orangeburg, NY), an EUSprobe (Olympus UM-2R, UM-3R), or a combination of these with a frequency range of 5.0 to 20 mega-hertz. EUS-guided fine-needle aspirations were performed using a 22-gauge or 25-gauge needle(Echo-1-22 needle; Wilson-Cook, Winston-Salem,NC). Reports of those examinations were reviewed and the following information was collected: tumor size, depth of tumor invasion (EUST classification),and the presence or absence of either enlarged lymph nodes or lymph nodes with abnormal echo-genicity (N0/N1 status). The full length of the oesophagus, the stomach, and the celiac axis were scanned endosonographically. Lymph nodes were classified as positive (N1) if they exhibited at least 2 of the following criteria: dimension>1cm, around shape with discrete margins, and hypoechoic texture Spiral CT scans of the chest and abdomen were obtained to exclude the possibility of distant metastases. Positron emission tomography (PET) scans were performed when available.504CANCER February 1, 2008 / Volume 112 / Number 3 Reference standard: Histopathologic assessment of resected specimens Patients underwent subtotal oesophagectomy and/or proximal gastrectomy and lymph node dissection with curative intent. Specimens from the resections were processed according to a standardized protocol. All resected lymph nodes were evaluated for cancer metastases. Reports of those findings were reviewed, and the following data obtained: size, extension, and location of the tumour; LVI status (re-evaluated); degree of differentiation; presence of Barrett mucosa; presence or absence of lymph node metastasis; and histologic type (squamous cell carcinoma or adenocarcinoma). All cancers were staged by both EUS and in the surgical specimen according to the TNM staging system of the American Joint Committee on Cancer/International Union Against Cancer (AJCC/UICC).19,20T1 cancers were subclassified into 2 groups based on depth of invasion: T1a (intramucosal) or T1b (sub-mucosal-infiltrating into the submucosa without invasion of the muscularis propria). Time between measurement of index test and reference standard: not specified				
2×2 table		Reference standard +	Reference standard −	Total	**2x2 for T1 staging vs T2-T4; not extracted in main review table as it did not meet the protocol.**
	Index test +	59	2	61	
	Index test −	6	20	26	
	Total	65	13	87	
2x2 table		Reference standard +	Reference standard −	Total	**2x2 for T1a staging vs T1b, T2-T4 (n=22, 25% had T2-4); used in main review table and downgraded for indirectness.**
	Index test +	28	3	31	
	Index test −	14	42	56	
	Total	42	45	87	
2x2 table		Reference standard +	Reference standard −	Total	**2x2 for N1 vs N0 staging**

Reference	**Cen 2008[1]**				
	Index test +	8	4	12	
	Index test −	13	62	75	
	Total	21	66	87	
Statistical measures	Index test EUS for T1 (vs T2-4); (n=87) Sensitivity: 0.91 (95% CI 0.81- 0.97) Specificity: 0.91 (95% CI 0.71, 0.99) Index test EUS for T1a (vs T1b, T2-4); (n=87) Sensitivity: 0.67 (95% CI 0.50- 0.80) Specificity: 0.93 (95% CI 0.82- 0.99) Index test: EUS for N1 status (n=87) Sensitivity: 0.38 (95% CI 0.18, 0.62) Specificity: 0.94 (95% CI 0.85, 0.98)				
Source of funding	Supported in part by the Dallas, cantu, Smith,and Park Families the Rivercreek Foundation.				
Limitations	Risk of bias: serious risk of bias due to lack of sufficient detail on assessment of index test and reference standard results, flow and timing. Indirectness: very serious population indirectness with the study including people with histology higher than stage 1 (n=22; 25%) but it being unclear if this was suspected before the EUS and histopathology assessment and n=6 people with squamous cell carcinoma.				
Comments					

Reference	**Pech 2006 [4]**
Study type	Prospective cohort
Study methodology	Data source: Patients with suspected early cancer in Barrett's oesophagus referred for endoscopic therapy at the Teaching Hospital, University of Mainz between October 1999 and October 2001 Recruitment: Consecutive
Number of patients	n = 100; n=66 analysed (and n=55 included in the analysis for this review; see details on 2x2 table section below)
Patient characteristics	Age, median (range): 64 years (58-72)

Reference	Pech 2006 [4]
	Gender (male to female ratio): 80/20 Ethnicity: not specified Setting: University hospital Country: Germany Inclusion criteria: Patients referred to the Teaching Hospital, University of Mainz between October 1999 and October 2001 with suspicion of early cancer in Barrett's oesophagus that were screened with high-resolution video endoscopy and chromoendoscopy with methylene blue or acetic acid staining, or both. Consecutive patients with confirmed early cancer in Barrett's oesophagus. Only patients without prior CT for staging, performed by the referring physicians were included High resolution video endoscopy and chromoendoscopy with methylene blue or acetic acid staining, or both was carried out using Fujinon Europe, Inc., Willich, Germany). Biopsies were taken from all observed lesions, as well as four-quadrant biopsies every 1-2cm over the entire Barrett's segment. Assessment of biopsies taken during the diagnostic procedures was usually carried out by at least two different gastroenterological pathologists. The histological criteria, classification and assessment of the grade of differentiation corresponded to the WHO classification Exclusion criteria: Patients in whom carcinoma could not be confirmed by experienced gastroenterological pathologists. Characteristics: Short segment/Long segment Barrett's oesophagus: 47/53
Target condition(s)	T staging (T1m and T1sm) and N staging
Index test(s) and reference standard	Index test: (Miniprobe) EUS All patients with proven cancer underwent intensive staging, using EUS with 7.5-MHz probes (Olympus UM, 7.5 MHz; Olympus Deutschland Ltd., Hamburg, Germany) and if elevated lesions were found, 12.5-MHz or 20-MHz HFPs (Fujinon VSP501) were used as well Index test: CT Helical CT of the chest and upper abdominal organs was carried out in all patients (TwinFlash; two-row helical CT, Elscint Ltd., Wiesbaden, Germany). Only patients without prior CT for staging, performed by the referring physicians were included. At least two radiologists were involved in reading the CT scan. All patients also received an abdominal ultrasound examination (Logiq 5 and Logiq 7; General Electrics, Fairfield, CT) to detect intraabdominal lesions. Depending on the appearance of the lymph nodes detected with CT and/or EUS, patients were assigned to three different categories: category 1: patients without any suspicious lymph nodes

<table>
<tr><td>Reference</td><td colspan="5">Pech 2006 [4]</td></tr>
<tr><td></td><td colspan="5">category 2: patients with mediastinal or celiac lymph nodes>1 cm in size or lymph nodes <1 cm at the tumour level without suspicious EUS characteristics
category 3: patients with lymph nodes <1 cm at the tumour level or round and hypoechoic lymph nodes with sharp margins on EUS, independent of size and location.
The accuracy of EUS was based on a threshold of group 3.

<u>Reference standard: Histology</u>
Based on endoscopic resection or surgical specimens. The results of T staging were compared with the pathological T category (pTx). For lymph node staging, lymph nodes were considered as non-malignant when the pathological assessment was negative or the long-term follow-up showed no progression.

The T category was assessed using HFPs in 66 of the 100 patients who had elevated and/or depressed lesions. EUS with HFPs was not carried out on endoscopically unequivocal mucosal neoplasia (type IIb lesions in the Paris classification)

Time between measurement of index test and reference standard: unclear</td></tr>
<tr><td>2×2 table</td><td></td><td>Reference standard +</td><td>Reference standard −</td><td>Total</td><td rowspan="4">EUS for T1m (mucosal carcinoma) vs T1sm (submucosal carcinoma); calculated including only people with T1m and T1sm on EUS and histology (n=55); excluding those with T2 (n=4) and T3(n=3) histology.
T1m assumed to correspond to T1a
T1sm assumed to correspond to T1b</td></tr>
<tr><td></td><td>Index test +</td><td>39</td><td>8</td><td>47</td></tr>
<tr><td></td><td>Index test −</td><td>5</td><td>3</td><td>8</td></tr>
<tr><td></td><td>Total</td><td>44</td><td>11</td><td>55</td></tr>
<tr><td>Statistical measures</td><td colspan="5"><u>Index test CT for staging T1 tumours</u>
Sensitivity: 1.00
Specificity: 0.00

<u>Index test EUS for T staging (T1m vs T1sm)</u>
Sensitivity: 0.89 (95% CI 0.75-0.96)
Specificity: 0.27 (95% CI 0.06-0.61)

<u>Index test EUS for N staging</u>
Sensitivity: 0.75
Specificity: 0.97

<u>Index test CT for N staging</u>
Sensitivity: 0.38</td></tr>
</table>

Reference	Pech 2006 [4]
	Specificity: 1.00
Source of funding	None
Limitations	Risk of bias: Serious risk of bias due to flow and timing (analysis based on 66/100 people who had HFPs) lack of clarity over the interpretation of the index test results without knowledge of the reference standard results and it being unclear for which participants reference standard was endoscopic or surgical. Indirectness: Serious population indirectness with the study including people with confirmed 'early' carcinoma and being it unclear if a stage higher than 1 was suspected (at least 7 of which had higher than stage 1 on histology)
Comments	

Reference	Pech 2010 [3]
Study type	Prospective randomised cross-over study
Study methodology	Data source: Patients referred for endoscopic treatment for Barrett's cancer between 2006 and 2007 Recruitment: consecutive
Number of patients	n = 43
Patient characteristics	Age, median (range): 66 (58-73) years Gender (male to female ratio): 34/9 Ethnicity: not specified Setting: Department of Internal Medicine, HSK Wiesbaden, Wiesbaden, Germany Country: Germany

Reference	Pech 2010 [3]
	Inclusion criteria: all patients with suspected early cancer in Barrett's oesophagus who were referred for endoscopic treatment. Patients were screened by high-resolution video endoscopy with acetic acid staining (Fuijinon EG-450HR or EG-450WR5 instruments; Fujinon Europe, Inc. Willich, Germany) Exclusion criteria: not specified
Target condition(s)	T staging (mucosal and submucosal cancer)
Index test(s) and reference standard	Participants were randomised to either HFPs or crEUS as the initial diagnostic method; afterwards all patients were re-examined with the alternative procedure by the same endosonographer. All examinations were performed by two experienced endosonographers with experience averaging more than 1000 EUS procedures in total and more than 200 oesophageal cancer staging procedures each per year. One day before EUS staging, upper endoscopy was performed by an experienced endoscopist who was not the endosonographer for the same patient. The assessment of macroscopic tumour type was performed prospectively at the first endoscopy performed in the hospital's medical department using the Japanese classification (since 2003, the Paris classification), which divides superficial neoplastic lesions into the following gross types: polypoid (type I), flat and slightly elevated (IIa), flat and level (IIb), flat depressed (IIc) and ulcerated (III). Biopsies were taken from all lesions seen, as were four-quadrant biopsies every 1-2cm over the entire Barrett's segment. The histological criteria, classification, and assessment of differentiation grade corresponded to the WHO classification. Patients with HGIN or type IIb lesions were excluded from this study because recent analysis demonstrated that this macroscopic type is almost never associated with submucosal invasion. <u>Index test: High- frequency mini-probes (HFPs)</u> 20-MHz HFPs (Fuijnon SP 501; Fujinon Europe). HFPs were used after instillation of water into the oesophageal lumen and suctioning of luminal air. Infiltration depth and lymph node status were assessed. <u>Index test: Conventional radial endoscopic ultrasonography (crEUS)</u> crEUS (Pentax EG-3630; 7.5-10 MHz; Pentax, Tokyo, Japan, with Hitachi EUB 6500, Hitachi Medical Systems GmbH, Wiesbaden, Germany). Infiltration depth and lymph node status were assessed. T and N staging was carried out using standard EUS criteria based on the TNM classification system. Mucosal cancer was defined as a hypoechoic thickening of the mucosal layer (second layer on EUS). Submucosal infiltration was defined as hypoechoic invasion or loss of the fourth layer using the 20 MHz HFPs and of the third layer using crEUS with 10 MHz. The frequency of the crEUS was then changed to 7.5 MHz to assess lymph node status. Criteria for malignant lymph nodes were: size 10mm or greater; round shape; hypoechoic pattern; clear visible borders. <u>Reference standard: Histology (from endoscopic resection or surgical specimens)</u>

<table>
<tr><td>Reference</td><td colspan="5">Pech 2010 [3]</td></tr>
<tr><td></td><td colspan="5">The results of the T staging were compared with the pathological T category (pTX). Only patients with histologically proven T stage were included in the analysis. Patients with suspected mucosal Barrett’s cancer or Barrett’s cancer with submucosal infiltration without suspect lymph nodes underwent (diagnostic) endoscopic resection using the ‘such-and-cut’ technique with a ligation device. The ligation device was reusable EuroLigator (WMT Inc., Wiesbaden, Germany). The resected specimens and histopathological assessments were processed by highly experienced pathologists.
All patients who were treated endoscopically were included in a follow-up protocol. Those patients with a suspected tumour staged T2 or higher and/or suspect lymph nodes were scheduled to undergo oesophageal resection. The results of the EUS assessments were compared with the histopathological findings after oesophageal resection.

