National Institute for Health and Care Excellence

Oesophago-gastric cancer: assessment and management in adults

[A] Evidence reviews for the management of luminal obstruction in adults with oesophageal cancer not amenable to treatment with curative intent

NICE guideline NG83

Evidence reviews underpinning recommendations 1.5.11 to 1.5.12 and recommendations for research in the NICE guideline

July 2023

Final

Disclaimer

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

Local commissioners and/or providers have a responsibility to enable the guideline to be applied when individual health professionals and their patients or service users wish to use it. They should do so in the context of local and national priorities for funding and developing services, and in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities. Nothing in this guideline should be interpreted in a way that would be inconsistent with compliance with those duties.

NICE guidelines cover health and care in England. Decisions on how they apply in other UK countries are made by ministers in the Welsh Government, Scottish Government, and Northern Ireland Executive. All NICE guidance is subject to regular review and may be updated or withdrawn.

Copyright

ISBN: 978-1-4731-5281-6

Contents

1 Palliative management of luminal obstruction

1.1 Review question

What is the optimal management of luminal obstruction for adults with cancer of the oesophagus or the oesophago-gastric junction not amenable to treatment with curative intent?

1.1.1 Introduction

Many people with oesophageal cancer or cancer of the oesophago-gastric junction present with dysphagia or gastric outlet obstruction and are subsequently diagnosed with advanced disease. NICE published recommendations on the optimal management of luminal obstruction in 2018, however a surveillance review found new evidence which suggested these recommendations could be updated.

This review will evaluate and summarise clinical evidence published from 2018 onwards on the efficacy of different interventions to manage luminal obstruction in the palliation of oesophago or oesophago-gastric junctional cancer and update recommendations in NG83, taking into account important outcomes such as dysphagia relief, treatment-related and disease-related morbidity and mortality and patient-reported health outcomes. For the health economic evidence, no cut-off date was implemented.

1.1.2 Summary of the protocol

Table 1: PICOS inclusion criteria

Population	Adults with cancer of the oesophagus or the oesophago-gastric junction not amenable to treatment with curative intent, who have symptoms of luminal obstruction and require palliation.

Interventions	• Stenting
	  ○ Self-expanding (metallic) stent
	  ○ Covered/uncovered stent
	  ○ Biodegradable stent
	  ○ Permanent/ removable stent
	  ○ Mode of delivery: radiological/ endoscopic
	  ○ Radioactive impregnated
	• Dilatation
	• Radiotherapy
	  ○ Intraluminal brachytherapy
	  ○ External beam radiotherapy
	• Surgery
	• Laser therapy

	• Systemic anti-cancer therapy (chemotherapy, immunotherapy, targeted therapies) • Enteral feeding tube
Comparator	• Each other • Combinations of the interventions listed above

Outcomes	• Symptom improvement (including time from intervention to improvement of symptoms). Symptoms are defined as:
	  ○ Weight loss/maintenance
	  ○ Vomiting
	  ○ Nausea
	  ○ Aspiration
	  ○ Cough
	  ○ Resumption of eating
	  ○ Swallowing (dysphagia)
	  ○ Pain
	• Symptom recurrence (including time from intervention to recurrence of symptoms)
	• Overall survival
	• Re-intervention
	• Technical success
	• Procedure-related mortality
	• Health-related quality of life
	• PROMS
	  ○ Chest pain
	  ○ Gastro-oesophageal reflux
	• Adverse event such as Gastrointestinal (GI)-related bleeding events, perforation, and pain
	• Resource use

Study type	• RCTs
	• Comparative cohort or observational studies (if RCTs unavailable or limited data to inform decision making). Included studies will be expected as a minimum to have matched or adjusted for the following confounding factors:
	  ○ Age
	  ○ Gender
	  ○ Stage of disease
	  ○ Performance status or comorbidities
	  ○ Degree of obstruction
	  ○ Site of obstruction
	  ○ Type of stent used

For the full protocol see appendix A.

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 appendix L.

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

1.1.3.1 Search methods

The searches for the clinical effectiveness evidence were run between 16th December 2022 and 4th January 2023. The following databases were searched: Central Register of Controlled Trials (Wiley), Cochrane Database of Systematic Reviews (Wiley), EMBASE (Ovid), Epistemonikos, MEDLINE (Ovid), MEDLINE-in-Process (Ovid) and Medline E-pubs (Ovid). The searches focused on the management of luminal obstruction. Full search strategies for each database are provided in appendix B.

The searches for the cost effectiveness evidence were run on 5th January 2023. The following databases were searched: EconLit (Ovid), Embase (Ovid), HTA (CRD), INAHTA, MEDLINE (Ovid), MEDLINE-in-Process (Ovid), Medline E-pubs (Ovid) and NHS Economic Evaluations Database (CRD). Full search strategies for each database are provided in appendix B.

A NICE information specialist conducted the searches. The MEDLINE strategy was quality assured a by trained NICE information specialist and all translated search strategies were peer reviewed to ensure their accuracy. Both procedures were adapted from the 2015 PRESS Guideline Statement.

1.1.3.2 Methods specific to this evidence review

1) Because the review question highlights that the population of interest should 'not be amenable to treatment with curative intent', the population section of the protocol was amended to reflect this during the review. This is an administrative change rather than a protocol deviation because the review question, which was agreed with the committee and NICE quality assurance team, is clear in specifying that this is the population of interest.

2) The protocol stated that evidence from observational studies would be searched for and included where there was limited data from RCTs to inform decision making. This was only undertaken for immunotherapy/targeted cancer treatments and enteral feeding because no RCT evidence was found for these interventions.

3) A large number of comparators and outcomes were reported in the previous version of this review (section 9.4 of the 2018 full guideline). The comparators and outcomes for which no new evidence was found are not replicated in this review, which only reports new comparators and outcomes and those from 2018 that have been updated.

1.1.4 Effectiveness evidence

1.1.4.1 Included studies

A systematic search carried out to identify potentially relevant studies found 4,201 references (see appendix B for the literature search strategy).

These 4,201 references were screened at title and abstract level against the review protocol, with 4,146 excluded at this level. 10% of references were screened separately by two reviewers with 96% agreement. Discrepancies were resolved by discussion.

The full texts of 55 studies (34 RCTs, 17 observational studies and 4 systematic reviews) were ordered for closer inspection. 4 of the RCT studies met the criteria specified in the review protocol (appendix A). No observational studies met the inclusion criteria, and no further studies were identified from systematic reviews used as a source for primary studies. For a summary of the 4 included studies see table 2.

The clinical evidence study selection is presented as a PRISMA diagram in appendix C.

See section 1.1.14 References – included studies for the full references of the included studies.

1.1.4.2 Excluded studies

Details of studies excluded at full text, along with reasons for exclusion are given in appendix J.

1.1.5 Summary of studies included in the effectiveness evidence

Studies included in the previous evidence review for this question are not reported here. Please see the previous version of this review (section 9.4 of the 2018 full guideline).

Table 2 Summary of studies included in the effectiveness evidence update

Study details	Setting / Location	Population	Intervention	Comparison	Risk of bias
Adamson 2021 N= 199 Study type: RCT Longest follow up time: Median 22.9 weeks (SEMS), 22.1 weeks (SEMS +EBRT)	Setting: Cancer centres and acute care hospitals Location: UK	Patients referred for an oesophageal stent as primary palliation for advanced oesophageal cancer dysphagia. ≥ 16 years	Self-expanding metal stent (SEMS) insertion with external beam radiotherapy (EBRT).	Self-expanding metal stent (SEMS)	Low
Didden 2018 N=98 Study type: RCT Median follow-up time was 54 days (range 0 – 184 days)	Setting: Hospitals Location: The Netherlands	A dysphagia score of at least 2 caused by a malignant stricture of the oesophagus or cardia. ≥ 18 years	Fully covered (FC-) oesophageal self-expandable metal stents (SEMSs).	Partially covered (PC-) oesophageal SEMSs	Low
Penniment 2018 N=220	Setting: Hospitals	Biopsy-proven oesophageal cancer (excluding Seifert 2 and	Chemoradiotherapy	Radiotherapy	Low

Study details	Setting / Location	Population	Intervention	Comparison	Risk of bias
Study type: RCT Median follow-up from randomisation was 4·4 years (IQR 2·6–6·4)	Location: UK, Australia, New Zealand, and Canada	3 lesions), and deemed unsuitable for, or unable to have, curative treatment. Dysphagia. ≥ 18 years			
Persson 2017 N=95 Study type: RCT Follow-up: 3 months	Setting: Hospitals Location: Sweden	Patients with incurable cancer in the oesophagus or the GEJ.	Fully covered oesophageal self-expandable metal stents (FC-SEMSs)	Partially covered oesophageal self-expandable metal stents (PC-SEMSs)	Low

See appendix D for full evidence tables.

1.1.6 Summary of the effectiveness evidence

The effectiveness evidence presented here is for comparators and outcomes that were reported in the studies included in this update. None of the update evidence modified the analyses undertaken for the previous guideline. Please see the previous version of this review (section 9.4 of the 2018 full guideline).

Table 3 – SEMS versus SEMS + EBRT

Outcomes	No. studies	Sample size	Effect size (HR or RR) (95% CI)	Quality of the evidence (GRADE)	Interpretation of effect
SEMS versus SEMS +EBRT. Numbers greater than 1 favour SEMS					
Overall survival[a]	1[c]	199	HR 1.06 [0.78, 1.45]	Low[e]	Unable to differentiate
Overall survival[b]	1[c]	199	RR 1.00 [0.89, 1.13]	Moderate[d]	Unable to differentiate
Deterioration of Dysphagia or death – 12 weeks	1[c]	199	RR 0.93 [0.66, 1.31]	Low[e]	Unable to differentiate
Dysphagia deterioration free survival	1[c]	199	HR 0.92 [0.68, 1.25]	Low[e]	Unable to differentiate
Time to first dysphagia stent complication or reintervention	1[c]	199	HR 0.79 [0.37, 1.67]	Low[e]	Unable to differentiate
GI related bleeding – patients with 1 or more event – longest follow up	1[c]	199	RR 0.58 [0.34, 1.00]	Moderate[d]	Unable to differentiate
GI related bleeding – patients with 1 or more event – 16 weeks	1[c]	199	RR 0.55 [0.27, 1.13]	Moderate[d]	Unable to differentiate
Dysphagia grade 3/4 toxicity – 16 weeks	1[c]	199	RR 0.86 [0.37, 1.98]	Low[e]	Unable to differentiate
Nausea grade 3/4 toxicity – 16 weeks	1[c]	199	RR 1.47 [0.48, 4.48]	Low[e]	Unable to differentiate

Outcomes	No. studies	Sample size	Effect size (HR or RR) (95% CI)	Quality of the evidence (GRADE)	Interpretation of effect
Vomiting grade 3/4 toxicity – 16 weeks	1[c]	199	RR 2.89 [0.95, 8.78]	Moderate[d]	Unable to differentiate
Aspiration grade 3/4 toxicity – 16 weeks	1[c]	199	RR 5.26 [0.26, 108.09]	Low[e]	Unable to differentiate
Stent related pain grade 3/4 toxicity – 16 weeks	1[c]	199	RR 1.40 [0.50, 3.89]	Low[e]	Unable to differentiate
Upper GI haemorrhage grade 3/4 toxicity – 16 weeks	1[c]	199	RR 0.53 [0.10, 2.81]	Low[e]	Unable to differentiate
Abdominal pain grade 3/4 toxicity – 16 weeks	1[c]	199	RR 2.63 [0.52, 13.23]	Low[e]	Unable to differentiate
EORTC QLQ-C30 and EORTC QLQ-OG25 questionnaires scales and WHO performance status (Global health, odynophagia, pain/discomfort, eating restrictions)	1[c]	199	See evidence statement in section 1.1.11.		

a. Overall survival data presented as a hazard ratio in 2023 update. New data not compatible for meta-analysis with 2018 outcome data.
b. Overall survival data presented as a risk ratio.
c. Adamson 2021
d. Downgraded once for imprecision because the 95% confidence interval crosses the line of no effect.

Outcomes	No. studies	Sample size	Effect size (HR or RR) (95% CI)	Quality of the evidence (GRADE)	Interpretation of effect
e. Downgraded twice for imprecision because the 95% confidence interval crosses the line of no effect and both minimally important differences (0.8 and 1.25).					

Table 4 – Fully covered SEMS versus partially covered SEMS

Outcomes	No. studies	Sample size	Effect size (HR or RR) (95% CI)	Quality	Interpretation of effect
Fully covered SEMS versus partially covered SEMS. Numbers greater than 1 favour partially covered SEMS					
Recurrent obstruction/dysphagia	1[a]	98	RR 0.84 [0.38, 1.83]	Low[c]	Unable to differentiate
Technical success	1[a]	98	RR 0.20 [0.01, 4.14]	Low[c]	Unable to differentiate
Severe pain > 7 days	1[a]	98	RR 1.02 [0.07, 15.86]	Low[c]	Unable to differentiate
Severe pain ≤ 7 days	1[a]	98	RR 1.02 [0.42, 2.50]	Low[c]	Unable to differentiate
Haemorrhage > 7 days	1[a]	98	RR 0.82 [0.23, 2.86]	Low[c]	Unable to differentiate
Stridor ≤ 7 days	1[a]	98	RR 5.10 [0.25, 103.58]	Low[c]	Unable to differentiate
Mild pain > 7 days	1[a]	98	RR 3.06 [0.13, 73.34]	Low[c]	Unable to differentiate
Stent migration – 1 week	1[b]	95	RR 0.98 [0.26, 3.69]	Low[c]	Unable to differentiate
Stent migration – 1 month	1[b]	95	RR 0.33 [0.04, 3.03]	Low[c]	Unable to differentiate
Stent migration – 3 months	1[b]	95	RR 0.24 [0.03, 2.11]	Low[c]	Unable to differentiate
Reinterventions – 1 week	1[b]	95	RR 0.82 [0.27, 2.49]	Low[c]	Unable to differentiate

Outcomes	No. studies	Sample size	Effect size (HR or RR) (95% CI)	Quality	Interpretation of effect
Reinterventions – 1 month	1[b]	95	RR 0.39 [0.08, 1.92]	Low[c]	Unable to differentiate
Reinterventions – 3 months	1[b]	95	RR 0.24 [0.03, 2.11]	Low[c]	Unable to differentiate
Median dysphagia scores using the Watson scale, Ogilvie scale and dysphagia module (QLQ-OG25)	1[b]	95	See evidence statement in section 1.1.11.		
Median quality of life (QLQ-C30)	1[b]	95	See evidence statement in section 1.1.11		
QLQ-C30, including global health status, functional, and symptom scales	1[a]	98	See evidence statement in section 1.1.11		

a. Didden 2018
b. Persson 2017
c. Downgraded twice for imprecision because the 95% confidence interval crosses the line of no effect and both minimally important differences (0.8 and 1.25).

Table 5 - Radiotherapy versus chemoradiotherapy

Outcomes	No. studies	Sample size	Effect size (HR or RR) (95% CI)	Quality	Interpretation of effect
Chemoradiotherapy versus radiotherapy. Numbers greater than 1 favour radiotherapy					
Dysphagia relief	1[a]	219	RR 0.84 [0.67, 1.04]	Moderate[c]	Unable to differentiate
Dysphagia deterioration	1[a]	219	RR 0.86 [0.55, 1.34]	Low[d]	Unable to differentiate

Outcomes	No. studies	Sample size	Effect size (HR or RR) (95% CI)	Quality	Interpretation of effect
Dysphagia progression free survival	1[a]	219	HR 0.89 [0.67, 1.18]	Moderate[c]	Unable to differentiate
Overall survival	1[a]	219	HR 0.98 [0.74, 1.30]	Low[d]	Unable to differentiate
Nausea and vomiting grade 1 – 90 days	1[a]	211	RR 0.58 [0.27, 1.27]	Low[d]	Unable to differentiate
Nausea and vomiting grade 2 – 90 days	1[a]	211	RR 1.47 [1.10, 1.96]	High	Favours radiotherapy
Nausea and vomiting grade 3– 90 days	1[a]	211	RR 1.36 [0.45, 4.15]	Low[d]	Unable to differentiate
Nausea and vomiting grade 4 – 90 days	1[a]	211	Not estimable[b]	Moderate[c]	Unable to differentiate
Chest pain – 90 days	1[a]	211	RR 0.32 [0.01, 7.87]	Low[d]	Unable to differentiate

a. Penniment 2018
b. No events in either arm.
c. Downgraded once for imprecision because the 95% confidence interval crosses the line of no effect.
d. Downgraded twice for imprecision because the 95% confidence interval crosses the line of no effect and both minimally important differences (0.8 and 1.25).

See appendix F for full GRADE tables.

1.1.7 Economic evidence

1.1.7.1 Included studies

A search was performed to identify published economic evidence of relevance to this review question. This search retrieved 338 studies. Based on title and abstract screening 320 of the studies could be confidently excluded. Sixteen studies were excluded following the full text review. Thus, for this review question there were two included studies.

1.1.7.2 Excluded studies

See appendix J for a list of references for excluded studies, with reason for exclusion.

1.1.8 Summary of included economic evidence

Table 6: Economic evidence profile

Study	Applicability	Limitations	Incremental			Uncertainty
			Cost (£)	Effects (QALYs)	ICER (£/QALY)	
Adamson 2021	Directly applicable	Minor (Multiple conflicts of interests)	SEMS: £4,628 SEMS + EBRT: £6,157 Incremental: £1,529	SEMS: 0.111 SEMS + EBRT: 0.108 Incremental: -0.003	SEMS dominates SEMS + ERBT	One way sensitivity analyses were completed but none changed the result of SEMS dominating
Rao 2009	Directly applicable	Potentially serious (Data used for costs and effects are 15 years old)	Cost: Plastic stent: £4,091 Uncovered self-expanding metal stent: £2,653 Covered self-expanding metal stent: £2,284	QALYs: Plastic stent: 0.332 Uncovered self-expanding metal stent: 0.352 Covered self-expanding metal stent: 0.354	Covered self-expanding metal stents dominate	PSA showed that covered self-expanding metal stents is 99% certain to be cost effective at all willingness to pay thresholds below $150,000/QALY

1.1.9 Economic model

No original economic modelling was developed for this review question.

1.1.11 Evidence statements

Some outcome data could not be converted into a risk ratio, hazard ratio or mean difference as per the review protocol, therefore this has been presented narratively, as evidence statements below. Studies included in the previous evidence review for this question are not reported here. Please see the previous version of this review (section 9.4 of the 2018 full guideline).

SEMS versus SEMS + EBRT

Evidence from one RCT (Adamson 2021) with a low risk of bias reported no time versus treatment interactions for the subscales of the EORTC QLQ-C30 and EORTC QLQ-OG25 questionnaires and WHO performance status (global health, odynophagia, pain/discomfort, eating restrictions) with all p values above 0.05.

Fully covered SEMS versus partially covered SEMS

Evidence from one RCT (Persson 2017) with a low risk of bias showed a reduction in median dysphagia scores from baseline to 3 months in both arms using the Watson scale, Ogilvie scale and dysphagia module (QLQ-OG25) without a statistically significant difference (p=0.107, 0.081 and 0.067 respectively).

Evidence from one RCT (Persson 2017) with a low risk of bias showed no statistically significant difference in median quality of life (QLQ-C30) at baseline, 1 week, 1 month or 3 months between fully covered SEMS and partially covered SEMS.

Evidence from one RCT (Didden 2018) with a low risk of bias showed no statistically significant differences in effect over time between the two SEMS types for all scales of the QLQ-C30, including global health status, functional, and symptom scales.

Radiotherapy versus chemoradiotherapy

Evidence from one RCT (Penniment 2018) with a low risk of bias showed no statistically significant differences in dysphagia relief, dysphagia deterioration, progression free survival, overall survival, nausea and vomiting grades 1, 3, and 4, and chest pain. However, people experienced more nausea and vomiting grade 2 for chemoradiotherapy compared with radiotherapy.

Economic evidence statement

Two economic studies were included in the evidence. One of the studies compared SEMS with SEMS + EBRT which found SEMS alone was less costly and more effective than SEMS + EBRT. The other study was comparing different types of stents (plastic, covered metal and uncovered metal), this study found that the covered metal stent was the most cost-effective option.

1.1.12 The committee's discussion and interpretation of the evidence

1.1.12.1. The outcomes that matter most

The primary outcomes identified in the protocol for this review related mostly to quality of life outcomes since the population group being considered here were not having treatment with curative intent. The committee were interested in symptom improvement (for symptoms related to dysphagia, such as pain and vomiting) and quality of life, though they agreed that overall survival was still an important outcome. Evidence was not found for many of the outcomes listed in the protocol. Prioritising outcomes was not necessary because only one result reached statistical significance (Penniment 2018: people experienced more nausea and vomiting grade 2 for chemoradiotherapy compared with radiotherapy).

1.1.12.2 The quality of the evidence

The committee noted that the evidence found was sparse, with only 4 studies meeting the inclusion criteria, and no included evidence matching many of the interventions they were interested in, such as enteral feeding in this population. The committee noted that the previous version of this guideline had only been published 2 years ago and this might explain the lack of new evidence. They noted that the study identified by NICEs surveillance process was included and was a high quality, UK-based health technology assessment that related directly to the recommendation in the previous version of this guideline to consider external beam radiotherapy (EBRT) after stenting for people with dysphagia who required palliation. The committee agreed that the quality of the evidence was sufficient to enable removal of the recommendation.

Two studies related to the choice between fully covered and partially covered self-expanding stents, however, since these did not add to the evidence base underpinning recommendations 1.5.9 and 1.5.10, the committee did not amend these recommendations since the new evidence did not add to that considered by the previous committee for these recommendations.

1.1.12.3 Benefits and harms

The previous committee recommended considering EBRT after stenting based on a small study of 79 people that provided moderate quality evidence that there might be some benefit to overall survival and dysphagia free survival associated with EBRT after stenting. When data from newer studies was added to this meta-analysis, the benefit disappeared and people who received EBRT after stenting fared no better on survival outcomes (or any other reported outcomes) than people who received a stent with no EBRT.

The source of this new data was Adamson 2021, which assessed SEMS alone versus SEMS and adjuvant EBRT and concluded that the data could not differentiate between them for all outcomes considered in this review. Therefore, for people with oesophageal and oesophago-gastric junctional cancer who had received stenting for long-term disease control, it was decided that EBRT should be removed from the guidelines as a treatment option to consider and a 'do not routinely offer' recommendation was added. For the outcome 'gastrointestinal related bleeding – patients with 1 or more events – longest follow-up point', the confidence intervals for the effect estimate only just touched the line of no effect (Relative Risk 0.58 [95% confidence intervals: 0.34, 1.00]), so on the balance of probabilities, the committee agreed that the outcome was likely to favour SEMS plus EBRT compared with SEMS alone

for this outcome. Furthermore, in the committee's experience, EBRT helps to limit bleeding for people experiencing it because of oesophageal and oesophago-gastric junctional cancer, and so they agreed that people who were bleeding, or at risk of bleeding were a group where EBRT could usefully be added to stenting.

The committee noted that with the exception of 1 result, the evidence could not differentiate for the comparisons 'fully covered SEMS versus partially covered SEMS' and 'radiotherapy versus chemoradiotherapy'. The exception was that people experienced more nausea and vomiting grade 2 for chemoradiotherapy compared with radiotherapy. Therefore, the committee did not make a recommendation for fully or partially covered SEMS because the evidence could not meaningfully differentiate between them and therefore the committee agreed that decisions made by the previous committee should stand.

1.1.12.4 Cost effectiveness and resource use

Only two health economic studies were identified that addressed the optimal management of dysphagia in adults with cancer of the oesophagus or the oesophago-gastric junction not amenable to treatment with curative intent. The ROCS study (Adamson 2021) assessed self-expanding metal stent (SEMS) alone versus SEMS and adjuvant external beam radiotherapy (EBRT) and concluded that SEMS alone was less costly and more effective than SEMS + EBRT in preventing dysphagia deterioration. The committee noted that the addition of EBRT did not significantly reduce the other costs for example primary and secondary care and medication. The other study (Rao 2009) investigated plastic stent versus uncovered SEMS versus covered SEMS and found that covered SEMS dominated (less costly and more effective) the other two options and was therefore the most cost-effective option. However, the committee felt that there was not strong enough evidence to add the specification of using covered SEMS to the recommendations due to the health economic evidence being 15 years old with significant limitations. These limitations included a one-year time horizon and patients that were treated were diagnosed between 1999 and 2003. Given the limited time horizon and how long ago the operations were performed, the committee felt that there was not strong enough evidence to support a particular type of stent. The committee agreed to remove the recommendation of using EBRT from the current guideline and replace it with a 'Do not routinely consider' recommendation but to give the option of using EBRT to a minority of patients who are bleeding. The committee acknowledged that the time horizon of the ROCS study (Adamson 2021) was limited and would have preferred it to be a lifetime model. However, the committee felt that this study was good supporting evidence to the clinical analyses which is why they were comfortable removing EBRT for most patients. These new recommendations are likely to be cost saving as it will be reducing the number of patients receiving EBRT.

The committee agreed that restricting EBRT to people with incurable oesophageal and oesophago-gastric junctional cancer who are bleeding at the cancer site should be a more effective use of resources. This is because EBRT is not widely available, and a more specific recommendation will mean that it can be more effectively targeted towards people who will benefit from it. For example, resources for EBRT could be more effectively directed to centres who manage people with incurable oesophageal and oesophago-gastric junctional cancer who are bleeding at the cancer site. Furthermore, people with oesophageal and oesophago-gastric junctional cancer who are not bleeding from the cancer site and their carers and relatives will not be inconvenienced by unnecessary EBRT and the drawbacks this involves, such as the inconvenience of travelling for unnecessary EBRT treatment and the side-effects associated with it. The committee did not know the exact proportion of

patients who bleed at the cancer site. However, if this proportion is similar to Adamson (2021), it will be around 5% meaning that only using EBRT in this population is likely to reduce the resource impact.

1.1.12.5 Other factors the committee took into account

In the experience of the committee, EBRT aids the cessation of prolonged bleeding after self-expanded stent insertion, which is caused by incurable oesophageal and oesophago-gastric junctional cancer. This is especially the case for people who have a known bleeding disorder. Therefore, they made a recommendation to consider EBRT for this indication. Cessation of bleeding is important to people who have incurable oesophageal and oesophago-gastric junctional cancer because it improves their quality of life and may prevent associated complications such as iron deficiency anaemia, haematochexia, melena, and haematemesis.

1.1.13 Recommendations supported by this evidence review

This evidence review supports the recommendations 1.5.11 and 1.5.12 and the research recommendations in appendix K.

1.1.14 References – included studies

1.1.14.1 Effectiveness evidence

Studies included in the previous evidence review for this question are not reported here. Please see the previous version of this review (section 9.4 of the 2018 full guideline).

Adamson, Douglas, Byrne, Anthony, Porter, Catharine et al. (2021) Palliative radiotherapy after oesophageal cancer stenting (ROCS): a multicentre, open-label, phase 3 randomised controlled trial. The lancet. Gastroenterology & hepatology 6(4): 292-303

Didden, Paul, Reijm, Agnes N, Erler, Nicole S et al. (2018) Fully vs. partially covered selfexpandable metal stent for palliation of malignant esophageal strictures: a randomized trial (the COPAC study). Endoscopy 50(10): 961-971

Penniment, Michael G, De Ieso, Paolo B, Harvey, Jennifer A et al. (2018) Palliative chemoradiotherapy versus radiotherapy alone for dysphagia in advanced oesophageal cancer: a multicentre randomised controlled trial (TROG 03.01). The lancet. Gastroenterology & hepatology 3(2): 114-124

Persson, Jan, Smedh, Ulrika, Johnsson, Ase et al. (2017) Fully covered stents are similar to semi-covered stents with regard to migration in palliative treatment of malignant strictures of the esophagus and gastric cardia: results of a randomized controlled trial. Surgical endoscopy 31(10): 4025-4033

1.1.14.2 Economic

Adamson, Douglas; Byrne, Anthony; Porter, Catharine et al. (2021) Palliative radiotherapy after oesophageal cancer stenting (ROCS): a multicentre, open-label, phase 3 randomised controlled trial. Palliative radiotherapy after oesophageal cancer stenting (ROCS): a multicentre, open-label, phase 3 randomised controlled trial. 6 (4); 292-303

Rao, C.; Haycock, A.; Zacharakis, E et al. (2009) Economic analysis of esophageal stenting for management of malignant dysphagia. Diseases of the Esophagus; 22 (4); 337-347

Appendices

Appendix A – Review protocol

Review protocol for oesophageal cancer: Management of luminal obstruction for adults with cancer of the oesophagus or the oesophago-gastric junction not amenable to treatment with curative intent.

