National Institute for Health and Care Excellence

Version 3.0 Final

Oesophago-gastric cancer

assessment and management in adults

NG83 Appendix D

Review protocols

January 2018

Final

Developed by the National Guideline Alliance, hosted by the Royal College of Obstetricians and Gynaecologists

Disclaimer
Healthcare professionals are expected to take NICE clinical guidelines fully into account when exercising their clinical judgement. However, the guidance does not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of each patient, in consultation with the patient and/or their guardian or carer.

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Appendix D:

D.1 Radical treatment

What are the specific information and support needs before and after treatment for adults with oesophago-gastric cancer who are suitable for radical treatment and their carers?

Item	Details
Area in the scope	Information and support needs specific to adults with oesophago-gastric cancer and their carers.
Review question in the scope	What are the specific information and support needs after surgical treatment of people with oesophago-gastric cancer?
Review question for the guideline	What are the specific information and support needs before and after treatment for adults with oesophago-gastric cancer who are suitable for radical treatment and their carers?
Objective	This review aims to identify the specific information and support services that are beneficial to adults and their carers before and after radical treatment for oesophago-gastric cancer
Population and directness	Adults who are candidates for or have undergone radical treatment for oesophago-gastric cancer and their carers:
Context	Information content and type with regards to radical treatment of oesophago-gastric cancer Support structures or services available for adults and carers who receive radical treatment of oesophago-gastric cancer
Themes	Themes will be identified from the literature, but expected themes are: Psychosocial support Holistic Needs Assessments Access to psychological support/counselling Financial and benefits advice Nutrition/artificial feeding Dietetic input/advice and counselling Community based support Secondary or Tertiary care support Named individual/key-worker or specialist nurse for point of contact Support groups/programmes and frequency of meetings Patient/carer Information: Use of personalised treatment plans Format, timing and availability of information at: diagnosis, pre-treatment, during treatment, end of treatment. Format of information about benefits and burdens of treatments that best supports patient decision making Verbal Written Web-based to include videos and social media Electronic data (e.g. mobile phone applications) online support forums Use of Information prescription (list of potentially useful leaflets as determined by healthcare professional for a particular patient)

Item	Details
	Quality of information available Use or understanding of jargon and terminology This should include information on: Availability and format of various feeds or aids. Enhanced Recovery Protocols (e.g. prehabilitation) Rehabilitation Information on surgery to include surgical approach, potential risks and complications, post-operative recovery and discharge Information on chemoradiotherapy to include how this is given, potential risks, side-effects and complications Long-term nutritional complications post-op (supplementation) Potential long term consequences of surgery Potential long term consequences of chemoradiotherapy Symptom management Post-operative nutritional needs/feeding Respite care Lifestyle, leisure, work and social issues Treatment failure/outcomes
Setting	Community, primary, secondary and tertiary care ideally in a UK context, but evidence from other countries will be considered if there is insufficient direct evidence
Stratified, subgroup and adjusted analyses	Timing of information: At diagnosis Pre-treatment During treatment End of treatment/discharge During follow-up Treatment received Chemo-radiotherapy Surgical treatment
Language	English
Study design	Study designs to be considered: Qualitative studies (for example, interviews, focus groups, observations) Surveys (which include qualitative data) Excluded: Since a mixed-methods approach is not planned, purely quantitative studies (including surveys with only descriptive quantitative (statistical) data) will be excluded..
Review strategy	Appraisal of methodological quality: The methodological quality of each study will be assessed using CASP qualitative study quality checklists and the overall quality of the evidence will be assessed by a GRADE approach (CER-QUAL) for each theme. The modified CER-QUAL approach we propose to use is outlined in Lewin S, Glenton C, Munthe-Kaas H, Carlsen B, Colvin CJ, Gülmezoglu M, et al. (2015) Using Qualitative Evidence in Decision Making for Health and Social Interventions: An Approach to Assess Confidence in Findings from Qualitative Evidence Syntheses (GRADE-CERQual). PLoS Med 12(10): e1001895. doi:10.1371/journal.pmed.1001895 Data synthesis: Thematic analysis of the data will be conducted and findings presented.
Equalities	Non-English support and information for non-English speakers or ethnic minorities