Time between measurement of index test and reference standard: 1 day</td></tr>
<tr><td>2×2 table</td><td></td><td>Reference standard +</td><td>Reference standard −</td><td>Total</td><td rowspan="4">2x2 only calculable for N staging; N1 status by crEUS for n=16 patients.</td></tr>
<tr><td></td><td>Index test +</td><td>3</td><td>1</td><td>4</td></tr>
<tr><td></td><td>Index test −</td><td>0</td><td>12</td><td>12</td></tr>
<tr><td></td><td>Total</td><td>3</td><td>13</td><td>16</td></tr>
<tr><td>Statistical measures</td><td colspan="5"><u>Index test HFP for (pT1m); (n=36)</u>
Sensitivity: 0.70 (95% CI 0.46-0.87)
Specificity: 0.69 (95% CI 0.41-0.88)

<u>Index test HFP for (pT1sm); (n=36)</u>
Sensitivity: 0.69 (95% CI 0.41-0.88)
Specificity: 0.75 (95% CI 0.50-0.90)

<u>Index test crEUS for (pT1m); (n=25)</u>
Sensitivity: 0.73 (95% CI 0.39-0.93)
Specificity: 0.78 (95% CI 0.49-0.94)

<u>Index tests crEUS for (pT1sm); (n=25)</u>
Sensitivity: 0.64 (0.36-0.86)
Specificity: 0.73 (0.39-0.93)

<u>Index test: crEUS for N1 status (n=16)</u>
Sensitivity: 1.00 (95% CI 0.29-1.00)
Specificity: 0.92 (95% CI 0.64-1.00)</td></tr>
</table>

Reference	**Pech 2010** [3]
Source of funding	Not specified
Limitations	Risk of bias: serious risk of bias due to lack of sufficient detail on patient selection (exclusion criteria not specified) Indirectness: serious population indirectness with the study including people with suspected 'early' carcinoma and being it unclear if a stage higher than 1 was suspected (information in the paper suggests T2 was suspected for some but it is unclear at which stage during the study)
Comments	

Reference	**Scotiniotis 2001**[5]
Study type	Retrospective study
Study methodology	Data source: EUS database established in 1993. Recruitment: not specified; people from database meeting inclusion criteria
Number of patients	n = 22
Patient characteristics	Age, mean (SD): 64 (8.7) years Gender (male to female ratio): 20/2 Ethnicity: not specified Setting: not specified Country: USA Inclusion criteria: Patients with Barrett's oesophagus and high-grade dysplasia or intramucosal carcinoma based on endoscopy, endoscopic biopsies and CT who underwent EUS between November 1993 and January 2000; who went oesophagectomy with surgical pathology available for comparison with EUS findings. Exclusion criteria: people who did not undergo surgery or whose endoscopic biopsy specimens obtained at the time of EUS demonstrated submucosal invasion (stage T1b) Other characteristics: mean length of Barrett's epithelium (SD; range): 7 (2.6- 2.11) cm

Reference	**Scotiniotis 2001[5]**
Target condition(s)	T staging (T1b vs Tcis/T1a ,T2,T3)
Index test(s) and reference standard	Index test: EUS EUS was performed with the patient under conscious sedation with a mechanical sector scanning echoendoscope system (GF-UM2O, Olympus America, Inc., Melville, N.Y.). The procedures were performed by 2 experienced endosonographers (G.G.G., M.L.K.). Images were obtained at 7.5 MHz and 12 MHz. Because all patients had HGD or ImCa on endoscopic biopsy, the determination that a lesion was superficial was based on preservation of the integrity of the submucosal layer as demonstrated by its endosonographic characteristics. Therefore, absence of disruption of the hyperechoic, third sonographic layer, or the interface between the second and third layers, beneath the lesion was interpreted as no submucosal invasion. Lesions with these findings were accorded stage Tcis/T1a rather than Tx or T0 because of the known HGD or ImCa on biopsy. Submucosal invasion (T1b) was diagnosed when there was hypoechoic disruption of the interface between the second and third sonographic layers and focal hypoechoic blurring or thickening of the third layer. Focal hypoechoic wall layer disruption extending into but not through the fourth hypoechoic layer indicated invasion into the muscularis propria (T2), and extending through the fourth sonographic layer indicated invasion into the adventitia and periesophageal tissue (T3). Staging of lymph nodes was complete in all cases. Lymph nodes were assessed along the length of the oesophagus and in the proximal gastric and celiac regions. For staging purposes, lymph nodes were classified as positive (N1) if they exhibited 2 of the following criteria: were greater than 1 cm in diameter, round with discrete margins, and/or hypoechoic. Lymph nodes were considered as not containing malignancy (N0) if they were small, isoechoic or hyperechoic, had a non-discrete margin, and were not round in shape. Reference standard: Histopathologic evaluation A single GI pathologist (E.E.F.) reviewed all endoscopic biopsy and esophagectomy specimens. Tissue was fixed in formalin, and sections were examined after staining with H&E. The diagnosis of Barrett's epithelium was established by the presence of specialized columnar epithelium in esophageal biopsy specimens. HGD arising in Barrett's epithelium was diagnosed by using an established classification scheme.28 ImCa (stage T1a) was defined as carcinoma cells extending beyond the basement membrane into the lamina propria or muscularis mucosae, but no beyond. Esophageal resection specimens were evaluated according to a standardized protocol in which the entire segment of Barrett's epithelium was sectioned. All resected lymph nodes were evaluated histologically. Time between measurement of index test and reference standard: not specified

2×2 table

	Reference standard +	Reference standard −	Total
Index test +	5	1	6
Index test −	0	16	16
Total	5	17	22

2x2 table for T1b vs Tcis/T1a, T2, T3

Reference	Scotiniotis 2001[5]
Statistical measures	Index test EUS for T1b vs Tcis/T1a, T2, T3 (n=22) Sensitivity: 1.00 (95% CI 0.48- 1.00) Specificity: 0.94 (95% CI 0.71- 1.00)
Source of funding	Two of the authors have served as paid consultants for, have received research assistance in the form of equipment donation from, and have received invited speaker honoraria from Olympus America, Inc.
Limitations	Risk of bias: serious risk of bias due to lack of sufficient detail on the interpretation of the index test and reference standard results. Indirectness: serious due to the inclusion of n=4 people with cancer stage T2 or T3.
Comments	

Reference	Thomas 2010[6]
Study type	Retrospective series
Study methodology	Data source: Patients with histologically proven high-grade intraepithelial neoplasia or intramucosal carcinoma complicating Barrett's oesophagus referred for further evaluation to one of two tertiary referral centres between March 2003 and September 2008. Recruitment: not specified
Number of patients	n = 50
Patient characteristics	Age, median (range): 69 (60-79) years Gender (male to female ratio): 32/18 Ethnicity: not specified Setting: tertiary referral centre Country: UK Inclusion criteria: patients with histologically proven high-grade intraepithelial neoplasia (HGIN) or intramucosal carcinoma (IMC) complicating Barrett's oesophagus referred for further evaluation to one of two tertiary referral centres. Exclusion criteria: not specified Other characteristics: length of Barrett's oesophagus ranged from 1 to 12 cm (median 4); Pre-EUS histology: n=31 (62%) high grade dysplasia, n=19 (38%) intramucosal carcinoma

Reference	**Thomas 2010[6]**				
Target condition(s)	T staging (T1m vs T0; T1sm vs T1m and T0); N staging (N1 vs N0)				
Index test(s) and reference standard	All the patients had undergone conventional white light endoscopy and were found to have HGIN or IMC based on Barrett's surveillance by the referring clinicians. The patients were further evaluated with high-resolution endoscopy using the Olympus Lucera video endoscope system (Olympus KeyMed Ltd., Southend-on-Sea, Essex, UK) and GIF H260 or Q240FZ Olympus gastroscopes followed by EUS assessment for depth of invasion and the presence of regional lymphadenopathy using conventional 7.5- to 20-MHz radial echoendoscopes. Targeted biopsies and/or four quadrant biopsies every 1–2 cm were taken to map the entire Barrett's segment. Visible lesions were classified according to the Paris classification. Index test: EUS All the patients had intravenous sedation with diazepam and pethidine or with midazolam and fentanyl. The patients were assessed by three experienced operators (G. P. Aithal and K. Ragunath in Nottingham, and I. Penman in Edinburgh) using radial EUS (GF-UM2000 or GF-UE260-AL5p (Olympus-Keymed). Endoscopically visible lesions were evaluated using a frequency of 7.5, 10, 12, and/or 20 MHz. The depth of invasion was assessed using a frequency of 20 MHz (mechanical radial scope GFUM2000) and 10 MHz (electronic radial scope GF-UE260- AL5). High-frequency probes were not used for any cases. Submucosal invasion was defined as hypoechoic involvement of the third layer or hypoechoic loss of the interface between the second and third layers on EUS. Lesions were staged based on the tumor node metastasis (TNM) classification. Clinically significant lymphadenopathy was defined as hypoechogenic, rounded nodes with clearly defined margins of 10 mm or more. Reference standard: Histology (of endoscopically or surgically resected specimens) Endoscopic mucosal resection was performed using either the cap technique (Olympus-Keymed) or the multiband mucosectomy technique (Duette, Cook, UK). The patients referred for surgery underwent conventional esophagectomy by a dedicated oesophageal surgical team. The resected specimens were reviewed by two expert gastrointestinal pathologists for the presence of HGIN or IMC in Barrett's oesophagus. Nodal positivity on EUS was based on the morphologic appearance of the nodes on EUS and not on fine-needle aspiration (FNA) sampling Time between measurement of index test and reference standard: not specified				
2×2 table		Reference standard +	Reference standard −	Total	**2x2 table calculated from narrative reporting for T1sm vs T0 and T1m T1m=T1a T1sm=T1b**
	Index test +	10	2	12	
	Index test −	8	26	34	
	Total	18	28	46	
2x2 table		Reference standard +	Reference standard −	Total	**N staging (N1 vs N0)**
	Index test +	1	1	2	

Reference	**Thomas 2010[6]**				
	Index test −	1	25	27	
	Total	2	26	29	
Statistical measures	Index test EUS for T1sm vs T1m+T0; (n=46) Sensitivity: 0.56 (95% CI 0.31-0.78) Specificity: 0.93 (95% CI 0.76-0.99) Index test EUS for N staging (N1 vs N0) (n=29) Sensitivity: 0.50 (95% CI 0.01- 0.99) Specificity: 0.96 (95% 0.81 - 1.00)				
Source of funding	Authors supported by speaker honorariums, educational grants, and research support from Olympus-Keymed and Cook, UK, educational support from Olympus Keymed and Cook, UK.				
Limitations	Risk of bias: very serious risk of bias due to lack of sufficient detail on patient selection, lack of detail on the interpretation of the index test and reference standard results. Indirectness: none				
Comments					

Appendix E – Forest plots

Coupled sensitivity and specificity forest plots

Figure 2: Mini-probe EUS (ref. standard: histology based on endoscopic or surgical resection) for T1a vs T1b (T1m vs T1sm) stage

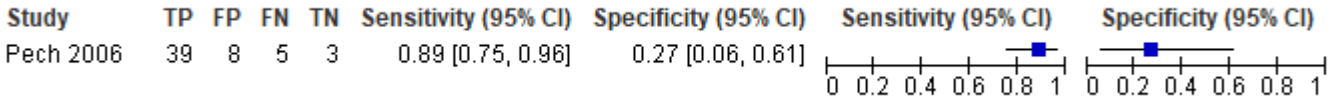


Figure 3: crEUS (ref. standard: histology based on surgical resection) for N1 vs N0 status

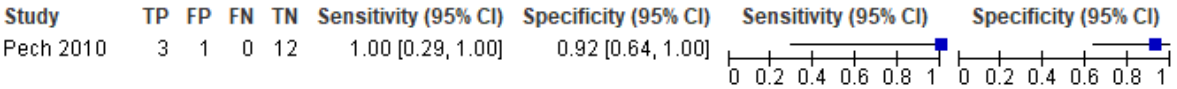


Figure 4: EUS (ref. standard: histopathological assessment of resected specimens) for T1a vs T1b, T2-4 stage

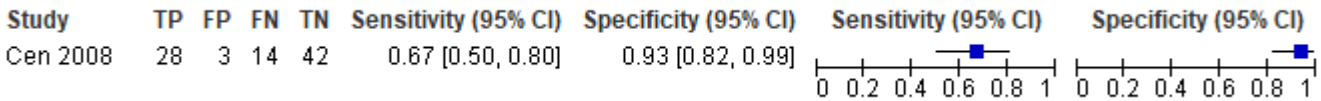


Figure 5: EUS (ref. standard: histopathological assessment of resected specimens) for N1 vs N0 status

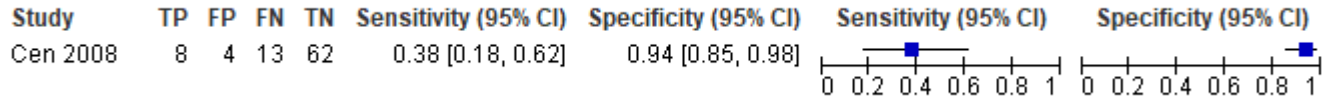


Figure 6: EUS (ref. standard: histology) for T1b vs T0, T1a

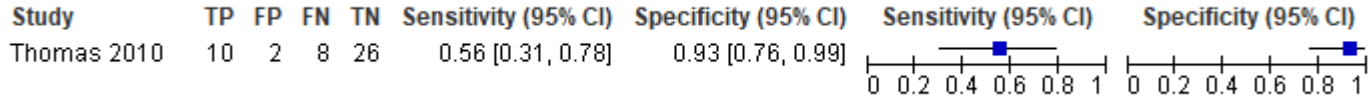
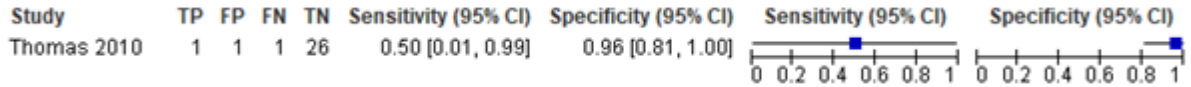