ID	Field	Content
0.	PROSPERO registration number	
1.	Review title	Management of luminal obstruction for adults with cancer of the oesophagus or the oesophago-gastric junction not amenable to treatment with curative intent.
2.	Review question	What is the optimal management of luminal obstruction for adults with cancer of the oesophagus or the oesophago-gastric junction not amenable to treatment with curative intent?
3.	Objective	This review aims to evaluate and summarise the efficacy of different interventions to treat luminal obstruction in the palliation of oesophago-gastric cancer. We aim to identify the most effective management for palliation of luminal obstruction when considering important outcomes such as disease-related

		morbidity and mortality, adverse events and patient reported health outcomes such as health related quality of life.
4.	Searches	The following databases will be searched: • Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews (CDSR) • Embase • Epistemonikos • MEDLINE Searches will be restricted by: • Studies from May 2017 (unrestricted for new terms added since original search) • English language • Human studies Search strategies are quality assured using an adaptation of the PRESS checklist and through two stages of peer review. The full search strategies for MEDLINE database will be published in the final review.
5.	Condition or domain being studied	Oesophago-gastric cancer
6.	Population	Inclusion: Adults with cancer of the oesophagus or the oesophago-gastric

		junction who have symptoms of luminal obstruction and require palliation. Exclusion: None

7.	Intervention	• Stenting (note what stent was used in the studies)
		  ○ Self-expanding (metallic) stent
		  ○ Covered/uncovered stent
		  ○ Biodegradable stent
		  ○ Permanent/ removable stent
		  ○ Mode of delivery: radiological/ endoscopic
		  ○ Radioactive impregnated
		• Dilatation
		• Radiotherapy
		  ○ Intraluminal brachytherapy
		  ○ External beam radiotherapy
		• Surgery
		• Laser therapy
		• Systemic anti-cancer therapy (chemotherapy, immunotherapy, targeted therapies)
		• Enteral feeding tube

8.	Comparator	• Each other • Combinations of the interventions listed above
9.	Types of study to be included	• RCTs • Comparative cohort or observational studies (if RCTs unavailable or limited data to inform decision making). Included studies will be expected as a minimum to have matched or adjusted for the following confounding factors:

		○ Age ○ Gender ○ Stage of disease ○ Performance status or comorbidities ○ Degree of obstruction ○ Site of obstruction ○ Type of stent used
10.	Other exclusion criteria	None
11.	Context	This review is an update of section 1.5 palliative management in NG83 Oesophago-gastric cancer: assessment and management in adults. A decision was taken to update this section following an exceptional surveillance review that found evidence from a UK based RCT that radiotherapy following stenting may not be clinically or cost effective.
12.	Primary outcomes (critical outcomes)	• Symptom improvement (including time from intervention to improvement of symptoms). Symptoms are defined as: ○ Weight loss/maintenance ○ Vomiting ○ Nausea ○ Aspiration ○ Cough ○ Resumption of eating ○ Swallowing (dysphagia) ○ Pain • Symptom recurrence (including time from intervention to recurrence of symptoms) • Overall survival • Re-intervention

		• Technical success
		• Procedure-related mortality
		• Health-related quality of life
		• PROMS
		  ○ Chest pain
		  ○ Gastro-oesophageal reflux
		• Adverse event such as Gastrointestinal (GI)-related bleeding events, perforation, and pain
		• Resource use

13.	Secondary outcomes (important outcomes)	None
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. 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).
15.	Risk of bias (quality) assessment	Risk of bias will be assessed using the appropriate checklist as described in Developing NICE guidelines: the manual. RCTs will be assessed using Cochrane RoB tool (2.0). Cohort studies and non-randomised trials will be assessed using ROBINS-I.
16.	Strategy for data synthesis	Pairwise meta-analyses will be performed in Cochrane Review Manager V5.3. A pooled relative risk will be calculated for dichotomous outcomes (using the Mantel–

		Haenszel method) reporting numbers of people having an event. A pooled mean difference will be calculated for continuous outcomes (using the inverse variance method) when the same scale will be used to measure an outcome across different studies. Where different studies presented continuous data measuring the same outcome but using different numerical scales these outcomes will be all converted to the same scale before meta-analysis is conducted on the mean differences. Where outcomes measured the same underlying construct but used different instruments/metrics, data will be analysed using standardised mean differences (SMDs, Hedges' g). Fixed effects models will be fitted unless there is significant statistical heterogeneity in the meta-analysis, defined as $I^2 \geq 50\%$, when random effects models will be used instead. Where 10 or more studies are included as part of a single meta-analysis, a funnel plot will be produced to graphically assess the potential for publication bias. • GRADE will be used to assess the quality of any pair-wise analysis of outcomes. Outcomes using evidence from RCTs will be rated as high quality initially and downgraded from this point. Reasons for upgrading the certainty of the evidence will also be considered.
17.	Analysis of sub-groups	For RCTs, where data allow, outcomes will be subgrouped by:

		○ Age, ○ gender, ○ stage of disease, ○ performance status or comorbidities ○ degree of obstruction ○ Site of obstruction ○ Type of stent used		
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	6th January 2023		
22.	Anticipated completion date	14th June 2023		
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** Guideline Development Team B **5b Named contact e-mail** OGcancerupdate@nice.org.uk **5e Organisational affiliation of the review** National Institute for Health and Care Excellence (NICE)		
25.	Review team members	From the centre for guidelines: • Technical lead: Chris Carmona • Technical analyst: Toby Mercer • Technical analyst: Anthony Gildea • Health economic adviser: Syed Mohiuddin • Health economist: Steph Armstrong • Information specialist: David Nicholls		
26.	Funding sources/sponsor	This systematic review is being completed by the Guideline Updates Team B 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: www.nice.org.uk
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	Oesophago-gastric cancer, Self-expanding metal STENT (SEMS), External Beam Radiotherapy (EBRT)
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

Appendix B – Literature search strategies

Background and development

Search design and peer review

A NICE information specialist conducted the literature searches for the evidence review. The searches were originally run between the 16th December 2022 and 4th January 2023. This search report is compliant with the requirements of the PRISMA Statement for Reporting Literature Searches in Systematic Reviews (for further details see: Rethlefsen M et al. PRISMA-S. *Systematic Reviews*, 10(1), 39).

The MEDLINE strategy below was quality assured (QA) by a trained NICE information specialist. All translated search strategies were peer reviewed to ensure their accuracy. Both procedures were adapted from the Peer Review of Electronic Search Strategies Guideline Statement (for further details see: McGowan J et al. PRESS 2015 Guideline Statement. *Journal of Clinical Epidemiology*, 75, 40-46).

The principal search strategy was developed in MEDLINE (Ovid interface) and adapted, as appropriate, for use in the other sources listed in the protocol, taking into account their size, search functionality and subject coverage.

Review management

The search results were managed in EPPI-Reviewer v5. Duplicates were removed in EPPI-R5 using a two-step process. First, automated deduplication is performed using a high-value algorithm. Second, manual deduplication is used to assess 'low probability' matches. All decisions made for the review can be accessed via the deduplication history.

Prior work

The search strategy was based on the terms used for the former NG83 and NG161 NICE guidelines. Modifications were made to these original search strategies for the specifications in the review protocol.

Limits and restrictions

English language limits were applied in adherence to standard NICE practice and the review protocol.

Limits to exclude conferences in Embase were applied in adherence to standard NICE practice and the review protocol.

The limit to remove animal studies in the searches was the standard NICE practice, which has been adapted from: Dickersin, K., Scherer, R., & Lefebvre, C. (1994). Systematic Reviews: Identifying relevant studies for systematic reviews. BMJ, 309(6964), 1286.

Search filters

Oesophago-gastric cancer: assessment and management in adults: evidence reviews for the management of luminal obstruction FINAL (July 2023)

Clinical searches

- RCT filters:
    - McMaster Therapy – Medline - "best balance of sensitivity and specificity" version.
      Haynes RB et al. (2005) Optimal search strategies for retrieving scientifically strong studies of treatment from Medline: analytical survey. *BMJ*, 330, 1179-1183.

    - McMaster Therapy – Embase "best balance of sensitivity and specificity" version.

      Wong SSL et al. (2006) Developing optimal search strategies for detecting clinically sound treatment studies in EMBASE. Journal of the Medical Library Association, 94(1), 41-47.

- Systematic reviews filters:

      Lee, E. et al. (2012) An optimal search filter for retrieving systematic reviews and meta-analyses. *BMC Medical Research Methodology,* 12(1), 51.

In MEDLINE, the standard NICE modifications were used: pubmed.tw added; systematic review.pt added from MeSH update 2019.

In Embase, the standard NICE modifications were used: pubmed.tw added to line medline.tw.

The terms used for observational studies are standard NICE practice that have been developed in house.

Cost effectiveness searches

The following search filters were applied to the search strategies in MEDLINE and Embase to identify cost-effectiveness studies:

- Glanville J et al. (2009) Development and Testing of Search Filters to Identify Economic Evaluations in MEDLINE and EMBASE. Alberta: Canadian Agency for Drugs and Technologies in Health (CADTH)

Several modifications have been made to these filters over the years that are standard NICE practice.

Key decisions

The search strategy was developed to find evidence on for the specified population and intervention in the review protocol.

Clinical searches

Main search – Databases

Database	Date searched	Database platform	Database segment or version	No. of results downloaded
Cochrane Central Register of Controlled Trials (CENTRAL)	4th January 2023	Wiley	Issue 12 of 12, December 2022	427
Cochrane Database of Systematic Reviews (CDSR)	4th January 2023	Wiley	Issue 12 of 12, December 2022	12
Embase (Ovid)	4th January 2023	Ovid	1974 to 2022 December 30	3378
Epistemonikos	4th January 2023	Epistemonikos	n/a	126
MEDLINE (Ovid)	4th January 2023	Ovid	1946 to December 30, 2022	1531
MEDLINE In-Process (Ovid)	4th January 2023	Ovid	1946 to December 30, 2022	0
MEDLINE Epub Ahead of Print	4th January 2023	Ovid	December 30, 2022	14

Search strategy history

Database name: MEDLINE

1 exp Esophageal Neoplasms/ (57733)
2 Stomach Neoplasms/ (108368)
3 exp Esophagogastric Junction/ (10061)
4 ((esophag* or oesophag*) adj4 (cancer or tumo?r or neoplasm* or adenocarcinoma or squamous or carcinoma)).tw. (50175)
5 (gastric* adj4 (cancer or tumo?r or neoplasm* or adenocarcinoma or squamous or carcinoma)).tw. (80313)
6 ((esophagogastric* or esophago-gastric* or oesophagogastric* or oesophago-gastric*) adj4 (cancer or tumo?r or neoplasm* or adenocarcinoma or squamous or carcinoma)).tw. (1835)
7 (gastro?esophag* adj4 (cancer or tumo?r or neoplasm* or adenocarcinoma or squamous or carcinoma)).tw. (1780)
8 (gullet adj4 (cancer or tumo?r or neoplasm* or adenocarcinoma or squamous or carcinoma)).tw. (9)
9 (stomach adj4 (cancer or tumo?r or neoplasm* or adenocarcinoma or squamous or carcinoma)).tw. (16156)
10 (junctional adj4 (cancer or tumo?r or neoplasm* or adenocarcinoma or squamous or carcinoma)).tw. (329)
11 or/1-10 (187431)
12 exp Deglutition Disorders/ (58161)
13 Gastric Outlet Obstruction/ (1803)
14 (dysphag* or deglutit* or swallow* or (pylor* adj4 stenos*)).tw. (55536)
15 Palliative Care/ (61494)
16 palliati*.tw. (74423)
17 ((intralumina* or intra-lumina* or lumina* or extra-lumina* or extralumina* or esophag* or oesophag* or airway* or (gastric adj4 outlet*)) adj4 (obstruct* or block* or narrow* or strictur* or tighten* or circumference* or occlusion* or imped* or patenc*)).tw. (42728)
18 or/12-17 (224227)
19 exp radiotherapy/ (205451)
20 (radiotherap* or (radiat* adj4 (treatment* or therap*))).tw. (244833)
21 exp Drug Therapy/ (1490967)

22 (chemotherap* or chemorad* or pharmacotherap*).tw. (463546)
23 exp combined modality therapy/ (294601)
24 antineoplastic combined chemotherapy protocols/ (158456)
25 brachytherapy/ (21573)
26 (brachytherap* or curietherap* or (radioisotop* adj4 plaque*)).tw. (17371)
27 exp "Prostheses and Implants"/ (579264)
28 stent*.tw. (100141)
29 (prosthe* or endoprosthe*).tw. (126843)
30 exp laser therapy/ (66088)
31 exp Lasers/ (58658)
32 laser*.ti,ab. (204832)
33 exp light coagulation/ (13182)
34 exp catheter ablation/ (38031)
35 (argon adj4 plasma adj4 coagulat*).tw. (1228)
36 Sclerotherapy/ (5853)
37 sclerotherap*.tw. (6810)
38 exp electrocoagulation/ (12516)
39 (electrocoagulat* or electro-coagulat* or galvanocauter* or thermocoagulat* or thermo-coagulat* or (surg* adj4 diatherm*) or (endocavitar* adj4 fulgurat*)).tw. (4785)
40 (therm* adj4 ablat*).tw. (4517)
41 ((polar or bipolar or therm*) adj4 coagulat*).tw. (1459)
42 exp photochemotherapy/ (25427)
43 (photochemo* or (photodynamic adj4 therap*)).tw. (24090)
44 Aminolevulinic Acid/ (6224)
45 (levulan* or Aminol?evulinate or (aminolaevulin* adj4 acid)).tw. (2896)
46 ((alcohol or ethanol) adj2 inject*).tw. (4114)
47 esophagectomy/ (12132)
48 (esophagectomy or oesophagectomy).tw. (11263)
49 *Esophagoscopy/mt [Methods] (1890)
50 ((esophag* or oesophag*) adj10 bypass).tw. (578)
51 Gastric Dilatation/ (1035)
52 ((gastric or stomach) adj4 (dilation* or dilatation*)).tw. (1296)
53 or/19-52 (2976075)
54 Enteral Nutrition/ (21628)

55 ((enteral or enteric or force* or non-oral or "non oral") adj4 (nutrition* or feed*)).tw. (18522)

56 (feeding adj4 tube*).tw. (7876)

57 Jejunostomy/ (2951)

58 jejunostom*.tw. (2896)

59 exp Antineoplastic Agents/ (1228934)

60 (antineoplastic* or anti-neoplastic* or polychemotherap* or CTX).tw. (34322)

61 ((anticancer* or anti-cancer* or antitumo?r* or anti-tumo?r* or anticarcinogen* or anticarcinogen*) adj4 (drug* or agent* or therap* or treat* or medicat* or protocol*)).tw. (114139)

62 (radiochemotherap* or chemoradiation*).tw. (15110)

63 (chemo adj1 (radiotherap* or radiation)).tw. (3916)

64 (combine* adj4 modal* adj4 (treat* or therap* or regimen* or manag* or intervention*)).tw. (4641)

65 ((tri-modal* or trimodal* or multi-modal* or multimodal* or target*) adj4 (treat* or therap* or regimen* or manag* or intervention*)).tw. (392511)

66 TMT.tw. (3783)

67 Radiation Oncology/ (5513)

68 radiotherapy.fs. (208019)

69 (radiotreat* or roentgentherap* or radiosurg*).tw. (12584)

70 ((radiat* or radio* or irradiat* or roentgen or x-ray or xray) adj4 (therap* or treat* or repair* or oncolog* or surg*)).tw. (245535)

71 (RT or RTx or XRT).tw. (211920)

72 Stereotaxic Techniques/ (15770)

73 ((stereotac* or stereotax*) adj4 (radiat* or surg* or procedure* or method* or technique* or technic*)).tw. (9478)

74 (SABR or SBRT or SRS).tw. (14476)

75 ((hypofraction* or hyperfraction*) adj4 (dose* or dosage* or accelerat* or expedite* or hasten* or quick* or radical* or modulat* or adjust* or regulat* or intens*)).tw. (1794)

76 (HFSRT or CAHRT or CHARTWEL or IMRT or AHRT or A-HYPO or HypoTRT).tw. (9885)

77 exp Immunotherapy/ (324889)

78 Immunotherap*.tw. (97769)

79 or/54-78 (2447591)

80 11 and 18 and 53 (7236)

81 11 and 18 and 79 (3355)
82 randomized controlled trial.pt. (582409)
83 randomi?ed.mp. (942914)
84 placebo.mp. (221753)
85 or/82-84 (999634)
86 (MEDLINE or pubmed).tw. (244396)
87 systematic review.tw. (197346)
88 systematic review.pt. (207266)
89 meta-analysis.pt. (171258)
90 intervention$.ti. (160241)
91 or/86-90 (534353)
92 Observational Studies as Topic/ (8390)
93 Observational Study/ (137757)
94 Epidemiologic Studies/ (9263)
95 exp Case-Control Studies/ (1377005)
96 exp Cohort Studies/ (2428763)
97 Cross-Sectional Studies/ (447683)
98 Controlled Before-After Studies/ (728)
99 Historically Controlled Study/ (230)
100 Interrupted Time Series Analysis/ (1736)
101 Comparative Study.pt. (1917963)
102 case control$.tw. (134744)
103 case series.tw. (78470)
104 (cohort adj (study or studies)).tw. (252955)
105 cohort analy$.tw. (9577)
106 (follow up adj (study or studies)).tw. (50527)
107 (observational adj (study or studies)).tw. (124693)
108 longitudinal.tw. (262380)
109 prospective.tw. (605080)
110 retrospective.tw. (594837)
111 cross sectional.tw. (392684)
112 or/92-111 (5028720)
113 85 or 91 or 112 (5917779)
114 80 and 113 (3154)
115 limit 114 to ed=20170504-20230103 (714)

116 81 and 113 (1401)
117 115 or 116 (1848)
118 limit 117 to english language (1619)
119 animals/ not humans/ (5052249)
120 118 not 119 (1612)
121 limit 120 to (letter or historical article or comment or editorial or news or case reports) (81)
122 120 not 121 (1531)

Database name: MEDLINE in Process

1 exp Esophageal Neoplasms/ (0)
2 Stomach Neoplasms/ (0)
3 exp Esophagogastric Junction/ (0)
4 ((esophag* or oesophag*) adj4 (cancer or tumo?r or neoplasm* or adenocarcinoma or squamous or carcinoma)).tw. (9)
5 (gastric* adj4 (cancer or tumo?r or neoplasm* or adenocarcinoma or squamous or carcinoma)).tw. (24)
6 ((esophagogastric* or esophago-gastric* or oesophagogastric* or oesophago-gastric*) adj4 (cancer or tumo?r or neoplasm* or adenocarcinoma or squamous or carcinoma)).tw. (3)
7 (gastro?esophag* adj4 (cancer or tumo?r or neoplasm* or adenocarcinoma or squamous or carcinoma)).tw. (1)
8 (gullet adj4 (cancer or tumo?r or neoplasm* or adenocarcinoma or squamous or carcinoma)).tw. (0)
9 (stomach adj4 (cancer or tumo?r or neoplasm* or adenocarcinoma or squamous or carcinoma)).tw. (0)
10 (junctional adj4 (cancer or tumo?r or neoplasm* or adenocarcinoma or squamous or carcinoma)).tw. (0)
11 or/1-10 (32)
12 exp Deglutition Disorders/ (0)
13 Gastric Outlet Obstruction/ (0)
14 (dysphag* or deglutit* or swallow* or (pylor* adj4 stenos*)).tw. (10)
15 Palliative Care/ (0)
16 palliati*.tw. (17)

17 ((intralumina* or intra-lumina* or lumina* or extra-lumina* or extralumina* or esophag* or oesophag* or airway* or (gastric adj4 outlet*)) adj4 (obstruct* or block* or narrow* or strictur* or tighten* or circumference* or occlusion* or imped* or patenc*)).tw. (11)

18 or/12-17 (37)

19 exp radiotherapy/ (0)

20 (radiotherap* or (radiat* adj4 (treatment* or therap*))).tw. (42)

21 exp Drug Therapy/ (0)

22 (chemotherap* or chemorad* or pharmacotherap*).tw. (74)

23 exp combined modality therapy/ (0)

24 antineoplastic combined chemotherapy protocols/ (0)

25 brachytherapy/ (0)

26 (brachytherap* or curietherap* or (radioisotop* adj4 plaque*)).tw. (1)

27 exp "Prostheses and Implants"/ (0)

28 stent*.tw. (27)

29 (prosthe* or endoprosthe*).tw. (22)

30 exp laser therapy/ (0)

31 exp Lasers/ (0)

32 laser*.ti,ab. (29)

33 exp light coagulation/ (0)

34 exp catheter ablation/ (0)

35 (argon adj4 plasma adj4 coagulat*).tw. (0)

36 Sclerotherapy/ (0)

37 sclerotherap*.tw. (2)

38 exp electrocoagulation/ (0)

39 (electrocoagulat* or electro-coagulat* or galvanocauter* or thermocoagulat* or thermo-coagulat* or (surg* adj4 diatherm*) or (endocavitar* adj4 fulgurat*)).tw. (2)

40 (therm* adj4 ablat*).tw. (2)

41 ((polar or bipolar or therm*) adj4 coagulat*).tw. (0)

42 exp photochemotherapy/ (0)

43 (photochemo* or (photodynamic adj4 therap*)).tw. (3)

44 Aminolevulinic Acid/ (0)

45 (levulan* or Aminol?evulinate or (aminolaevulin* adj4 acid)).tw. (0)

46 ((alcohol or ethanol) adj2 inject*).tw. (0)

47 esophagectomy/ (0)

48 (esophagectomy or oesophagectomy).tw. (8)

49 *Esophagoscopy/mt [Methods] (0)

50 ((esophag* or oesophag*) adj10 bypass).tw. (0)

51 Gastric Dilatation/ (0)

52 ((gastric or stomach) adj4 (dilation* or dilatation*)).tw. (0)

53 or/19-52 (193)

54 Enteral Nutrition/ (0)

55 ((enteral or enteric or force* or non-oral or "non oral") adj4 (nutrition* or feed*)).tw. (2)

56 (feeding adj4 tube*).tw. (1)

57 Jejunostomy/ (0)

58 jejunostom*.tw. (1)

59 exp Antineoplastic Agents/ (0)

60 (antineoplastic* or anti-neoplastic* or polychemotherap* or CTX).tw. (2)

61 ((anticancer* or anti-cancer* or antitumo?r* or anti-tumo?r* or anticarcinogen* or anticarcinogen*) adj4 (drug* or agent* or therap* or treat* or medicat* or protocol*)).tw. (18)

62 (radiochemotherap* or chemoradiation*).tw. (4)

63 (chemo adj1 (radiotherap* or radiation)).tw. (1)

64 (combine* adj4 modal* adj4 (treat* or therap* or regimen* or manag* or intervention*)).tw. (0)

65 ((tri-modal* or trimodal* or multi-modal* or multimodal* or target*) adj4 (treat* or therap* or regimen* or manag* or intervention*)).tw. (149)

66 TMT.tw. (2)

67 Radiation Oncology/ (0)

68 radiotherapy.fs. (0)

69 (radiotreat* or roentgentherap* or radiosurg*).tw. (2)

70 ((radiat* or radio* or irradiat* or roentgen or x-ray or xray) adj4 (therap* or treat* or repair* or oncolog* or surg*)).tw. (44)

71 (RT or RTx or XRT).tw. (60)

72 Stereotaxic Techniques/ (0)

73 ((stereotac* or stereotax*) adj4 (radiat* or surg* or procedure* or method* or technique* or technic*)).tw. (1)

74 (SABR or SBRT or SRS).tw. (5)

75 ((hypofraction* or hyperfraction*) adj4 (dose* or dosage* or accelerat* or expedite* or hasten* or quick* or radical* or modulat* or adjust* or regulat* or intens*)).tw. (1)

76 (HFSRT or CAHRT or CHARTWEL or IMRT or AHRT or A-HYPO or HypoTRT).tw. (3)

77 exp Immunotherapy/ (0)

78 Immunotherap*.tw. (39)
79 or/54-78 (293)
80 11 and 18 and 53 (0)
81 11 and 18 and 79 (0)
82 randomized controlled trial.pt. (0)
83 randomi?ed.mp. (208)
84 placebo.mp. (37)
85 or/82-84 (214)
86 (MEDLINE or pubmed).tw. (143)
87 systematic review.tw. (119)
88 systematic review.pt. (3)
89 meta-analysis.pt. (0)
90 intervention$.ti. (66)
91 or/86-90 (245)
92 Observational Studies as Topic/ (0)
93 Observational Study/ (0)
94 Epidemiologic Studies/ (0)
95 exp Case-Control Studies/ (0)
96 exp Cohort Studies/ (0)
97 Cross-Sectional Studies/ (0)
98 Controlled Before-After Studies/ (0)
99 Historically Controlled Study/ (0)
100 Interrupted Time Series Analysis/ (0)
101 Comparative Study.pt. (0)
102 case control$.tw. (28)
103 case series.tw. (24)
104 (cohort adj (study or studies)).tw. (143)
105 cohort analy$.tw. (8)
106 (follow up adj (study or studies)).tw. (5)
107 (observational adj (study or studies)).tw. (65)
108 longitudinal.tw. (96)
109 prospective.tw. (176)
110 retrospective.tw. (278)
111 cross sectional.tw. (274)
112 or/92-111 (840)

113 85 or 91 or 112 (1184)

114 80 and 113 (0)

115 81 and 113 (0)

116 114 or 115 (0)

117 limit 116 to english language (0)

118 animals/ not humans/ (0)

119 117 not 118 (0)

120 limit 119 to (letter or historical article or comment or editorial or news or case reports) (0)

121 119 not 120 (0)

Database name: MEDLINE ePubs

1 exp Esophageal Neoplasms/ (0)

2 Stomach Neoplasms/ (0)

3 exp Esophagogastric Junction/ (0)

4 ((esophag* or oesophag*) adj4 (cancer or tumo?r or neoplasm* or adenocarcinoma or squamous or carcinoma)).tw. (713)

5 (gastric* adj4 (cancer or tumo?r or neoplasm* or adenocarcinoma or squamous or carcinoma)).tw. (1004)

6 ((esophagogastric* or esophago-gastric* or oesophagogastric* or oesophago-gastric*) adj4 (cancer or tumo?r or neoplasm* or adenocarcinoma or squamous or carcinoma)).tw. (42)

7 (gastro?esophag* adj4 (cancer or tumo?r or neoplasm* or adenocarcinoma or squamous or carcinoma)).tw. (52)

8 (gullet adj4 (cancer or tumo?r or neoplasm* or adenocarcinoma or squamous or carcinoma)).tw. (0)

9 (stomach adj4 (cancer or tumo?r or neoplasm* or adenocarcinoma or squamous or carcinoma)).tw. (113)

10 (junctional adj4 (cancer or tumo?r or neoplasm* or adenocarcinoma or squamous or carcinoma)).tw. (3)

11 or/1-10 (1722)

12 exp Deglutition Disorders/ (0)

13 Gastric Outlet Obstruction/ (0)

14 (dysphag* or deglutit* or swallow* or (pylor* adj4 stenos*)).tw. (1126)

15 Palliative Care/ (0)

16 palliati*.tw. (1662)

17 ((intralumina* or intra-lumina* or lumina* or extra-lumina* or extralumina* or esophag* or oesophag* or airway* or (gastric adj4 outlet*)) adj4 (obstruct* or block* or narrow* or strictur* or tighten* or circumference* or occlusion* or imped* or patenc*)).tw. (504)

18 or/12-17 (3218)

19 exp radiotherapy/ (0)

20 (radiotherap* or (radiat* adj4 (treatment* or therap*))).tw. (3108)

21 exp Drug Therapy/ (0)

22 (chemotherap* or chemorad* or pharmacotherap*).tw. (5760)