Item	Details
	Non-written support and information for those who are illiterate or with communication problems
Key papers	1. Adams, E., Boulton, M., Watson, E. The information needs of partners and family members of cancer patients: a systematic literature review. Patient Education and Counseling. 2009;77:179–186. 2. Richards M, Corner J and Maher J, The National Cancer Survivorship Initiative: new and emerging evidence on the ongoing needs of cancer survivors. British Journal of Cancer, 2011. 105 S1-4 4. Armes, J. et al. Patients' supportive care needs beyond the end of treatment: a prospective, longitudinal survey. Journal of Clinical. Oncology. 27, 6172–6179 (2009). 5. Brennan J et al. Refinement of the Distress Management Problem list as the basis for a holistic therapeutic conversation among UK patients with cancer. Psycho-oncology. 2011. Online10:1002 7. Ziegler, L., Newell, R., Stafford, N., Lewin, R. A literature review of head and neck cancer patients information needs, experiences and views regarding decision-making. Eur J Cancer Care (Engl). 2004;13:119–126. 8. Iconomou, G., Vagenakis, A.G., Kalofonos, H.P. The informational needs, satisfaction with communication, and psychological status of primary caregivers of cancer patients receiving chemotherapy. Support Care Cancer. 2001;9:591–596. 9. Woolf, S.H., Chan, E.C.Y., Harris, R., Sheridan, S.L., Braddock, C.H. III, Kaplan, R.M., Krist, A., O'Connor, A.M., Tunis, S. Promoting informed choice: transforming health care to dispense knowledge for decision making. Annals of Internal Medicine. 2005;143:293–300. 10. Goldzweigh G, Merims, S, Ganon R, Peretz T, Baider L (2012) Coping and distress among spouse caregivers to older patients with cancer: An intricate path. Journal of Geriatric Oncology. Vol 3, issue 4 376 - 385 11. Kitrungote, L., Cohen, M.Z. Quality of life of family caregivers of patients with cancer: a literature review. Oncology Nurse Forum. 2006;33:625–632. 12. Rutten, L.J.F., Arora, N.K., Bakos, A.D., Aziz, N., Rowland, J. Information needs and sources of information among cancer patients: a systematic review of research (1980–2003). Patient Education Counselling. 2005;57:250–261. 13. Randers, I., Naslund, E., Stockeld, D., Mattiasson, A.C. Information needs following a diagnosis of oesophageal cancer, self-perceived information needs of patients and family members compared with the perceptions of healthcare professionals: a pilot study. European Journal of Cancer Care (2007;16:277–285. 14. Macmillan living with and beyond cancer: http://www.ncsi.org.uk/wp-content/uploads/Living-with-and-beyond-2013.pdf 15. Jenkins, V., Fallowfield, L., Saul, J. Information needs of patients with cancer: results from a large study in UK cancer centres. British Journal of Cancer. 2001;84:48. 16. Morrison, V., Henderson, B.J., Zinovieff, F., Davies, G., Cartmell, R., Hall, A. et al, Common, important, and unmet needs of cancer outpatients. European Journal of Oncology Nursing. 2012;16:115–123 17. Koutsopoulou S, Papathanassoglou E, Katapodi M, Patiraki E (2010) A critical review of the evidence for nurses as information providers to cancer patients. Journal of Clinical Nursing. 19, 5-6, 749-765. 18. Gaston, C.M. and G. Mitchell, Information giving and decision-making in patients with advanced cancer: A systematic review. Social Science & Medicine, 2005. 61(10): p. 2252- 2264. 19. National cancer survivorship initiative: http://www.ncsi.org.uk 20. Harrison, J.D., Young, J.M., Price, M.A., Butow, P.N. and Solomon, M.J. (2009) What are the unmet supportive care needs of people with cancer? A systematic review. Supportive Care in Cancer, 17, 1117-1128.