Figure 4: **Figure 7: EUS (ref. standard: histology) for N1 vs N0 status**

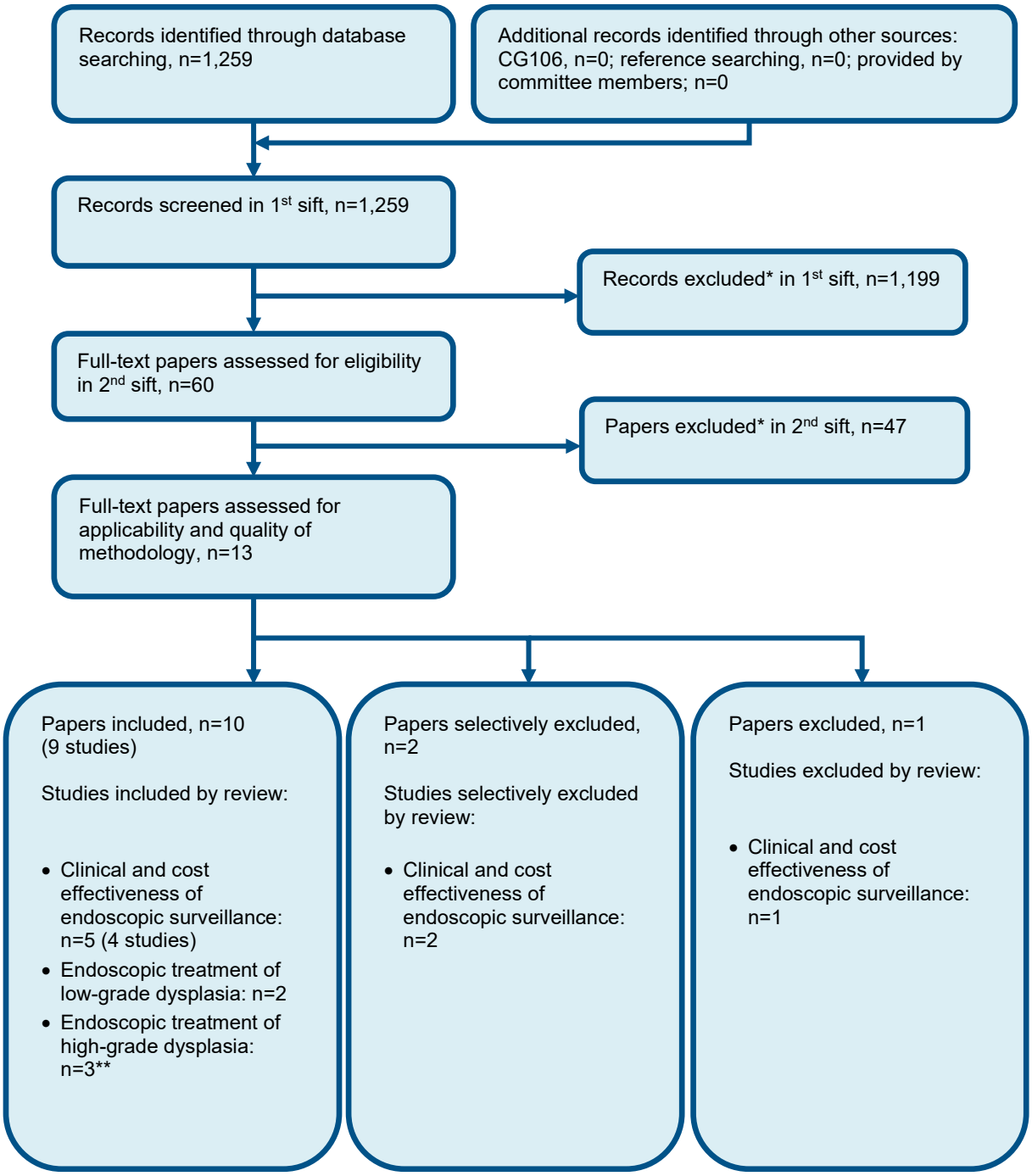


Source: <Insert Source text here>

Figure 5: EUS (ref. standard: histopathologic evaluation) for T1b vs Tcis/T1a, T2 or T3

Source: <Insert Source text here>

Appendix F – 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 G – Excluded studies

Clinical studies

Table 9: Studies excluded from the clinical review

Study	Reason for exclusion
Ahn, H. S., Lee, H. J., Yoo, M. W. et al. (2009) Diagnostic accuracy of T and N stages with endoscopy, stomach protocol CT, and endoscopic ultrasonography in early gastric cancer. Journal of Surgical Oncology 99(1): 20-7	- Population not relevant to this review protocol *Participants with gastric cancer*
Akahoshi, K., Chijiiwa, Y., Hamada, S. et al. (1997) Endoscopic ultrasonography: a promising method for assessing the prospects of endoscopic mucosal resection in early gastric cancer. Endoscopy 29(7): 614-9	- Population not relevant to this review protocol
Arima, M., Arima, H., Tada, M. et al. (2007) Diagnostic accuracy of tumor staging and treatment outcomes in patients with superficial esophageal cancer. Esophagus 4(4): 145-153	- Population not relevant to this review protocol *No patient with adenocarcinoma included*
Bajbouj, M., Vieth, M., Rosch, T. et al. (2010) Probe-based confocal laser endomicroscopy compared with standard four-quadrant biopsy for evaluation of neoplasia in Barrett's esophagus. Endoscopy 42(6): 435-40	- No relevant outcomes *study reports on the detection of neoplasia but no data on the diagnostic accuracy of staging*

Study	Reason for exclusion
Bar-Shalom, R., Guralnik, L., Tsalic, M. et al. (2005) The additional value of PET/CT over PET in FDG imaging of oesophageal cancer. European Journal of Nuclear Medicine & Molecular Imaging 32(8): 918-24	- Population not relevant to this review protocol *Initial diagnosis was higher than stage 1 cancer*
Bartel, M. J., Wallace, T. M., Gomez-Esquivel, R. D. et al. (2017) Role of EUS in patients with suspected Barrett's esophagus with high-grade dysplasia or early esophageal adenocarcinoma: impact on endoscopic therapy. Gastrointestinal Endoscopy 86(2): 292-298	- Population not relevant to this review protocol *Patients with low grade dysplasia and non dysplastic Barrett's oesophagus included*
Bergeron, E. J., Lin, J., Chang, A. C. et al. (2014) Endoscopic ultrasound is inadequate to determine which T1/T2 esophageal tumors are candidates for endoluminal therapies. Journal of Thoracic & Cardiovascular Surgery 147(2): 765-71: Discussion 771	- Population not relevant to this review protocol
Bhandari, P., Kandaswamy, P., Cowlishaw, D. et al. (2012) Acetic acid-enhanced chromoendoscopy is more cost-effective than protocol-guided biopsies in a high-risk Barrett's population. Diseases of the Esophagus 25(5): 386-392	- Population not relevant to this review protocol *suspected high grade dysplasia on biopsy and true diagnosis was low-grade dysplasia, high-grade dysplasia, non-dysplasric barrett's and cancer; no relevant data on staging*
Binmoeller, K. F., Seifert, H., Seitz, U. et al. (1995) Ultrasonic esophagoprobe for TNM staging of highly stenosing esophageal carcinoma. Gastrointestinal Endoscopy 41(6): 547-52	- Population not relevant to this review protocol *people with oesophageal malignancy likely not related to Barrett's oesophagus and including suspected stage higher than 1.*
Boerwinkel, D. F., Holz, J. A., Kara, M. A. et al. (2014) Effects of autofluorescence imaging on detection and treatment of early neoplasia in	- No relevant outcomes *neoplasia detection with no data on staging*

Study	Reason for exclusion
patients with Barrett's esophagus. Clinical Gastroenterology & Hepatology 12(5): 774-81	
Cen, P., Hofstetter, W. L., Correa, A. M. et al. (2008) Lymphovascular invasion as a tool to further subclassify T1b esophageal adenocarcinoma. Cancer 112(5): 1020-7	- Conference abstract
Chen, Y., Aguirre, A. D., Hsiung, P. L. et al. (2007) Ultrahigh resolution optical coherence tomography of Barrett's esophagus: preliminary descriptive clinical study correlating images with histology. Endoscopy 39(7): 599-605	- No relevant outcomes *No staging data; incorrect population: not suspected stage 1, including low and high grade dysplasia, non-dysplastic Barrett's, carcinoma and Barrett's epithelium.*
Choi, J. Y., Lee, K. S., Kwon, O. J. et al. (2005) Improved detection of second primary cancer using integrated [18F] fluorodeoxyglucose positron emission tomography and computed tomography for initial tumor staging. Journal of Clinical Oncology 23(30): 7654-7659	- Population not relevant to this review protocol *Participants with different type of cancers not relevant to the protocol*
Choi, J., Kim, S. G., Kim, J. S. et al. (2010) Comparison of endoscopic ultrasonography (EUS), positron emission tomography (PET), and computed tomography (CT) in the preoperative locoregional staging of resectable esophageal cancer. Surgical Endoscopy 24(6): 1380-6	- Population not relevant to this review protocol *More than 90% participants with SCC*
Cuellar, S. L., Carter, B. W., Macapinlac, H. A. et al. (2014) Clinical staging of patients with early esophageal adenocarcinoma: does FDG-PET/CT have a role?. Journal of Thoracic Oncology: Official Publication of the International Association for the Study of Lung Cancer 9(8): 1202-6	- Population not relevant to this review protocol *people with adenocarcinoma of the distal oesophagus and or gastroesophageal junction. not related to Barrett's oesophagus*

Study	Reason for exclusion
Curvers, W. L., Singh, R., Song, L. M. W. K. et al. (2008) Endoscopic tri-modal imaging for detection of early neoplasia in Barrett's oesophagus: A multi-centre feasibility study using high-resolution endoscopy, autofluorescence imaging and narrow band imaging incorporated in one endoscopy system. Gut 57(2): 167-172	- No relevant outcomes *diagnostic accuracy for high-grade dysplasia/carcinoma (of unspecified stage) together; no staging data.*
Eloubeidi, M. A., Cerfolio, R. J., Bryant, A. S. et al. (2011) Efficacy of endoscopic ultrasound in patients with esophageal cancer predicted to have N0 disease. European Journal of Cardio-Thoracic Surgery 40(3): 636-41	- Population not relevant to this review protocol *mixed population of high-grade dysplasia, adenocarcinoma, squamous cell carcinoma where only 29% was related to Barrett's oesophagus*
Esaki, M., Matsumoto, T., Moriyama, T. et al. (2006) Probe EUS for the diagnosis of invasion depth in superficial esophageal cancer: A comparison between a jelly-filled method and a water-filled balloon method. Gastrointestinal Endoscopy 63(3): 389-395	- Population not relevant to this review protocol *squamous cell carcinoma*
Everson, M. A., Lovat, L. B., Graham, D. G. et al. (2019) Virtual chromoendoscopy by using optical enhancement improves the detection of Barrett's esophagus-associated neoplasia. Gastrointestinal Endoscopy 89(2): 247-256.e4	- No relevant outcomes *diagnostic accuracy of different endoscopists in detecting dysplasia from images obstained from HD imaging or iScan images + interobserver agreement; no staging data*
Fang, T. C., Oh, Y. S., Szabo, A. et al. (2016) Utility of dysphagia grade in predicting endoscopic ultrasound T-stage of non-metastatic esophageal cancer. Diseases of the Esophagus 29(6): 642-8	- Study does not contain an intervention relevant to this review protocol

Study	Reason for exclusion
Flamen, P., Lerut, A., Van Cutsem, E. et al. (2000) Utility of positron emission tomography for the staging of patients with potentially operable esophageal carcinoma. Journal of Clinical Oncology 18(18): 3202-10	- Population not relevant to this review protocol *Participants with SCC included*
Fortun, P. J., Anagnostopoulos, G. K., Kaye, P. et al. (2006) Acetic acid-enhanced magnification endoscopy in the diagnosis of specialized intestinal metaplasia, dysplasia and early cancer in Barrett's oesophagus. Alimentary Pharmacology and Therapeutics 23(6): 735-742	- No relevant outcomes *detection of metaplasia, dysplasia, cancer; no staging data*
Gamal, G. H. (2019) Does PET/CT give incremental staging information in cancer oesophagus compared to CECT?. Egyptian Journal of Radiology and Nuclear Medicine 50(1)	- Population not relevant to this review protocol *Participants included were with advanced stage disease*
Giganti, F., Ambrosi, A., Petrone, M. C. et al. (2016) Prospective comparison of MR with diffusion-weighted imaging, endoscopic ultrasound, MDCT and positron emission tomography-CT in the pre-operative staging of oesophageal cancer: results from a pilot study. British Journal of Radiology 89(1068): 20160087	- Population not relevant to this review protocol *people with oesophagogastric junction cancer (Sewert type I, not arising in the context of Barrett's oesophagus)*
Goda, K., Takeuchi, M., Ishihara, R. et al. (2021) Diagnostic utility of a novel magnifying endoscopic classification system for superficial Barrett's esophagus-related neoplasms: a nationwide multicenter study. Esophagus 18(4): 713-723	- Study does not contain an intervention relevant to this review protocol
Gossner, L., May, A., Pech, O. et al. (2000) Chromoendoscopy with methylene blue by Barrett's oesophagus with serious dysplasias or early cancer. Zeitschrift fur gastroenterologie. 38(8): 663	- Study not reported in English

Study	Reason for exclusion
Gossner, L., Pech, O., May, A. et al. (2006) Comparison of methylene blue-directed biopsies and four-quadrant biopsies in the detection of high-grade intraepithelial neoplasia and early cancer in Barrett's oesophagus. Digestive and Liver Disease 38(10): 724-729	- No relevant outcomes *detection of high-grade dysplasia/cancer; no relevant staging data*
Grimm, H., Binmoeller, K. F., Hamper, K. et al. (1993) Endosonography for preoperative locoregional staging of esophageal and gastric cancer. Endoscopy 25(3): 224-230	- Population not relevant to this review protocol *Majority were higher than stage 1 cancer.*
Hansen, C. P.; Oskarsson, K.; Mortensen, D. (2000) Computed tomography for staging of oesophageal cancer. Annales Chirurgiae et Gynaecologiae 89(1): 14-8	- Population not relevant to this review protocol *Participants with SCC included*
Heidemann, J., Schilling, M. K., Schmassmann, A. et al. (2000) Accuracy of endoscopic ultrasonography in preoperative staging of esophageal carcinoma. Digestive Surgery 17(3): 219-224	- Population not relevant to this review protocol *suspected higher than stage 1 adenocarcinoma*
Ito, B., Niwa, Y., Ando, N. et al. (2005) Diagnosis of the depth of invasion of esophageal carcinoma using digital radiography. European Journal of Radiology 54(3): 377-82	- Population not relevant to this review protocol *Participants with SCC*
Jayasekera, C., Taylor, A. C. F., Desmond, P. V. et al. (2012) Added value of narrow band imaging and confocal laser endomicroscopy in detecting Barretts esophagus neoplasia. Endoscopy 44(12): 1089-1095	- No relevant outcomes *No staging data*