23 exp combined modality therapy/ (0)

24 antineoplastic combined chemotherapy protocols/ (0)

25 brachytherapy/ (0)

26 (brachytherap* or curietherap* or (radioisotop* adj4 plaque*)).tw. (236)

27 exp "Prostheses and Implants"/ (0)

28 stent*.tw. (1805)

29 (prosthe* or endoprosthe*).tw. (1522)

30 exp laser therapy/ (0)

31 exp Lasers/ (0)

32 laser*.ti,ab. (3350)

33 exp light coagulation/ (0)

34 exp catheter ablation/ (0)

35 (argon adj4 plasma adj4 coagulat*).tw. (9)

36 Sclerotherapy/ (0)

37 sclerotherap*.tw. (101)

38 exp electrocoagulation/ (0)

39 (electrocoagulat* or electro-coagulat* or galvanocauter* or thermocoagulat* or thermo-coagulat* or (surg* adj4 diatherm*) or (endocavitar* adj4 fulgurat*)).tw. (51)

40 (therm* adj4 ablat*).tw. (79)

41 ((polar or bipolar or therm*) adj4 coagulat*).tw. (9)

42 exp photochemotherapy/ (0)

43 (photochemo* or (photodynamic adj4 therap*)).tw. (334)

44 Aminolevulinic Acid/ (0)

45 (levulan* or Aminol?evulinate or (aminolaevulin* adj4 acid)).tw. (9)

46 ((alcohol or ethanol) adj2 inject*).tw. (25)

47 esophagectomy/ (0)

48 (esophagectomy or oesophagectomy).tw. (261)

49 *Esophagoscopy/mt [Methods] (0)

50 ((esophag* or oesophag*) adj10 bypass).tw. (5)

51 Gastric Dilatation/ (0)

52 ((gastric or stomach) adj4 (dilation* or dilatation*)).tw. (12)

53 or/19-52 (15060)

54 Enteral Nutrition/ (0)

55 ((enteral or enteric or force* or non-oral or "non oral") adj4 (nutrition* or feed*)).tw. (235)

56 (feeding adj4 tube*).tw. (187)

57 Jejunostomy/ (0)

58 jejunostom*.tw. (36)

59 exp Antineoplastic Agents/ (0)

60 (antineoplastic* or anti-neoplastic* or polychemotherap* or CTX).tw. (441)

61 ((anticancer* or anti-cancer* or antitumo?r* or anti-tumo?r* or anticarcinogen* or anticarcinogen*) adj4 (drug* or agent* or therap* or treat* or medicat* or protocol*)).tw. (1533)

62 (radiochemotherap* or chemoradiation*).tw. (201)

63 (chemo adj1 (radiotherap* or radiation)).tw. (63)

64 (combine* adj4 modal* adj4 (treat* or therap* or regimen* or manag* or intervention*)).tw. (50)

65 ((tri-modal* or trimodal* or multi-modal* or multimodal* or target*) adj4 (treat* or therap* or regimen* or manag* or intervention*)).tw. (7960)

66 TMT.tw. (91)

67 Radiation Oncology/ (0)

68 radiotherapy.fs. (0)

69 (radiotreat* or roentgentherap* or radiosurg*).tw. (284)

70 ((radiat* or radio* or irradiat* or roentgen or x-ray or xray) adj4 (therap* or treat* or repair* or oncolog* or surg*)).tw. (3363)

71 (RT or RTx or XRT).tw. (2409)

72 Stereotaxic Techniques/ (0)

73 ((stereotac* or stereotax*) adj4 (radiat* or surg* or procedure* or method* or technique* or technic*)).tw. (179)

74 (SABR or SBRT or SRS).tw. (414)

75 ((hypofraction* or hyperfraction*) adj4 (dose* or dosage* or accelerat* or expedite* or hasten* or quick* or radical* or modulat* or adjust* or regulat* or intens*)).tw. (14)

76 (HFSRT or CAHRT or CHARTWEL or IMRT or AHRT or A-HYPO or HypoTRT).tw. (111)

77 exp Immunotherapy/ (0)

78 Immunotherap*.tw. (1895)

79 or/54-78 (17175)

80 11 and 18 and 53 (40)

81 11 and 18 and 79 (18)

82 randomized controlled trial.pt. (1)

83 randomi?ed.mp. (12150)

84 placebo.mp. (2413)

85 or/82-84 (12924)

86 (MEDLINE or pubmed).tw. (8644)

87 systematic review.tw. (8831)

88 systematic review.pt. (196)

89 meta-analysis.pt. (85)

90 intervention$.ti. (3557)

91 or/86-90 (15399)

92 Observational Studies as Topic/ (0)

93 Observational Study/ (2)

94 Epidemiologic Studies/ (0)

95 exp Case-Control Studies/ (0)

96 exp Cohort Studies/ (0)

97 Cross-Sectional Studies/ (0)

98 Controlled Before-After Studies/ (0)

99 Historically Controlled Study/ (0)

100 Interrupted Time Series Analysis/ (0)

101 Comparative Study.pt. (0)

102 case control$.tw. (2093)

103 case series.tw. (2210)

104 (cohort adj (study or studies)).tw. (8276)

105 cohort analy$.tw. (291)

106 (follow up adj (study or studies)).tw. (537)

107 (observational adj (study or studies)).tw. (3896)

108 longitudinal.tw. (6432)
109 prospective.tw. (10612)
110 retrospective.tw. (16617)
111 cross sectional.tw. (9821)
112 or/92-111 (46028)
113 85 or 91 or 112 (65751)
114 80 and 113 (13)
115 81 and 113 (7)
116 114 or 115 (14)
117 limit 116 to english language (14)
118 animals/ not humans/ (0)
119 117 not 118 (14)
120 limit 119 to (letter or historical article or comment or editorial or news or case reports) (0)
121 119 not 120 (14)

Database name: Embase

1 exp esophagus tumor/ (99190)
2 stomach tumor/ (30814)
3 exp gastroesophageal junction/ (7336)
4 ((esophag* or oesophag*) adj4 (cancer or tumo?r or neoplasm* or adenocarcinoma or squamous or carcinoma)).tw. (82705)
5 (gastric* adj4 (cancer or tumo?r or neoplasm* or adenocarcinoma or squamous or carcinoma)).tw. (129546)
6 ((esophagogastric* or esophago-gastric* or oesophagogastric* or oesophago-gastric*) adj4 (cancer or tumo?r or neoplasm* or adenocarcinoma or squamous or carcinoma)).tw. (3606)
7 (gastro?esophag* adj4 (cancer or tumo?r or neoplasm* or adenocarcinoma or squamous or carcinoma)).tw. (4104)
8 (gullet adj4 (cancer or tumo?r or neoplasm* or adenocarcinoma or squamous or carcinoma)).tw. (8)
9 (stomach adj4 (cancer or tumo?r or neoplasm* or adenocarcinoma or squamous or carcinoma)).tw. (19247)

10 (junctional adj4 (cancer or tumo?r or neoplasm* or adenocarcinoma or squamous or carcinoma)).tw. (601)

11 or/1-10 (258793)

12 exp dysphagia/ (89936)

13 pylorus stenosis/ (5157)

14 (dysphag* or deglutit* or swallow* or (pylor* adj4 stenos*)).tw. (101417)

15 palliative therapy/ (106946)

16 palliati*.tw. (137772)

17 ((intralumina* or intra-lumina* or lumina* or extra-lumina* or extralumina* or esophageal* or oesophageal* or airway* or (gastric adj4 outlet*)) adj4 (obstruct* or block* or narrow* or strictur* or tighten* or circumference* or occlusion* or imped* or patenc*)).tw. (67884)

18 or/12-17 (365361)

19 exp radiotherapy/ (622904)

20 (radiotherap* or (radiat* adj4 (treatment* or therap*))).tw. (434327)

21 exp chemotherapy/ (794495)

22 (chemotherap* or chemorad* or pharmacotherap*).tw. (842479)

23 exp multimodality cancer therapy/ (73566)

24 antineoplastic agent/ (345274)

25 brachytherapy/ (43517)

26 (brachytherap* or curietherap* or (radioisotop* adj4 plaque*)).tw. (35372)

27 stent/ or prosthesis/ (127533)

28 stent*.tw. (195047)

29 (prosthe* or endoprosthe*).tw. (165339)

30 exp laser therapy/ (29465)

31 exp laser/ (175854)

32 laser*.ti,ab. (321983)

33 exp laser coagulation/ (23632)

34 exp catheter ablation/ (40895)

35 (argon adj4 plasma adj4 coagulat*).tw. (3343)

36 sclerotherapy/ (12980)

37 sclerotherap*.tw. (11368)

38 exp electrocoagulation/ (7895)

39 (electrocoagulat* or electro-coagulat* or galvanocauter* or thermocoagulat* or thermo-coagulat* or (surg* adj4 diatherm*) or (endocavitar* adj4 fulgurat*)).tw. (6316)

40 (therm* adj4 ablat*).tw. (8555)

41 ((polar or bipolar or therm*) adj4 coagulat*).tw. (2396)

42 exp photochemotherapy/ (51371)

43 (photochemo* or (photodynamic adj4 therap*)).tw. (32928)

44 aminolevulinic acid/ (10549)

45 (levulan* or Aminol?evulinate or (aminolaevulin* adj4 acid)).tw. (3702)

46 ((alcohol or ethanol) adj2 inject*).tw. (6191)

47 esophagus resection/ (24917)

48 (esophagectomy or oesophagectomy).tw. (20023)

49 esophagoscopy/ (13092)

50 ((esophag* or oesophag*) adj10 bypass).tw. (946)

51 stomach distension/ (5301)

52 ((gastric or stomach) adj4 (dilation* or dilatation*)).tw. (1937)

53 or/19-52 (2640782)

54 enteric feeding/ (38416)

55 ((enteral or enteric or force* or non-oral or "non oral") adj4 (nutrition* or feed*)).tw. (32210)

56 (feeding adj4 tube*).tw. (13975)

57 jejunostomy/ (6605)

58 jejunostom*.tw. (5627)

59 exp antineoplastic agent/ (2645191)

60 (antineoplastic* or anti-neoplastic* or polychemotherap* or CTX).tw. (53621)

61 ((anticancer* or anti-cancer* or antitumo?r* or anti-tumo?r* or anticarcinogen* or anticarcinogen*) adj4 (drug* or agent* or therap* or treat* or medicat* or protocol*)).tw. (172199)

62 (radiochemotherap* or chemoradiation*).tw. (33727)

63 (chemo adj1 (radiotherap* or radiation)).tw. (10888)

64 (combine* adj4 modal* adj4 (treat* or therap* or regimen* or manag* or intervention*)).tw. (7151)

65 ((tri-modal* or trimodal* or multi-modal* or multimodal* or target*) adj4 (treat* or therap* or regimen* or manag* or intervention*)).tw. (677666)

66 TMT.tw. (7390)

67 radiation oncology/ (6710)

68 radiotherapy.fs. (368199)

69 (radiotreat* or roentgentherap* or radiosurg*).tw. (22765)

70 ((radiat* or radio* or irradiat* or roentgen or x-ray or xray) adj4 (therap* or treat* or repair* or oncolog* or surg*)).tw. (426755)

71 (RT or RTx or XRT).tw. (367944)

72 stereotactic procedure/ (3097)

73 ((stereotac* or stereotax*) adj4 (radiat* or surg* or procedure* or method* or technique* or technic*)).tw. (19713)

74 (SABR or SBRT or SRS).tw. (35624)

75 ((hypofraction* or hyperfraction*) adj4 (dose* or dosage* or accelerat* or expedite* or hasten* or quick* or radical* or modulat* or adjust* or regulat* or intens*)).tw. (3545)

76 (HFSRT or CAHRT or CHARTWEL or IMRT or AHRT or A-HYPO or HypoTRT).tw. (26589)

77 exp immunotherapy/ (289060)

78 Immunotherap*.tw. (183672)

79 or/54-78 (4185080)

80 11 and 18 and 53 (12590)

81 11 and 18 and 79 (8059)

82 randomized controlled trial.pt. (0)

83 randomi?ed.mp. (1414458)

84 placebo.mp. (506560)

85 or/82-84 (1642222)

86 (MEDLINE or pubmed).tw. (374967)

87 exp systematic review/ or systematic review.tw. (461735)

88 meta-analysis/ (266686)

89 intervention$.ti. (250557)

90 or/86-89 (897044)

91 Clinical study/ (161427)

92 Case control study/ (197071)

93 Family study/ (25730)

94 Longitudinal study/ (183789)

95 Retrospective study/ (1360440)

96 comparative study/ (985057)

97 Prospective study/ (819362)

98 Randomized controlled trials/ (241913)

99 97 not 98 (809614)

100 Cohort analysis/ (939008)

101 cohort analy$.tw. (17924)
102 (Cohort adj (study or studies)).tw. (427879)
103 (Case control$ adj (study or studies)).tw. (164526)
104 (follow up adj (study or studies)).tw. (71399)
105 (observational adj (study or studies)).tw. (234795)
106 (epidemiologic$ adj (study or studies)).tw. (118877)
107 (cross sectional adj (study or studies)).tw. (314224)
108 case series.tw. (138159)
109 prospective.tw. (1047317)
110 retrospective.tw. (1173000)
111 or/91-96,99-110 (5112914)
112 85 or 90 or 111 (6843536)
113 80 and 112 (4246)
114 limit 113 to dc=20170504-20230104 (1864)
115 81 and 112 (2886)
116 114 or 115 (3624)
117 limit 116 to english language (3411)
118 nonhuman/ not (human/ and nonhuman/) (5121069)
119 117 not 118 (3404)
120 (letter or editorial).pt. (1999682)
121 119 not 120 (3378)

Database name: Cochrane Library

#1 MeSH descriptor: [Esophageal Neoplasms] explode all trees 1866
#2 MeSH descriptor: [Stomach Neoplasms] this term only 2936
#3 MeSH descriptor: [Esophagogastric Junction] explode all trees 499
#4 ((esophag* or oesophag*) near/4 (cancer or tumor or tumour or neoplasm* or adenocarcinoma or squamous or carcinoma)):ti,ab,kw 6383
#5 (gastric* near/4 (cancer or tumor or tumour or neoplasm* or adenocarcinoma or squamous or carcinoma)):ti,ab,kw 7936
#6 ((esophagogastric* or esophago-gastric* or oesophagogastric* or oesophago-gastric*) near/4 (cancer or tumor or tumour or neoplasm* or adenocarcinoma or squamous or carcinoma)):ti,ab,kw 522

#7 ((gastroesophag* or gastrooesophag* or gastro-esophag*) near/4 (cancer or tumor or tumour or neoplasm* or adenocarcinoma or squamous or carcinoma)):ti,ab,kw 1116

#8 (gullet near/4 (cancer or tumor or tumour or neoplasm* or adenocarcinoma or squamous or carcinoma)):ti,ab,kw 15

#9 (stomach near/4 (cancer or tumor or tumour or neoplasm* or adenocarcinoma or squamous or carcinoma)):ti,ab,kw 6578

#10 (junctional near/4 (cancer or tumor or tumour or neoplasm* or adenocarcinoma or squamous or carcinoma)):ti,ab,kw 58

#11 {OR #1-#10} 14930

#12 MeSH descriptor: [Deglutition Disorders] explode all trees 3183

#13 MeSH descriptor: [Gastric Outlet Obstruction] this term only 38

#14 (dysphag* or deglutit* or swallow* or (pylor* near/4 stenos*)):ti,ab,kw 9804

#15 MeSH descriptor: [Palliative Care] this term only 1805

#16 palliati*:ti,ab,kw 9159

#17 ((intralumina* or intra-lumina* or lumina* or extra-lumina* or extralumina* or esophageal* or oesophageal* or airway* or (gastric near/4 outlet*)) near/4 (obstruct* or block* or narrow* or strictur* or tighten* or circumference* or occlusion* or imped* or patenc*)):ti,ab,kw 5454

#18 {OR #12-#17} 25580

#19 MeSH descriptor: [Radiotherapy] explode all trees 6712

#20 (radiotherap* or (radiat* near/4 (treatment* or therap*))):ti,ab,kw 42668

#21 MeSH descriptor: [Drug Therapy] explode all trees 148743

#22 (chemotherap* or chemorad* or pharmacotherap*):ti,ab,kw 99708

#23 MeSH descriptor: [Combined Modality Therapy] explode all trees 23275

#24 MeSH descriptor: [Antineoplastic Combined Chemotherapy Protocols] this term only 15378

#25 MeSH descriptor: [Brachytherapy] this term only 730

#26 (brachytherap* or curietherap* or (radioisotop* near/4 plaque*)):ti,ab,kw 2467

#27 MeSH descriptor: [Prostheses and Implants] explode all trees 18961

#28 stent*:ti,ab,kw 17585

#29 (prosthe* or endoprosthe*):ti,ab,kw 16196

#30 MeSH descriptor: [Laser Therapy] explode all trees 4603

#31 MeSH descriptor: [Lasers] explode all trees 2633

#32 laser*:ti,ab 20985

#33 MeSH descriptor: [Light Coagulation] explode all trees 767

#34 MeSH descriptor: [Catheter Ablation] explode all trees 1647

#35 (argon near/4 plasma near/4 coagulat*):ti,ab,kw 271

#36 MeSH descriptor: [Sclerotherapy] this term only 510

#37 sclerotherap*:ti,ab,kw 1688

#38 MeSH descriptor: [Electrocoagulation] explode all trees 763

#39 (electrocoagulat* or electro-coagulat* or galvanocauter* or thermocoagulat* or thermo-coagulat* or (surg* near/4 diatherm*) or (endocavitar* near/4 fulgurat*)):ti,ab,kw 1207

#40 (therm* near/4 ablat*):ti,ab,kw 589

#41 ((polar or bipolar or therm*) near/4 coagulat*):ti,ab,kw 209

#42 MeSH descriptor: [Photochemotherapy] explode all trees 1012

#43 (photochemo* or (photodynamic near/4 therap*)):ti,ab,kw 2892

#44 MeSH descriptor: [Aminolevulinic Acid] this term only 509

#45 (levulan* or Aminolevulinate or Aminolaevulinate or (aminolaevulin* near/4 acid)):ti,ab,kw 431

#46 ((alcohol or ethanol) near/2 inject*):ti,ab,kw 324

#47 MeSH descriptor: [Esophagectomy] this term only 456

#48 (esophagectomy or oesophagectomy):ti,ab,kw 1500

#49 MeSH descriptor: [Esophagoscopy] this term only and with qualifier(s): [methods - MT] 99

#50 ((esophag* or oesophag*) near/10 bypass):ti,ab,kw 62

#51 MeSH descriptor: [Gastric Dilatation] this term only 25

#52 ((gastric or stomach) near/4 (dilation* or dilatation*)):ti,ab,kw 71

#53 {OR #19-#52} 318371

#54 MeSH descriptor: [Enteral Nutrition] this term only 2014

#55 ((enteral or enteric or force* or non-oral or "non oral") near/4 (nutrition* or feed*)):ti,ab,kw 6819

#56 (feeding near/4 tube*):ti,ab,kw 1787

#57 MeSH descriptor: [Jejunostomy] this term only 79

#58 jejunostom*:ti,ab,kw 338

#59 MeSH descriptor: [Antineoplastic Agents] explode all trees 13351

#60 (antineoplastic* or anti-neoplastic* or polychemotherap* or CTX):ti,ab,kw 31681

#61 ((anticancer* or anti-cancer* or antitumor* or antitumour* or anti-tumor* or anti-tumour* or anticarcinogen* or anticarcinogen*) near/4 (drug* or agent* or therap* or treat* or medicat* or protocol*)):ti,ab,kw 4564

#62 (radiochemotherap* or chemoradiation*):ti,ab,kw 4220

#63 (chemo near/1 (radiotherap* or radiation)):ti,ab,kw 1208

#64 (combine* near/4 modal* near/4 (treat* or therap* or regimen* or manag* or intervention*)):ti,ab,kw 16887

#65 ((tri-modal* or trimodal* or multi-modal* or multimodal* or target*) near/4 (treat* or therap* or regimen* or manag* or intervention*)):ti,ab,kw 32575

#66 TMT:ti,ab,kw 824

#67 MeSH descriptor: [Radiation Oncology] this term only 53

#68 (radiotreat* or roentgentherap* or radiosurg*):ti,ab,kw 997

#69 ((radiat* or radio* or irradiat* or roentgen or x-ray or xray) near/4 (therap* or treat* or repair* or oncolog* or surg*)):ti,ab,kw 40146

#70 (RT or RTx or XRT):ti,ab,kw 17834

#71 MeSH descriptor: [Stereotaxic Techniques] this term only 102

#72 ((stereotac* or stereotax*) near/4 (radiat* or surg* or procedure* or method* or technique* or technic*)):ti,ab,kw 1419

#73 (SABR or SBRT or SRS):ti,ab,kw 2242

#74 ((hypofraction* or hyperfraction*) near/4 (dose* or dosage* or accelerat* or expedite* or hasten* or quick* or radical* or modulat* or adjust* or regulat* or intens*)):ti,ab,kw 695

#75 (HFSRT or CAHRT or CHARTWEL or IMRT or AHRT or A-HYPO or HypoTRT):ti,ab,kw 1834

#76 MeSH descriptor: [Immunotherapy] explode all trees 8819

#77 Immunotherap*:ti,ab,kw 12363

#78 {OR #54-#77} 150123

#79 #11 AND #18 AND #53 with Cochrane Library publication date Between May 2017 and Jan 2023, in Cochrane Reviews, Cochrane Protocols 6

#80 #11 AND #18 AND #53 with Publication Year from 2017 to 2023, in Trials 154

#81 #11 AND #18 AND #78 in Cochrane Reviews, Cochrane Protocols 6

#82 #11 AND #18 AND #78 in Trials 278

#83 {OR #79-#82} 373

#84 "conference":pt or (clinicaltrials or trialsearch):so 658360

#85 #83 NOT #84 270

Database name: Epistemonikos

Oesophago-gastric cancer: assessment and management in adults: evidence reviews for the management of luminal obstruction FINAL (July 2023)

1

(title:((esophag* OR gastric* OR esophagogastric* OR oesophagogastric* OR esophago-gastric* OR oesophago-gastric* OR gastroesophag* OR gastro-esophag* OR gastrooesophag* OR gastro-oesophag* OR gullet* OR stomach* OR junctional)) OR abstract:((esophag* OR gastric* OR esophagogastric* OR oesophagogastric* OR esophago-gastric* OR oesophago-gastric* OR gastroesophag* OR gastro-esophag* OR gastrooesophag* OR gastro-oesophag* OR gullet* OR stomach* OR junctional))) AND (title:((cancer OR tumor OR tumour OR neoplasm* OR adenocarcinoma OR squamous OR carcinoma)) OR abstract:((cancer OR tumor OR tumour OR neoplasm* OR adenocarcinoma OR squamous OR carcinoma)))

2

(title:((dysphag* OR deglutit* OR swallow* OR pylor* stenos* OR palliati*)) OR abstract:((dysphag* OR deglutit* OR swallow* OR pylor* stenos* OR palliati*))) OR (title:((intralumina* OR intra-lumina* OR lumina* OR extra-lumina* OR extralumina* OR esophageal* OR airway* OR gastric outlet*) AND (obstruct* OR block* OR narrow* OR strictur* OR tighten* OR circumference* OR occlusion* OR imped* OR patenc*)) OR abstract:((intralumina* OR intra-lumina* OR lumina* OR extra-lumina* OR extralumina* OR esophageal* OR airway* OR gastric outlet*) AND (obstruct* OR block* OR narrow* OR strictur* OR tighten* OR circumference* OR occlusion* OR imped* OR patenc*)))

3

(title:((radiotherap* OR chemotherap* OR chemorad* OR pharmacotherap* OR brachytherap* OR curietherap* OR stent* OR prosthe* OR endoprosthe* OR laser* OR sclerotherap* OR esophagectomy OR (radioisotop* AND plaque*) OR (argon AND plasma AND coagulat*) OR (electrocoagulat* OR electro-coagulat* OR galvanocauter* OR thermocoagulat* OR thermo-coagulat* OR (surg* AND diatherm*) OR (endocavitar* AND fulgurat*)) OR (therm* AND ablat*) OR ((?polar OR therm*) AND coagulat*) OR (esophag* AND bypass) OR (photochemo* OR (photodynamic AND therap*)) OR (levulan* OR Aminol?evulinate OR (aminolaevulin* AND acid)) OR ((alcohol OR ethanol) AND inject*) OR ((gastric OR stomach) AND (dilation* OR dilatation*)) OR (radiat* AND (treatment* OR therap*)))) OR abstract:((radiotherap* OR chemotherap* OR chemorad* OR pharmacotherap* OR brachytherap* OR curietherap* OR stent* OR prosthe* OR endoprosthe* OR laser* OR sclerotherap* OR esophagectomy OR (radioisotop* AND plaque*) OR (argon AND plasma AND coagulat*) OR (electrocoagulat* OR electro-coagulat*

OR galvanocauter* OR thermocoagulat* OR thermo-coagulat* OR (surg* AND diatherm*) OR (endocavitar* AND fulgurat*)) OR (therm* AND ablat*) OR ((?polar OR therm*) AND coagulat*) OR (esophag* AND bypass) OR (photochemo* OR (photodynamic AND therap*)) OR (levulan* OR Aminol?evulinate OR (aminolaevulin* AND acid)) OR ((alcohol OR ethanol) AND inject*) OR ((gastric OR stomach) AND (dilation* OR dilatation*)) OR (radiat* AND (treatment* OR therap*)))))

1 AND 2 and 3 -- section limited to 2017 to 2022 (study limits also applied)

4

(title:(((enteral OR enteric OR force* OR non-oral OR "non oral" OR tube*) AND (nutrition* OR feed*))) OR abstract:(((enteral OR enteric OR force* OR non-oral OR "non oral" OR tube*) AND (nutrition* OR feed*)))) OR (title:(jejunostom*) OR abstract:(jejunostom*)) OR (title:((antineoplastic* OR anti-neoplastic* OR polychemotherap* OR CTX)) OR abstract:((antineoplastic* OR anti-neoplastic* OR polychemotherap* OR CTX))) OR (title:(((anticancer* OR anti-cancer* OR antitumor* OR antitumour* OR anti-tumor* OR anti-tumour* OR anticarcinogen* OR anticarcinogen*) AND (drug* OR agent* OR therap* OR treat* OR medicat* OR protocol*))) OR abstract:(((anticancer* OR anti-cancer* OR antitumor* OR antitumour* OR anti-tumor* OR anti-tumour* OR anticarcinogen* OR anticarcinogen*) AND (drug* OR agent* OR therap* OR treat* OR medicat* OR protocol*)))) OR (title:((radiochemotherap* OR chemoradiation*)) OR abstract:((radiochemotherap* OR chemoradiation*))) OR (title:((chemo AND (radiotherap* OR radiation))) OR abstract:((chemo AND (radiotherap* OR radiation)))) OR (title:((combine* AND modal* AND (treat* OR therap* OR regimen* OR manag* OR intervention*))) OR abstract:((combine* AND modal* AND (treat* OR therap* OR regimen* OR manag* OR intervention*)))) OR (title:(((tri-modal* OR trimodal* OR multi-modal* OR multimodal* OR target*) AND (treat* OR therap* OR regimen* OR manag* OR intervention*))) OR abstract:(((tri-modal* OR trimodal* OR multi-modal* OR multimodal* OR target*) AND (treat* OR therap* OR regimen* OR manag* OR intervention*)))) OR (title:(TMT) OR abstract:(TMT)) OR (title:((radiotreat* OR roentgentherap* OR radiosurg*)) OR abstract:((radiotreat* OR roentgentherap* OR radiosurg*))) OR (title:(((radiat* OR radio* OR irradiat* OR roentgen OR x-ray OR xray) AND (therap* OR treat* OR repair* OR oncolog* OR surg*))) OR abstract:(((radiat* OR radio* OR irradiat* OR roentgen OR x-ray OR xray) AND (therap* OR treat* OR repair* OR oncolog* OR surg*)))) OR (title:((RT OR RTx OR XRT)) OR abstract:((RT OR RTx OR XRT))) OR (title:(((stereotac* OR stereotax*) AND (radiat* OR surg* OR procedure* OR method* OR

technique* OR technic*))) OR abstract:(((stereotac* OR stereotax*) AND (radiat* OR surg* OR procedure* OR method* OR technique* OR technic*)))) OR (title:((SABR OR SBRT OR SRS)) OR abstract:((SABR OR SBRT OR SRS))) OR (title:(((hypofraction* OR hyperfraction*) AND (dose* OR dosage* OR accelerat* OR expedite* OR hasten* OR quick* OR radical* OR modulat* OR adjust* OR regulat* OR intens*))) OR abstract:(((hypofraction* OR hyperfraction*) AND (dose* OR dosage* OR accelerat* OR expedite* OR hasten* OR quick* OR radical* OR modulat* OR adjust* OR regulat* OR intens*)))) OR (title:((HFSRT OR CAHRT OR CHARTWEL OR IMRT OR AHRT OR A-HYPO OR HypoTRT)) OR abstract:((HFSRT OR CAHRT OR CHARTWEL OR IMRT OR AHRT OR A-HYPO OR HypoTRT))) OR (title:(Immunotherap*) OR abstract:(Immunotherap*))