Item	Details
	McNair AG, Brookes ST, Kinnersley P, Blazeby JM (2013) What surgeons should tell patients with oesophago-gastric cancer: a cross sectional study of information needs. , 39(11):1278-86. Blencowe et al. (2015) Assessing the quality of written information provision for surgical procedures: a case study in oesophagectomy. British Medical Journal Steer CB (2016) Supportive care in older adults with cancer - An update of research in 2015. J Geriatr Oncol. (was unable to access full article) Graham & Wikman (2015) Dis Esophagus. Toward improved survivorship: supportive care needs of esophageal cancer patients, a literature review. Malmström et al. (2013) Patients' experiences of supportive care from a long-term perspective after oesophageal cancer surgery - a focus group study. Eur J Oncol Nurs. Henselmans et al. (2012) Postoperative information needs and communication barriers of esophageal cancer patients. Patient Educ Couns. Jul;88(1):138-46. Smets EM et al. (2012) Addressing patients' information needs: a first evaluation of a question prompt sheet in the pretreatment consultation for patients with esophageal cancer. Dis Esophagus. Wittmann et al. (2011) Comparison of patients' needs and doctors' perceptions of information requirements related to a diagnosis of oesophageal or gastric cancer. Eur J Cancer Care (Engl). 20(2):187-95.

D.2 Palliative management

What are the specific information and support needs for adults with oesophago-gastric cancer who are suitable for palliative treatments and care only?

Item	Details
Area in the scope	Information and support needs specific to adults with oesophago-gastric cancer and their carers
Review question in the scope	What are the information and support needs to manage dysphagia in people with oesophago-gastric cancer?
Review question for the guideline	What are the specific information and support needs of adults with oesophago-gastric cancer who are suitable for palliative treatments and care only?
Objective	This review aims to identify the information and support needs specific to those with oesophago-gastric cancer who are suitable for palliative treatments and care only and their carers.
Background	It is important for people living with oesophago-gastric cancer and their carers to have access to the right information and support at the right time. Information about the diagnostic tests, the disease itself, treatment options, complications associated with oesophago-gastric cancer and treatments, available clinical trials and practical issues is vital. Patients with oesophago-gastric cancer and those supporting them must cope with the stresses created by a potentially physically demanding, debilitating and life threatening illness and health impairment. These effects may be magnified if the right information and support is not available. In 2004, the National Audit Office found that nearly 40% of cancer patients did not receive information they required. National approaches by leading cancer charities and the National Cancer Action Team (NCAT) have aimed to improve this. There is no standard agreement or approach how best to provide the full array of information needed at various times during and after the cancer treatment. However, it is documented that information should be tailored to the individual needs. It is evident that satisfaction improves and anxiety decreases when information is provided at the right time.There are many approaches to informing cancer patients about their

Item	Details
	diagnosis, disease and treatment. The key is to ensure that the right information, at the right time and in a format accessible by the patient (e.g. paper materials, electronic materials, visual and audio materials) is available. Information related to the practical issues is generic and this must not be overlooked as evidence indicates that issues such as finance and work concerns are as important as the disease and treatment itself to patients and carers. A system of providing such information that is up to date, accurate, and reliable and in a language that carers and patients can read and understand needs to be agreed and monitored. Many of the support needs of adults living with oesophago-gastric cancer are generic to all adults living with cancers. The approach to these is described in Improving Supportive and Palliative Care for Adults with Cancer NICE 2004. However there are specific information and support needs that are particular to those with oesophago-gastric cancer. This is not limited to information about the treatments specific to oesophago gastric cancer but also about the particular nutritional issues that face those with dysphagia, stents, reduced gastric capacity, delayed gastric emptying and upper gastro-intestinal obstruction. There is often a need for specific information about dietary changes and food preparation to deal with such issues. There can be need for psychological support to deal with the impact this has on the social function of eating and drinking and the emotional consequences of this. There are sometimes difficult decisions about what forms of clinically assisted nutrition or hydration should be used particularly in more advanced disease which need skilled support.
Population and directness	Adults suitable only for palliative treatments and care for oesophago-gastric cancer and their carers
Context and likely themes (information)	Context: Impact on eating and drinking Information content and type with regards to palliative treatment of oesophago-gastric cancer Support structures or services required for adults with oesophago-gastric cancer who are suitable for palliative treatment and care only Themes: Themes will be identified from the literature, but expected themes are: Psychosocial support: Support groups/programmes and frequency of meetings Dietetic input/advice and counselling Psychological support/counselling Timing of support Frequency of support or assessments Community based support Secondary or Tertiary care support Named individual or specialist nurse for point of contact Patient/carer information: Use of personalised treatment plans Format, timing and availability of information at: diagnosis, pre-treatment, during treatment, end of treatment. Format of information about benefits and burdens of treatments that best supports patient decision making Verbal Written Web-based to include videos and social media Electronic data (e.g. mobile phone applications) online support forums