Study	Reason for exclusion
Joshi, B. P., Duan, X., Kwon, R. S. et al. (2016) Multimodal endoscope can quantify wide-field fluorescence detection of Barrett's neoplasia. Endoscopy 48(2): A1-A13	- No relevant outcomes *detection of neoplasia/carcinoma with no staging data*
Kara, M. A., Smits, M. E., Rosmolen, W. D. et al. (2005) A randomized crossover study comparing light-induced fluorescence endoscopy with standard videoendoscopy for the detection of early neoplasia in Barrett's esophagus. Gastrointestinal Endoscopy 61(6): 671-8	- No relevant outcomes *detection of high-grade dysplasia/carcinoma; no staging data*
Kato, H., Miyazaki, T., Nakajima, M. et al. (2005) The incremental effect of positron emission tomography on diagnostic accuracy in the initial staging of esophageal carcinoma. Cancer 103(1): 148-56	- Population not relevant to this review protocol *More than 90% participants with SCC*
Kaushik, N., Khalid, A., Brody, D. et al. (2007) Endoscopic ultrasound compared with laparoscopy for staging esophageal cancer. Annals of Thoracic Surgery 83(6): 2000-2	- Population not relevant to this review protocol *adenocarcinoma not specified to be related to Barrett's oesophagus, includes small percentage of squamous cell carcinoma and people suspected of adenocarcinoma higher than stage 1*
Klamt, A. L., Neyeloff, J. L., Santos, L. M. et al. (2021) Echoendoscopy in Preoperative Evaluation of Esophageal Adenocarcinoma and Gastroesophageal Junction: Systematic Review and Meta-analysis. Ultrasound in Medicine & Biology 47(7): 1657-1669	- Systematic review used as source of primary studies
Krasna, M. J., Flowers, J. L., Attar, S. et al. (1996) Combined thoracoscopic/laparoscopic staging of esophageal cancer. Journal of Thoracic & Cardiovascular Surgery 111(4): 800-6; discussion 806	- Population not relevant to this review protocol *mixed population with squamous cell carcinoma; no relevant index tests*

Study	Reason for exclusion
Kutup, A., Link, B. C., Schurr, P. G. et al. (2007) Quality control of endoscopic ultrasound in preoperative staging of esophageal cancer. Endoscopy 39(8): 715-9	- Population not relevant to this review protocol *60% participants with SCC*
Latos, W., Bugaj, A. M., Sieron, A. et al. (2019) Stratification of the dysplasia and neoplasia risk using autofluorescence endoscopic surveillance of Barrett's esophagus. Photodiagnosis & Photodynamic Therapy 25: 285-291	- No relevant outcomes *detection of dysplasia; no staging data*
Lee, G., Hoseok, I., Kim, S. J. et al. (2014) Clinical implication of PET/MR imaging in preoperative esophageal cancer staging: Comparison with PET/CT, endoscopic ultrasonography, and CT. Journal of Nuclear Medicine 55(8): 1242-1247	- Population not relevant to this review protocol *people with squamous cell carcinoma (and suspected higher than stage 1)*
Lerut, T., Flamen, P., Ectors, N. et al. (2000) Histopathologic validation of lymph node staging with FDG-PET scan in cancer of the esophagus and gastroesophageal junction: A prospective study based on primary surgery with extensive lymphadenectomy. Annals of Surgery 232(6): 743-52	- Population not relevant to this review protocol *primary tumour histology included squamous cell carcinoma in 24%, 36% adenocarcinoma of the gastroesophageal junction.*
Li, J.; Zhu, S.; Liu, Z. (2012) SU-E-J-181: Explore the Value of 18F-FDG, PET and CT Scan for the Clinical Stage of Esophageal Carcinoma. Medical Physics 39(6part9): 3694	- Conference abstract
Lightdale, C. J. and Kulkarni, K. G. (2005) Role of endoscopic ultrasonography in the staging and follow-up of esophageal cancer. Journal of Clinical Oncology 23(20): 4483-9	- Review article but not a systematic review

Study	Reason for exclusion
Lok, K. H., Lee, C. K., Yiu, H. L. et al. (2008) Current utilization and performance status of endoscopic ultrasound in a community hospital. Journal of Digestive Diseases 9(1): 41-7	- Population not relevant to this review protocol *Includes participants with gastric cancer and submucosal tumours*
Longcroft-Wheaton, G., Brown, J., Basford, P. et al. (2013) Duration of acetowhitening as a novel objective tool for diagnosing high risk neoplasia in Barrett's esophagus: a prospective cohort trial. Endoscopy 45(6): 426-32	- No relevant outcomes *detection of metaplasia/neoplasia but no staging data*
Longcroft-Wheaton, G., Duku, M., Mead, R. et al. (2010) Acetic acid spray is an effective tool for the endoscopic detection of neoplasia in patients with barrett's esophagus. Clinical Gastroenterology and Hepatology 8(10): 843-847	- No relevant outcomes *detection of neoplasia/dysplasia/cancer but no staging data*
Lowe, V. J., Booya, F., Fletcher, J. G. et al. (2005) Comparison of positron emission tomography, computed tomography, and endoscopic ultrasound in the initial staging of patients with esophageal cancer. Molecular imaging and biology : MIB : the official publication of the Academy of Molecular Imaging 7(6): 422-430	- Population not relevant to this review protocol *includes squamous cell carcinoma and suspected stages higher than 1*
Luketich, J. D., Meehan, M., Nguyen, N. T. et al. (2000) Minimally invasive surgical staging for esophageal cancer. Surgical Endoscopy 14(8): 700-702	- Population not relevant to this review protocol *suspected stage 1 and higher*
Luketich, J. D., Schauer, P., Landreneau, R. et al. (1997) Minimally invasive surgical staging is superior to endoscopic ultrasound in detecting lymph node metastases in esophageal cancer. Journal of Thoracic & Cardiovascular Surgery 114(5): 817-21; discussion 821	- Population not relevant to this review protocol *majority had adenocarcinoma of the gastroesophageal junction or squamous cell carcinoma*

Study	Reason for exclusion
Marzola, M. C., De Manzoni, G., Grassetto, G. et al. (2012) Extended staging of oesophageal cancer using FDG-PET - a critical appraisal. European Journal of Radiology 81(1): 21-30	- Systematic review used as source of primary studies
Meining, A., Dittler, H. J., Wolf, A. et al. (2002) You get what you expect? A critical appraisal of imaging methodology in endosonographic cancer staging. Gut 50(5): 599-603	- Population not relevant to this review protocol *Tumours of the oesophagus, stomach and pancreas stages T1-T3*
Meister, T., Domagk, D., Heinzow, H. S. et al. (2013) Miniprobe endoscopic ultrasound accurately stages esophageal cancer and guides therapeutic decisions in the era of neoadjuvant therapy: Results of a multicenter cohort analysis. Surgical Endoscopy 27(8): 2813-2819	- Population not relevant to this review protocol *stages 1-4; 22% squamous cell carcinoma*
Meltzer, C. C., Luketich, J. D., Friedman, D. et al. (2000) Whole-body FDG positron emission tomographic imaging for staging esophageal cancer comparison with computed tomography. Clinical Nuclear Medicine 25(11): 882-7	- Population not relevant to this review protocol *Mixed sample of people with adenocarcinoma (unclear suspected stage) and squamous cell carcinoma*
Mennigen, R., Tuebergen, D., Koehler, G. et al. (2008) Endoscopic ultrasound with conventional probe and miniprobe in preoperative staging of esophageal cancer. Journal of gastrointestinal surgery : official journal of the Society for Surgery of the Alimentary Tract 12(2): 256-262	- Population not relevant to this review protocol *19% squamous cell carcinoma and unclear if suspected stage 1.*
Menzel, J., Hoepffner, N., Nottberg, H. et al. (1999) Preoperative staging of esophageal carcinoma: miniprobe sonography versus conventional endoscopic ultrasound in a prospective histopathologically verified study. Endoscopy 31(4): 291-7	- Population not relevant to this review protocol *Participants with SCC included*

Study	Reason for exclusion
Meyers, B. F., Downey, R. J., Decker, P. A. et al. (2007) The utility of positron emission tomography in staging of potentially operable carcinoma of the thoracic esophagus: results of the American College of Surgeons Oncology Group Z0060 trial. Journal of Thoracic & Cardiovascular Surgery 133(3): 738-45	- Population not relevant to this review protocol *Mixed populations with oesophageal and squamous cell carcinoma of clinically staged from 1-3 at baseline.*
Montravers, F., Grahek, D., Kerrou, K. et al. (2000) 14. FDG CDET (2D Dual-Head Coincidence Gamma Camera) in the Primary Staging of Oesophageal Cancer. Histopathological Correlation. Clinical Positron Imaging 3(4): 168	- Conference abstract
Moorjani, N., Junemann-Ramirez, M., Judd, O. et al. (2007) Endoscopic ultrasound in esophageal carcinoma: comparison with multislice computed tomography and importance in the clinical decision making process. Minerva Chirurgica 62(4): 217-23	- Population not relevant to this review protocol *Majority of participants with other type of carcinomas included*
Mortensen, M. B., Edwin, B., Hunerbein, M. et al. (2007) Impact of endoscopic ultrasonography (EUS) on surgical decision-making in upper gastrointestinal tract cancer: an international multicenter study. Surgical Endoscopy 21(3): 431-8	- Population not relevant to this review protocol *People with upper gastrointestinal tract cancer including squamous cell carcinoma, adenocarcinoma of the stomach, pancreatic adenocarcinoma), mostly stage higher than 1.*
Moschetta, M., Ianora, A. A., Marzullo, A. et al. (2010) Vessel probe CT protocol in the study of esophageal carcinoma: can it improve preoperative T staging?. European Journal of Surgical Oncology 36(7): 663-9	- Population not relevant to this review protocol *- More than 50% particpants included with SCC- All participants included were suspected with advanced stage disease*

Study	Reason for exclusion
Moss, A., Bourke, M. J., Hourigan, L. F. et al. (2010) Endoscopic resection for Barrett's high-grade dysplasia and early esophageal adenocarcinoma: an essential staging procedure with long-term therapeutic benefit. American Journal of Gastroenterology 105(6): 1276-83	- No relevant outcomes *Study do not report sensitivity and specificity*
Muijs, C. T., Beukema, J. C., Pruim, J. et al. (2010) A systematic review on the role of FDG-PET/CT in tumour delineation and radiotherapy planning in patients with esophageal cancer. Radiotherapy & Oncology 97(2): 165-71	- Systematic review used as source of primary studies
Natsugoe, S., Nakashima, S., Matsumoto, M. et al. (2002) Biologic and imaging diagnosis of lymph node metastasis in esophageal carcinoma. Journal of Surgical Oncology 81(1): 25-32	- Population not relevant to this review protocol *All participants with SCC*
Nattermann, C. and Dancygier, H. (1993) Endoscopic ultrasound in the preoperative TN-staging of oesophageal carcinoma. A comparative study between endosonography and computed tomography. Ultraschall in der Medizin 14(3): 100-105	- Study not reported in English
Nguyen, N. T., Roberts, P. F., Follette, D. M. et al. (2001) Evaluation of minimally invasive surgical staging for esophageal cancer. American Journal of Surgery 182(6): 702-6	- Population not relevant to this review protocol *mixed population with adenocarcinoma not specified to be related to Barrett's and >20%squamous cell carcinoma*
Nishimaki, T., Tanaka, O., Ando, N. et al. (1999) Evaluation of the accuracy of preoperative staging in thoracic esophageal cancer. Annals of Thoracic Surgery 68(6): 2059-64	- Population not relevant to this review protocol *Participants with SCC*

Study	Reason for exclusion
Nishimura, H., Tanigawa, N., Hiramatsu, M. et al. (2006) Preoperative esophageal cancer staging: magnetic resonance imaging of lymph node with ferumoxtran-10, an ultrasmall superparamagnetic iron oxide. Journal of the American College of Surgeons 202(4): 604-11	- Population not relevant to this review protocol *Participants with SCC*
Nobel, T. B., Barbetta, A., Hsu, M. et al. (2019) Ongoing Challenges with Clinical Assessment of Nodal Status in T1 Esophageal Adenocarcinoma. Journal of the American College of Surgeons 229(4): 366-373	- Population not relevant to this review protocol *mixed population of adenocarcinoma (unclear if related to Barrett's) and squamous cell carcinoma*
Nobel, T. B., Curry, M., Gennarelli, R. et al. (2019) Higher clinical suspicion is needed for prompt diagnosis of esophageal adenocarcinoma in young patients. Journal of Thoracic & Cardiovascular Surgery 16: 16	- Study does not contain an intervention relevant to this review protocol
Noble, F., Bailey, D., Panel, Swcis Upper Gastrointestinal Tumour et al. (2009) Impact of integrated PET/CT in the staging of oesophageal cancer: a UK population-based cohort study. Clinical Radiology 64(7): 699-705	- Population not relevant to this review protocol *mixed population with adenocarcinoma and squamous cell carcinoma >20%*
Onbas, O., Eroglu, A., Kantarci, M. et al. (2006) Preoperative staging of esophageal carcinoma with multidetector CT and virtual endoscopy. European Journal of Radiology 57(1): 90-5	- Population not relevant to this review protocol *Participants with Squamous cell carcinoma*
Parry, K., Haverkamp, L., Bruijnen, R. C. et al. (2016) Staging of adenocarcinoma of the gastroesophageal junction. European Journal of Surgical Oncology 42(3): 400-6	- Population not relevant to this review protocol *adenocarcinoma of the gastroesophageal junction*