1 and 2 and 4 - study limits applied, no date limit

Study limits

Broad synthesis - interventions

Primary study - RCT

Structured summary

Systematic review - interventions

Cost-effectiveness searches

Main search – Databases

Database	Date searched	Database platform	Database segment or version	No. of results downloaded
MEDLINE (Ovid)	5th January 2023	Ovid	1946 to January 04, 2022	52
MEDLINE in Process (Ovid)	5th January 2023	Ovid	1946 to January 04, 2022	0
MEDLINE epub (Ovid)	5th January 2023	Ovid	January 04, 2022	0
Embase (Ovid)	5th January 2023	Ovid	1974 to 2022 January 04	306

EconLit (Ovid)	5th January 2023	Ovid	1886 to December 22, 2022	0
NHS Economic Evaluation Database (NHS EED) (legacy database)	5th January 2023	CRD	Up to 2015	12
CRD HTA	5th January 2023	CRD	Up to 2018	5
INAHTA	5th January 2023	INAHTA		20

Search strategy history

Database name: MEDLINE

1 exp Esophageal Neoplasms/ (57701)

2 Stomach Neoplasms/ (108215)

3 exp Esophagogastric Junction/ (10048)

4 ((esophag* or oesophag*) adj4 (cancer or tumo?r or neoplasm* or adenocarcinoma or squamous or carcinoma)).tw. (50134)

5 (gastric* adj4 (cancer or tumo?r or neoplasm* or adenocarcinoma or squamous or carcinoma)).tw. (80116)

6 ((esophagogastric* or esophago-gastric* or oesophagogastric* or oesophago-gastric*) adj4 (cancer or tumo?r or neoplasm* or adenocarcinoma or squamous or carcinoma)).tw. (1837)

7 (gastro?esophag* adj4 (cancer or tumo?r or neoplasm* or adenocarcinoma or squamous or carcinoma)).tw. (1764)

8 (gullet adj4 (cancer or tumo?r or neoplasm* or adenocarcinoma or squamous or carcinoma)).tw. (9)

9 (stomach adj4 (cancer or tumo?r or neoplasm* or adenocarcinoma or squamous or carcinoma)).tw. (16173)

10 (junctional adj4 (cancer or tumo?r or neoplasm* or adenocarcinoma or squamous or carcinoma)).tw. (327)

11 or/1-10 (187207)

12 exp Deglutition Disorders/ (58386)

13 Gastric Outlet Obstruction/ (1809)

14 (dysphag* or deglutit* or swallow* or (pylor* adj4 stenos*)).tw. (55636)

15 Palliative Care/ (61868)

16 palliati*.tw. (74856)

17 ((intralumina* or intra-lumina* or lumina* or extra-lumina* or extralumina* or esophag* or oesophag* or airway* or (gastric adj4 outlet*)) adj4 (obstruct* or block* or narrow* or strictur* or tighten* or circumference* or occlusion* or imped* or patenc*)).tw. (42666)

18 or/12-17 (224836)

19 exp radiotherapy/ (204717)

20 (radiotherap* or (radiat* adj4 (treatment* or therap*))).tw. (244461)

21 exp Drug Therapy/ (1483432)

22 (chemotherap* or chemorad* or pharmacotherap*).tw. (462351)

23 exp combined modality therapy/ (293061)

24 antineoplastic combined chemotherapy protocols/ (157309)

25 brachytherapy/ (21487)

26 (brachytherap* or curietherap* or (radioisotop* adj4 plaque*)).tw. (17274)

27 exp "Prostheses and Implants"/ (579841)

28 stent*.tw. (100106)

29 (prosthe* or endoprosthe*).tw. (127201)

30 exp laser therapy/ (66004)

31 exp Lasers/ (58787)

32 laser*.ti,ab. (204928)

33 exp light coagulation/ (13152)

34 exp catheter ablation/ (38247)

35 (argon adj4 plasma adj4 coagulat*).tw. (1222)

36 Sclerotherapy/ (5871)

37 sclerotherap*.tw. (6825)

38 exp electrocoagulation/ (12526)

39 (electrocoagulat* or electro-coagulat* or galvanocauter* or thermocoagulat* or thermo-coagulat* or (surg* adj4 diatherm*) or (endocavitar* adj4 fulgurat*)).tw. (4822)

40 (therm* adj4 ablat*).tw. (4531)

41 ((polar or bipolar or therm*) adj4 coagulat*).tw. (1457)

42 exp photochemotherapy/ (25424)

43 (photochemo* or (photodynamic adj4 therap*)).tw. (24134)

44 Aminolevulinic Acid/ (6256)

45 (levulan* or Aminol?evulinate or (aminolaevulin* adj4 acid)).tw. (2900)

46 ((alcohol or ethanol) adj2 inject*).tw. (4110)

47 esophagectomy/ (12151)

48 (esophagectomy or oesophagectomy).tw. (11290)

49 *Esophagoscopy/mt [Methods] (1874)

50 ((esophag* or oesophag*) adj10 bypass).tw. (577)

51 Gastric Dilatation/ (1032)

52 ((gastric or stomach) adj4 (dilation* or dilatation*)).tw. (1300)

53 or/19-52 (2969038)

54 Enteral Nutrition/ (21654)

55 ((enteral or enteric or force* or non-oral or "non oral") adj4 (nutrition* or feed*)).tw. (18566)

56 (feeding adj4 tube*).tw. (7879)

57 Jejunostomy/ (2946)

58 jejunostom*.tw. (2917)

59 exp Antineoplastic Agents/ (1225511)

60 (antineoplastic* or anti-neoplastic* or polychemotherap* or CTX).tw. (34311)

61 ((anticancer* or anti-cancer* or antitumo?r* or anti-tumo?r* or anticarcinogen* or anticarcinogen*) adj4 (drug* or agent* or therap* or treat* or medicat* or protocol*)).tw. (113735)

62 (radiochemotherap* or chemoradiation*).tw. (15079)

63 (chemo adj1 (radiotherap* or radiation)).tw. (3925)

64 (combine* adj4 modal* adj4 (treat* or therap* or regimen* or manag* or intervention*)).tw. (4619)

65 ((tri-modal* or trimodal* or multi-modal* or multimodal* or target*) adj4 (treat* or therap* or regimen* or manag* or intervention*)).tw. (390246)

66 TMT.tw. (3823)

67 Radiation Oncology/ (5455)

68 radiotherapy.fs. (207805)

69 (radiotreat* or roentgentherap* or radiosurg*).tw. (12610)

70 ((radiat* or radio* or irradiat* or roentgen or x-ray or xray) adj4 (therap* or treat* or repair* or oncolog* or surg*)).tw. (245454)

71 (RT or RTx or XRT).tw. (211292)

72 Stereotaxic Techniques/ (15722)

73 ((stereotac* or stereotax*) adj4 (radiat* or surg* or procedure* or method* or technique* or technic*)).tw. (9498)

74 (SABR or SBRT or SRS).tw. (14497)

75 ((hypofraction* or hyperfraction*) adj4 (dose* or dosage* or accelerat* or expedite* or hasten* or quick* or radical* or modulat* or adjust* or regulat* or intens*)).tw. (1761)

76 (HFSRT or CAHRT or CHARTWEL or IMRT or AHRT or A-HYPO or HypoTRT).tw. (9897)

77 exp Immunotherapy/ (324353)

78 Immunotherap*.tw. (97419)

79 or/54-78 (2442240)

80 11 and 18 and 53 (7219)

81 11 and 18 and 79 (3352)

82 Cost-Benefit Analysis/ (91382)

83 Quality-Adjusted Life Years/ (15309)

84 Markov Chains/ (15875)

85 exp Models, Economic/ (16167)

86 cost*.ti. (121336)

87 (cost* adj2 utilit*).tw. (6185)

88 (cost* adj2 (effective* or assess* or evaluat* or analys* or model* or benefit* or threshold* or quality or expens* or saving* or reduc*)).tw. (214616)

89 (economic* adj2 (evaluat* or assess* or analys* or model* or outcome* or benefit* or threshold* or expens* or saving* or reduc*)).tw. (36839)

90 (qualit* adj2 adjust* adj2 life*).tw. (14662)

91 QALY*.tw. (11650)

92 (incremental* adj2 cost*).tw. (14236)

93 ICER.tw. (4649)

94 utilities.tw. (7374)

95 markov*.tw. (22354)

96 (dollar* or USD or cents or pound or pounds or GBP or sterling* or pence or euro or euros or yen or JPY).tw. (45139)

97 ((utility or effective*) adj2 analys*).tw. (20052)

98 (willing* adj2 pay*).tw. (7518)

99 (EQ5D* or EQ-5D*).tw. (10308)

100 ((euroqol or euro-qol or euroquol or euro-quol or eurocol or euro-col) adj3 ("5" or five)).tw. (2777)

101 (european* adj2 quality adj3 ("5" or five)).tw. (521)
102 or/82-101 (399905)
103 80 and 102 (149)
104 limit 103 to ed=20170504-20230105 (22)
105 81 and 102 (45)
106 104 or 105 (61)
107 limit 106 to english language (53)
108 animals/ not humans/ (5044488)
109 107 not 108 (53)
110 limit 109 to (letter or historical article or comment or editorial or news or case reports) (1)
111 109 not 110 (52)

Database name: MEDLINE in Process

Database: Ovid MEDLINE(R) In-Process & In-Data-Review Citations <1946 to January 04, 2023>
Search Strategy:
---
1 exp Esophageal Neoplasms/ (0)
2 Stomach Neoplasms/ (0)
3 exp Esophagogastric Junction/ (0)
4 ((esophag* or oesophag*) adj4 (cancer or tumo?r or neoplasm* or adenocarcinoma or squamous or carcinoma)).tw. (22)
5 (gastric* adj4 (cancer or tumo?r or neoplasm* or adenocarcinoma or squamous or carcinoma)).tw. (40)
6 ((esophagogastric* or esophago-gastric* or oesophagogastric* or oesophago-gastric*) adj4 (cancer or tumo?r or neoplasm* or adenocarcinoma or squamous or carcinoma)).tw. (2)
7 (gastro?esophag* adj4 (cancer or tumo?r or neoplasm* or adenocarcinoma or squamous or carcinoma)).tw. (1)
8 (gullet adj4 (cancer or tumo?r or neoplasm* or adenocarcinoma or squamous or carcinoma)).tw. (0)
9 (stomach adj4 (cancer or tumo?r or neoplasm* or adenocarcinoma or squamous or carcinoma)).tw. (2)

10 (junctional adj4 (cancer or tumo?r or neoplasm* or adenocarcinoma or squamous or carcinoma)).tw. (0)

11 or/1-10 (61)

12 exp Deglutition Disorders/ (0)

13 Gastric Outlet Obstruction/ (0)

14 (dysphag* or deglutit* or swallow* or (pylor* adj4 stenos*)).tw. (18)

15 Palliative Care/ (0)

16 palliati*.tw. (20)

17 ((intralumina* or intra-lumina* or lumina* or extra-lumina* or extralumina* or esophag* or oesophag* or airway* or (gastric adj4 outlet*)) adj4 (obstruct* or block* or narrow* or strictur* or tighten* or circumference* or occlusion* or imped* or patenc*)).tw. (8)

18 or/12-17 (45)

19 exp radiotherapy/ (0)

20 (radiotherap* or (radiat* adj4 (treatment* or therap*))).tw. (55)

21 exp Drug Therapy/ (0)

22 (chemotherap* or chemorad* or pharmacotherap*).tw. (143)

23 exp combined modality therapy/ (0)

24 antineoplastic combined chemotherapy protocols/ (0)

25 brachytherapy/ (0)

26 (brachytherap* or curietherap* or (radioisotop* adj4 plaque*)).tw. (3)

27 exp "Prostheses and Implants"/ (0)

28 stent*.tw. (63)

29 (prosthe* or endoprosthe*).tw. (42)

30 exp laser therapy/ (0)

31 exp Lasers/ (0)

32 laser*.ti,ab. (55)

33 exp light coagulation/ (0)

34 exp catheter ablation/ (0)

35 (argon adj4 plasma adj4 coagulat*).tw. (0)

36 Sclerotherapy/ (0)

37 sclerotherap*.tw. (2)

38 exp electrocoagulation/ (0)

39 (electrocoagulat* or electro-coagulat* or galvanocauter* or thermocoagulat* or thermo-coagulat* or (surg* adj4 diatherm*) or (endocavitar* adj4 fulgurat*)).tw. (2)

40 (therm* adj4 ablat*).tw. (7)

41 ((polar or bipolar or therm*) adj4 coagulat*).tw. (0)

42 exp photochemotherapy/ (0)

43 (photochemo* or (photodynamic adj4 therap*)).tw. (7)

44 Aminolevulinic Acid/ (0)

45 (levulan* or Aminol?evulinate or (aminolaevulin* adj4 acid)).tw. (0)

46 ((alcohol or ethanol) adj2 inject*).tw. (0)

47 esophagectomy/ (0)

48 (esophagectomy or oesophagectomy).tw. (16)

49 *Esophagoscopy/mt [Methods] (0)

50 ((esophag* or oesophag*) adj10 bypass).tw. (0)

51 Gastric Dilatation/ (0)

52 ((gastric or stomach) adj4 (dilation* or dilatation*)).tw. (0)

53 or/19-52 (354)

54 Enteral Nutrition/ (0)

55 ((enteral or enteric or force* or non-oral or "non oral") adj4 (nutrition* or feed*)).tw. (5)

56 (feeding adj4 tube*).tw. (1)

57 Jejunostomy/ (0)

58 jejunostom*.tw. (2)

59 exp Antineoplastic Agents/ (0)

60 (antineoplastic* or anti-neoplastic* or polychemotherap* or CTX).tw. (3)

61 ((anticancer* or anti-cancer* or antitumo?r* or anti-tumo?r* or anticarcinogen* or anticarcinogen*) adj4 (drug* or agent* or therap* or treat* or medicat* or protocol*)).tw. (45)

62 (radiochemotherap* or chemoradiation*).tw. (8)

63 (chemo adj1 (radiotherap* or radiation)).tw. (2)

64 (combine* adj4 modal* adj4 (treat* or therap* or regimen* or manag* or intervention*)).tw. (2)

65 ((tri-modal* or trimodal* or multi-modal* or multimodal* or target*) adj4 (treat* or therap* or regimen* or manag* or intervention*)).tw. (242)

66 TMT.tw. (4)

67 Radiation Oncology/ (0)

68 radiotherapy.fs. (0)

69 (radiotreat* or roentgentherap* or radiosurg*).tw. (2)

70 ((radiat* or radio* or irradiat* or roentgen or x-ray or xray) adj4 (therap* or treat* or repair* or oncolog* or surg*)).tw. (63)

71 (RT or RTx or XRT).tw. (60)

72 Stereotaxic Techniques/ (0)

73 ((stereotac* or stereotax*) adj4 (radiat* or surg* or procedure* or method* or technique* or technic*)).tw. (2)

74 (SABR or SBRT or SRS).tw. (4)

75 ((hypofraction* or hyperfraction*) adj4 (dose* or dosage* or accelerat* or expedite* or hasten* or quick* or radical* or modulat* or adjust* or regulat* or intens*)).tw. (0)

76 (HFSRT or CAHRT or CHARTWEL or IMRT or AHRT or A-HYPO or HypoTRT).tw. (0)

77 exp Immunotherapy/ (0)

78 Immunotherap*.tw. (72)

79 or/54-78 (461)

80 11 and 18 and 53 (0)

81 11 and 18 and 79 (0)

82 Cost-Benefit Analysis/ (0)

83 Quality-Adjusted Life Years/ (0)

84 Markov Chains/ (0)

85 exp Models, Economic/ (0)

86 cost*.ti. (34)

87 (cost* adj2 utilit*).tw. (0)

88 (cost* adj2 (effective* or assess* or evaluat* or analys* or model* or benefit* or threshold* or quality or expens* or saving* or reduc*)).tw. (107)

89 (economic* adj2 (evaluat* or assess* or analys* or model* or outcome* or benefit* or threshold* or expens* or saving* or reduc*)).tw. (20)

90 (qualit* adj2 adjust* adj2 life*).tw. (4)

91 QALY*.tw. (3)

92 (incremental* adj2 cost*).tw. (3)

93 ICER.tw. (2)

94 utilities.tw. (1)

95 markov*.tw. (7)

96 (dollar* or USD or cents or pound or pounds or GBP or sterling* or pence or euro or euros or yen or JPY).tw. (10)

97 ((utility or effective*) adj2 analys*).tw. (6)

98 (willing* adj2 pay*).tw. (1)

99 (EQ5D* or EQ-5D*).tw. (1)

100 ((euroqol or euro-qol or euroquol or euro-quol or eurocol or euro-col) adj3 ("5" or five)).tw. (2)

101 (european* adj2 quality adj3 ("5" or five)).tw. (1)
102 or/82-101 (152)
103 80 and 102 (0)
104 81 and 102 (0)
105 103 or 104 (0)
106 limit 105 to english language (0)
107 animals/ not humans/ (0)
108 106 not 107 (0)
109 limit 108 to (letter or historical article or comment or editorial or news or case reports) (0)
110 108 not 109 (0)

Database name: MEDLINE ePubs

Database: Ovid MEDLINE(R) Epub Ahead of Print <January 04, 2023>
Search Strategy:
---
1 exp Esophageal Neoplasms/ (0)
2 Stomach Neoplasms/ (0)
3 exp Esophagogastric Junction/ (0)
4 ((esophag* or oesophag*) adj4 (cancer or tumo?r or neoplasm* or adenocarcinoma or squamous or carcinoma)).tw. (713)
5 (gastric* adj4 (cancer or tumo?r or neoplasm* or adenocarcinoma or squamous or carcinoma)).tw. (998)
6 ((esophagogastric* or esophago-gastric* or oesophagogastric* or oesophago-gastric*) adj4 (cancer or tumo?r or neoplasm* or adenocarcinoma or squamous or carcinoma)).tw. (43)
7 (gastro?esophag* adj4 (cancer or tumo?r or neoplasm* or adenocarcinoma or squamous or carcinoma)).tw. (50)
8 (gullet adj4 (cancer or tumo?r or neoplasm* or adenocarcinoma or squamous or carcinoma)).tw. (0)
9 (stomach adj4 (cancer or tumo?r or neoplasm* or adenocarcinoma or squamous or carcinoma)).tw. (114)

10 (junctional adj4 (cancer or tumo?r or neoplasm* or adenocarcinoma or squamous or carcinoma)).tw. (3)

11 or/1-10 (1717)

12 exp Deglutition Disorders/ (0)

13 Gastric Outlet Obstruction/ (0)

14 (dysphag* or deglutit* or swallow* or (pylor* adj4 stenos*)).tw. (1119)

15 Palliative Care/ (0)

16 palliati*.tw. (1667)

17 ((intralumina* or intra-lumina* or lumina* or extra-lumina* or extralumina* or esophag* or oesophag* or airway* or (gastric adj4 outlet*)) adj4 (obstruct* or block* or narrow* or strictur* or tighten* or circumference* or occlusion* or imped* or patenc*)).tw. (508)

18 or/12-17 (3220)

19 exp radiotherapy/ (0)

20 (radiotherap* or (radiat* adj4 (treatment* or therap*))).tw. (3117)

21 exp Drug Therapy/ (0)

22 (chemotherap* or chemorad* or pharmacotherap*).tw. (5748)

23 exp combined modality therapy/ (0)

24 antineoplastic combined chemotherapy protocols/ (0)

25 brachytherapy/ (0)

26 (brachytherap* or curietherap* or (radioisotop* adj4 plaque*)).tw. (237)

27 exp "Prostheses and Implants"/ (0)

28 stent*.tw. (1785)

29 (prosthe* or endoprosthe*).tw. (1502)

30 exp laser therapy/ (0)

31 exp Lasers/ (0)

32 laser*.ti,ab. (3351)

33 exp light coagulation/ (0)

34 exp catheter ablation/ (0)

35 (argon adj4 plasma adj4 coagulat*).tw. (10)

36 Sclerotherapy/ (0)

37 sclerotherap*.tw. (101)

38 exp electrocoagulation/ (0)

39 (electrocoagulat* or electro-coagulat* or galvanocauter* or thermocoagulat* or thermo-coagulat* or (surg* adj4 diatherm*) or (endocavitar* adj4 fulgurat*)).tw. (51)

40 (therm* adj4 ablat*).tw. (76)

41 ((polar or bipolar or therm*) adj4 coagulat*).tw. (9)

42 exp photochemotherapy/ (0)

43 (photochemo* or (photodynamic adj4 therap*)).tw. (339)

44 Aminolevulinic Acid/ (0)

45 (levulan* or Aminol?evulinate or (aminolaevulin* adj4 acid)).tw. (11)

46 ((alcohol or ethanol) adj2 inject*).tw. (23)

47 esophagectomy/ (0)

48 (esophagectomy or oesophagectomy).tw. (256)

49 *Esophagoscopy/mt [Methods] (0)

50 ((esophag* or oesophag*) adj10 bypass).tw. (5)

51 Gastric Dilatation/ (0)

52 ((gastric or stomach) adj4 (dilation* or dilatation*)).tw. (12)

53 or/19-52 (15006)

54 Enteral Nutrition/ (0)

55 ((enteral or enteric or force* or non-oral or "non oral") adj4 (nutrition* or feed*)).tw. (235)

56 (feeding adj4 tube*).tw. (183)

57 Jejunostomy/ (0)

58 jejunostom*.tw. (36)

59 exp Antineoplastic Agents/ (0)

60 (antineoplastic* or anti-neoplastic* or polychemotherap* or CTX).tw. (438)

61 ((anticancer* or anti-cancer* or antitumo?r* or anti-tumo?r* or anticarcinogen* or anticarcinogen*) adj4 (drug* or agent* or therap* or treat* or medicat* or protocol*)).tw. (1497)

62 (radiochemotherap* or chemoradiation*).tw. (194)

63 (chemo adj1 (radiotherap* or radiation)).tw. (62)

64 (combine* adj4 modal* adj4 (treat* or therap* or regimen* or manag* or intervention*)).tw. (50)

65 ((tri-modal* or trimodal* or multi-modal* or multimodal* or target*) adj4 (treat* or therap* or regimen* or manag* or intervention*)).tw. (7886)

66 TMT.tw. (91)

67 Radiation Oncology/ (0)

68 radiotherapy.fs. (0)

69 (radiotreat* or roentgentherap* or radiosurg*).tw. (289)

70 ((radiat* or radio* or irradiat* or roentgen or x-ray or xray) adj4 (therap* or treat* or repair* or oncolog* or surg*)).tw. (3365)

71 (RT or RTx or XRT).tw. (2421)

72 Stereotaxic Techniques/ (0)

73 ((stereotac* or stereotax*) adj4 (radiat* or surg* or procedure* or method* or technique* or technic*)).tw. (178)

74 (SABR or SBRT or SRS).tw. (408)

75 ((hypofraction* or hyperfraction*) adj4 (dose* or dosage* or accelerat* or expedite* or hasten* or quick* or radical* or modulat* or adjust* or regulat* or intens*)).tw. (13)

76 (HFSRT or CAHRT or CHARTWEL or IMRT or AHRT or A-HYPO or HypoTRT).tw. (111)

77 exp Immunotherapy/ (0)

78 Immunotherap*.tw. (1895)

79 or/54-78 (17075)

80 11 and 18 and 53 (41)

81 11 and 18 and 79 (18)

82 Cost-Benefit Analysis/ (0)

83 Quality-Adjusted Life Years/ (0)

84 Markov Chains/ (0)

85 exp Models, Economic/ (0)

86 cost*.ti. (1694)

87 (cost* adj2 utilit*).tw. (218)

88 (cost* adj2 (effective* or assess* or evaluat* or analys* or model* or benefit* or threshold* or quality or expens* or saving* or reduc*)).tw. (4977)

89 (economic* adj2 (evaluat* or assess* or analys* or model* or outcome* or benefit* or threshold* or expens* or saving* or reduc*)).tw. (1040)

90 (qualit* adj2 adjust* adj2 life*).tw. (414)

91 QALY*.tw. (340)

92 (incremental* adj2 cost*).tw. (354)

93 ICER.tw. (158)

94 utilities.tw. (172)

95 markov*.tw. (557)

96 (dollar* or USD or cents or pound or pounds or GBP or sterling* or pence or euro or euros or yen or JPY).tw. (798)

97 ((utility or effective*) adj2 analys*).tw. (539)

98 (willing* adj2 pay*).tw. (225)
99 (EQ5D* or EQ-5D*).tw. (406)
100 ((euroqol or euro-qol or euroquol or euro-quol or eurocol or euro-col) adj3 ("5" or five)).tw. (111)
101 (european* adj2 quality adj3 ("5" or five)).tw. (24)
102 or/82-101 (7873)
103 80 and 102 (0)
104 81 and 102 (0)
105 103 or 104 (0)
106 limit 105 to english language (0)
107 animals/ not humans/ (0)
108 106 not 107 (0)
109 limit 108 to (letter or historical article or comment or editorial or news or case reports) (0)
110 108 not 109 (0)

Database name: Embase

Database: Embase <1974 to 2023 January 04>
Search Strategy:
---
1 exp esophagus tumor/ (99267)
2 stomach tumor/ (30818)
3 exp gastroesophageal junction/ (7350)
4 ((esophag* or oesophag*) adj4 (cancer or tumo?r or neoplasm* or adenocarcinoma or squamous or carcinoma)).tw. (82787)
5 (gastric* adj4 (cancer or tumo?r or neoplasm* or adenocarcinoma or squamous or carcinoma)).tw. (129674)
6 ((esophagogastric* or esophago-gastric* or oesophagogastric* or oesophago-gastric*) adj4 (cancer or tumo?r or neoplasm* or adenocarcinoma or squamous or carcinoma)).tw. (3608)
7 (gastro?esophag* adj4 (cancer or tumo?r or neoplasm* or adenocarcinoma or squamous or carcinoma)).tw. (4110)

8 (gullet adj4 (cancer or tumo?r or neoplasm* or adenocarcinoma or squamous or carcinoma)).tw. (8)

9 (stomach adj4 (cancer or tumo?r or neoplasm* or adenocarcinoma or squamous or carcinoma)).tw. (19261)

10 (junctional adj4 (cancer or tumo?r or neoplasm* or adenocarcinoma or squamous or carcinoma)).tw. (602)

11 or/1-10 (259010)

12 exp dysphagia/ (89987)

13 pylorus stenosis/ (5160)

14 (dysphag* or deglutit* or swallow* or (pylor* adj4 stenos*)).tw. (101495)

15 palliative therapy/ (107043)

16 palliati*.tw. (137888)

17 ((intralumina* or intra-lumina* or lumina* or extra-lumina* or extralumina* or esophageal* or oesophageal* or airway* or (gastric adj4 outlet*)) adj4 (obstruct* or block* or narrow* or strictur* or tighten* or circumference* or occlusion* or imped* or patenc*)).tw. (67923)

18 or/12-17 (365604)

19 exp radiotherapy/ (623397)

20 (radiotherap* or (radiat* adj4 (treatment* or therap*))).tw. (434718)

21 exp chemotherapy/ (795281)

22 (chemotherap* or chemorad* or pharmacotherap*).tw. (843318)

23 exp multimodality cancer therapy/ (73569)

24 antineoplastic agent/ (345346)