Item	Details
	Use of Information prescription (list of potentially useful leaflets as determined by healthcare professional for a particular patient) Quality of information available Use or understanding of jargon and terminology This should include information on: Support groups and organisations Personalised care plans (holistic needs assessment) Availability and format of dietetic support Respite care Support and benefits available to carers Information and support about financial issues and those relating to work Information about palliative treatments Chemotherapy Radiotherapy Information about palliative interventions including stenting Information about nutritional needs, diet and nutritional support Timing of referral to specialist palliative care services Content Prognosis of disease Work and social impact Dysphagia Weight loss Specific information about diet for patients who have stents Nutrition/ Clinically Assisted Nutrition and Hydration Supplements Psychological difficulties Information and availability of a named individual for point of contact Information and availability of patient support groups or patient support pathways Lifestyle, leisure, work, finances and social issues Use or understanding of jargon and terminology Treatments received or available and their associated complications End of life care planning Advance care planning
Setting	Community, primary, secondary care ideally in UK setting, but evidence from other countries will be considered if there is insufficient direct evidence
Stratified, subgroup and adjusted analyses	Palliative treatment Palliative care/end of life care
Language	English
Study design	Study designs to be considered: Qualitative studies (for example, interviews, focus groups, observations) Surveys (which include qualitative data) Excluded: Since a mixed-methods approach is not planned, purely quantitative studies (including surveys with only descriptive quantitative (statistical) data) will be excluded.
Search strategy	Sources to be searched: Medline, Medline In-Process, CENTRAL, CDSR, DARE, HTA, Embase, Web of Science, Psychinfo, Cinahl Date limit:1990

Item	Details
	Rationale for date limit: First patient information leaflets and patient needs data available since this date. Supplementary search techniques: Snowballing techniques will be used to ensure a thorough representation of the published literature this will involve exploration of reference lists from key narrative and systematic reviews where appropriate or necessary.
Review strategy	Appraisal of methodological quality: The methodological quality of each study will be assessed using CASP qualitative study quality checklists and the overall quality of the evidence will be assessed using the GRADE approach (CER-QUAL) for each theme. The modified CER-QUAL approach we propose to use is outlined in Lewin S, Glenton C, Munthe-Kaas H, Carlsen B, Colvin CJ, Gülmezoglu M, et al. (2015) Using Qualitative Evidence in Decision Making for Health and Social Interventions: An Approach to Assess Confidence in Findings from Qualitative Evidence Syntheses (GRADE-CERQual). PLoS Med 12(10): e1001895. doi:10.1371/journal.pmed.1001895 Data synthesis: Thematic analysis of the data will be conducted and findings presented.
Equalities	Non-English support and information for non-English speakers or ethnic minorities Non-written support and information for those who are illiterate or with communication problems
Notes/additional information	Link with NICE palliative care and patient experience guidelines Aim to prioritise issues relating to impact on eating and drinking from a social and nutritional perspective.
Key Papers	Arends, J., Bodoky, G., Bozzetti, F., et al. (2006) ESPEN Guidelines on Enteral Nutrition: Non-surgical oncology. Clinical Nutrition. 25 (2), 245–259. Isenring, E.A., Capra, S., Bauer, J.D. (2004) Nutrition intervention is beneficial in oncology outpatients receiving radiotherapy to the gastrointestinal or head and neck area. British Journal of Cancer, 91 (3), 447 – 452. Steer CB (2016) Supportive care in older adults with cancer - An update of research in 2015. J Geriatr Oncol. (was unable to access full article) Andreassen et al. (2007) Information needs following a diagnosis of oesophageal cancer; self-perceived information needs of patients and family members compared with the perceptions of healthcare professionals: a pilot study. Eur J Cancer Care (Engl). 16(3):277-85. Andreassen S1, Randers I, Näslund E, Stockeld D, Mattiasson AC. (2005) Family members' experiences, information needs and information seeking in relation to living with a patient with oesophageal cancer. Eur J Cancer Care (Engl). 14(5):426-34.