Study	Reason for exclusion
Pfau, P. R., Perlman, S. B., Stanko, P. et al. (2007) The role and clinical value of EUS in a multimodality esophageal carcinoma staging program with CT and positron emission tomography. Gastrointestinal Endoscopy 65(3): 377-84	- Study does not contain an intervention relevant to this review protocol
Pham, T., Roach, E., Falk, G. L. et al. (1998) Staging of oesophageal carcinoma by endoscopic ultrasound: preliminary experience. Australian & New Zealand Journal of Surgery 68(3): 209-12	- Population not relevant to this review protocol
Pohl, H., Koch, M., Khalifa, A. et al. (2007) Evaluation of endocytoscopy in the surveillance of patients with Barrett's esophagus. Endoscopy 39(6): 492-496	- Population not relevant to this review protocol *not suspected stage 1, includes non-dysplastic and low-grade dysplasia; no relevant outcomes*
Puli, S. R., Reddy, J. B., Bechtold, M. L. et al. (2008) Staging accuracy of esophageal cancer by endoscopic ultrasound: a meta-analysis and systematic review. World Journal of Gastroenterology 14(10): 1479-90	- Systematic review used as source of primary studies
Purandare, N. C., Pramesh, C. S., Karimundackal, G. et al. (2014) Incremental value of 18F-FDG PET/CT in therapeutic decision-making of potentially curable esophageal adenocarcinoma. Nuclear Medicine Communications 35(8): 864-9	- Population not relevant to this review protocol *Advanced stage disease*
Qumseya, B. J., Brown, J., Abraham, M. et al. (2014) Role of endoscopic ultrasound in Barrett's esophagus with HGD or cancer: A systematic review and meta-analysis. Gastrointestinal Endoscopy: ab190	- Conference abstract

Study	Reason for exclusion
Qumseya, B. J., Brown, J., Abraham, M. et al. (2015) Diagnostic performance of EUS in predicting advanced cancer among patients with Barrett's esophagus and high-grade dysplasia/early adenocarcinoma: systematic review and meta-analysis. Gastrointestinal Endoscopy 81(4): 865-74.e2	- Systematic review used as source of primary studies
Rice, T. W.; Boyce, G. A.; Sivak, M. V. (1991) Esophageal ultrasound and the preoperative staging of carcinoma of the esophagus. Journal of Thoracic & Cardiovascular Surgery 101(3): 536-43; discussion 543	- Population not relevant to this review protocol *mixed population of suspected stage 1 and higher than stage 1*
Roedl, J. B., Colen, R. R., King, K. et al. (2008) Visual PET/CT scoring for nonspecific 18F-FDG uptake in the differentiation of early malignant and benign esophageal lesions. AJR. American Journal of Roentgenology 191(2): 515-21	- Study does not contain an intervention relevant to this review protocol
Roedl, J. B., Sahani, D. V., Colen, R. R. et al. (2008) Tumour length measured on PET-CT predicts the most appropriate stage-dependent therapeutic approach in oesophageal cancer. European Radiology 18(12): 2833-40	- Population not relevant to this review protocol *Stages 1-4*
Salminen, J. T., Farkkila, M. A., Ramo, O. J. et al. (1999) Endoscopic ultrasonography in the preoperative staging of adenocarcinoma of the distal oesophagus and oesophagogastric junction. Scandinavian Journal of Gastroenterology 34(12): 1178-82	- Population not relevant to this review protocol *mixed population of adenocarcinoma of the distal oesophagus and oesophagogastric junction; very limited number of people with adenocarcinoma associated with Barrett's.*
Sami, S. S., Subramanian, V., Butt, W. M. et al. (2015) High definition versus standard definition white light endoscopy for detecting dysplasia in	- No relevant outcomes

Study	Reason for exclusion
patients with Barrett's esophagus. Diseases of the Esophagus 28(8): 742-749	*detection of dysplasia and no diagnostic accuracy data*
Sandha, G. S., Severin, D., Postema, E. et al. (2008) Is positron emission tomography useful in locoregional staging of esophageal cancer? Results of a multidisciplinary initiative comparing CT, positron emission tomography, and EUS. Gastrointestinal Endoscopy 67(3): 402-9	- Population not relevant to this review protocol *mixed population with adenocarcinoma (not specified to be related to Barrett's), squamous cell carcinoma and unspecified poorly differentiated carcinoma*
Sazuka, T., Akai, T., Uesato, M. et al. (2016) Assessment for diagnosis of lymph node metastasis in esophageal cancer using endoscopic ultrasound elastography. Esophagus 13: 254-263	- Population not relevant to this review protocol *Participants with Squamous cell carcinoma*
Scholer, A. J., Uppal, A., Chang, S. C. et al. (2020) Inaccurate pretreatment staging can impact survival in early stage esophageal adenocarcinoma. Journal of Surgical Oncology 122(5): 914-922	- Study does not contain an intervention relevant to this review protocol
Schreurs, L. M., Janssens, A. C., Groen, H. et al. (2016) Value of EUS in Determining Curative Resectability in Reference to CT and FDG-PET: The Optimal Sequence in Preoperative Staging of Esophageal Cancer?. Annals of Surgical Oncology 23(suppl5): 1021-1028	- Study does not contain an intervention relevant to this review protocol
Schreurs, L. M., Pultrum, B. B., Koopmans, K. P. et al. (2008) Better assessment of nodal metastases by PET/CT fusion compared to side-by-side PET/CT in oesophageal cancer. Anticancer Research 28(3b): 1867-73	- Study does not contain an intervention relevant to this review protocol

Study	Reason for exclusion
Shen, H., Li, X., Meng, L. et al. (2012) Confirmation of histology of PET positive lymph nodes recovered by hand-video-assisted thoracoscopy surgery. Gene 509(1): 173-7	- Population not relevant to this review protocol *squamous cell carcinoma*
Shi, H., Ma, S., Zhao, P. et al. (2017) Endoscopic ultrasonography for preoperative staging of esophageal carcinoma. Scandinavian Journal of Gastroenterology 52(10): 1052-1056	- Population not relevant to this review protocol *people with oesophageal carcinoma of various stages (including large number with stages 3 and 4) and unclear if related to Barrett's oesophagus*
Shimpi, R. A., George, J., Jowell, P. et al. (2007) Staging of esophageal cancer by EUS: staging accuracy revisited. Gastrointestinal Endoscopy 66(3): 475-82	- Population not relevant to this review protocol *includes very small sample (n=9) part of which were referred for known oesophageal adenocarcinoma without a preceding history of Barrett's oesophagus.*
Shin, S., Kim, H. K., Choi, Y. S. et al. (2014) Clinical stage T1-T2N0M0 oesophageal cancer: accuracy of clinical staging and predictive factors for lymph node metastasis. European Journal of Cardio-Thoracic Surgery 46(2): 274-9; discussion 279	- Population not relevant to this review protocol *More than 90% participants with squamous cell carcinoma*
Sihvo, E. I. T., Rasanen, J. V., Knuuti, M. J. et al. (2004) Adenocarcinoma of the esophagus and the esophagogastric junction: Positron emission tomography improves staging and prediction of survival in distant but not in locoregional disease. Journal of Gastrointestinal Surgery 8(8): 988-996	- Population not relevant to this review protocol *The majority was people with carcinoma located on the oesophageal junction (Siewert type 2) and it was unclear if this was in the context of Barrett"s oesophagus.*
Silva, F. B., Dinis-Ribeiro, M., Vieth, M. et al. (2011) Endoscopic assessment and grading of Barrett's esophagus using magnification	- No relevant outcomes

Study	Reason for exclusion
endoscopy and narrow-band imaging: accuracy and interobserver agreement of different classification systems (with videos). Gastrointestinal Endoscopy 73(1): 7-14	*diagnostic accuracy for detection of dysplastic and non-dysplastic specialised intestinal metaplasia (SIM)*
Singh, R., Shahzad, M. A., Tam, W. et al. (2013) Preliminary feasibility study using a novel narrow-band imaging system with dual focus magnification capability in Barrett's esophagus: is the time ripe to abandon random biopsies?. Digestive Endoscopy 25suppl2: 151-6	- No relevant outcomes *accuracy of detecting non-dysplastic or dysplastic Barrett's including carcinoma with no staging data; population does not meet protocol: not suspected stage 1*
Staiger, W., Ronellenfitsch, U., Hofheinz, R. D. et al. (2010) Endoscopic ultrasound in the pre-therapeutic staging of gastroesophageal adenocarcinoma: The diagnostic value in defining patients eligible for a neoadjuvant chemotherapy regimen. Wideochirurgia I Inne Techniki Maloinwazyjne 5(1): 1-6	- Population not relevant to this review protocol *Participants with advanced stage disease included*
Subasinghe, D. and Samarasekera, D. N. (2010) A study comparing endoscopic ultrasound (EUS) and computed tomography (CT) in staging oesophageal cancer and their role in clinical decision making. Journal of Gastrointestinal Cancer 41(1): 38-42	- Study does not contain an intervention relevant to this review protocol
Sun, G., Tian, J., Gorospe, E. C. et al. (2013) Utility of baseline positron emission tomography with computed tomography for predicting endoscopic resectability and survival outcomes in patients with early esophageal adenocarcinoma. Journal of Gastroenterology & Hepatology 28(6): 975-81	- Study does not contain an intervention relevant to this review protocol

Study	Reason for exclusion
Takashima, S., Takeuchi, N., Shiozaki, H. et al. (1991) Carcinoma of the esophagus: CT vs MR imaging in determining resectability. AJR. American Journal of Roentgenology 156(2): 297-302	- Population not relevant to this review protocol *Patients with SCC*
Tan, R., Yao, S. Z., Huang, Z. Q. et al. (2014) Combination of FDG PET/CT and contrast-enhanced MSCT in detecting lymph node metastasis of esophageal cancer. Asian Pacific Journal of Cancer Prevention: Apjcp 15(18): 7719-24	- Population not relevant to this review protocol *majority had squamous cell carcinoma*
Tekola, B. D., Sauer, B. G., Wang, A. Y. et al. (2014) Accuracy of endoscopic ultrasound in the diagnosis of T2N0 esophageal cancer. Journal of Gastrointestinal Cancer 45(3): 342-6	- Population not relevant to this review protocol *people with oesophageal tumours at various locations, including adenocarcinoma, squamous cell carcinoma, histologic grade G1: well-differentiated G2: moderately differentiated G3: poorly differentiated G4: undifferentiated*
Thekkek, N., Lee, M. H., Polydorides, A. D. et al. (2015) Quantitative evaluation of in vivo vital-dye fluorescence endoscopic imaging for the detection of Barrett's-associated neoplasia. Journal of Biomedical Optics 20(5): 56002	- No relevant outcomes *mixed population of metaplasia and neoplasia; no staging data, study looking at detection of metaplasia/neoplasia*
Tholoor, S., Bhattacharyya, R., Tsagkournis, O. et al. (2014) Acetic acid chromoendoscopy in Barrett's esophagus surveillance is superior to the standardized random biopsy protocol: results from a large cohort study (with video). Gastrointestinal Endoscopy 80(3): 417-24	- Population not relevant to this review protocol *not limited to suspected stage 1 or high-grade dysplasia on biopsy, also includes low-grade dysplasia; no relevant outcomes*
Thosani, N., Singh, H., Kapadia, A. et al. (2012) Diagnostic accuracy of EUS in differentiating mucosal versus submucosal invasion of superficial	- Systematic review used as source of primary studies

Study	Reason for exclusion
esophageal cancers: a systematic review and meta-analysis. Gastrointestinal Endoscopy 75(2): 242-53	
Thota, P. N., Sada, A., Sanaka, M. R. et al. (2017) Correlation between endoscopic forceps biopsies and endoscopic mucosal resection with endoscopic ultrasound in patients with Barrett's esophagus with high-grade dysplasia and early cancer. Surgical Endoscopy 31(3): 1336-1341	- Population not relevant to this review protocol *includes people with non-dysplastic Barrett's and low-grade dysplasia; No sensitivity or specificity data reported.*
Thurau, K., Palmes, D., Franzius, C. et al. (2011) Impact of PET-CT on primary staging and response control on multimodal treatment of esophageal cancer. World Journal of Surgery 35(3): 608-16	- Population not relevant to this review protocol *mixed population of squamous cell carcinoma, adenocarcinoma, anaplastic carcinoma*
Tio, T. L., Coene, P. P., Schouwink, M. H. et al. (1989) Esophagogastric carcinoma: preoperative TNM classification with endosonography. Radiology 173(2): 411-417	- Population not relevant to this review protocol *population was not limited to suspected stage 1.*
Umeoka, S., Koyama, T., Watanabe, G. et al. (2010) Preoperative local staging of esophageal carcinoma using dual-phase contrast-enhanced imaging with multi-detector row computed tomography: value of the arterial phase images. Journal of Computer Assisted Tomography 34(3): 406-12	- Population not relevant to this review protocol *Participants with SCC*
van Heijl, M., Omloo, J. M., van Berge Henegouwen, M. I. et al. (2009) Diagnostic strategies for pre-treatment staging of patients with oesophageal cancer. Digestive Surgery 26(2): 149-55	- Study does not contain an intervention relevant to this review protocol

Study	Reason for exclusion
van Vliet, E. P., Heijenbrok-Kal, M. H., Hunink, M. G. et al. (2008) Staging investigations for oesophageal cancer: a meta-analysis. British Journal of Cancer 98(3): 547-57	- Systematic review used as source of primary studies
van Westreenen, H. L., Cobben, D. C., Jager, P. L. et al. (2005) Comparison of 18F-FLT PET and 18F-FDG PET in esophageal cancer. Journal of Nuclear Medicine 46(3): 400-4	- Population not relevant to this review protocol *includes people with squamous cell carcinoma and overall population was staged 1-3 not suspected stage 1.*
van Westreenen, H. L., Westerterp, M., Sloof, G. W. et al. (2007) Limited additional value of positron emission tomography in staging oesophageal cancer. British Journal of Surgery 94(12): 1515-20	- Population not relevant to this review protocol *oesophageal cancer unclear if related to Barrett's*
van Zoonen, M., van Oijen, M. G., van Leeuwen, M. S. et al. (2012) Low impact of staging EUS for determining surgical resectability in esophageal cancer. Surgical Endoscopy 26(10): 2828-34	- Population not relevant to this review protocol *mixed population of squamous cell carcinoma and adenocarcinoma*
Vazquez-Sequeiros, E., Levy, M. J., Clain, J. E. et al. (2006) Routine vs. selective EUS-guided FNA approach for preoperative nodal staging of esophageal carcinoma. Gastrointestinal Endoscopy 63(2): 204-11	- Population not relevant to this review protocol *mixed population of adenocarcinoma and squamous cell carcinoma*
Vickers, J. (1998) Role of endoscopic ultrasound in the preoperative assessment of patients with oesophageal cancer. Annals of the Royal College of Surgeons of England 80(4): 233-9	- Population not relevant to this review protocol *mixed population of people with normal oesophagus, benign oesophageal pathology and oesophageal cancer the majority of which was T3*