25 brachytherapy/ (43561)

26 (brachytherap* or curietherap* or (radioisotop* adj4 plaque*)).tw. (35416)

27 stent/ or prosthesis/ (127599)

28 stent*.tw. (195197)

29 (prosthe* or endoprosthe*).tw. (165447)

30 exp laser therapy/ (29482)

31 exp laser/ (175966)

32 laser*.ti,ab. (322158)

33 exp laser coagulation/ (23636)

34 exp catheter ablation/ (40923)

35 (argon adj4 plasma adj4 coagulat*).tw. (3346)

36 sclerotherapy/ (12984)

37 sclerotherap*.tw. (11374)

38 exp electrocoagulation/ (7896)

39 (electrocoagulat* or electro-coagulat* or galvanocauter* or thermocoagulat* or thermo-coagulat* or (surg* adj4 diatherm*) or (endocavitar* adj4 fulgurat*)).tw. (6322)

40 (therm* adj4 ablat*).tw. (8565)

41 ((polar or bipolar or therm*) adj4 coagulat*).tw. (2396)

42 exp photochemotherapy/ (51407)

43 (photochemo* or (photodynamic adj4 therap*)).tw. (32956)

44 aminolevulinic acid/ (10550)

45 (levulan* or Aminol?evulinate or (aminolaevulin* adj4 acid)).tw. (3703)

46 ((alcohol or ethanol) adj2 inject*).tw. (6194)

47 esophagus resection/ (24917)

48 (esophagectomy or oesophagectomy).tw. (20045)

49 esophagoscopy/ (13096)

50 ((esophag* or oesophag*) adj10 bypass).tw. (946)

51 stomach distension/ (5302)

52 ((gastric or stomach) adj4 (dilation* or dilatation*)).tw. (1937)

53 or/19-52 (2642556)

54 enteric feeding/ (38463)

55 ((enteral or enteric or force* or non-oral or "non oral") adj4 (nutrition* or feed*)).tw. (32228)

56 (feeding adj4 tube*).tw. (13981)

57 jejunostomy/ (6605)

58 jejunostom*.tw. (5628)

59 exp antineoplastic agent/ (2646450)

60 (antineoplastic* or anti-neoplastic* or polychemotherap* or CTX).tw. (53664)

61 ((anticancer* or anti-cancer* or antitumo?r* or anti-tumo?r* or anticarcinogen* or anticarcinogen*) adj4 (drug* or agent* or therap* or treat* or medicat* or protocol*)).tw. (172355)

62 (radiochemotherap* or chemoradiation*).tw. (33777)

63 (chemo adj1 (radiotherap* or radiation)).tw. (10902)

64 (combine* adj4 modal* adj4 (treat* or therap* or regimen* or manag* or intervention*)).tw. (7157)

65 ((tri-modal* or trimodal* or multi-modal* or multimodal* or target*) adj4 (treat* or therap* or regimen* or manag* or intervention*)).tw. (678536)

66 TMT.tw. (7398)

67 radiation oncology/ (6734)

68 radiotherapy.fs. (368199)

69 (radiotreat* or roentgentherap* or radiosurg*).tw. (22782)

70 ((radiat* or radio* or irradiat* or roentgen or x-ray or xray) adj4 (therap* or treat* or repair* or oncolog* or surg*)).tw. (427113)

71 (RT or RTx or XRT).tw. (368229)

72 stereotactic procedure/ (3097)

73 ((stereotac* or stereotax*) adj4 (radiat* or surg* or procedure* or method* or technique* or technic*)).tw. (19732)

74 (SABR or SBRT or SRS).tw. (35659)

75 ((hypofraction* or hyperfraction*) adj4 (dose* or dosage* or accelerat* or expedite* or hasten* or quick* or radical* or modulat* or adjust* or regulat* or intens*)).tw. (3545)

76 (HFSRT or CAHRT or CHARTWEL or IMRT or AHRT or A-HYPO or HypoTRT).tw. (26604)

77 exp immunotherapy/ (289399)

78 Immunotherap*.tw. (183961)

79 or/54-78 (4187896)

80 11 and 18 and 53 (12593)

81 11 and 18 and 79 (8061)

82 cost utility analysis/ (11659)

83 quality adjusted life year/ (33328)

84 cost*.ti. (186389)

85 (cost* adj2 utilit*).tw. (11958)

86 (cost* adj2 (effective* or assess* or evaluat* or analys* or model* or benefit* or threshold* or quality or expens* or saving* or reduc*)).tw. (362218)

87 (economic* adj2 (evaluat* or assess* or analys* or model* or outcome* or benefit* or threshold* or expens* or saving* or reduc*)).tw. (62149)

88 (qualit* adj2 adjust* adj2 life*).tw. (25571)

89 QALY*.tw. (25098)

90 (incremental* adj2 cost*).tw. (26905)

91 ICER.tw. (12087)

92 utilities.tw. (14288)

93 markov*.tw. (37726)

94 (dollar* or USD or cents or pound or pounds or GBP or sterling* or pence or euro or euros or yen or JPY).tw. (68308)
95 ((utility or effective*) adj2 analys*).tw. (35415)
96 (willing* adj2 pay*).tw. (13577)
97 (EQ5D* or EQ-5D*).tw. (23892)
98 ((euroqol or euro-qol or euroquol or euro-quol or eurocol or euro-col) adj3 ("5" or five)).tw. (4734)
99 (european* adj2 quality adj3 ("5" or five)).tw. (882)
100 or/82-99 (597503)
101 80 and 100 (300)
102 limit 101 to dc=20170504-20230105 (109)
103 81 and 100 (179)
104 101 or 103 (325)
105 limit 104 to english language (307)
106 nonhuman/ not (human/ and nonhuman/) (5123711)
107 105 not 106 (307)
108 (letter or editorial).pt. (2001099)
109 107 not 108 (306)

Database name: Econlit

1 ((esophag* or oesophag*) adj4 (cancer or tumo?r or neoplasm* or adenocarcinoma or squamous or carcinoma)).tw. (4)
2 (gastric* adj4 (cancer or tumo?r or neoplasm* or adenocarcinoma or squamous or carcinoma)).tw. (9)
3 ((esophagogastric* or esophago-gastric* or oesophagogastric* or oesophago-gastric*) adj4 (cancer or tumo?r or neoplasm* or adenocarcinoma or squamous or carcinoma)).tw. (0)
4 (gastro?esophag* adj4 (cancer or tumo?r or neoplasm* or adenocarcinoma or squamous or carcinoma)).tw. (0)
5 (gullet adj4 (cancer or tumo?r or neoplasm* or adenocarcinoma or squamous or carcinoma)).tw. (0)
6 (stomach adj4 (cancer or tumo?r or neoplasm* or adenocarcinoma or squamous or carcinoma)).tw. (7)
7 (junctional adj4 (cancer or tumo?r or neoplasm* or adenocarcinoma or squamous or carcinoma)).tw. (0)

8 or/1-7 (19)

9 (dysphag* or deglutit* or swallow* or (pylor* adj4 stenos*)).tw. (64)

10 palliati*.tw. (129)

11 ((intralumina* or intra-lumina* or lumina* or extra-lumina* or extralumina* or esophag* or oesophag* or airway* or (gastric adj4 outlet*)) adj4 (obstruct* or block* or narrow* or strictur* or tighten* or circumference* or occlusion* or imped* or patenc*)).tw. (2)

12 or/9-11 (194)

13 (radiotherap* or (radiat* adj4 (treatment* or therap*))).tw. (90)

14 (chemotherap* or chemorad* or pharmacotherap*).tw. (167)

15 (brachytherap* or curietherap* or (radioisotop* adj4 plaque*)).tw. (7)

16 stent*.tw. (47)

17 (prosthe* or endoprosthe*).tw. (29)

18 laser*.ti,ab. (124)

19 (argon adj4 plasma adj4 coagulat*).tw. (0)

20 sclerotherap*.tw. (0)

21 (electrocoagulat* or electro-coagulat* or galvanocauter* or thermocoagulat* or thermo-coagulat* or (surg* adj4 diatherm*) or (endocavitar* adj4 fulgurat*)).tw. (0)

22 (therm* adj4 ablat*).tw. (0)

23 ((polar or bipolar or therm*) adj4 coagulat*).tw. (0)

24 (photochemo* or (photodynamic adj4 therap*)).tw. (2)

25 (levulan* or Aminol?evulinate or (aminolaevulin* adj4 acid)).tw. (0)

26 ((alcohol or ethanol) adj2 inject*).tw. (0)

27 (esophagectomy or oesophagectomy).tw. (2)

28 ((esophag* or oesophag*) adj10 bypass).tw. (0)

29 ((gastric or stomach) adj4 (dilation* or dilatation*)).tw. (0)

30 or/13-29 (450)

31 ((enteral or enteric or force* or non-oral or "non oral") adj4 (nutrition* or feed*)).tw. (23)

32 (feeding adj4 tube*).tw. (2)

33 jejunostom*.tw. (0)

34 (antineoplastic* or anti-neoplastic* or polychemotherap* or CTX).tw. (12)

35 ((anticancer* or anti-cancer* or antitumo?r* or anti-tumo?r* or anticarcinogen* or anticarcinogen*) adj4 (drug* or agent* or therap* or treat* or medicat* or protocol*)).tw. (17)

36 (radiochemotherap* or chemoradiation*).tw. (0)

37 (chemo adj1 (radiotherap* or radiation)).tw. (0)

38 (combine* adj4 modal* adj4 (treat* or therap* or regimen* or manag* or intervention*)).tw. (0)

39 ((tri-modal* or trimodal* or multi-modal* or multimodal* or target*) adj4 (treat* or therap* or regimen* or manag* or intervention*)).tw. (1590)

40 TMT.tw. (118)

41 radiotherapy.fs. (0)

42 (radiotreat* or roentgentherap* or radiosurg*).tw. (3)

43 ((radiat* or radio* or irradiat* or roentgen or x-ray or xray) adj4 (therap* or treat* or repair* or oncolog* or surg*)).tw. (106)

44 (RT or RTx or XRT).tw. (124)

45 ((stereotac* or stereotax*) adj4 (radiat* or surg* or procedure* or method* or technique* or technic*)).tw. (2)

46 (SABR or SBRT or SRS).tw. (149)

47 ((hypofraction* or hyperfraction*) adj4 (dose* or dosage* or accelerat* or expedite* or hasten* or quick* or radical* or modulat* or adjust* or regulat* or intens*)).tw. (0)

48 (HFSRT or CAHRT or CHARTWEL or IMRT or AHRT or A-HYPO or HypoTRT).tw. (14)

49 Immunotherap*.tw. (10)

50 or/31-49 (2141)

51 8 and 12 and 30 (0)

52 8 and 12 and 50 (0)

Database name: CRD databases

1	MeSH DESCRIPTOR Esophageal Neoplasms EXPLODE ALL TREES	298
2	MeSH DESCRIPTOR Stomach Neoplasms	427
3	MeSH DESCRIPTOR Esophagogastric Junction EXPLODE ALL TREES	28
4	(((esophag* or oesophag*) NEAR4 (cancer or tumo?r or neoplasm* or adenocarcinoma or squamous or carcinoma)))	364
5	((gastric* NEAR4 (cancer or tumo?r or neoplasm* or adenocarcinoma or squamous or carcinoma)))	430
6	(((esophagogastric* or esophago-gastric* or oesophagogastric* or oesophago-gastric*) NEAR4 (cancer or tumo?r or neoplasm* or adenocarcinoma or squamous or carcinoma)))	11

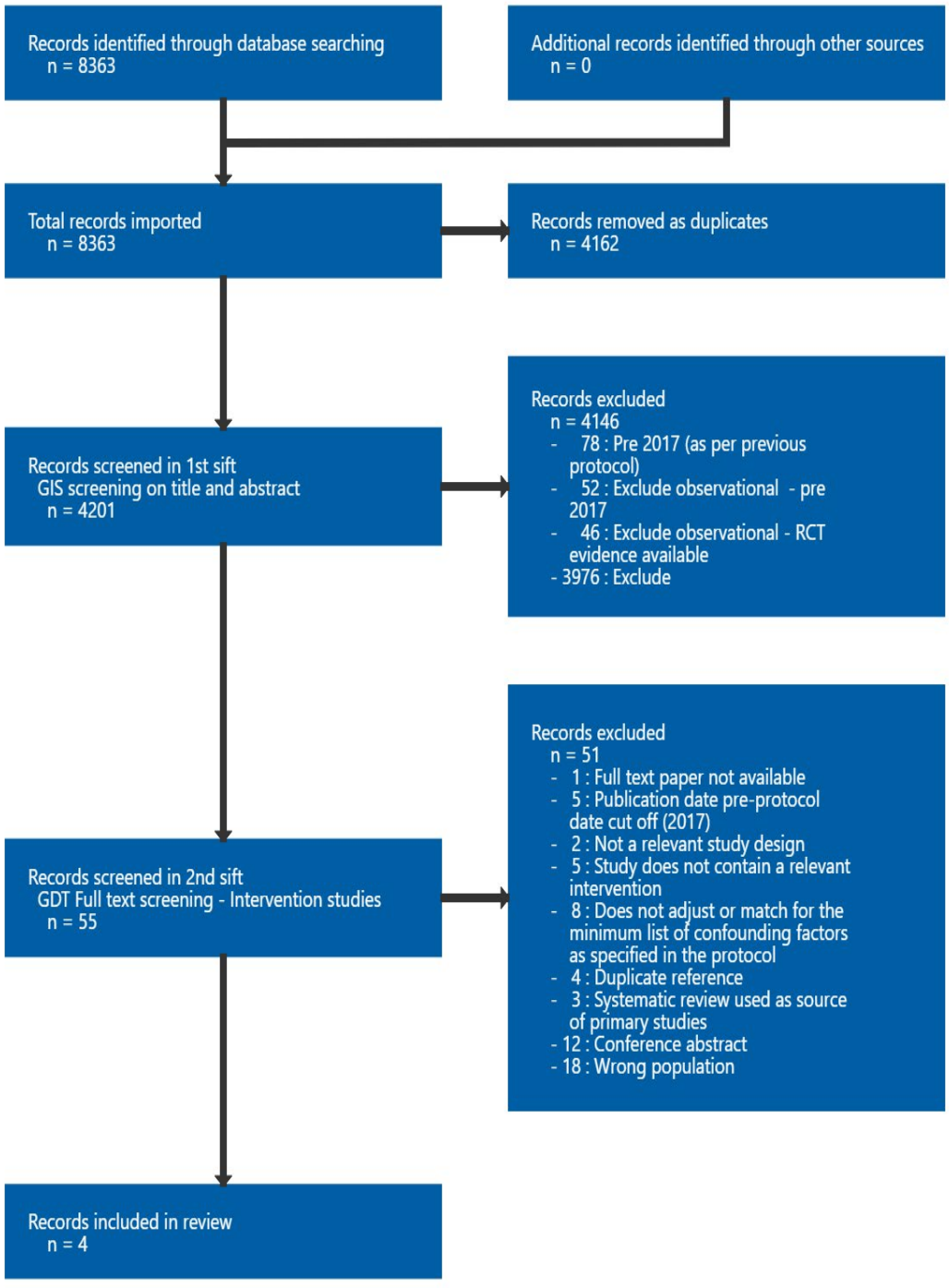
7	((gastro?esophag* NEAR4 (cancer or tumo?r or neoplasm* or adenocarcinoma or squamous or carcinoma)))	15
8	((gullet NEAR4 (cancer or tumo?r or neoplasm* or adenocarcinoma or squamous or carcinoma)))	0
9	((stomach NEAR4 (cancer or tumo?r or neoplasm* or adenocarcinoma or squamous or carcinoma)))	445
10	((junctional NEAR4 (cancer or tumo?r or neoplasm* or adenocarcinoma or squamous or carcinoma)))	0
11	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10	830
12	MeSH DESCRIPTOR Deglutition Disorders EXPLODE ALL TREES	334
13	MeSH DESCRIPTOR Gastric Outlet Obstruction	15
14	((dysphag* or deglutit* or swallow* or (pylor* NEAR4 stenos*)))	296
15	MeSH DESCRIPTOR Palliative Care	333
16	(palliati*)	873
17	(((intralumina* or intra-lumina* or lumina* or extra-lumina* or extralumina* or esophag* or oesophag* or airway* or (gastric NEAR4 outlet*)) NEAR4 (obstruct* or block* or narrow* or strictur* or tighten* or circumference* or occlusion* or imped* or patenc*)))	214
18	#12 OR #13 OR #14 OR #15 OR #16 OR #17	1533
19	MeSH DESCRIPTOR radiotherapy EXPLODE ALL TREES	890
20	((radiotherap* or (radiat* NEAR4 (treatment* or therap*))))	1839
21	MeSH DESCRIPTOR Drug Therapy EXPLODE ALL TREES	8236
22	((chemotherap* or chemorad* or pharmacotherap*))	4527
23	MeSH DESCRIPTOR combined modality therapy EXPLODE ALL TREES	1811
24	MeSH DESCRIPTOR antineoplastic combined chemotherapy protocols	1085
25	MeSH DESCRIPTOR brachytherapy	133
26	((brachytherap* or curietherap* or (radioisotop* NEAR4 plaque*)))	205
27	MeSH DESCRIPTOR Prostheses and Implants EXPLODE ALL TREES	2817
28	(stent*)	1401
29	((prosthe* or endoprosthe*))	1625
30	MeSH DESCRIPTOR laser therapy EXPLODE ALL TREES	453

31	MeSH DESCRIPTOR lasers EXPLODE ALL TREES	137
32	(laser*)	988
33	MeSH DESCRIPTOR light coagulation EXPLODE ALL TREES	66
34	MeSH DESCRIPTOR catheter ablation EXPLODE ALL TREES	385
35	((argon NEAR4 plasma NEAR4 coagulat*))	23
36	MeSH DESCRIPTOR Sclerotherapy	75
37	(sclerotherap*)	120
38	MeSH DESCRIPTOR electrocoagulation EXPLODE ALL TREES	85
39	((electrocoagulat* or electro-coagulat* or galvanocauter* or thermocoagulat* or thermo-coagulat* or (surg* NEAR4 diatherm*) or (endocavitar* NEAR4 fulgurat*)))	115
40	((therm* NEAR4 ablat*))	59
41	(((polar or bipolar or therm*) NEAR4 coagulat*))	14
42	MeSH DESCRIPTOR photochemotherapy EXPLODE ALL TREES	143
43	((photochemo* or (photodynamic NEAR4 therap*)))	216
44	MeSH DESCRIPTOR Aminolevulinic Acid	22
45	((levulan* or Aminol?evulinate or (aminolaevulin* NEAR4 acid)))	16
46	(((alcohol or ethanol) NEAR2 inject*))	37
47	MeSH DESCRIPTOR esophagectomy	84
48	((esophagectomy or oesophagectomy))	119
49	MeSH DESCRIPTOR Esophagoscopy WITH QUALIFIER MT	21
50	(((esophag* or oesophag*) NEAR10 bypass))	3
51	MeSH DESCRIPTOR Gastric Dilatation	0
52	(((gastric or stomach) NEAR4 (dilation* or dilatation*)))	1
53	#19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52	####
54	MeSH DESCRIPTOR Enteral Nutrition	228
55	(((enteral or enteric or force* or non-oral or "non oral") NEAR4 (nutrition* or feed*)))	347
56	((feeding NEAR4 tube*))	52

57	MeSH DESCRIPTOR Jejunostomy	10
58	(jejunostom*)	24
59	MeSH DESCRIPTOR Antineoplastic Agents EXPLODE ALL TREES	3797
60	((antineoplastic* or anti-neoplastic* or polychemotherap* or CTX))	2732
61	(((anticancer* or anti-cancer* or antitumo?r* or anti-tumo?r* or anticarcinogen* or anticarcinogen*) NEAR4 (drug* or agent* or therap* or treat* or medicat* or protocol*)))	183
62	((radiochemotherap* or chemoradiation*))	94
63	((chemo NEAR1 (radiotherap* or radiation)))	27
64	((combine* NEAR4 modal* NEAR4 (treat* or therap* or regimen* or manag* or intervention*)))	946
65	(((tri-modal* or trimodal* or multi-modal* or multimodal* or target*) NEAR4 (treat* or therap* or regimen* or manag* or intervention*)))	615
66	(TMT)	1
67	MeSH DESCRIPTOR Radiation Oncology	15
68	((radiotreat* or roentgentherap* or radiosurg*))	154
69	(((radiat* or radio* or irradiat* or roentgen or x-ray or xray) NEAR4 (therap* or treat* or repair* or oncolog* or surg*)))	1978
70	((RT or RTx or XRT))	319
71	MeSH DESCRIPTOR Stereotaxic Techniques	40
72	(((stereotac* or stereotax*) NEAR4 (radiat* or surg* or procedure* or method* or technique* or technic*)))	81
73	((SABR or SBRT or SRS))	73
74	(((hypofraction* or hyperfraction*) NEAR4 (dose* or dosage* or accelerat* or expedite* or hasten* or quick* or radical* or modulat* or adjust* or regulat* or intens*)))	8
75	((HFSRT or CAHRT or CHARTWEL or IMRT or AHRT or A-HYPO or HypoTRT))	47
76	MeSH DESCRIPTOR Immunotherapy EXPLODE ALL TREES	917
77	(Immunotherap*)	279

78	#54 OR #55 OR #56 OR #57 OR #58 OR #59 OR #60 OR #61 OR #62 OR #63 OR #64 OR #65 OR #66 OR #67 OR #68 OR #69 OR #70 OR #71 OR #72 OR #73 OR #74 OR #75 OR #76 OR #77	8873
79	(#11 AND #18 AND #53) FROM 2017 TO 2023	0
80	(#11 AND #18 AND #78)	27
81	#79 OR #80	27
82	(#79 OR #80) IN NHSEED	12
83	(#79 OR #80) IN HTA	5

Appendix C – Effectiveness evidence study selection



Appendix D – Effectiveness evidence

Studies included in the previous evidence review for this question are not reported here. Please see the previous version of this review (section 9.4 of the 2018 full guideline).

Adamson, 2021

Bibliographic Reference	Adamson, Douglas; Byrne, Anthony; Porter, Catharine; Blazeby, Jane; Griffiths, Gareth; Nelson, Annmarie; Sewell, Bernadette; Jones, Mari; Svobodova, Martina; Fitzsimmons, Deborah; Nixon, Lisette; Fitzgibbon, Jim; Thomas, Stephen; Millin, Anthony; Crosby, Tom; Staffurth, John; Hurt, Christopher; Palliative radiotherapy after oesophageal cancer stenting (ROCS): a multicentre, open-label, phase 3 randomised controlled trial.; The lancet. Gastroenterology & hepatology; 2021; vol. 6 (no. 4); 292-303

Study details

Secondary publication of another included study- see primary study for details	N/A
Other publications associated with this study included in review	Adamson, Douglas, Blazeby, Jane, Porter, Catharine et al. (2021) Palliative radiotherapy combined with stent insertion to reduce recurrent dysphagia in oesophageal cancer patients: the ROCS RCT. Health technology assessment (Winchester, England) 25(31): 1-144
Trial registration number and/or trial name	NCT01915693
Study type	Randomised controlled trial (RCT)
Study location	UK
Study setting	Cancer centres and acute care hospitals
Study dates	16 December 2013 to 24 August 2018
Sources of funding	NIHR Health Technology Assessment Programme
Inclusion criteria	• Incurable oesophageal cancer confirmed using histology (high-grade dysplasia) and clinical or radiological evidence of invasive tumour

	• Age 16 years or older • Have an expected survival time • Of at least 12 weeks • Deemed clinically able to tolerate the study treatments
Exclusion criteria	• Patients planned to receive endoscopic treatment of the tumour, other than dilatation, in the peri-treatment period (except for required emergency interventions) • Those with a tumour size too large • Length greater than 12 cm (or tumour growth within 2 cm of the upper oesophageal sphincter) • Patients with a tracheo-oesophageal fistula • Patients with a pacemaker in the proposed radiotherapy field • Patients who had previous radiotherapy to the area of the proposed radiotherapy field • Patients who were pregnant • Patients in whom brachytherapy or external beam radiation therapy was already planned after stent insertion
Intervention(s)	**Self-expanding metal stent (SEMS) insertion with adjuvant external beam radiotherapy (EBRT).** Stent type and length were determined by the treating clinician. When possible, the stent length was chosen to ensure that at least 2 cm of normal oesophagus was covered by the stent above and below the tumour. Usual care was implemented in both groups according to local MDT practice to include, as needed, post-stent dietetic advice, referral for palliative and supportive care interventions (e.g., blood transfusion and supportive oncology), and community-based healthcare and social-care follow-up. In the EBRT group, the study protocol mandated that radiotherapy begin within 4 weeks of stent insertion and preferably 2 weeks. Treatment dose was prespecified at each centre, preferably 20 Gy in five fractions over 1 week or, at the treating clinician's discretion, 30 Gy in ten fractions over 2 weeks. Treatment was administered according to each centre's normal radiotherapy procedures without corrections for inhomogeneity in dose calculation. In the event of severe radiotherapy side-effects or treatment machine unavailability, gaps in treatment of up to 7 calendar days were allowed. If the patient missed more than 7 consecutive calendar days during radiotherapy treatment, then they were withdrawn from the trial and further treatment given at the clinician's discretion. Radiotherapy quality assurance was monitored by the NIHR Radiotherapy Trial Quality Assurance Group.
Comparator	SEMS insertion alone, which is usual care.
Number of participants	199

Duration of follow-up	12 weeks
Loss to follow-up	1 person in each arm
Methods of analysis	Originally the sample size calculation was based on a time-to-event analysis for the primary endpoint requiring 496 participants. However, during the recruitment phase of the trial, in view of lower than expected eligible patient numbers and substantial missing data after 12 weeks reflecting patient deterioration, the independent data monitoring committee (IDMC) recommended a revised sample size calculation, based on comparison of proportions with an event by week 12 rather than a time-to-event analysis. No early analysis was done that might have influenced this recommendation. To detect a reduction in the proportion of patients with deterioration from 40% to 20% required 164 patients (82 patients per group; 80% power at a two-sided α level of 5%), with a total of 220 to be recruited to allow for 25% loss to follow-up. This difference in proportions was larger than that for the original sample size sought but was in line with the difference sought in other studies of stent or non-stent interventions for malignant dysphagia. The changes were approved by the independent trial steering committee and ratified by the funder following further independent review. All statistical analyses followed a predefined statistical analysis plan agreed with the IDMC. Their modified intention-to-treat (ITT) population was defined as all patients who had a stent inserted (otherwise no benefit from radiotherapy was expected) and returned a baseline EORTC QLQ-OG25 (an eligibility criteria). The per-protocol (PP) population was defined as the subgroup of the modified ITT population that was alive and had not withdrawn from trial treatment at 4 weeks after stent insertion, and, in the EBRT arm, had received at least one fraction of radiotherapy to compare those who could have received radiotherapy in the usual care arm with those who did in the EBRT arm. Analysis of the primary binary endpoint of deterioration in dysphagia symptoms by 12 weeks was primarily done in the modified ITT population with complete case data. Complete cases were defined as having complete data for the dysphagia subscale of the QLQ-OG25 questionnaire at baseline, week 4, week 8, and week 12, or having died with complete data before week 12. In the absence of a documented dysphagia-related event, missing dysphagia scores between two non-event dysphagia scores were assumed to be no event. Multivariable logistic regression was used to adjust for randomisation stratification factors and obtain odds ratios (ORs) and 95% CIs for any treatment effect in the primary analysis and all sensitivity analyses. They did three sensitivity analyses: using the same complete case population but treating death by 12 weeks without earlier deterioration as no deterioration; imputing missing data using a best-case scenario that assumed no deterioration in a missing QLQ-OG25 form immediately before an QLQ-OG25 form that showed deterioration (or a dysphagia-related primary event), or that assumed no deterioration in a missing QLQ-OG25

	form immediately before death; and imputing missing data using a worst-case scenario that assumed deterioration in a missing QLQ-OG25 form immediately before an QLQ-OG25 form that showed deterioration (or a dysphagia-related primary event), or that assumed deterioration in a missing QLQ-OG25 form immediately before death. As further sensitivity analyses, all analyses were repeated in the PP population. As a secondary endpoint per IDMC guidance, DDFS was calculated in the ITT population from the date of stent insertion to the date of deterioration in dysphagia (as per the primary outcome definition). They analysed overall survival and DDFS using Kaplan-Meier plots and Cox regression (with the usual care group as the reference for the treatment effect measured by hazard ratios [HRs] and 95% CIs), with patients without events being censored at the time of last contact and adjusted for randomisation stratification factors with treating centre included as a shared frailty. They tested the model fit and assumptions using Cox-Snell residuals and Schoenfeld's global test. QoL data and WHO performance status scores, prespecified in the statistical analysis plan, were analysed by the same method: the distributions of the variables were tested for normality with the Shapiro Wilk test, kernel density, normal probability, and normal quantile plots, and either mean scores (or median scores if the was evidence of non-normality) plotted accordingly. Box plots were used to show the median, IQR, upper and lower adjacent values, and any outliers as dots, at each timepoint. Mean values were plotted with 95% CIs against time. Linear mixed models were used to compare differences between trial groups for each subscale or single item on the EORTC QLQ-C30, EORTC QLQ-OG25, and WHO performance status. They included time as a categorical covariate using the week of observation from week 1 to week 16, after which the proportion of missing data became too high (>30% of randomly assigned patients returning questionnaires). If an intermediate value was missing, the corresponding time was skipped. Covariates included trial group, age, time 0 score, and randomisation stratification factors. The mixed model residuals were tested for normality. Time to first morbidity event was compared between trial groups by competing risks regression (used to calculate sub-hazard ratios and 95% CIs), with death as a competing risk, adjusted for randomisation stratification factors, and with cumulative incidence functions plotted by trial group and median time to event calculated with the stci command in STATA. Treatment-emergent grade 3–4 toxicity was reported in the modified ITT population. Risk ratios were calculated in a post-hoc analysis to compare rates of toxicities and post-stent chemotherapy or additional radiotherapy between treatment arms.
Additional comments	The number of participants who were male and female in each arm was not provided.