D.3 Multidisciplinary teams

What is the most effective organisation of local and specialist MDT services for adults with oesophago-gastric cancer?

Item	Details
Area in the scope	Organisation of specialist teams

Item	Details
Review question in the scope	What is the most effective organisation of specialist care teams for people with oesophago-gastric cancer (including curative surgery)?
Review question for the guideline	What is the most effective organisation of local and specialist MDT services for adults with oesophago-gastric cancer?
Objective	For patients diagnosed with oesophagogastric cancer there are three defined levels of care: The diagnostic process Local care Specialist care Diagnostic units may be separate to the local Tier 2 hospital but all patients diagnosed with oesophagogastric cancer will initially be managed in a local unit (Tier 2 hospital), where there will be a local upper GI team but no specialist oesophagogastric team. Tier 3 hospitals will have a specialist oesophagogastric cancer team (specialist unit), but may also provide level 1 (diagnostic) and level 2 (local care) services to the local population. Currently, patients with oesophago-gastric cancer are discussed in a formal multidisciplinary team (MDT) meeting in order to plan the most appropriate management. Local units have a regular local MDT meeting to discuss patients with a diagnosis of oesophagogastric cancer. Some specialist oesophagogastric cancer units have regular specialist MDTs to discuss patients who are being considered for radical (usually multimodal) treatment, however this is not the case for all specialist MDTs across the UK. Patients suitable for radical treatment are referred to the specialist oesophagogastric cancer teams, while patients suitable for palliative treatment may be managed either in the local unit or in the specialist centre. In order to identify the most effective organisation and delivery of MDT services for those with oesophago-gastric cancer we aim to explore the outcomes associated with the management of patients within local and specialist MDTs. Additionally we aim to identify which subgroups of patients might benefit the most from referral from local to specialist MDTs.
Population and directness	Adults with newly diagnosed or recurrent oesophago-gastric cancer
Intervention	• Referral between local and specialist OG MDTs of: • all patients (suitable for either palliative or radical/multi-modality treatments) or • only patients suitable for radical/muti-modality treatment
Comparison	Each other
Outcomes	• Time to decision to treat (NHS England 31/62 day targets) • Change in staging decisions of local or specialist MDTs • Change in management decisions of local or specialist MDTs • Frequency of MDTs (how often meeting occurs) • Discussion time (for each patient) time from initial presentation in local MDT to referral to first discussion at specialist MDTs • Overall survival. • Disease-free survival. • Disease-related morbidity. • Treatment-related morbidity. • Treatment-related mortality.

Item	Details
	• Health-related quality of life. • Patient-reported outcome measures. • Patient satisfaction • Probability of radical treatment
Importance of outcomes	Preliminary classification of the outcomes for decision making: **Critical Outcomes (up to 3 outcomes)** • Time to decision to treat (NHS England 31/62 day target) • Change in staging decisions of local or specialist MDTs • Change in management decisions of local or specialist MDTs **Important but not critical outcomes (up to 3 outcomes)** • Frequency of MDTs (how often meeting occurs) • Discussion time (for each patient) time from initial presentation in local MDT to referral to first discussion at specialist MDTs **Of limited importance (1 outcome)** • Patient satisfaction
Setting	All settings in which MDT services comparable to those in UK are available.
Stratified, subgroup and adjusted analyses	Stratified analyses: • Anatomical tumour site • Curative or palliative intent • Quorate MDTs (the proportion of the MDTs that are quorate (with attendance from the required core members) would be a surrogate for the quality of decision making)
Language	English
Study design	• Systematic reviews of RCTs • RCTs (Blinding will predictably only be possible for patients) • Conference abstracts of RCTs will be considered if adequate useful information is reported and the full text publication is unavailable. • Comparative cohort or observational studies (only if RCTs unavailable or limited data to inform decision making)
Search strategy	Sources to be searched: Medline, Medline In-Process, CENTRAL, CDSR, DARE, HTA, Embase, Web of Science Date limit:2000 Rationale for date limit: MDT widely used since 2000. Supplementary search techniques: Snowballing techniques will be used to ensure a thorough representation of the published literature this will involve exploration of reference lists from key narrative and systematic reviews where appropriate or necessary.
Review strategy	**Appraisal of methodological quality:** The methodological quality of each study will be assessed using an appropriate checklist: ROBIS for systematic reviews Cochrane risk of bias tool for RCTs Cochrane risk of bias tool for non-randomised studies The quality of the evidence for an outcome (i.e. across studies) will be assessed using GRADE. **Synthesis of data:** Meta-analysis will be conducted where appropriate. **Minimum important differences**