Study	Reason for exclusion
Vickers, J. and Alderson, D. (1998) Oesophageal cancer staging using endoscopic ultrasonography. British Journal of Surgery 85(7): 994-8	- Population not relevant to this review protocol *mixed population of adenocarcinoma and squamous cell carcinoma*
Vilgrain, V., Mompoint, D., Palazzo, L. et al. (1990) Staging of esophageal carcinoma: comparison of results with endoscopic sonography and CT. AJR. American Journal of Roentgenology 155(2): 277-81	- Population not relevant to this review protocol *Participants with SCC*
Vu, C., Tsang, S., Doig, L. et al. (2007) The preferred choice for radial endosonographic staging of esophageal cancer: Standard echoendoscope or nonoptic esophagoprobe?. Surgical Endoscopy and Other Interventional Techniques 21(9): 1617-1622	- Population not relevant to this review protocol *people suspected of oesophageal cancer, unclear if related to Barrett's oesophagus and including people with more advanced stages (T3 and T4); no relevant outcomes (does not report sensitivity or specificity data)*
Wang, L., Song, H., Wang, M. et al. (2021) Utilization of Ultrasonic Image Characteristics Combined with Endoscopic Detection on the Basis of Artificial Intelligence Algorithm in Diagnosis of Early Upper Gastrointestinal Cancer. Journal of Healthcare Engineering 2021: 2773022	- Population not relevant to this review protocol *unclear if cancer was related to Barrett's oesophagus, no mentioning of Barrett's oesophagus; comparison does not meet protocol*
Waterhouse, D. J., Bano, S., Januszewicz, W. et al. (2021) First-in-human pilot study of snapshot multispectral endoscopy for early detection of Barrett's-related neoplasia. Journal of Biomedical Optics 26(10): 10	- Study does not contain an intervention relevant to this review protocol
Waterhouse, D. J., Joseph, J., Neves, A. A. et al. (2016) Design and validation of a near-infrared fluorescence endoscope for detection of early esophageal malignancy. Journal of Biomedical Optics 21(8): 84001	- Study does not contain an intervention relevant to this review protocol

Study	Reason for exclusion
Waterman, M. and Gralnek, I. M. (2009) Capsule endoscopy of the esophagus. Journal of Clinical Gastroenterology 43(7): 605-12	- Review article but not a systematic review
Waxman, I. (1998) Clinical impact of high-frequency ultrasound probe sonography during diagnostic endoscopy--a prospective study. Endoscopy 30suppl1: A166-8	- Study does not contain an intervention relevant to this review protocol
Waxman, I., Raju, G. S., Critchlow, J. et al. (2006) High-frequency probe ultrasonography has limited accuracy for detecting invasive adenocarcinoma in patients with Barrett's esophagus and high-grade dysplasia or intramucosal carcinoma: a case series. American Journal of Gastroenterology 101(8): 1773-9	- No relevant outcomes *detection of high-grade dysplasia/cancer*
Weaver, S. R., Blackshaw, G. R., Lewis, W. G. et al. (2004) Comparison of special interest computed tomography, endosonography and histopathological stage of oesophageal cancer. Clinical Radiology 59(6): 499-504	- Population not relevant to this review protocol *Participants with SCC included*
Weir, D. G. (1971) The diagnostic accuracy of endoscopy of the oesophagus and stomach with and without histology. Journal of the Irish Medical Association 64(426): 664-8	- Study does not contain an intervention relevant to this review protocol
Werbrouck, E., De Hertogh, G., Sagaert, X. et al. (2016) Oesophageal biopsies are insufficient to predict final histology after endoscopic resection in early Barrett's neoplasia. United European Gastroenterology Journal 4(5): 663-668	- Population not relevant to this review protocol *includes people with non-dysplastic Barrett's, low-grade dysplasia*

Study	Reason for exclusion
Westerterp, M., Van Westreenen, H. L., Sloof, G. W. et al. (2006) Role of positron emission tomography in the (re-)staging of oesophageal cancer. Scandinavian Journal of Gastroenterology - Supplement: 116-22	- Systematic review used as source of primary studies
Wildi, S. M., Wallace, M. B., Glenn, T. F. et al. (2003) Accuracy of esophagoscopy performed by a non-physician endoscopist with a 4-mm diameter battery-powered endoscope. Gastrointestinal Endoscopy 57(3): 305-10	- Study does not contain an intervention relevant to this review protocol
Williams, R. N., Ubhi, S. S., Sutton, C. D. et al. (2009) The early use of PET-CT alters the management of patients with esophageal cancer. Journal of Gastrointestinal Surgery 13(5): 868-73	- Population not relevant to this review protocol *mixed population with cancer of the oesophagus and squamous cell carcinoma; no relevant outcomes: no diagnostic accuracy of staging*
Wo, J. M., Ray, M. B., Mayfield-Stokes, S. et al. (2001) Comparison of methylene blue-directed biopsies and conventional biopsies in the detection of intestinal metaplasia and dysplasia in Barrett's esophagus: a preliminary study. Gastrointestinal Endoscopy 54(3): 294-301	- No relevant outcomes *detection of dysplasia; incorrect population: people undergoing surveillance for heartburn or Barrett's oesophagus*
Woolf, G. M., Riddell, R. H., Irvine, E. J. et al. (1989) A study to examine agreement between endoscopy and histology for the diagnosis of columnar lined (Barrett's) esophagus. Gastrointestinal Endoscopy 35(6): 541-4	- Population not relevant to this review protocol *Participants with oesophageal malignancy excluded*
Wray, A.; Rice, P.; Love, M. (2012) Endoscopic ultrasound in Barrett's oesophagitis with dysplasia. Ulster Medical Journal 81(2): 70-3	- No relevant outcomes *analysis of 9 patients with complex Barrett's oesophagitis with stage T1-4 on EUS with data relevant to the detection of 'invasive disease', no data on T1, T1a vs T1b classification.*

Study	Reason for exclusion
Wren, S. M.; Stijns, P.; Srinivas, S. (2002) Positron emission tomography in the initial staging of esophageal cancer. Archives of Surgery 137(9): 1001-6; discussion 1006	- Population not relevant to this review protocol *Participants include patients with SCC*
Yanai, H., Yoshida, T., Harada, T. et al. (1996) Endoscopic ultrasonography of superficial esophageal cancers using a thin ultrasound probe system equipped with switchable radial and linear scanning modes. Gastrointestinal Endoscopy 44(5): 578-82	- Population not relevant to this review protocol *Participants with SCC*
Yang, D., King, W., Aihara, H. et al. (2022) Effect of endoscopic submucosal dissection on histologic diagnosis in Barrett's esophagus visible neoplasia. Gastrointestinal Endoscopy 95(4): 626-633	- Population not relevant to this review protocol *people with lesions were more frequently located in the distal esophagus and/or gastroesophageal junction; includes people with low-grade dysplasia*
Yano, M., Motoori, M., Tanaka, K. et al. (2012) Preoperative staging of clinically node-negative esophageal cancer by the combination of18 f-fluorodeoxyglucose positron emission tomography and computed tomography (FDG-PET/CT). Esophagus 9(4): 210-216	- Population not relevant to this review protocol *Patients with SCC*
Yasuda, K., Kamaguchi, M., Morikawa, J. et al. (2005) Role of endoscopic ultrasonography in the diagnosis of early esophageal carcinoma. Gastrointestinal Endoscopy Clinics of North America 15(1): 93-99	- Review article but not a systematic review
Yokoyama, A., Ichimasa, K., Ishiguro, T. et al. (2012) Is it proper to use non-magnified narrow-band imaging for esophageal neoplasia screening? Japanese single-center, prospective study. Digestive Endoscopy 24(6): 412-8	- Population not relevant to this review protocol *mixed results with squamous cell carcinoma, high grade and low grade neoplasia; no relevant outcomes*

Study	Reason for exclusion
Yoshikane, H., Tsukamoto, Y., Niwa, Y. et al. (1994) Superficial esophageal carcinoma: evaluation by endoscopic ultrasonography. American Journal of Gastroenterology 89(5): 702-7	- Population not relevant to this review protocol *Participants with SCC*
You, J. J., Wong, R. K., Darling, G. et al. (2013) Clinical utility of 18F-fluorodeoxyglucose positron emission tomography/computed tomography in the staging of patients with potentially resectable esophageal cancer. Journal of Thoracic Oncology: Official Publication of the International Association for the Study of Lung Cancer 8(12): 1563-9	- Population not relevant to this review protocol *oesophageal cancer of various stages, unclear if related to Barrett's oesophagus*
Young, J. A.; Hughes, H. E.; Lee, F. D. (1980) Evaluation of endoscopic brush and biopsy touch smear cytology and biopsy histology in the diagnosis of carcinoma of the lower oesophagus and cardia. Journal of Clinical Pathology 33(9): 811-4	- Population not relevant to this review protocol *people with malignant lesions at the junction of the lower oesophagus and cardia; non-specified to be related to Barrett's*
Young, P. E., Gentry, A. B., Acosta, R. D. et al. (2010) Endoscopic ultrasound does not accurately stage early adenocarcinoma or high-grade dysplasia of the esophagus. Clinical Gastroenterology & Hepatology 8(12): 1037-41	- Systematic review used as source of primary studies
Yuki, T., Amano, Y., Kushiyama, Y. et al. (2006) Evaluation of modified crystal violet chromoendoscopy procedure using new mucosal pit pattern classification for detection of Barrett's dysplastic lesions. Digestive & Liver Disease 38(5): 296-300	- Study does not contain an intervention relevant to this review protocol

Study	Reason for exclusion
Zacharias, T., Barrier, A., Montravers, F. et al. (2004) Cardio-esophageal cancer. Is 18Fluorodeoxyglucose positron emission tomography worthwhile?. Hepato-Gastroenterology 51(57): 741-3	- Population not relevant to this review protocol *More than 70% participants with SCC*
Zhang, C., Shi, Z., Kalendralis, P. et al. (2021) Prediction of lymph node metastases using pre-treatment PET radiomics of the primary tumour in esophageal adenocarcinoma: an external validation study. British Journal of Radiology 94(1118): 20201042	- Population not relevant to this review protocol *people with oesophageal adenocarcinomas not specified to be related to Barrett's oesophagus*
Zhang, X., Watson, D. I., Lally, C. et al. (2005) Endoscopic ultrasound for preoperative staging of esophageal carcinoma. Surgical Endoscopy 19(12): 1618-21	- Population not relevant to this review protocol *mixed population with adenocarcinoma and squamous cell carcinoma*
Zhang, Y., He, S., Dou, L. et al. (2019) Esophageal cancer N staging study with endoscopic ultrasonography. Oncology Letters 17(1): 863-870	- Population not relevant to this review protocol *Participants included with SCC*
Zheng, S., Chen, Z., Huang, C. et al. (2019) [99mTc]3PRGD2 for integrin receptor imaging of esophageal cancer: a comparative study with [18F]FDG PET/CT. Annals of Nuclear Medicine 33(2): 135-143	- Population not relevant to this review protocol
Zhou, S. S., Yan, S., Chen, W. C. et al. (2014) Accuracy of endoscopic ultrasound in preoperative staging of early esophageal cancer: A Meta-analysis. World Chinese Journal of Digestology 22(7): 988-999	- Study not reported in English
Ziegler, K., Sanft, C., Zeitz, M. et al. (1991) Evaluation of endosonography in TN staging of oesophageal cancer. Gut 32(1): 16-20	- Population not relevant to this review protocol

Study	Reason for exclusion
	squamous cell carcinoma
Zuccaro, G., Jr., Rice, T. W., Goldblum, J. et al. (1999) Endoscopic ultrasound cannot determine suitability for esophagectomy after aggressive chemoradiotherapy for esophageal cancer. American Journal of Gastroenterology 94(4): 906-12	- Population not relevant to this review protocol *Advanced stage disease*

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 H – Review protocols

H.1 Review protocol for clinical and cost effectiveness of endoscopic and radiological staging techniques

ID	Field	Content
0.	PROSPERO registration number	CRD42022309286
1.	Review title	Clinical and cost effectiveness of endoscopic and radiological staging techniques
2.	Review question	For adults with suspected stage 1 carcinoma, what is the clinical and cost effectiveness of different endoscopic and radiological staging techniques?
3.	Objective	To determine which strategy for staging with different endoscopic and radiological techniques is clinically and cost effective.
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 • Epistemonikos Searches will be restricted by: • English language studies • Human studies • Letters and comments are excluded

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

7.	Intervention	• endoscopic staging techniques
		  ○ high resolution endoscopy with biopsies
		  ○ Chromoendoscopy (e.g. narrow band imaging)
		
		• radiological staging techniques

		○ EUS (endoscopic ultrasound including mini probes) ○ CT ○ CT PET
8.	Comparator	• Within group (e.g. endoscopic staging technique vs. endoscopic staging technique) • Each other (e.g. endoscopic staging technique vs. radiological staging technique •
9.	Types of study to be included	• RCT • Systematic Reviews Published NMAs and IPDs will be considered for inclusion.
10.	Other exclusion criteria	Non-English language studies. 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 people with suspected stage 1 adenocarcinoma, different endoscopic and radiological techniques are used for staging. This review aims to assess the clinical and cost effectiveness of the different techniques
12.	Primary outcomes (critical outcomes)	All outcomes are considered equally important for decision making and therefore have all been rated as critical: • Health related quality of life • Progression to higher stage of cancer • Mortality • Adverse events (staging perforation, bleeding, pain, allergic reaction to contrast + complications of oesophagectomy Time point: any time point available; no minimum follow-up

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) 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 vs. T1b Subgrouping: If serious or very serious heterogeneity (I2>50%) is present, sub-grouping will occur according to the following strategies: none

18.	Type and method of review	☒	Intervention
		☐	Diagnostic
		☐	Prognostic
		☐	Qualitative
		☐	Epidemiologic
		☐	Service Delivery
		☐	Other (please specify)
19.	Language	English	
20.	Country	England	
21.	Anticipated or actual start date		
22.	Anticipated completion date		
23.	Stage of review at time of this submission	Review stage	Started / Completed
		Preliminary searches	☐ / ☐
		Piloting of the study selection process	☐ / ☐
		Formal screening of search results against eligibility criteria	☐ / ☐
		Data extraction	☐ / ☐

		Risk of bias (quality) assessment	☐	☐
		Data analysis	☐	☐
24.	Named contact	5a. Named contact National Guideline Centre 5b Named contact e-mail @nice.org.uk 5e Organisational affiliation of the review National Institute for Health and Care Excellence (NICE) and National Guideline Centre		
25.	Review team members	From the National Guideline Centre: Norma O Flynn Gill Ritchie Amy Crisp Lina Gulhane Stephen Deed Vimal Bedia Muksitur Rahman Melina Vasileiou Maheen Qureshi		
26.	Funding sources/sponsor	This systematic review is being completed by the National Guideline Centre which receives funding from NICE.		