Study arms

- Self-expanding metal stent (SEMS) insertion with adjuvant external beam radiotherapy (EBRT) (N = 97)
- SEMS insertion alone (usual care) (N = 102)

Characteristics

Arm-level characteristics

Characteristic	Self-expanding metal stent (SEMS) insertion with adjuvant external beam radiotherapy (EBRT) (N = 97)	SEMS insertion alone (usual care) (N = 102)
median age (years) Median (IQR)	72 (65.3 to 79.9)	73.5 (65.4 to 81.5)

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

Overall bias and Directness	Risk of bias judgement	Low *(Although this was an unblinded study, the outcomes were measured objectively, and blinding was impossible because of the nature of the interventions.)*
Overall bias and Directness	Overall Directness	Directly applicable

Didden, 2018

Bibliographic Reference	Didden, Paul; Reijm, Agnes N; Erler, Nicole S; Wolters, Leonieke M M; Tang, Thjon J; Ter Borg, Pieter C J; Leeuwenburgh, Ivonne; Bruno, Marco J; Spaander, Manon C W; Fully vs. partially covered selfexpandable metal stent for palliation of malignant esophageal strictures: a randomized trial (the COPAC study).; Endoscopy; 2018; vol. 50 (no. 10); 961-971

Study details

Secondary publication of another included study- see primary study for details	N/A

Other publications associated with this study included in review	N/A
Trial registration number and/or trial name	NCT01661686
Study type	Randomised controlled trial (RCT)
Study location	The Netherlands
Study setting	Hospitals
Study dates	August 2012 to April 2016
Sources of funding	One investigator received funding for research from Scientific and lecturers for Boston Scientific and Cook Medical.
Inclusion criteria	• Incurable oesophageal cancer confirmed using histology (high-grade dysplasia) and clinical or radiological evidence of invasive tumour • A specified dysphagia score • Of at least 2 • Age 18 years or older
Exclusion criteria	• Patients with a tracheo-oesophageal fistula • Previous treatment with self-expandable metal stents • A tumour located close to the upper oesophageal sphincter (within 2 cm of it) • Deemed clinically unable to tolerate the study treatments
Intervention(s)	**Fully covered (FC-) oesophageal self-expandable metal stents (SEMS).** SEMS placement was performed by experienced endoscopists, who had placed over 20 oesophageal SEMSs before participating in this study. The stents used were the WallFlex fully covered oesophageal stent and the WallFlex partially covered oesophageal stent, with the only difference being the extent of the covering. For the FC-SEMSs, the entire surface is covered with a silicone covering. While for the partially covered (PC-) SEMSs, 1.65 cm at both ends are uncovered. Both ends are flare shaped and radiopaque markers are located on both ends and at the centre. The

	diameter of the stents is 18 mm, with a diameter of 23 mm for both flares. Lengths of 10, 12, and 15 cm are available. Patients underwent oesophageal stent placement while under conscious sedation. A forward-viewing endoscope was used, and a guidewire was advanced across the stricture. Where the endoscope could not be passed through the stricture, the guidewire was advanced under fluoroscopic guidance. The location of the stricture was divided according to the recommendations of the American Joint Committee on Cancer (AJCC) on oesophageal cancer: proximal, upper border located <25 cm from the incisors; mid, 25 – 30 cm from the incisors; distal, >30 cm from the incisors. The length of the stent was determined as the stricture length + a minimum of 2 cm on both sides. The stent was advanced over the guidewire until it passed the distal end of the stenosis, thereafter the SEMS was deployed under endoscopic or fluoroscopic guidance. If insertion was carried out fluoroscopically, the upper edge of the stenosis was marked by the submucosal injection of a contrast agent. When the distal end of the stent was below the esophago-gastric junction, a lifelong daily dose of 40mg proton pump inhibitor was prescribed to prevent gastroesophageal reflux.
Comparator	Partially covered (PC-) oesophageal SEMS
Number of participants	98
Duration of follow-up	6 months
Loss to follow-up	1 person in the FC-SEMS arm, 2 people in the PC-SEMs arm
Methods of analysis	For the sample size, they used the number of patients with recurrent dysphagia as the clinically important treatment effect (Δ). Based on previous studies, recurrent dysphagia after PC-SEMS insertion was set at approximately 40%, with a difference of at least 25% as a clinically important treatment effect. Using the Pearson chi-squared test with the power fixed to 80% and a two-sided significance level of α = 0.05, the required sample size was 49 patients per treatment. They performed an intention-to-treat analysis with follow-up data from randomisation until 6 months after treatment or until an endpoint had been reached. Patients who did not receive an intervention (SEMS) were excluded from the analysis. Results with respect to technical and clinical success rate were analysed as dichotomous data and compared using the Fisher’s

	exact test and Pearson chi-squared test, respectively. Clinical success was defined as an improvement of dysphagia (at least a 1-point reduction in the dysphagia score) during follow-up. Recurrent obstruction and adverse events were compared as dichotomous data between the two arms using the chi-squared test. The Kaplan-Meier method and log-rank test were used to compare the time to recurrent obstruction. Cox regression analyses were performed to determine the factors associated with recurrent obstruction and major adverse events, which were expressed as hazards ratios (HRs) with corresponding 95 % confidence intervals (CIs). HRQoL scores were investigated by analysis of repeated measurements. Specifically, mixed-effects models were fitted that included time, treatment group, and their interaction as fixed factors, and a random intercept to consider the correlation between repeated measurements within the same patient. A linear mixed model was used to analyse the scale Global health status (QL2), and (ordinal) cumulative logit mixed models were used to analyse the other scales. Because many patients died before the end of follow-up, resulting in non-ignorable missing values in the HRQoL scales, sensitivity analysis was performed using two different imputation strategies (last observation carried-forward and worst-value imputation). Tests were considered statistically significant if the P value was <0.05.

Study arms

Fully covered oesophageal self-expandable metal stents (SEMSs) (N = 49)

Partially covered oesophageal self-expandable metal stents (SEMSs) (N = 49)

Characteristics

Arm-level characteristics

Characteristic	Fully covered oesophageal self-expandable metal stents (SEMSs) (N = 49)	Partially covered oesophageal self-expandable metal stents (SEMSs) (N = 49)
Mean age (SD) (years) Mean (SD)	69.2 (12.2)	70.8 (11.4)
% Female (%) Nominal	29.2	26.5

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

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low *(Although this was an unblinded study, the outcomes were measured objectively, and blinding was impossible because of the nature of the interventions.)*
Overall bias and Directness	Overall Directness	Directly applicable

Penniment, 2018

Bibliographic Reference	Penniment, Michael G; De Ieso, Paolo B; Harvey, Jennifer A; Stephens, Sonya; Au, Heather-Jane; O'Callaghan, Christopher J; Kneebone, Andrew; Ngan, Samuel Y; Ward, Iain G; Roy, Rajarshi; Smith, Jennifer G; Nijjar, Tirath; Biagi, James J; Mulroy, Liam A; Wong, Rebecca; TROG 03.01/CCTG ES.2, group; Palliative chemoradiotherapy versus radiotherapy alone for dysphagia in advanced oesophageal cancer: a multicentre randomised controlled trial (TROG 03.01).; The lancet. Gastroenterology & hepatology; 2018; vol. 3 (no. 2); 114-124

Study details

Secondary publication of another included study- see primary study for details	N/A
Other publications associated with this study included in review	N/A
Trial registration number and/or trial name	NCT00193882 TROG 03.01
Study type	Randomised controlled trial (RCT)
Study location	UK, Australia, New Zealand, and Canada
Study setting	Hospitals
Study dates	7 July 2003 to 21 March 2012

Sources of funding	National Health and Medical Research Council of Australia, Canadian Cancer Society Research Institute, Canadian Cancer Trials Group, Trans Tasman Radiation Oncology Group, and Cancer Australia
Inclusion criteria	• Incurable oesophageal cancer confirmed using histology (high-grade dysplasia) and clinical or radiological evidence of invasive tumour • A specified dysphagia score • Grade 1–4 on the Mellow scale • Age 18 years or older • A specified performance status • Eastern Cooperative Oncology Group performance status 0–2 • Adequate haematological and renal function • Neutrophil count >1·5×10⁹ cells per L, platelet count >100×10⁹ cells per L, and calculated creatinine clearance ≥50 mL/min
Exclusion criteria	• Patients with a tracheo-oesophageal fistula • Patients who were pregnant • Or lactating • Seifert 2 and 3 lesions • Prior chemotherapy • Prior chest radiotherapy for oesophageal cancer • Or for other active malignancies in the chest • Stent in situ • Inadequate contraception • Non-adherence to study methods • Blood tests were required within 2 weeks of randomisation, and staging CT scans of the chest and abdomen were required within 8 weeks of randomisation.
Intervention(s)	**Chemoradiotherapy** The protocol required radiotherapy to be prescribed according to the International Commission on Radiation Units and Measurements (ICRU) Report 5017 and Report 62.18 Gross tumour volume was defined as primary tumour and adjacent involved locoregional lymph nodes, based on CT and endoscopy, with or without endoscopic ultrasound. Investigations including barium swallow and PET were not mandated by the protocol, but diagnostic information from both were used if available. Clinical target volume included gross disease and potential sites of locoregional microscopic extension, defined as gross tumour volume plus 3·0 cm superiorly and inferiorly and 0·5 cm radially. Planning target volume was defined as clinical target volume plus 1·0 cm in all dimensions. For lower oesophageal lesions within a few centimetres of the stomach, the oesophago-gastric junction was included in the gross tumour volume. The subsequent expansion to clinical target volume distally was reduced to 2·0 cm.

	The planned radiotherapy dose in both groups was 35 Gy in 15 fractions over 3 weeks for study participants enrolled in Australia and New Zealand and 30 Gy in ten fractions over 2 weeks for participants enrolled in Canada and the UK. Overall treatment time was not to exceed 25 days for the 3-week course or 18 days for the 2 week course. The biologically equivalent doses for the schedules using an α/β ratio of 10 for tumour and acute reacting tissue are 42 Gy and 39 Gy, respectively, a difference of less than 10%. The trial protocol stipulated the use of a parallel opposed two-field anteroposterior–posteroanterior (AP–PA) megavoltage photon beam technique. Doses were to be prescribed to the midplane central axis, with total dose to the ICRU reference point within 5% of the prescribed dose, maximum dose to planning target volume within 10% of the total dose, and spinal cord dose less than 40 Gy. Chemotherapy consisted of intravenous cisplatin (either 80 mg/m² on day 1 or 20 mg/m² per day on days 1–4 at the clinician's discretion) with intravenous fluorouracil 800 mg/m² per day on days 1–4 of radiotherapy (continuous infusion). Patients received dexamethasone and a 5-HT3 receptor antagonist before cisplatin and were pre-hydrated as per institutional protocols. An independent senior radiation oncologist and a senior data manager audited pre-treatment patient characteristics, radiotherapy plans, and chemotherapy prescriptions for 72 (33%) patients. Patients were selected for audit at randomisation by taking the first five patients from each centre, then one in five patients at random subsequently. Audits were done after treatment. Minor recording errors and protocol deviations were found, but major deviations were rare. Patients were assessed weekly during treatment, with blood tests continuing until the neutrophil count exceeded 1·0 × 10^9 cells per L and platelet count exceeded 100 × 10^9 cells per L. Follow-up assessments were planned for week 5, then every 4 weeks for the first year, and every 3 months thereafter. Dysphagia was graded using the Mellow scale (0=able to eat all solids; 1=able to eat only some solids, 2=able to eat only soft foods, 3=able to drink liquids only, 4=complete dysphagia). Acute toxic effects were graded according to the National Cancer Institute Common Toxicity Criteria version 2.0, and late toxic effects (more than 13 weeks after commencing radiotherapy) were graded using the late radiation morbidity criteria described by The Radiation Therapy Oncology Group and the European Organisation for Research and Treatment of Cancer. At weeks 9 and 13, patients were asked to rate the change in their swallowing on a 7-point scale, from "very much worse" to "very much better". This was added to the protocol in December, 2006, after the first 79 patients had been randomised.
Comparator	**Radiotherapy alone.**

Number of participants	220
Duration of follow-up	13 weeks
Loss to follow-up	Nobody was lost to follow-up
Methods of analysis	The sample size was calculated to enable the detection of a 15% absolute difference in dysphagia relief rate (from 75% in the radiotherapy group to 90% in the chemoradiotherapy group), with 80% power using a two-sided test at the 5% significance level. This required 100 patients per treatment group. To allow for some losses to follow-up, the recruitment target was 220 patients. An interim analysis on the primary endpoint (dysphagia relief) was done after 139 patients had been randomly assigned, with the stopping criterion being a highly significant difference ($p<0·005$) between the two treatment groups. The stopping criterion was not met, so the trial continued, and the results were not revealed to trial investigators until the trial was closed. A Safety and Data Monitoring Committee formally reviewed treatment-related toxic effects annually. No unexpected and severe toxic effects were reported to the Trial Management Committee. Patients' data were analysed according to their randomised treatment arm (intention-to-treat), except for the exclusion of one patient who was found not to have oesophageal cancer after randomisation. Patients who did not commence any protocol treatment were excluded from the toxicity analyses. Dysphagia relief rate was defined as the number of patients with complete or partial dysphagia relief as a percentage of the total number of randomised patients. The investigators used the Fisher exact test to compare the rates between treatment groups, and they calculated exact 95% CI for each group and for the difference between groups. For those patients who obtained any relief, even at only one assessment, they used the Wilcoxon rank sum test to compare the treatment groups for time from start of radiotherapy to first relief or to first complete relief, and for the duration of any relief. Dysphagia progression-free survival and overall survival from the date of randomisation were estimated using the Kaplan-Meier method. Dysphagia progression-free survival events were progression of dysphagia, or death from any cause. All deaths were counted as events for overall survival. Survival times for patients who had not experienced the relevant event were censored at the close-out date (Dec 2, 2013) or, if lost to follow-up, at their dates of last contact. The logit transformation and the Brookmeyer-Crowley method were used to obtain 95% CI for percentages of patients surviving at 1 and 2 years and median survival times, respectively.

	The Mantel-Cox log rank test was used to compare subgroups. The reverse Kaplan-Meier method was used to estimate the overall follow-up time—ie, counting surviving and lost patients as events, and censoring deaths. To find out which patients would benefit most from the protocol treatments, ten potential prespecified prognostic factors were tested in post-hoc univariate analyses of dysphagia relief and dysphagia progression-free survival. These were M stage, pre-treatment dysphagia, histological subtype, tumour length, performance status, bodyweight loss, pre-treatment haemoglobin, age group, sex, and radiotherapy fractionation. For overall survival, they also tested extent of disease (locoregional, limited disseminated, extensive disseminated), NM stage (N0M0, N+M0, M1), and liver metastases. Locoregional disease was defined as locally unresectable disease without metastases, limited disseminated disease was defined as nodal metastases confined to the thorax and either coeliac axis or neck region (excluding supraclavicular nodes), and extensive disseminated disease as distant metastases, positive supraclavicular nodes, or concurrent metastases in both coeliac and neck regions. N and M stages were retrospectively revised in line with the Union for International Cancer Control's TNM Staging Criteria, 7th edition, before analysis. Multivariable analyses were done both to adjust the comparisons of dysphagia relief, dysphagia progression-free survival, and overall survival between treatment groups for the stratification variables (M stage and dysphagia, not hospital), and to find the most important prognostic factors affecting these three outcomes. Exact logistic regression with conditional maximum likelihood inference was used for dysphagia relief rates, and Cox proportional hazards regression was used for dysphagia progression-free survival and overall survival. All statistical tests were two-sided, and the criterion of significance was a p value of less than 0·05 with no adjustments for multiple comparisons. They used R statistical software for survival analyses and Cytel Studio 7.0 for non-parametric tests and logistic regression. Nearly all patients were followed until death, so it was considered unnecessary to estimate late toxicity incidence using the Kaplan-Meier method. Crude incidences of worst grades of acute and late toxicities are reported instead. The Cochran-Armitage trend test was used to compare individual toxic effects between treatment groups, and the Fisher exact test was used to compare the overall incidence of any grade 3–4 toxic effects.

Study arms

Chemoradiotherapy (N = 111)

Radiotherapy (N = 109)

Characteristics

Arm-level characteristics

Characteristic	Chemoradiotherapy (N = 111)	Radiotherapy (N = 109)
median age (years) Median (IQR)	62 (57 to 70)	67 (60 to 72)
% Female (%) Nominal	17	16

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

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low *(Although this was an unblinded study, the outcomes were measured objectively, and blinding was impossible because of the nature of the interventions.)*
Overall bias and Directness	Overall Directness	Directly applicable

Persson, 2017

Bibliographic Reference	Persson, Jan; Smedh, Ulrika; Johnsson, Ase; Ohlin, Bo; Sundbom, Magnus; Nilsson, Magnus; Lundell, Lars; Sund, Berit; Johnsson, Erik; Fully covered stents are similar to semi-covered stents with regard to migration in palliative treatment of malignant strictures of the esophagus and gastric cardia: results of a randomized controlled trial.; Surgical endoscopy; 2017; vol. 31 (no. 10); 4025-4033

Study details

Secondary publication of another included study- see primary study for details	N/A
Other publications associated with this study	N/A

included in review	
Trial registration number and/or trial name	Not provided
Study type	Randomised controlled trial (RCT)
Study location	Sweden
Study setting	Hospitals
Study dates	2011 to 2014
Sources of funding	This study was supported by the Gothenburg Medical Society, the Assar Gabrielsson's Fund, Sweden and ALF-LUA via the Department of Surgery, Sahlgrenska University Hospital.
Inclusion criteria	• Incurable oesophageal cancer confirmed using histology (high-grade dysplasia) and clinical or radiological evidence of invasive tumour • Biopsy-verified squamous cell carcinoma or adenocarcinoma in the oesophagus or the GEJ where stent-treatment is applicable • A specified dysphagia score • Swallowing difficulties with a severity of dysphagia of 2–4 according to Ogilvie • Older than 18 years of age
Exclusion criteria	• A tumour located close to the upper oesophageal sphincter • Need for a stent with the upper margin less than 2 cm from the upper oesophageal sphincter • Other concurrent malignancy that might impact the life span and/or QoL of the patient • Need of more than one stent to bridge the tumour
Intervention(s)	**Fully covered oesophageal self-expandable metal stents (FC-SEMSs)** The Wallflex stent is made of a multiple-wired mesh of Nitinol and has a full silicone internal covering with progressive step-flared ends. The body diameter of the stent used was 18 mm, and the flare diameters were 25 mm proximally, and 23 mm distally. This stent was available in three lengths: 103, 123, and 153 mm. All available stent lengths were used in both groups. Many patients undergoing the endoscopic procedure were treated under conscious sedation with midazolam, and alfentanil or pethidine in addition. The upper and when possible also the lower margin of the tumour was marked with a metal clip. If it was impossible to pass the tumour with the endoscope, the length of the obstruction was determined by the

	radiological findings or by the use of an “on the table” conventional contrast X-ray. Under fluoroscopic X-ray guidance, a guide-wire was passed down to the stomach. When the endoscope had been removed, the stent was inserted over the wire and positioned in relation to the clips. The length of the stent was chosen according to the length of the stricture, and the stent was placed with at least a 2 cm proximal and distal overlap to the upper and lower margins of the tumour. In cases where the stent was positioned with its distal end below the cardia, the distal overlap was aimed at 1 cm. Dilatation was not done routinely to be able to pass the tumour with the endoscope. However, if there were difficulties passing the stricture with the introducer of the stent, a dilatation was performed up to a maximum of 12 mm. Technical failure was defined as inability to place a stent due to technical problems during the initial procedure, or any other event on day 0 that made further participation impossible. Immediately after stent placement, its position was documented with a postero-anterior and lateral chest X-ray. The majority of the patients were examined in the standing position. The patients received additional written and oral information after receiving the stent. These instructions included advice on diet and ingesting only liquid nutrients for the first 3 days after the procedure.
Comparator	**Partially covered oesophageal self-expandable metal stents (PC-SEMSs)** The Ultraflex stent consists of a knitted nickel-titanium alloy (Nitinol) wire tube and has a polyurethane layer, which covers the midsection of the stent extending to within 1.5 cm of either end of the stent. The stent used in this study had a proximal flare of 23 mm and an inner body diameter of 18 mm. It was available in three lengths: 100, 120, and 150 mm.
Number of participants	95
Duration of follow-up	3 months
Loss to follow-up	Nobody was lost to follow-up
Methods of analysis	A sample size of 43 patients in each group was calculated based on an estimate that the expected rate of migration in the conventional PC-SEMSs group was 10% and in the group with FC-SEMS 35%, whereupon a corresponding difference could be detected with a power of 80% and a significance level of 95%, ($p<0.05$). The SPSS statistical program was applied for data analysis. The point prevalence of data was compared using parametric or non-parametric tests where appropriate. A p-value of less than 0.05 was considered statistically significant.

Study arms

Fully covered oesophageal self-expandable metal stents (FC-SEMSs) (N = 48)

Partially covered oesophageal self-expandable metal stents (PC-SEMSs) (N = 47)

Characteristics

Arm-level characteristics

Characteristic	Fully covered oesophageal self-expandable metal stents (FC-SEMSs) (N = 48)	Partially covered oesophageal self-expandable metal stents (PC-SEMSs) (N = 47)
median age (years) Nominal	71.2	72.2
median age (years) Range	56.8 to 91	48.2 to 91
% Female (%) Nominal	27.1	23.4

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

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low *(This was an unblinded study - blinding was not possible. Therefore, the risk of bias is low for objective outcomes, such as mortality, but there is a moderate risk of bias for subjective outcomes, such as adverse events.)*
Overall bias and Directness	Overall Directness	Directly applicable

Appendix E – Forest plots

No outcomes were reported by more than one study so no meta-analysis was undertaken. Forest plots included in the previous evidence review for this question are not reported here. Please see the previous version of this review (section 9.4 of the 2018 full guideline).

Appendix F – GRADE tables

GRADE tables included in the previous evidence review for this question are not reported here. Please see the previous version of this review (section 9.4 of the 2018 full guideline).

Table 7: SEMS + EBRT versus SEMS

Certainty assessment							Summary of findings				
							Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	With SEMS	With SEMS + EBRT		Risk with SEMS	Risk difference with SEMS + EBRT
Overall survival – as a risk ratio. Numbers greater than 1 favour SEMS											
199 (1 RCT – Adamson 2021)	not serious	not serious	not serious	serious[a]	none	⨁⨁⨁◯ Moderate	86/102 (84.3%)	82/97 (84.5%)	**RR 1.00** (0.89 to 1.13)	843 per 1,000	**0 fewer per 1,000** (from 93 fewer to 110 more)
Overall survival – as a hazard ratio. Numbers greater than 1 favour SEMS											

Certainty assessment							Summary of findings				
199 (1 RCT – Adamson 2021)	not serious	not serious	not serious	very serious[d]	none	⨁⨁◯◯ Low	N/A[b]	N/A[b]	**HR 1.06** (0.78 to 1.45)	N/A[b]	N/A[b]

Deterioration of dysphagia or death – 12 weeks. Numbers greater than 1 favour SEMS

149[c] (1 RCT – Adamson 2021)	not serious	not serious	not serious	very serious[d]	none	⨁⨁◯◯ Low	36/74 (48.6%)	34/75 (45.3%)	**RR 0.93** (0.66 to 1.31)	486 per 1,000	**34 fewer per 1,000** (from 165 fewer to 151 more)

Dysphagia deterioration free survival. Numbers greater than 1 favour SEMS

199 (1 RCT – Adamson 2021)	not serious	not serious	not serious	very serious[d]	none	⨁⨁◯◯ Low	N/A[b]	N/A[b]	**HR 0.92** (0.68 to 1.25)	N/A[b]	N/A[b]

Time to first dysphagia stent complication or reintervention. Numbers greater than 1 favour SEMS

199 (1 RCT – Adamson 2021)	not serious	not serious	not serious	very serious[d]	none	⨁⨁◯◯ Low	N/A[b]	N/A[b]	**HR 0.79** (0.37 to 1.67)	N/A[b]	N/A[b]

Certainty assessment							Summary of findings				
GI related bleeding – patients with 1 or more events longest follow up. Numbers greater than 1 favour SEMS											
199 (1 RCT – Adamson 2021)	not serious	not serious	not serious	serious[a]	none	⨁⨁⨁◯ Moderate	29/102 (28.4%)	16/97 (16.5%)	**RR 0.58** (0.34 to 1.00)	284 per 1,000	**119 fewer per 1,000** (from 188 fewer to 0 fewer)
GI related bleeding – patients with 1 or more event – 16 weeks. Numbers greater than 1 favour SEMS											
199 (1 RCT – Adamson 2021)	not serious	not serious	not serious	serious[a]	none	⨁⨁⨁◯ Moderate	19/102 (18.6%)	10/97 (10.3%)	**RR 0.55** (0.27 to 1.13)	186 per 1,000	**84 fewer per 1,000** (from 136 fewer to 24 more)
Dysphagia grade 3 or 4 toxicity – 16 weeks. Numbers greater than 1 favour SEMS											
199 (1 RCT – Adamson 2021)	not serious	not serious	not serious	very serious[d]	none	⨁⨁◯◯ Low	11/102 (10.8%)	9/97 (9.3%)	**RR 0.86** (0.37 to 1.98)	108 per 1,000	**15 fewer per 1,000** (from 68 fewer to 106 more)
Nausea grade 3 or 4 toxicity – 16 weeks. Numbers greater than 1 favour SEMS											

Certainty assessment							Summary of findings				
199 (1 RCT – Adamson 2021)	not serious	not serious	not serious	very serious[d]	none	⨁⨁◯◯ Low	5/102 (4.9%)	7/97 (7.2%)	**RR 1.47** (0.48 to 4.48)	49 per 1,000	**23 more per 1,000** (from 25 fewer to 171 more)

Vomiting grade 3 or 4 toxicity – 16 weeks. Numbers greater than 1 favour SEMS

199 (1 RCT – Adamson 2021)	not serious	not serious	not serious	serious[a]	none	⨁⨁⨁◯ Moderate	4/102 (3.9%)	11/97 (11.3%)	**RR 2.89** (0.95 to 8.78)	39 per 1,000	**74 more per 1,000** (from 2 fewer to 305 more)

Aspiration grade 3 or 4 toxicity - 16 weeks. Numbers greater than 1 favour SEMS

199 (1 RCT – Adamson 2021)	not serious	not serious	not serious	very serious[d]	none	⨁⨁◯◯ Low	0/102 (0.0%)	2/97 (2.1%)	**RR 5.26** (0.26 to 108.09)	0 per 1,000	**0 fewer per 1,000** (from 0 fewer to 0 fewer)

Stent related pain grade 3 or 4 toxicity – 16 weeks. Numbers greater than 1 favour SEMS

Certainty assessment							Summary of findings				
199 (1 RCT – Adamson 2021)	not serious	not serious	not serious	very serious[d]	none	⨁⨁◯◯ Low	6/102 (5.9%)	8/97 (8.2%)	**RR 1.40** (0.50 to 3.89)	59 per 1,000	**24 more per 1,000** (from 29 fewer to 170 more)

Upper GI haemorrhage grade 3 or 4 toxicity – 16 weeks. Numbers greater than 1 favour SEMS

199 (1 RCT – Adamson 2021)	not serious	not serious	not serious	very serious[d]	none	⨁⨁◯◯ Low	4/102 (3.9%)	2/97 (2.1%)	**RR 0.53** (0.10 to 2.81)	39 per 1,000	**18 fewer per 1,000** (from 35 fewer to 71 more)

Abdominal pain grade 3 or 4 toxicity – 16 weeks. Numbers greater than 1 favour SEMS

199 (1 RCT – Adamson 2021)	not serious	not serious	not serious	very serious[d]	none	⨁⨁◯◯ Low	2/102 (2.0%)	5/97 (5.2%)	**RR 2.63** (0.52 to 13.23)	20 per 1,000	**32 more per 1,000** (from 9 fewer to 240 more)

CI: confidence interval; **HR:** hazard Ratio; **RR:** risk ratio

Explanations

a. Downgraded once for imprecision because the 95% confidence interval crosses the line of no effect.

b. This is a hazard ratio therefore there are no study event rates or absolute effects.

c. Participants in this meta-analysis are fewer because it only includes participants for which all dysphagia subscale data is available.

d. Downgraded twice for imprecision because the 95% confidence interval crosses the line of no effect and both minimally important differences (0.8 and 1.25).