Item	Details
	Default values will be used of: 0.80 and 1.25 for dichotomous outcomes; 0.5 times SD for continuous outcomes, unless more appropriate values are identified by the guideline committee or in the literature. **Double sifting, data extraction and methodological quality assessment** Sifting, data extraction and appraisal of methodological quality and GRADE assessment will be performed by the systematic reviewer. Quality control will be performed by the senior systematic reviewer. Dual sifting will be performed on at least 10% of records and where possible all records. Dual quality assessment and data extraction will be performed when capacity allows.
Equalities	No equalities issues identified for this question.
Notes	***Comments from committee subgroup during protocol drafting:*** ***RW 12 May 2016*** Is the core membership of a local MDT defined – as it is with an sMDT? If not should this be clarified as it may help decide who needs an sMDT discussion? e.g palliative case may access oncological care only via sMDT in some regions. ***NM 13 May 2016*** Membership of local MDT is clearly defined in peer review I am fairly sure ***DE 12 May 2016*** My reading of the peer review measures, is that the core membership of the local MDT is defined (and interestingly is not too dissimilar from that required in an sMDT) The sMDT discussion should really include ALL patients. I appreciate that PR requires discussion of all patients with a core member of the sMDT, but in practice this is effectively at the meeting. This doesn't limit where the treatment can be given (ie palliative local or specialist) ***Reply from NM 13 May 2016*** Agree with DJE, but not everyone does this, so this is a point which needs to be determined by this review
Key Papers	M. R. Stephens, W. G. Lewis, A. E. Brewster et al., "Multidisciplinary team management is associated with improved outcomes after surgery for esophageal cancer," Diseases of the Esophagus, vol. 19, no. 3, pp. 164–171, 2006. A. R. Davies, D. A. C. Deans, I. Penman et al., "The multidisciplinary team meeting improves staging accuracy and treatment selection for gastro-esophageal cancer," Diseases of the Esophagus, vol. 19, no. 6, pp. 496–503, 2006 Kersten C, Cvancarova M, Mjåland S, Mjåland O. Does in-house availability of multidisciplinary teams increase survival in upper gastrointestinal-cancer? World J Gastrointest Oncol. 2013 Mar 15;5(3):60-7. doi: 10.4251/wjgo.v5.i3.60. National Oesophago-gastric cancer audit 2015: http://www.hscic.gov.uk/catalogue/PUB19627/clin-audi-supp-prog-oeso-gast-2015-rep.pdf

D.4 Surgical services

What is the optimal provision and organisation of surgical services for people with oesophago-gastric cancer?