27.	Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.	
28.	Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: [NICE guideline webpage].	
29.	Other registration details		
30.	Reference/URL for published protocol		
31.	Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: • notifying registered stakeholders of publication • publicising the guideline through NICE's newsletter and alerts • issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.	
32.	Keywords	Barrett's Oesophagus	
33.	Details of existing review of same topic by same authors		
34.	Current review status	☒	Ongoing
		☐	Completed but not published

		☐	Completed and published
		☐	Completed, published and being updated
		☐	Discontinued
35..	Additional information		
36.	Details of final publication	www.nice.org.uk	

H.2 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 I – 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.

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 10: Database parameters, filters and limits applied

Database	Dates searched	Search filter used
Medline (OVID)	1946 – 28 April 2022	Randomised controlled trials Systematic review studies Exclusions (animal studies, letters, comments, editorials, case studies/reports) English language
Embase (OVID)	1974 – 28 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 28 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.	Neoplasm Staging/
38.	((neoplasm* or cancer* or tumour* or tumor* or tnm*) adj2 (staging* or stage* or restage* or restaging* or understage* or understaging* or overstage* or overstaging* or classif*)).ti,ab,kf.
39.	Endoscopy, Gastrointestinal/ or Esophagoscopy/ or Gastroscopy/ or Proctoscopy/
40.	(endoscop* or esophagoscop* or esophagogastroduodenoscop* or esophagograph* or colonoscop* or proctoscop* or gastroscop* or spectroscop*).ti,ab,kf.
41.	Colouring agents/ or Chromogenic Compounds/ or Fluorescent dyes/ or *Indigo Carmine/
42.	(chromoscop* or chromoendoscop* or high resolution colonoscop* or dye spray* or indigo carmine or acetic acid or narrow band imag*).ti,ab,kf.
43.	Ultrasonography/

44.	Elasticity Imaging Techniques/
45.	Endosonography/
46.	Microscopy, Acoustic/
47.	Ultrasonography, Doppler/ or Ultrasonography, Doppler, Duplex/ or Ultrasonography, Doppler, Pulsed/
48.	(ultrasonograph* or ultrasound* or ultra sound* or sonograph* or sonogram* or echograph* or echotomograph* or elastography* or elastosonograph* or sonoelastograph* or doppler or endosonograph* or acoustic microscop* or mini probe* or miniprobe* or ultrasonic biomicroscop*).ti,ab,kf.
49.	Tomography/
50.	exp Tomography, Emission-Computed/
51.	exp Tomography, X-Ray/
52.	tomograph*.ti,ab,kf.
53.	tomodensitometry.ti,ab,kf.
54.	exp Positron-Emission Tomography/
55.	exp Diffusion Magnetic Resonance Imaging/
56.	(Diffusion weighted or DWI).ti,ab,kf.
57.	(CT or MDCT or CAT or PET or PETCT or SPECT).ti,ab,kf.
58.	((radioisotop* or isotop* or gamma camera) adj3 (scan* or imag*)).ti,ab,kf.
59.	or/37-58
60.	36 and 59
61.	randomized controlled trial.pt.
62.	controlled clinical trial.pt.
63.	randomi#ed.ab.
64.	placebo.ab.
65.	randomly.ab.
66.	clinical trials as topic.sh.
67.	trial.ti.
68.	or/61-67
69.	Meta-Analysis/
70.	Meta-Analysis as Topic/
71.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
72.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
73.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
74.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
75.	(search* adj4 literature).ab.
76.	(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.
77.	cochrane.jw.
78.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
79.	or/69-78
80.	60 and (68 or 79)

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.	*cancer staging/
37.	((neoplasm* or cancer* or tumour* or tumor* or tnm*) adj2 (staging* or stage* or restage* or restaging* or understage* or understaging* or overstage* or overstaging* or classif*)).ti,ab,kf.
38.	esophagogastroduodenoscopy/ or esophagography/ or esophagoscopy/
39.	(endoscop* or esophagoscop* or esophagogastroduodenoscop* or esophagograph* or colonoscop* or proctoscop* or gastroscop* or spectroscop*).ti,ab,kf.
40.	*Colouring agent/ or *chromoendoscopy/ or *Indigo Carmine/ or *high resolution endoscopy/ or *magnifying endoscopy/
41.	(chromoscop* or chromoendoscop* or high resolution colonoscop* or dye spray* or indigo carmine or acetic acid or narrow band imag*).ti,ab,kf.
42.	*Endoscopic ultrasonography/ or *Echography/
43.	*Elastograph/ or *Elastography/

44.	*Endoscopic ultrasonography/
45.	Microscopy, Acoustic/
46.	*Doppler Ultrasonography/ or *duplex Doppler ultrasonography/ or *pulsed Doppler ultrasonography/
47.	(ultrasonograph* or ultrasound* or ultra sound* or sonograph* or sonogram* or echograph* or echotomograph* or elastography* or elastosonograph* or sonoelastograph* or doppler or endosonograph* or acoustic microscop* or mini probe* or miniprobe* or ultrasonic biomicroscop*).ti,ab,kf.
48.	*tomography/
49.	exp *computer assisted tomography/ or exp *emission tomography/
50.	exp *whole body tomography/ or exp *x-ray tomography/
51.	tomograph*.ti,ab,kf.
52.	tomodensitometry.ti,ab,kf.
53.	*positron emission tomography/ or *computer assisted emission tomography/ or *positron emission tomography-computed tomography/ or *whole body pet/
54.	*diffusion weighted imaging/
55.	(Diffusion weighted or DWI).ti,ab,kf.
56.	(CT or MDCT or CAT or PET or PETCT or SPECT).ti,ab,kf.
57.	((radioisotop* or isotop* or gamma camera) adj3 (scan* or imag*)).ti,ab,kf.
58.	or/36-57
59.	35 and 58
60.	random*.ti,ab.
61.	factorial*.ti,ab.
62.	(crossover* or cross over*).ti,ab.
63.	((doubl* or singl*) adj blind*).ti,ab.
64.	(assign* or allocat* or volunteer* or placebo*).ti,ab.
65.	crossover procedure/
66.	single blind procedure/
67.	randomized controlled trial/
68.	double blind procedure/
69.	or/60-68
70.	systematic review/
71.	Meta-Analysis/
72.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
73.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
74.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
75.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
76.	(search* adj4 literature).ab.
77.	(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.
78.	cochrane.jw.
79.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
80.	or/70-79
81.	59 and (69 or 80)

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: [Neoplasm Staging] explode all trees
#18.	((neoplasm* or cancer* or tumour* or tumor* or tnm*) near/2 (staging* or stage* or restage* or restaging* or understage* or understaging* or overstage* or overstaging* or classif*)):ti,ab
#19.	MeSH descriptor: [Endoscopy, Gastrointestinal] this term only
#20.	MeSH descriptor: [Esophagoscopy] this term only
#21.	MeSH descriptor: [Gastroscopy] this term only
#22.	MeSH descriptor: [Proctoscopy] this term only
#23.	(endoscop* or esophagoscop* or esophagogastroduodenoscop* or esophagograph* or colonoscop* or proctoscop* or gastroscop* or spectroscop*):ti,ab
#24.	MeSH descriptor: [Coloring Agents] this term only
#25.	MeSH descriptor: [Chromogenic Compounds] this term only
#26.	MeSH descriptor: [Fluorescent Dyes] this term only
#27.	MeSH descriptor: [Indigo Carmine] this term only
#28.	(chromoscop* or chromoendoscop* or high resolution colonoscop* or dye spray* or indigo carmine or acetic acid or narrow band imag*):ti,ab
#29.	MeSH descriptor: [Ultrasonography] this term only
#30.	MeSH descriptor: [Elasticity Imaging Techniques] this term only
#31.	MeSH descriptor: [Endosonography] this term only
#32.	MeSH descriptor: [Microscopy, Acoustic] this term only
#33.	MeSH descriptor: [Ultrasonography, Doppler] this term only
#34.	MeSH descriptor: [Ultrasonography, Doppler, Duplex] this term only
#35.	MeSH descriptor: [Ultrasonography, Doppler, Pulsed] this term only
#36.	(ultrasonograph* or ultrasound* or ultra sound* or sonograph* or sonogram* or echograph* or echotomograph* or elastography* or elastosonograph* or sonoelastograph* or doppler or endosonograph* or acoustic microscop* or mini probe* or miniprobe* or ultrasonic biomicroscop*):ti,ab
#37.	MeSH descriptor: [Tomography] this term only
#38.	MeSH descriptor: [Tomography, Emission-Computed] explode all trees
#39.	MeSH descriptor: [Tomography, X-Ray] explode all trees
#40.	tomograph*:ti,ab

#41.	tomodensitometry:ti,ab
#42.	MeSH descriptor: [Positron-Emission Tomography] explode all trees
#43.	MeSH descriptor: [Diffusion Magnetic Resonance Imaging] explode all trees
#44.	(Diffusion weighted or DWI):ti,ab
#45.	(CT or MDCT or CAT or PET or PETCT or SPECT):ti,ab
#46.	((radioisotop* or isotop* or gamma camera) near/3 (scan* or imag*)):ti,ab
#47.	(or #17-#46)
#48.	#16 and #47
#49.	conference:pt or (clinicaltrials or trialsearch):so
#50.	#48 not #49

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:("neoplasm* classif*" OR "neoplasm* staging*" OR "cancer* classif*" OR "cancer* staging*" OR "tumour* classif*" OR "tumour* staging*" OR "tumor* classif*" OR "tumor* staging*" OR "classif* staging*" OR cancer* OR "tnm* classif*" OR "tnm* staging*" OR endoscop* OR esophagoscop* OR esophagogastroduodenoscop* OR esophagograph* OR colonoscop* OR proctoscop* OR gastroscop* OR spectroscop* OR chromoscop* OR chromoendoscop* OR "high resolution colonoscop*" OR "dye spray*" OR "indigo carmine" OR "acetic acid" OR "narrow band imag*" OR ultrasonograph* OR ultrasound* OR "ultra sound*" OR sonograph* OR sonogram* OR echograph* OR echotomograph* OR elastography* OR elastosonograph* OR sonoelastograph* OR doppler OR endosonograph* OR "acoustic microscop*" OR "mini probe*" OR "miniprobe*" OR "ultrasonic biomicroscop*" OR tomograph* OR tomodensitometry OR "Diffusion Magnetic Resonance Imaging" OR "Diffusion weighted") OR abstract:("neoplasm* classif*" OR "neoplasm* staging*" OR "cancer* classif*" OR "cancer* staging*" OR "tumour* classif*" OR "tumour* staging*" OR "tumor* classif*" OR "tumor* staging*" OR "classif* staging*" OR cancer* OR "tnm* classif*" OR "tnm* staging*" OR endoscop* OR esophagoscop* OR esophagogastroduodenoscop* OR esophagograph* OR colonoscop* OR proctoscop* OR gastroscop* OR spectroscop* OR chromoscop* OR chromoendoscop* OR "high resolution colonoscop*" OR "dye spray*" OR "indigo carmine" OR "acetic acid" OR "narrow band imag*" OR ultrasonograph* OR ultrasound* OR "ultra sound*" OR sonograph* OR sonogram* OR echograph* OR echotomograph* OR elastography* OR elastosonograph* OR sonoelastograph* OR doppler OR endosonograph* OR "acoustic microscop*" OR "mini probe*" OR "miniprobe*" OR "ultrasonic biomicroscop*" OR tomograph* OR tomodensitometry OR "Diffusion Magnetic Resonance Imaging" OR "Diffusion weighted")

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 11: 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