Table 8: Fully covered versus partially covered SEMS

Certainty assessment							Summary of findings				
							Study event rates (%)			Anticipated absolute effects	
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	With partially covered SEMS	With Fully covered	Relative effect (95% CI)	Risk with partially covered SEMS	Risk difference with Fully covered
Recurrent obstruction / dysphagia. Numbers greater than 1 favour partially covered SEMS											
97 (1 RCT – Didden 2018)	not serious	not serious	not serious	very serious[a]	none	⨁⨁◯◯ Low	11/49 (22.4%)	9/48 (18.8%)	**RR 0.84** (0.38 to 1.83)	224 per 1,000	**36 fewer per 1,000** (from 139 fewer to 186 more)
Technical Success. Numbers greater than 1 favour partially covered SEMS											

Certainty assessment							Summary of findings				
97 (1 RCT – Didden 2018)	not serious	not serious	not serious	very serious[a]	none	⨁⨁◯◯ Low	47/49 (95.9%)	48/48 (100.0%)	**RR 0.20** (0.01 to 4.14)	959 per 1,000	**767 fewer per 1,000** (from 950 fewer to 1,000 more)

Severe pain > 7 days. Numbers greater than 1 favour partially covered SEMS

97 (1 RCT – Didden 2018)	not serious	not serious	not serious	very serious[a]	none	⨁⨁◯◯ Low	1/49 (2.0%)	1/48 (2.1%)	**RR 1.02** (0.07 to 15.86)	20 per 1,000	**0 fewer per 1,000** (from 19 fewer to 303 more)

Severe pain ≤ 7 days. Numbers greater than 1 favour partially covered SEMS

97 (1 RCT – Didden 2018)	not serious	not serious	not serious	very serious[a]	none	⨁⨁◯◯ Low	8/49 (16.3%)	8/48 (16.7%)	**RR 1.02** (0.42 to 2.50)	163 per 1,000	**3 more per 1,000** (from 95 fewer to 245 more)

Haemorrhage > 7 days. Numbers greater than 1 favour partially covered SEMS

Certainty assessment							Summary of findings				
97 (1 RCT – Didden 2018)	not serious	not serious	not serious	very serious[a]	none	⨁⨁◯◯ Low	5/49 (10.2%)	4/48 (8.3%)	**RR 0.82** (0.23 to 2.86)	102 per 1,000	**18 fewer per 1,000** (from 79 fewer to 190 more)

Stridor ≤ 7 days. Numbers greater than 1 favour partially covered SEMS

97 (1 RCT – Didden 2018)	not serious	not serious	not serious	very serious[a]	none	⨁⨁◯◯ Low	0/49 (0.0%)	2/48 (4.2%)	**RR 5.10** (0.25 to 103.58)	0 per 1,000	**0 fewer per 1,000** (from 0 fewer to 0 fewer)

Mild pain > 7 days. Numbers greater than 1 favour partially covered SEMS

97 (1 RCT – Didden 2018)	not serious	not serious	not serious	very serious[a]	none	⨁⨁◯◯ Low	0/49 (0.0%)	1/48 (2.1%)	**RR 3.06** (0.13 to 73.34)	0 per 1,000	**0 fewer per 1,000** (from 0 fewer to 0 fewer)

Stent migration 1 week. Numbers greater than 1 favour partially covered SEMS

Certainty assessment							Summary of findings				
95 (1 RCT – Persson 2017)	not serious	not serious	not serious	very serious[a]	none	⨁⨁◯◯ Low	4/47 (8.5%)	4/48 (8.3%)	**RR 0.98** (0.26 to 3.69)	85 per 1,000	**2 fewer per 1,000** (from 63 fewer to 229 more)

Stent migration 1 month. Numbers greater than 1 favour partially covered SEMS

95 (1 RCT – Persson 2017)	not serious	not serious	not serious	very serious[a]	none	⨁⨁◯◯ Low	3/47 (6.4%)	1/48 (2.1%)	**RR 0.33** (0.04 to 3.03)	64 per 1,000	**43 fewer per 1,000** (from 61 fewer to 130 more)

Stent migration 3 months. Numbers greater than 1 favour partially covered SEMS

95 (1 RCT – Persson 2017)	not serious	not serious	not serious	very serious[a]	none	⨁⨁◯◯ Low	4/47 (8.5%)	1/48 (2.1%)	**RR 0.24** (0.03 to 2.11)	85 per 1,000	**65 fewer per 1,000** (from 83 fewer to 94 more)

Reinterventions 1 week. Numbers greater than 1 favour partially covered SEMS

Certainty assessment							Summary of findings				
95 (1 RCT – Persson 2017)	not serious	not serious	not serious	very serious[a]	none	⨁⨁◯◯ Low	6/47 (12.8%)	5/48 (10.4%)	**RR 0.82** (0.27 to 2.49)	128 per 1,000	**23 fewer per 1,000** (from 93 fewer to 190 more)

Reinterventions 1 month. Numbers greater than 1 favour partially covered SEMS

95 (1 RCT – Persson 2017)	not serious	not serious	not serious	very serious[a]	none	⨁⨁◯◯ Low	5/47 (10.6%)	2/48 (4.2%)	**RR 0.39** (0.08 to 1.92)	106 per 1,000	**65 fewer per 1,000** (from 98 fewer to 98 more)

Reinterventions 3 months. Numbers greater than 1 favour partially covered SEMS

95 (1 RCT – Persson 2017)	not serious	not serious	not serious	very serious[a]	none	⨁⨁◯◯ Low	4/47 (8.5%)	1/48 (2.1%)	**RR 0.24** (0.03 to 2.11)	85 per 1,000	**65 fewer per 1,000** (from 83 fewer to 94 more)

CI: confidence interval; **RR:** risk ratio

Explanations

a. Downgraded twice for imprecision because the 95% confidence interval crosses the line of no effect and both minimally important differences (0.8 and 1.25).

Table 9: Radiotherapy versus chemoradiotherapy

Certainty assessment							Summary of findings				
							Study event rates (%)			Anticipated absolute effects	
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	With Radiotherapy	With Chemotherapy	Relative effect (95% CI)	Risk with Radiotherapy	Risk difference with Chemotherapy
Dysphagia relief. Numbers greater than 1 favour radiotherapy											
219 (1 RCT – Penniment 2018)	not serious	not serious	not serious	serious[a]	none	⨁⨁⨁◯ Moderate	38/109 (34.9%)	50/110 (45.5%)	**RR 0.84** (0.67 to 1.04)	349 per 1,000	**56 fewer per 1,000** (from 115 fewer to 14 more)
Dysphagia deterioration. Numbers greater than 1 favour radiotherapy											

Certainty assessment							Summary of findings				
219 (1 RCT – Penniment 2018)	not serious	not serious	not serious	very serious[d]	none	⨁⨁◯◯ Low	31/109 (28.4%)	27/110 (24.5%)	**RR 0.86** (0.55 to 1.34)	284 per 1,000	**40 fewer per 1,000** (from 128 fewer to 97 more)

Progression free survival. Numbers greater than 1 favour radiotherapy

0 (1 RCT – Penniment 2018)	not serious	not serious	not serious	serious[a]	none	⨁⨁⨁◯ Moderate	N/A[b]	N/A[b]	**HR 0.89** (0.67 to 1.18)	N/A[b]	N/A[b]

Overall survival. Numbers greater than 1 favour radiotherapy

0 (1 RCT – Penniment 2018)	not serious	not serious	not serious	very serious[d]	none	⨁⨁◯◯ Low	N/A[b]	N/A[b]	**HR 0.98** (0.74 to 1.30)	N/A[b]	N/A[b]

Nausea and vomiting grade 1 - 90 days. Numbers greater than 1 favour radiotherapy

211 (1 RCT – Penniment 2018)	not serious	not serious	not serious	very serious[d]	none	⨁⨁◯◯ Low	15/104 (14.4%)	9/107 (8.4%)	**RR 0.58** (0.27 to 1.27)	144 per 1,000	**61 fewer per 1,000** (from 105 fewer to 39 more)

Certainty assessment							Summary of findings				
Nausea and vomiting grade 2 - 90 days. Numbers greater than 1 favour radiotherapy											
211 (1 RCT – Penniment 2018)	not serious	not serious	not serious	not serious	none	⨁⨁⨁⨁ High	41/104 (39.4%)	62/107 (57.9%)	**RR 1.47** (1.10 to 1.96)	394 per 1,000	**185 more per 1,000** (from 39 more to 378 more)
Nausea and vomiting grade 3 - 90 days. Numbers greater than 1 favour radiotherapy											
211 (1 RCT – Penniment 2018)	not serious	not serious	not serious	very serious[d]	none	⨁⨁◯◯ Low	5/104 (4.8%)	7/107 (6.5%)	**RR 1.36** (0.45 to 4.15)	48 per 1,000	**17 more per 1,000** (from 26 fewer to 151 more)
Nausea and vomiting grade 4 - 90 days. Numbers greater than 1 favour radiotherapy											
211 (1 RCT – Penniment 2018)	not serious	not serious	not serious	serious[a]	none	⨁⨁⨁◯ Moderate	0/104 (0.0%)	0/107 (0.0%)	not estimable[c]	0 per 1,000	not estimable[c]
Chest pain - 90 days. Numbers greater than 1 favour radiotherapy											

Certainty assessment							Summary of findings				
211 (1 RCT – Penniment 2018)	not serious	not serious	not serious	very serious[d]	none	⨁⨁◯◯ Low	1/104 (1.0%)	0/107 (0.0%)	**RR 0.32** (0.01 to 7.87)	10 per 1,000	**7 fewer per 1,000** (from 10 fewer to 66 more)

CI: confidence interval; **HR:** hazard Ratio; **RR:** risk ratio

Explanations

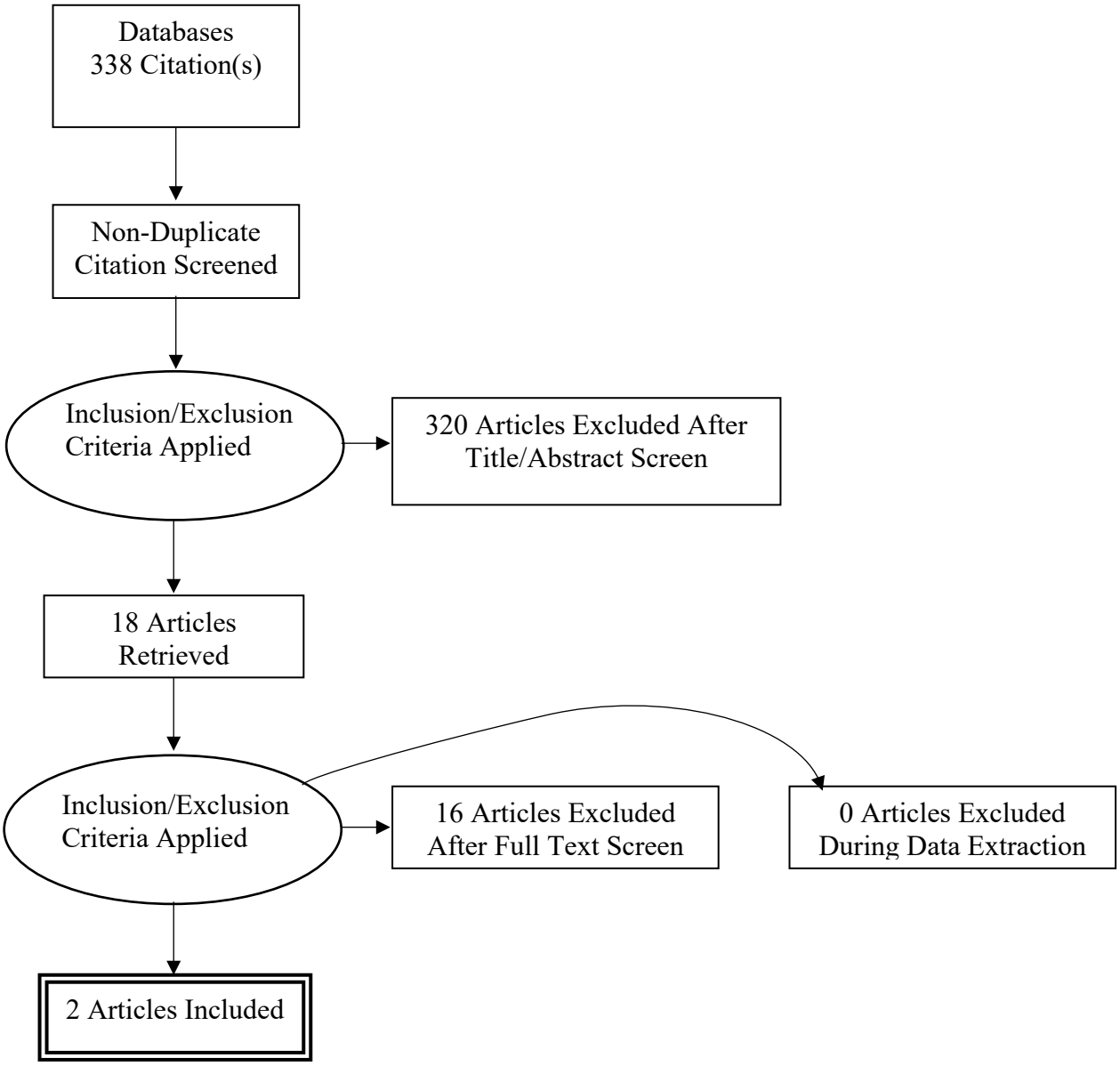
a. Downgraded once for imprecision because the 95% confidence interval crosses the line of no effect.

b. This is a hazard ratio therefore there are no study event rates or absolute effects.

c. Not estimable because there were no events in either arm.

d. Downgraded twice for imprecision because the 95% confidence interval crosses the line of no effect and both minimally important differences (0.8 and 1.25).

Appendix G – Economic evidence study selection



Appendix H – Economic evidence tables

Study	Study type	Study quality	Setting	Intervention	Methods of analysis	Results	Limitations	Additional comments
Adamson 2021	Cost utility study Decision tree and Markov model	Directly applicable Potentially serious limitations	UK NHS and PSS perspective (costing year not reported)	Patients (aged ≥16 years) with incurable oesophageal carcinoma receiving stent insertion for primary management of dysphagia Self-expanding metal stent (SEMS) n=102 Self-expanding metal stent (SEMS) and adjuvant external beam radiotherapy (EBRT) n=97	Health states: Swallowing improved; Swallowing worsening; Death Time horizon: 12 weeks (sensitivity analysis 12 months) No discounting	Cost: SEMS: £4,628 SEMS + EBRT: £6,157 Incremental: £1,529 QALYs: SEMS: 0.111 SEMS + EBRT: 0.108 Incremental: -0.003 ICER: SEMS dominates SEMS + ERBT	One way sensitivity analyses were completed but none changed the result of SEMS dominating SEMS + EBRT	Multiple authors have received funding from different pharmaceutical companies. The study was unable to investigate different EBRT schedules.

Study	Study type	Study quality	Setting	Intervention	Methods of analysis	Results	Limitations	Additional comments
Rao2009	Cost-utility study Decision tree	Directly applicable Potentially serious limitations	UK (costs converted from GBP to USD) NHS and PSS perspective (costing year 2007)	Patients diagnosed with esophageal cancer which are unsuitable for curative resection who have malignant dysphagia Plastic stent Uncovered self-expanding metal stent Covered self-expanding metal stent	Clinical outcomes were obtained from meta-analysed data of randomised and non-randomised studies. A weighted 30-day mean was then used for mortality, re-intervention, perforation, and haemorrhage Costs were obtained from NHS reference costs with the cost of the stent obtained from the manufacturer Health states: Successful; Haemorrhage; Perforation; and Death with those in the first three health states able to have a further stent if required 1-year time horizon	Cost: Plastic stent: $8,059 Uncovered self-expanding metal stent: $5,226 Covered self-expanding metal stent: $4,499 QALYs: Plastic stent: 0.3324 Uncovered self-expanding metal stent: 0.3522 Covered self-expanding metal stent: 0.3535 Covered self-expanding metal stents dominate	PSA showed that covered self-expanding metal stents is 99% certain to be cost effective at all willingness to pay thresholds below $150,000/QALY	

Study	Study type	Study quality	Setting	Intervention	Methods of analysis	Results	Limitations	Additional comments
					No discounting			

Study identification Adamson et al		
Category	**Rating**	**Comments**
Applicability		
1.1 Is the study population appropriate for the review question?	Yes	
1.2 Are the interventions appropriate for the review question?	Yes	
1.3 Is the system in which the study was conducted sufficiently similar to the current UK context?	Yes	
1.4 Is the perspective for costs appropriate for the review question?	Yes	
1.5 Is the perspective for outcomes appropriate for the review question?	Yes	
1.6 Are all future costs and outcomes discounted appropriately?	Yes	Time horizon under a year
1.7 Are QALYs, derived using NICE's preferred methods, or an appropriate social care-related equivalent used as an outcome? If not, describe rationale and outcomes used in line with analytical perspectives taken (item 1.5 above).	Yes	

Study identification Adamson et al		
Category	**Rating**	**Comments**
1.8 OVERALL JUDGEMENT	**DIRECTLY APPLICABLE**	There is no need to use section 2 of the checklist if the study is considered 'not applicable'.
Limitations		
2.1 Does the model structure adequately reflect the nature of the topic under evaluation?	Yes	
2.2 Is the time horizon sufficiently long to reflect all important differences in costs and outcomes?	Yes	
2.3 Are all important and relevant outcomes included?	Yes	
2.4 Are the estimates of baseline outcomes from the best available source?	Yes	
2.5 Are the estimates of relative intervention effects from the best available source?	Yes	
2.6 Are all important and relevant costs included?	Yes	
2.7 Are the estimates of resource use from the best available source?	Yes	
2.8 Are the unit costs of resources from the best available source?	Yes	
2.9 Is an appropriate incremental analysis presented or can it be calculated from the data?	Yes	
2.10 Are all important parameters whose values are uncertain subjected to appropriate sensitivity analysis?	Yes	
2.11 Has no potential financial conflict of interest been declared?	No	Multiple financial conflicts were declared for a number of the authors
2.12 OVERALL ASSESSMENT	**MINOR LIMITATIONS**	
Study identification		

Study identification Adamson et al		
Category	**Rating**	**Comments**

Rao et al		
Category	**Rating**	**Comments**
Applicability		
1.1 Is the study population appropriate for the review question?	Yes	
1.2 Are the interventions appropriate for the review question?	Yes	
1.3 Is the system in which the study was conducted sufficiently similar to the current UK context?	Yes	
1.4 Is the perspective for costs appropriate for the review question?	Yes	Used NICE perspective but then converted the costs into USD
1.5 Is the perspective for outcomes appropriate for the review question?	Yes	
1.6 Are all future costs and outcomes discounted appropriately?	Yes	
1.7 Are QALYs, derived using NICE's preferred methods, or an appropriate social care-related equivalent used as an outcome? If not, describe rationale and outcomes used in line with analytical perspectives taken (item 1.5 above).	Yes	
1.8 OVERALL JUDGEMENT	**DIRECTLY APPLICABLE**	
Limitations		
2.1 Does the model structure adequately reflect the nature of the topic under evaluation?	Yes	
2.2 Is the time horizon sufficiently long to reflect all important differences in costs and outcomes?	Yes	1 year

Study identification Adamson et al		
Category	**Rating**	**Comments**
2.3 Are all important and relevant outcomes included?	Yes	
2.4 Are the estimates of baseline outcomes from the best available source?	Partly	Best available at the time but then converted into USD
2.5 Are the estimates of relative intervention effects from the best available source?	Partly	Best available at the time
2.6 Are all important and relevant costs included?	Yes	
2.7 Are the estimates of resource use from the best available source?	Partly	Best available at the time
2.8 Are the unit costs of resources from the best available source?	Partly	Best available at the time (2006/2007)
2.9 Is an appropriate incremental analysis presented or can it be calculated from the data?	Yes	
2.10 Are all important parameters whose values are uncertain subjected to appropriate sensitivity analysis?	Yes	
2.11 Has no potential financial conflict of interest been declared?	Yes	
2.12 OVERALL ASSESSMENT	**POTENTIALLY SERIOUS LIMITATIONS**	

Appendix I – Health economic model

No original health economic modelling was undertaken for this review.

Appendix J – Excluded studies

Intervention studies

Study	Code [Reason]
Adamson, Douglas, Blazeby, Jane, Porter, Catharine et al. (2021) Palliative radiotherapy combined with stent insertion to reduce recurrent dysphagia in oesophageal cancer patients: the ROCS RCT. Health technology assessment (Winchester, England) 25(31): 1-144	- Duplicate reference *This is a mirror publication of Adamson 2021 published in the Lancet. We have included this study in our evidence review. Additional relevant information in the HTA has also been included in our evidence tables.*
Adenis, A., Kulkarni, A., Girotto, G.C. et al. (2019) Health-related quality of life (HRQoL) of pembrolizumab (pembro) versus physician choice single-agent paclitaxel, docetaxel, or irinotecan in subjects with advanced/metastatic adenocarcinoma (ACC) or squamous cell carcinoma (SCC) of the esophagus that has progressed after first-line standard therapy (KEYNOTE- 181). Journal of Clinical Oncology 37(supplement15)	- Conference abstract
Adenis, Antoine, Kulkarni, Amit S, Girotto, Gustavo C et al. (2022) Impact of Pembrolizumab Versus Chemotherapy as Second-Line Therapy for Advanced Esophageal Cancer on Health-Related Quality of Life in KEYNOTE-181. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 40(4): 382-391	- Does not adjust or match for the minimum list of confounding factors as specified in the protocol
Bandyopadhyay, S., Biswas, L., Banerjee, B. et al. (2022) A PROSPECTIVE AND COMPARATIVE STUDY ON CONCURRENT RADIOTHERAPY WITH GEFITINIB VERSUS RADIOTHERAPY ALONE IN THE TREATMENT OF ELDERLY PATIENTS WITH CARCINOMA OESOPHAGUS. Asian Journal of Pharmaceutical and Clinical Research 15(7): 144-148	- Wrong population *Not clear if population are palliative only* - Study does not contain a relevant intervention *Intervention's primary aim not palliative management of luminal obstruction*
Bascoul-Mollevi, C, Gourgou, S, Galais, M-P et al. (2017) Health-related quality of life results from the PRODIGE 5/ACCORD 17 randomised trial of FOLFOX versus fluorouracil-cisplatin regimen in oesophageal cancer. European journal of cancer (Oxford, England : 1990) 84: 239-249	- Wrong population *Mixed population with some amenable to treatment with curative intent*

Study	Code [Reason]
Boshier, P.R., Klevebro, F., Schmidt, A. et al. (2022) Impact of Early Jejunostomy Tube Feeding on Clinical Outcome and Parameters of Body Composition in Esophageal Cancer Patients Receiving Multimodal Therapy. Annals of Surgical Oncology 29(9): 5689-5697	- Wrong population *Curative population*
Byrne, A.T., Adamson, D., Porter, C. et al. (2020) Radiotherapy after esophageal cancer stenting (ROCS): A pragmatic randomized controlled trial evaluating the role of palliative radiotherapy in maintaining swallow. Journal of Clinical Oncology 38(15)	- Full text paper not available *Full text not available and reference appears to be a duplicate*
Cools-Lartigue, J., Jones, D., Zourikian, T. et al. (2013) The management of dysphagia in esophageal adenocarcinoma patients undergoing neoadjuvant chemotherapy: Can invasive tube feeding be avoided?. Journal of Clinical Oncology 31(15suppl1)	- Conference abstract
Dijksterhuis, W.P.M., Verhoeven, R.H.A., Meijer, S.L. et al. (2019) Increased assessment of HER2 in metastatic gastroesophageal cancer patients: A nationwide population-based cohort study. Annals of Oncology 30(supplement5): v312	- Wrong population - Not a relevant study design
Dijksterhuis, W.P.M., Verhoeven, R.H.A., Meijer, S.L. et al. (2019) Increased assessment of HER2 in metastatic gastroesophageal cancer patients: A nationwide population-based cohort study. Annals of Oncology 30(supplement5): v312	- Duplicate reference
Dijksterhuis, W.P.M., Verhoeven, R.H.A., Meijer, S.L. et al. (2020) Increased assessment of HER2 in metastatic gastroesophageal cancer patients: a nationwide population-based cohort study. Gastric Cancer 23(4): 579-590	- Duplicate reference
Dinshaw, K A, Sharma, V, Pendse, A M et al. (1991) The role of intraluminal radiotherapy and concurrent 5-fluorouracil infusion in the management of carcinoma esophagus: a pilot study. Journal of surgical oncology 47(3): 155-60	- Publication date pre-protocol date cut off (2017)
Doosti-Irani, Amin, Mansournia, Mohammad Ali, Cheraghi, Zahra et al. (2021) Network meta-analysis of palliative treatments in patients with esophageal cancer. Critical reviews in oncology/hematology 168: 103506	- Systematic review used as source of primary studies *No relevant studies post cut-off date found*