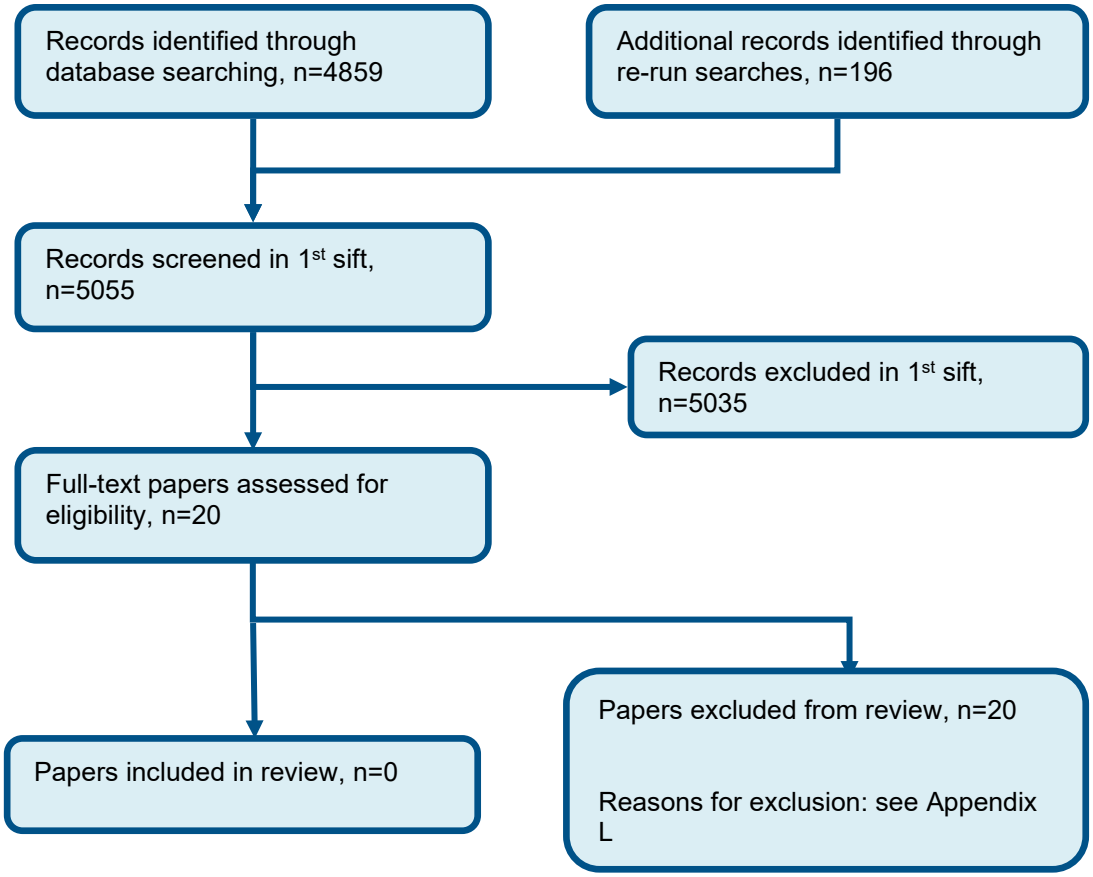
#1.	MeSH DESCRIPTOR Barrett Esophagus EXPLODE ALL TREES
#2.	(barrett*)
#3.	(speciali*) AND (epithel* or oesophag* or esophag* or mucos*)
#4.	(column*) AND (epithel* or oesophag* or esophag* or mucos* or lined or lining or metaplas*)
#5.	#1 OR #2 OR #3 OR #4
#6.	MeSH DESCRIPTOR Precancerous Conditions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

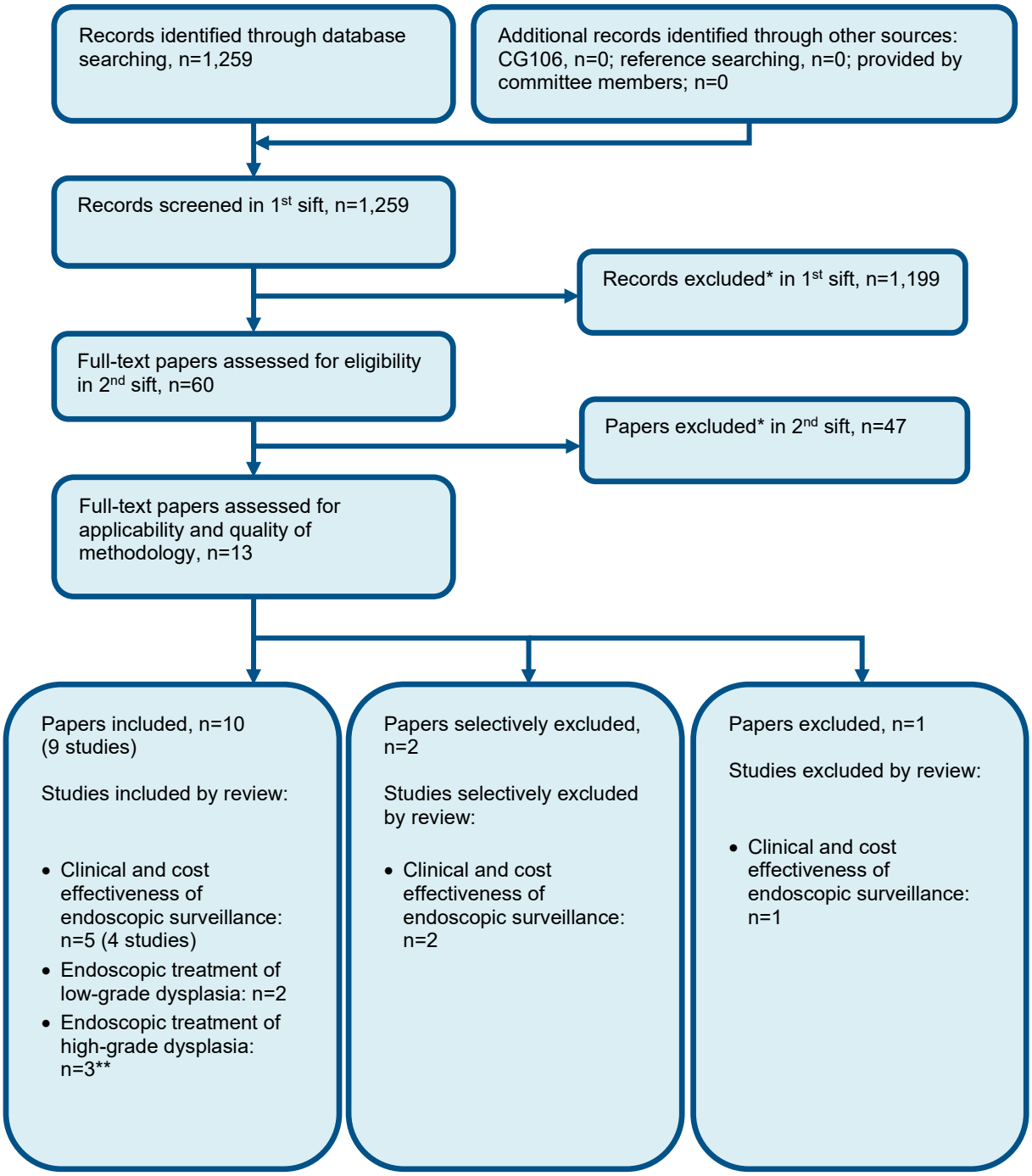
1.	("Barrett Esophagus"[mh]) OR (Barrett*) OR (Esophageal Neoplasms)[mh]

Appendix J – Effectiveness evidence study selection

Figure 6: Flow chart of clinical study selection for the review of clinical and cost-effectiveness of endoscopic and radiological staging techniques



Appendix K – Economic evidence study selection



* Non-relevant population, intervention, comparison, design or setting; non-English language
** One article identified was applicable to Q4.1 and Q4.2, for the purposes of this diagram they have been included under Q4.1 only.

Appendix L – Excluded studies

Clinical studies

Table 12: Studies excluded from the clinical review

Study	Reason for exclusion
Borovicka, J., Fischer, J., Neuweiler, J. et al. (2006) Autofluorescence endoscopy in surveillance of Barrett's esophagus: a multicenter randomized trial on diagnostic efficacy. Endoscopy 38(9): 867-72	- Population not relevant to this review protocol *The majority had non-dysplastic Barrett's oesophagus*
Canto, M. I., Anandasabapathy, S., Brugge, W. et al. (2014) In vivo endomicroscopy improves detection of Barrett's esophagus-related neoplasia: a multicenter international randomized controlled trial (with video). Gastrointestinal Endoscopy 79(2): 211-21	- No relevant outcomes *partially incorrect outcome: detection of neoplasia including high grade dysplasia or cancer (stage not specified); incorrect population: only 24% had suspected or confirmed neoplasia at study entry and it is unclear if that was stage 1.*
Chen, Y. Q.; Wang, G. M.; Zhang, H. M. (2013) Endoscopic acetic acid-Lugol's iodine double staining for diagnosis of early esophageal cancer. World Chinese Journal of Digestology 21(20): 1972-1976	- Full text paper not available
Curvers, W. L., van Vilsteren, F. G., Baak, L. C. et al. (2011) Endoscopic trimodal imaging versus standard video endoscopy for detection of early Barrett's neoplasia: a multicenter, randomized, crossover study in general practice. Gastrointestinal Endoscopy 73(2): 195-203	- No relevant outcomes
Hedenstrom, P., Marschall, H. U., Nilsson, B. et al. (2018) High clinical impact and diagnostic accuracy of EUS-guided biopsy sampling of subepithelial lesions: a prospective, comparative study. Surgical Endoscopy 32(3): 1304-1313	- No relevant outcomes *examining the malignancy of lesions not limited to the oesophagus*
Hoffman, A., Gotz, M., Vieth, M. et al. (2007) Confocal endomicroscopy in comparison with acetic acid support magnification endoscopy by Barrett's oesophagus - a randomised, prospective study with a cross-over design. Zeitschrift fur Gastroenterologie 45(8): 775	- Full text paper not available
Jiang, L., Gao, K., Zheng, J. et al. (2010) A randomized controlled trial of preoperative	- Study not reported in English

Study	Reason for exclusion
assessment of esophageal carcinoma with multi-slice computer tomography and mini-probe endoscopic ultrasonography in the selection of surgical programs. Chinese Journal of Clinical Oncology 37(22): 1300-1303	
Kara, M. A., Peters, F. P., Ten Kate, F. J. W. et al. (2005) Endoscopic video autofluorescence imaging may improve the detection of early neoplasia in patients with Barrett's esophagus. Gastrointestinal Endoscopy 61(6): 679-685	- Population not relevant to this review protocol *Mixed population of people referred for endoscopy due to regular surveillance (non-dysplastic Barrett's), evaluation of newly diagnosed high-grade dysplasia or oesophageal carcinoma or follow-up after endoscopic treatment of high-grade dysplasia or carcinoma; outcome was detection of high-grade dysplasia and carcinoma*
Kara, M. A., Smits, M. E., Rosmolen, W. D. et al. (2005) A randomized crossover study comparing light-induced fluorescence endoscopy with standard videoendoscopy for the detection of early neoplasia in Barrett's esophagus. Gastrointestinal Endoscopy 61(6): 671-8	- Population not relevant to this review protocol *Mixed population of non-dysplastic Barrett's oesophagus, high and low grade dysplasia, indefinite for dysplasia; no relevant outcome: diagnostic accuracy data for detection of high-grade dysplasia/ carcinoma (of unspecified stage)*
Matthes, K., Bounds, B. C., Collier, K. et al. (2006) EUS staging of upper GI malignancies: results of a prospective randomized trial. Gastrointestinal Endoscopy 64(4): 496-502	- Population not relevant to this review protocol *People with UGI malignancy not all located in the oesophagus; no relevant outcomes*
May, A., Gunter, E., Roth, F. et al. (2004) Accuracy of staging in early oesophageal cancer using high resolution endoscopy and high resolution endosonography: a comparative, prospective, and blinded trial. Gut 53(5): 634-40	- Population not relevant to this review protocol *includes people with squamous cell carcinoma (19%); suspicion of 'early oesophageal carcinoma' not limited to stage 1*
Ono, S., Kawada, K., Dohi, O. et al. (2021) Linked Color Imaging Focused on Neoplasm Detection in the Upper Gastrointestinal Tract : A Randomized Trial. Annals of Internal Medicine 174(1): 18-24	- Population not relevant to this review protocol *people with known previous or current cancer of the GI tract; outcome was detection of neoplastic lesions not limited to the oesophagus*
Pohl, J., May, A., Rabenstein, T. et al. (2007) Comparison of computed virtual chromoendoscopy and conventional chromoendoscopy with acetic acid for detection of neoplasia in Barrett's esophagus. Endoscopy 39(7): 594-8	- No relevant outcomes *diagnostic accuracy data for detection of high-grade dysplasia/early cancer combined (with stage not specified)*
Ragunath, K., Krasner, N., Raman, V. S. et al. (2003) A randomized, prospective cross-over	- Population not relevant to this review protocol

Study	Reason for exclusion
trial comparing methylene blue-directed biopsy and conventional random biopsy for detecting intestinal metaplasia and dysplasia in Barrett's esophagus. Endoscopy 35(12): 998-1003	*Included people with dysplasia without mucosal abnormalities who were receiving follow up endoscopies and excluded those with nodules or mucosal irregularities suspicious of dysplasia or cancer; no relevant outcomes (diagnostic accuracy data for detection of high-grade dysplasia/cancer (of unspecified stage) combined)*
Russell, I. T., Edwards, R. T., Gliddon, A. E. et al. (2013) Cancer of Oesophagus or Gastricus - New Assessment of Technology of Endosonography (COGNATE): report of pragmatic randomised trial. Health Technology Assessment (Winchester, England) 17(39): 1-170	- Population not relevant to this review protocol *people with known oesophageal cancer not limited to the oesophagus or related to Barrett's oesophagus and not limited to suspected stage 1*
Sharma, P., Hawes, R. H., Bansal, A. et al. (2013) Standard endoscopy with random biopsies versus narrow band imaging targeted biopsies in Barrett's oesophagus: a prospective, international, randomised controlled trial. Gut 62(1): 15-21	- No relevant outcomes *diagnostic accuracy data for detection of high-grade dysplasia/cancer (stage not specified)*
Siemsen, M., Knigge, U., Jensen, F. et al. (2000) A prospective randomized comparison of radial and curved array endosonography in preoperative staging of oesophageal cancer. Endoscopy 32: a20	- Full text paper not available
Siemsen, M., Svendsen, L. B., Knigge, U. et al. (2003) A prospective randomized comparison of curved array and radial echoendoscopy in patients with esophageal cancer. Gastrointestinal Endoscopy 58(5): 671-6	- Population not relevant to this review protocol *people with cancer of the oesophagus or cardia 37% of which was squamous cell carcinoma*
Wang, F., Liu, P., Zhao, K. et al. (2016) Magnifying endoscopy combined with narrow-band imaging for targeted biopsy of superficial lesions in esophagus. Chinese Journal of Gastroenterology 21(10): 597-601	- Study not reported in English
Zuo, X. L., Li, Z., Li, C. Q. et al. (2017) Probe-based endomicroscopy for in vivo detection of gastric intestinal metaplasia and neoplasia: a multicenter randomized controlled trial. Endoscopy 49(11): 1033-1042	- Population not relevant to this review protocol *People with H pylori infection or gastritis undergoing surveillance for gastric intestinal metaplasia, intraepithelial neoplasia or cancer.*

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.