Study	Code [Reason]
Dua, K.S., DeWitt, J.M., Kessler, W.R. et al. (2018) A phase 3, single-blinded, multicenter, prospective, non-infeiority, ramdomized, controlled, trial on the performance of a novel esophageal stent with an anti-reflux valve. Gastrointestinal Endoscopy 87(6supplement1): ab144-ab145	- Wrong population *Unclear if population were not amenable for treatment with curative intent*
Dutton, Susan J, Ferry, David R, Blazeby, Jane M et al. (2014) Gefitinib for oesophageal cancer progressing after chemotherapy (COG): a phase 3, multicentre, double-blind, placebo-controlled randomised trial. The Lancet. Oncology 15(8): 894-904	- Wrong population *Treatment intended for curative intent*
Ferry, D.R., Dutton, S.J., Mansoor, W. et al. (2012) Phase III multi-centre, randomised, double-blind, placebo-controlled trial of gefitinib versus placebo in esophageal cancer progressing after chemotherapy, COG (cancer oesophagus gefitinib). Annals of Oncology 23(suppl9): ix12	- Conference abstract
Fuccio, L., Mandolesi, D., Farioli, A. et al. (2017) Brachytherapy for the palliation of dysphagia owing to esophageal cancer: A systematic review and meta-analysis of prospective studies. Digestive and Liver Disease 49(supplement2): e79	- Systematic review used as source of primary studies *No relevant studies post cut-off date found.*
Fuchs, K H, Freys, S M, Schaube, H et al. (1991) Randomized comparison of endoscopic palliation of malignant esophageal stenoses. Surgical endoscopy 5(2): 63-7	- Publication date pre-protocol date cut off (2017)
Furuta, Mitsuhiro, Yokota, Tomoya, Tsushima, Takahiro et al. (2019) Comparison of enteral nutrition with total parenteral nutrition for patients with locally advanced unresectable esophageal cancer harboring dysphagia in definitive chemoradiotherapy. Japanese journal of clinical oncology 49(10): 910-918	- Does not adjust or match for the minimum list of confounding factors as specified in the protocol - Wrong population
Hall, P S, Lord, S R, Collinson, M et al. (2017) A randomised phase II trial and feasibility study of palliative chemotherapy in frail or elderly patients with advanced gastroesophageal cancer (321GO). British journal of cancer 116(4): 472-478	- Wrong population *Contains population with gastric cancer - data for Oesophago or Oesophago-junctional cancer not separated out.*
Hamada, Tsuyoshi, Hakuta, Ryunosuke, Takahara, Naminatsu et al. (2017) Covered versus uncovered metal stents for malignant gastric outlet obstruction: Systematic review and meta-analysis.	- Systematic review used as source of primary studies *No relevant studies post cut-off date found*

Study	Code [Reason]
Digestive endoscopy : official journal of the Japan Gastroenterological Endoscopy Society 29(3): 259-271	
Heier, S K, Rothman, K A, Heier, L M et al. (1995) Photodynamic therapy for obstructing esophageal cancer: light dosimetry and randomized comparison with Nd:YAG laser therapy. Gastroenterology 109(1): 63-72	- Publication date pre-protocol date cut off (2017)
Hulshof, M.C.C.M., Geijsen, E.D., Rozema, T. et al. (2021) Randomized Study on Dose Escalation in Definitive Chemoradiation for Patients with Locally Advanced Esophageal Cancer (ARTDECO Study). Journal of Clinical Oncology 39(25): 2816-2824	- Wrong population *Mixed population without and with dysphagia* - Study does not contain a relevant intervention *Primary aim of intervention wasn't palliative treatment for luminal obstruction.*
Hutt, E., Da silva, A., Pannier, D. et al. (2017) Impact of early palliative care on overall survival of patients with metastatic upper gastrointestinal cancers treated with first-line chemotherapy: Phase III EPIC trial. Annals of Oncology 28(supplement5): v267	- Not a relevant study design *Appears to be a protocol for an ongoing trial*
Kachnic, L.A., Moughan, J., Hong, T.S. et al. (2022) Patient-Reported Outcomes (PROs) in NRG Oncology RTOG 1010: Phase III Trial Evaluating the Addition of Trastuzumab to Trimodality Treatment of HER2 Overexpressing (HER2+) Esophageal Adenocarcinoma (EAC). International Journal of Radiation Oncology Biology Physics 114(3supplement): 14	- Conference abstract
Krishna, A., Hasib, A.G., Vidyasagar et al. (2019) A prospective, comparative study of response and toxicities of HDR intraluminal brachytherapy with chemoradiation and chemoradiation alone in the treatment of carcinoma esophagus. Journal of Contemporary Brachytherapy 11(5): 494	- Conference abstract
Krishna, A, Fernandes, D, Ms, A et al. (2021) OC-0111 Intraluminal brachytherapy with chemoradiation versus chemoradiation alone in carcinoma of esophagus. Radiotherapy and oncology 158: S79-S80	- Conference abstract
Lu, Ping, Yang, Xiaoyu, Huang, Yanmei et al. (2011) Antitumor activity of a combination of rAd2p53 adenoviral gene therapy and radiotherapy in esophageal carcinoma. Cell biochemistry and biophysics 59(3): 147-52	- Wrong population *Treatment intended for curative intent.*

Study	Code [Reason]
Luo, Honglei, Jiang, Wei, Ma, Li et al. (2020) Icotinib With Concurrent Radiotherapy vs Radiotherapy Alone in Older Adults With Unresectable Esophageal Squamous Cell Carcinoma: A Phase II Randomized Clinical Trial. JAMA network open 3(10): e2019440	- Study does not contain a relevant intervention *Intervention not for luminal obstruction specifically*
Matsutani, Takeshi, Nomura, Tsutomu, Hagiwara, Nobutoshi et al. (2016) Comparison of Postoperative Pain Following Laparoscopic Versus Open Gastrostomy/Jejunostomy in Patients with Complete Obstruction Caused by Advanced Esophageal Cancer. Journal of Nippon Medical School = Nippon Ika Daigaku zasshi 83(6): 228-234	- Does not adjust or match for the minimum list of confounding factors as specified in the protocol
Min, Yang Won, Jang, Eun Young, Jung, Ji Hey et al. (2017) Comparison between gastrostomy feeding and self-expandable metal stent insertion for patients with esophageal cancer and dysphagia. PloS one 12(6): e0179522	- Does not adjust or match for the minimum list of confounding factors as specified in the protocol - Wrong population *Unclear if population are palliative only / not amenable to treatment with curative intent*
Modi, R., Mikhail, S., Hinton, A. et al. (2017) Outcomes of nutritional interventions to treat dysphagia in esophageal cancer: A population-based study. Gastrointestinal Endoscopy 85(5supplement1): ab153	- Does not adjust or match for the minimum list of confounding factors as specified in the protocol
Moehler, M., Maderer, A., Thuss-Patience, P. et al. (2018) Cisplatin/5-fluorouracil 1/-panitumumab for patients with nonresectable, advanced or metastatic esophageal squamous cell cancer: A randomized phase III AIO/EORTC trial with an extensive biomarker program. Annals of Oncology 29(supplement5): v103	- Conference abstract
Moehler, M.H., Thuss-Patience, P.C., Brenner, B. et al. (2017) Cisplatin/5-FU (CF) +/- panitumumab (P) for patients (pts) with non-resectable, advanced, or metastatic esophageal squamous cell cancer (ESCC): An open-label, randomized AIO/TTD/BDGO/EORTC phase III trial (POWER). Journal of Clinical Oncology 35(15supplement1)	- Conference abstract
Moehler, M, Maderer, A, Thuss-Patience, P C et al. (2020) Cisplatin and 5-fluorouracil with or without epidermal growth factor receptor inhibition panitumumab for patients with non-resectable, advanced or metastatic oesophageal squamous cell cancer: a prospective, open-label, randomised phase III AIO/EORTC trial (POWER). Annals of	- Wrong population *Population not luminal obstruction specifically* - Study does not contain a relevant intervention *Treatment not aimed at palliation of luminal obstruction.*

Study	Code [Reason]
oncology : official journal of the European Society for Medical Oncology 31(2): 228-235	
Nagata, K., Tsujimoto, H., Nagata, H. et al. (2019) Nutritional benefit of laparoscopic jejunostomy during neoadjuvant chemotherapy for obstructing esophageal cancer. Molecular and Clinical Oncology 11(6): 612-616	- Wrong population *Population not palliative only/ not amenable to treatment with curative intent*
Noronha, V., Patil, V.M., Menon, N.S. et al. (2022) Phase III randomized controlled trial comparing chemotherapy to best supportive care in advanced esophageal and gastroesophageal junction cancer. Journal of Clinical Oncology 40(16supplement1)	- Conference abstract
Perez Cano, E., Jimenez Lopez, Y., Sierra Torres, M.I. et al. (2022) INDIRECT COMPARISON OF NIVOLUMAB, PEMBROLIZUMAB AND CAMRELIZUMAB IN PATIENTS WITH UNRESECTABLE AND/OR ADVANCED SQUAMOUS CELL CARCINOMA OF THE OESOPHAGUS IN A SECOND-LINE SETTING. European Journal of Hospital Pharmacy 29(suppl1): a57-a58	- Conference abstract
Roussel, A, Bleiberg, H, Dalesio, O et al. (1989) Palliative therapy of inoperable oesophageal carcinoma with radiotherapy and methotrexate: final results of a controlled clinical trial. International journal of radiation oncology, biology, physics 16(1): 67-72	- Publication date pre-protocol date cut off (2017)
Siddiqui, A A, Glynn, C, Loren, D et al. (2009) Self-expanding plastic esophageal stents versus jejunostomy tubes for the maintenance of nutrition during neoadjuvant chemoradiation therapy in patients with esophageal cancer: a retrospective study. Diseases of the esophagus : official journal of the International Society for Diseases of the Esophagus 22(3): 216-22	- Wrong population *Population not palliative/not amenable to treatment with curative intent*
Song, Joo Hye, Ko, Jaehyun, Min, Yang Won et al. (2020) Comparison between Percutaneous Gastrostomy and Self-Expandable Metal Stent Insertion for the Treatment of Malignant Esophageal Obstruction, after Propensity Score Matching. Nutrients 12(9)	- Does not adjust or match for the minimum list of confounding factors as specified in the protocol
Sunde, B, Johnsen, G, Jacobsen, A-B et al. (2019) Effects of neoadjuvant chemoradiotherapy vs chemotherapy alone on the relief of dysphagia in esophageal	- Wrong population *Not a palliative population*

Study	Code [Reason]
cancer patients: secondary endpoint analysis in a randomized trial. Diseases of the esophagus: official journal of the International Society for Diseases of the Esophagus 32(2)	
Van Cutsem, E., Kato, K., Ajani, J.A. et al. (2022) Tislelizumab versus chemotherapy as second-line treatment for advanced or metastatic esophageal squamous cell carcinoma (ESCC, RATIONALE 302): Impact on health-related quality of life (HRQoL). Journal of Clinical Oncology 40(16supplement1)	- Conference abstract
Wang, Tan, Wen, Qiuyue, Zhang, Yingqiang et al. (2021) Percutaneous Gastrostomy Compared with Esophageal Stent Placement for the Treatment of Esophageal Cancer with Dysphagia. Journal of vascular and interventional radiology: JVIR 32(8): 1215-1220	- Wrong population *Not a palliative population/population who were not amenable to treatment with curative intent.*
Wu, S.-X., Wang, L.V.-H., Luo, H.-L. et al. (2018) Randomised phase III trial of concurrent chemoradiotherapy with extended nodal irradiation and erlotinib in patients with inoperable oesophageal squamous cell cancer. European Journal of Cancer 93: 99-107	- Study does not contain a relevant intervention *Intervention's primary aim not palliative treatment of luminal obstruction*
Wu, X., Zhang, K., Guo, Z. et al. Immunotherapy with or without radiotherapy for metastatic or recurrent esophageal squamous cell carcinoma: A real-world study. Clinical and Translational Radiation Oncology 38: 130-137	- Wrong population - Does not adjust or match for the minimum list of confounding factors as specified in the protocol
Yang, C W, Lin, H H, Hsieh, T Y et al. (2015) Palliative enteral feeding for patients with malignant esophageal obstruction: a retrospective study. BMC palliative care 14: 58	- Duplicate reference
Yang, C., Lin, H., Hsieh, T. et al. (2015) Palliative enteral feeding for patients with malignant esophageal obstruction: A retrospective study Cancer palliative care. BMC Palliative Care 14(1): 58	- Does not adjust or match for the minimum list of confounding factors as specified in the protocol
Zhao, Peng, Zhang, Ming-Qiu, Zhang, Yong-Li et al. (2017) Application of esophageal irradiation stents coated with 125I particles in advanced esophageal cancer. Journal of B.U.ON.: official journal of the Balkan Union of Oncology 22(1): 265-269	- Publication date pre-protocol date cut off (2017) *2016 publication*

Study	Code [Reason]
Zhao, X., Guo, W., Chen, Z. et al. (2019) Comparison of efficacy and safety of secondline palliative chemotherapy with paclitaxel plus raltitrexed and paclitaxel alone in patients with metastatic gastric adenocarcinoma: A randomized phase II trial. Journal of Clinical Oncology 37(supplement15)	- Conference abstract
Zhu, Guang-Yu, Lu, Jian, Wang, Chao et al. (2021) A novel irradiation stent versus conventional irradiation stent for malignant dysphagia: A prospective randomized controlled trial. Journal of cancer research and therapeutics 17(5): 1261-1268	- Wrong population *Does not state the population are not amenable to treatment with curative intent.*

Economic studies

Study	Code [Reason]
Dimofte, Gabriel, Crumpei, Felicia, Trifina, Liviu et al. (2004) Cost-effectiveness of endoscopically placed stents in the palliation of locally advanced esophageal carcinoma. Romanian journal of gastroenterology 13(1): 17-22	- Full text paper not available
Faramarzi, A., Daroudi, R., Nahvijou, A. et al. (2019) Economic evaluation of treatments for patients with esophageal cancer: A systematic review. International Journal of Cancer Management 12(3): e86631	- Systematic review used as source of primary studies *All references check and none were relevant.*
Farndon, M A, Wayman, J, Clague, M B et al. (1998) Cost-effectiveness in the management of patients with oesophageal cancer. The British journal of surgery 85(10): 1394-8	- Study out of date *From 1998*
Fisher, Alexander V, Hanlon, Bret, Fernandes-Taylor, Sara et al. (2020) Natural history and cost analysis of surgical bypass versus endoscopic stenting for the palliative management of malignant gastric outlet obstruction. HPB: the official journal of the International Hepato Pancreato Biliary Association 22(4): 529-536	- Does not contain a population of people with oesophageal cancer *Malignant gastric outlet obstruction so the wrong part of the gastric tract*
Gregory, M.H., Chandrasekhara, V., Hollander, T. et al. (2021) ID: 3526919 COST EFFECTIVENESS ANALYSIS OF PARTIALLY COVERED, FULLY COVERED, AND SUTURED FULLY COVERED SELF EXPANDING METAL	- Conference abstract

Study	Code [Reason]
STENTS FOR PALLIATION OF MALIGNANT ESOPHAGEAL DYSPHAGIA. Gastrointestinal Endoscopy 93(6supplement): ab312	
Homs, M.Y.V., Steyerberg, E.W., Eijkenboom, W.M.H. et al. (2004) Single-dose brachytherapy versus metal stent placement for the palliation of dysphagia from oesophageal cancer: Multicentre randomised trial. Lancet 364(9444): 1497-1504	- Not correct perspective *Societal perspective for costs which is not NICE's reference case*
Janmaat, Vincent T, Bruno, Marco J, Polinder, Suzanne et al. (2016) Cost-Effectiveness of Cetuximab for Advanced Esophageal Squamous Cell Carcinoma. PloS one 11(4): e0153943	- Does not contain a population of people with oesophageal cancer *No mention of luminal obstruction*
Lam, Simon W, Wai, Maya, Lau, Jessica E et al. (2017) Cost-Effectiveness Analysis of Second-Line Chemotherapy Agents for Advanced Gastric Cancer. Pharmacotherapy 37(1): 94-103	- USA study *Costs from a USA perspective which is not NICE's reference case*
Nicholson, D.A., Haycox, A., Kay, C.L. et al. (1999) The cost effectiveness of metal oesophageal stenting in malignant disease compared with conventional therapy. Clinical Radiology 54(4): 212-215	- Study out of date *From 1999* - Not a cost utility study *Did not use QALYs which is not NICE's reference case*
Ramanaden, D N; Crimmins, R; Smith, P M (2000) Atkinson tubes are a good cost-effective means of palliating inoperable oesophageal malignant strictures: an eight-year experience. European journal of gastroenterology & hepatology 12(7): 751-3	- Not a cost utility study *No outcome measure (ICER or NMB) which is not NICE's reference case*
Sculpher, M J, Sargeant, I R, Loizou, L A et al. (1995) A cost analysis of Nd:YAG laser ablation versus endoscopic intubation for the palliation of malignant dysphagia. European journal of cancer (Oxford, England : 1990) 31a(10): 1640-6	- Study out of date
Shenfine, J., McNamee, P., Steen, N. et al. (2009) A randomized controlled clinical trial of palliative therapies for patients with inoperable esophageal cancer. American Journal of Gastroenterology 104(7): 1674-1685	- Study out of date *Operations done before 2001. No explanation where the costs were obtained from or what year they are from*
Shenfine, J, McNamee, P, Steen, N et al. (2005) A pragmatic randomised controlled trial of the cost-effectiveness of palliative therapies for patients with inoperable oesophageal cancer. Health technology	- Study out of date *Costs sourced from 1998.*

Study	Code [Reason]
assessment (Winchester, England) 9(5): iii-121	
Wenger, Urs, Johnsson, Erik, Bergquist, Henrik et al. (2005) Health economic evaluation of stent or endoluminal brachytherapy as a palliative strategy in patients with incurable cancer of the oesophagus or gastro-oesophageal junction: results of a randomized clinical trial. European journal of gastroenterology & hepatology 17(12): 1369-77	- Not a cost utility study *Does not use QALYs which is not NICE's reference case. Also based in Sweden in 2003*
Xinopoulos, D., Dimitroulopoulos, D., Moschandrea, I. et al. (2004) Natural course of inoperable esophageal cancer treated with metallic expandable stents: Quality of life and cost-effectiveness analysis. Journal of Gastroenterology and Hepatology (Australia) 19(12): 1397-1402	- Study out of date *Based in Greece in 2000 used QLQ-C30 rather than EQ-5D.*
Xinopoulos, D., Dimitroulopoulos, D., Tsamakidis, K. et al. (2005) Palliative treatment of advanced esophageal cancer with metal-covered expandable stents. A cost-effectiveness and quality of life study. Journal of B.U.ON. 10(4): 523-528	- Study out of date *Based in Greece in 2000 used QLQ-C30 rather than EQ-5D.*

Appendix K– Research recommendations – full details

K1.1 Research recommendation

What is the effectiveness and cost-effectiveness of external beam radiotherapy (EBRT) in addition to self-expanding stents in preventing or reducing bleeding in people with oesophago-gastric cancer who are undergoing palliative treatment of dysphagia symptoms with no curative intent?

K1.1.1 Why this is important

People who have incurable oesophageal and oesophago-gastric junctional cancer commonly experience tumour bleeding with symptoms such as coughing up blood (haematemesis), blood in the stools (melena), and anaemia and this may be triggered by inserting a self-expanding stent. The committee agreed that it would be useful to understand how effective EBRT is for preventing or treating bleeding from the tumour site.

K1.1.2 Rationale for research recommendation

External beam radiotherapy in addition to self-expanding stents in preventing or reducing bleeding

Importance to 'patients' or the population	Blood loss and its management reduces the quality of life for people with incurable cancer. Therefore, EBRT in addition to self-expanding stents to reduce or stop bleeding should be investigated.
Relevance to NICE guidance	EBRT (in addition to self-expanding stents) has been given a 'consider' recommendation for people with oesophageal and oesophago-gastric junctional cancer who are bleeding from the cancer site. However, this recommendation is based on expert clinical advice because no clear RCT evidence is available.
Relevance to the NHS	Access to EBRT is a limited resource and better targeting of people who would benefit most would make best and most cost-effective use of this resource..
National priorities	Medium
Current evidence base	Limited RCT data
Equality considerations	Because EBRT is a limited resource, directing it to indications where it is effective should reduce health inequalities by ensuring that the treatment is available for people who need it most.

K1.1.3 Modified PICO table

External beam radiotherapy in addition to self-expanding stents in preventing or reducing bleeding

Population	People with incurable oesophageal and oesophago-gastric junctional cancer who have had a stent inserted and are bleeding

Intervention	External beam radiotherapy (EBRT) in addition to a self-expanding stent
Comparators	Self-expanding stent alone
Outcomes	Quality of life, survival analysis, change in bleeding (for example: haematemesis, melena, anaemia), change in dysphagia, adverse events.
Study design	RCT
Timeframe	Until death (this is a palliative intervention)
Additional information	If possible, conduct a subgroup analysis to compare the results of older compared with younger people.

K1.2 Research recommendation

In people experiencing partial or complete luminal obstruction resulting from incurable oesophago-gastric cancer, is enteral feeding an effective and cost effective method of preserving quality of life and survival, when the first line management of dysphagia (for example, self-expanding stents) has failed or is contraindicated?

K1.1.1 Why this is important

The committee hoped to see RCT evidence for this but it was not available. It can be challenging to manage dysphagia in people with oesophago-gastric cancer who are undergoing palliative treatment with no curative intent. People who have dysphagia with incurable oesophago-gastric cancer have a poor quality of life, so finding treatments is important for them.

K1.1.2 Rationale for research recommendation

Enteral feeding compared to self-expanding stents for the palliation of dysphagia

Importance to ‘patients’ or the population	Little is known about how effective enteral tube feeding is after self-expanding stents have been tried in reducing the consequences of dysphagia for people with incurable oesophageal and oesophago-gastric junctional cancer or when self-expanding stents are contraindicated. The ability to get adequate nutrition is of key importance to their quality of life.
Relevance to NICE guidance	The committee requested that we find evidence on this subject to inform this review. However, no relevant evidence could be found.
Relevance to the NHS	The outcome should improve the quality of life for people who have dysphagia with incurable oesophageal and oesophago-gastric junctional cancer.
National priorities	Medium
Current evidence base	None
Equality considerations	None known

K1.1.3 Modified PICO table

Enteral feeding compared to self-expanding stents for the palliation of dysphagia

Population	People with incurable oesophageal and oesophago-gastric junctional cancer who have dysphagia.
Intervention	Enteral tube feeding following failure of self-expanding stents or where they are contra-indicated.
Comparator	Self-expanding stents alone or best supportive care without self-expanding stents if self-expanding stents are contraindicated.
Outcomes	Quality of life, length of hospital stay, survival analysis,, adverse events.
Study design	RCT
Timeframe	Until death (this is a palliative intervention)
Additional information	None

Appendix L – Methods

This guideline was developed using the methods described in the 2022 NICE guidelines manual.
Declarations of interest were recorded according to the NICE conflicts of interest policy.

Developing the review questions and outcomes

The 1 review question developed for this guideline was based on the key area identified in the guideline scope. It was drafted by the NICE guideline development team and refined and validated by the guideline committee.
The review question was based on the following frameworks:

- Population, Intervention, Comparator and Outcome [and Study type] (PICO)
- Full literature searches, critical appraisals and evidence reviews were completed for all review questions.

Reviewing research evidence

Review protocols

The review protocol was developed with the guideline committee to outline the inclusion and exclusion criteria used to select studies for each evidence review.

Searching for evidence

Evidence was searched for the review question using the methods specified in the 2022 NICE guidelines manual.

Selecting studies for inclusion

All references identified by the literature searches and from other sources (for example, previous versions of the guideline or studies identified by committee members) were uploaded into EPPI reviewer software (version 5) and de-duplicated. Titles and abstracts were assessed for possible inclusion using the criteria specified in the review protocol. 10% of the abstracts were reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer.
The full text of potentially eligible studies was retrieved and assessed according to the criteria specified in the review protocol. A standardised form was used to extract data from included studies.

Appraising the quality of evidence

Intervention studies (relative effect estimates)

RCTs and quasi-randomised controlled trials were quality assessed using the Cochrane Risk of Bias Tool. Evidence on each outcome for each individual study was classified into one of the following groups:

- Low risk of bias – The true effect size for the study is likely to be close to the estimated effect size.
- Moderate risk of bias – There is a possibility the true effect size for the study is substantially different to the estimated effect size.

- High risk of bias – It is likely the true effect size for the study is substantially different to the estimated effect size.
- Critical risk of bias (ROBINS-I only) - It is very likely the true effect size for the study is substantially different to the estimated effect size.

Each individual study was also classified into one of three groups for directness, based on if there were concerns about the population, intervention, comparator and/or outcomes in the study and how directly these variables could address the specified review question. Studies were rated as follows:

- Direct – No important deviations from the protocol in population, intervention, comparator and/or outcomes.
- Partially indirect – Important deviations from the protocol in one of the following areas: population, intervention, comparator and/or outcomes.
- Indirect – Important deviations from the protocol in at least two of the following areas: population, intervention, comparator and/or outcomes.

Minimally important differences (MIDs) and clinical decision thresholds

The Core Outcome Measures in Effectiveness Trials (COMET) database was searched to identify published minimal clinically important difference thresholds relevant to this guideline that might aid the committee in identifying clinical decision thresholds for the purpose of GRADE. Identified MIDs were assessed to ensure they had been developed and validated in a methodologically rigorous way, and were applicable to the populations, interventions and outcomes specified in this guideline. In addition, the Guideline Committee were asked to prospectively specify any outcomes where they felt a consensus clinical decision threshold could be defined from their experience. In particular, any questions looking to evaluate non-inferiority (that one treatment is not meaningfully worse than another) required a clinical decision threshold to be defined to act as a non-inferiority margin.

Clinical decision thresholds were used to assess imprecision using GRADE and aid interpretation of the size of effects for different outcomes. For relative risks and hazard ratios, where no other clinical decision threshold was available, a default clinical decision threshold for dichotomous outcomes of 0.8 to 1.25 was used. Odds ratios were converted to risk ratios before presentation to the committee to aid interpretation.

GRADE for intervention studies analysed using pairwise analysis.

GRADE was used to assess the quality of evidence for the outcomes specified in the review protocol. Data from randomised controlled trials (which were quality assessed using the Cochrane risk of bias tool) were initially rated as high quality while data from other study types were initially rated as low quality. The quality of the evidence for each outcome was downgraded or not from this initial point, based on the criteria given in Table 10. These criteria were used to apply preliminary ratings, but were overridden in cases where, in the view of the analyst or committee the uncertainty identified was unlikely to have a meaningful impact on decision making.

Table 10: Rationale for downgrading quality of evidence for intervention studies

GRADE criteria	Reasons for downgrading quality
Risk of bias	Not serious: If less than 33.3% of the weight in a meta-analysis came from studies at moderate or high risk of bias, the overall outcome was not downgraded.

GRADE criteria	Reasons for downgrading quality
	Serious: If greater than 33.3% of the weight in a meta-analysis came from studies at moderate or high risk of bias, the outcome was downgraded one level. Very serious: If greater than 33.3% of the weight in a meta-analysis came from studies at high risk of bias, the outcome was downgraded two levels. Extremely serious: If greater than 33.3% of the weight in a meta-analysis came from studies at critical risk of bias, the outcome was downgraded three levels
Indirectness	Not serious: If less than 33.3% of the weight in a meta-analysis came from partially indirect or indirect studies, the overall outcome was not downgraded. Serious: If greater than 33.3% of the weight in a meta-analysis came from partially indirect or indirect studies, the outcome was downgraded one level. Very serious: If greater than 33.3% of the weight in a meta-analysis came from indirect studies, the outcome was downgraded two levels.
Inconsistency	Concerns about inconsistency of effects across studies, occurring when there is unexplained variability in the treatment effect demonstrated across studies (heterogeneity), after appropriate pre-specified subgroup analyses have been conducted. This was assessed using the I^2 statistic. N/A: Inconsistency was marked as not applicable if data on the outcome was only available from one study. Not serious: If the I^2 was less than 33.3%, the outcome was not downgraded. Serious: If the I^2 was between 33.3% and 66.7%, the outcome was downgraded one level. Very serious: If the I^2 was greater than 66.7%, the outcome was downgraded two levels.
Imprecision	If an MID other than the line of no effect was defined for the outcome, the outcome was downgraded once if the 95% confidence interval for the effect size crossed one line of the MID, and twice if it crosses both lines of the MID. If the line of no effect was defined as an MID for the outcome, it was downgraded once if the 95% confidence interval for the effect size crossed the line of no effect (i.e., the outcome was not statistically significant), and twice if the sample size of the study was sufficiently small that it is not plausible any realistic effect size could have been detected. Outcomes meeting the criteria for downgrading above were not downgraded if the confidence interval was sufficiently narrow that the upper and lower bounds would correspond to clinically equivalent scenarios.
Publication bias	Where 10 or more studies were included as part of a single meta-analysis, a funnel plot was produced to graphically assess the potential for publication bias. When a funnel plot showed convincing evidence of publication bias, or the review team became aware of other evidence of publication bias (for example,

GRADE criteria	Reasons for downgrading quality
	evidence of unpublished trials where there was evidence that the effect estimate differed in published and unpublished data), the outcome was downgraded once. If no evidence of publication bias was found for any outcomes in a review (as was often the case), this domain was excluded from GRADE profiles to improve readability.