Item	Details
Area in the scope	Organisation of specialist teams
Review question in the scope	What is the optimal provision of surgical services for curative treatment for people with oesophago-gastric cancer (for example: size of catchment population, number of curative operations per year, enhanced recovery)
Review question for the guideline	What is the optimal provision and organisation of surgical services for people with oesophago-gastric cancer?
Objective	There is a clear relationship between numbers of resections of oesophago-gastric cancer and outcomes, and this has been the main driver of centralisation of specialist oesophagogastric cancer surgical services. The first major centralization occurred in 2001 with the publication of IOG. Size of catchment population has been the main criterion upon which such centralisation has been based, and IOG recommended 1 million as the minimum population for a specialist OG centre. In recent years, there has been further, but slower, centralisation, with a number of units now covering populations of 2 million or more. The optimum catchment area for such specialist centres remains unclear. The volume – outcome relationship also exists for individual surgeons. The requirement for 24 hour a day and 7 day a week specialist surgical cover, and the increasing practice of dual Consultant Surgeon operating, have clouded any clear recommendations of minimal numbers of resections per Consultant. It remains unclear what are the minimal numbers of surgeons for a specialist unit and what is the minimal number of resections each Surgeon should carry out. Whilst all surgery with curative intent should be carried out in the Specialist Centre, it may be appropriate for some palliative (especially emergency) surgery to take place in the local units. This review aims to explore the optimal provision and organisation of surgical services for people with oesophago-gastric cancer.
Population and directness	People with newly diagnosed or recurrent oesophago-gastric cancer suitable for surgical intervention (see subgroup analysis section of protocol).

Intervention	• High volume vs Low volume
	  ○ Size of catchment population
	  ○ Resections per unit
	  ○ Resections per consultant
	  ○ Number of consultants in unit
	• *Discussion about difficulty defining high vol vs low vol. Agreed that reviewer will note how this has been defined in studies*

Comparison	As above

Outcomes and prioritisation	• **Critical outcomes**
	• Survival (30 day, 90 day, 1 year).
	• Post-operative complications:
	  ○ (e.g. respiratory complications, anastomotic leak are the main ones, but we would be interested in other reported postoperative complications)
	  ○ Reoperation/return to theatre (this may not be a negative outcome because good units re-intervene early)
	• Adequacy of surgery
	  ○ Lymph node harvest
	  ○ Resection margin (R0, R1, R2)

Item	Details
	○ **Important but not critical outcomes:** • Time to Recurrence/ Disease-free survival. • PROMs/HRQoL/Patient satisfaction • Length of Hospital stay ○ **Of Limited Importance** • Tumour deemed inoperable/unresectable at surgery • **Not important:** • Length of ICU Stay • Treatment-related morbidity.
Setting	Settings in which people with oesophago-gastric cancer are offered surgery.
Stratified, subgroup and adjusted analyses	In the presence of heterogeneity, the following subgroups will be considered for sensitivity analysis: • Setting (this may need to be a stratified analysis rather than subgroup analysis): ○ Specialist OG units which offer curative and palliative surgery for oesophago-gastric cancer. Vs ○ non-specialist units which offer palliative surgery when appropriate for oesophago-gastric cancer • Treatment intent: ○ Palliative intent vs ○ Curative intent
Language	English
Study design	• Systematic reviews of RCTs • RCTs (Blinding will predictably only be possible for patients) • Conference abstracts of RCTs will be considered if adequate useful information is reported and the full text publication is unavailable. • Comparative cohort or observational studies (only if RCTs unavailable or limited data to inform decision making)
Search strategy	Sources to be searched: Medline, Medline In-Process, CENTRAL, CDSR, DARE, HTA, Embase, Web of Science use volume outcome as a search term Date limit:last 15 years Rationale for date limit: Studies exploring surgical outcomes associated with surgical service provision published in the last 15 years. Supplementary search techniques: Snowballing techniques will be used to ensure a thorough representation of the published literature. This will involve exploration of reference lists from key narrative and systematic reviews where appropriate or necessary.
Review strategy	**Appraisal of methodological quality:** The methodological quality of each study will be assessed using an appropriate checklist: ROBIS for systematic reviews Cochrane risk of bias tool for RCTs Cochrane risk of bias tool for non-randomised studies The quality of the evidence for an outcome (i.e. across studies) will be assessed using GRADE. **Synthesis of data:** Meta-analysis will be conducted where appropriate. **Minimum important differences**

Item	Details
	Default values will be used of: 0.80 and 1.25 for dichotomous outcomes; 0.5 times SD for continuous outcomes, unless more appropriate values are identified by the guideline committee or in the literature. **Double sifting, data extraction and methodological quality assessment** Sifting, data extraction and appraisal of methodological quality and GRADE assessment will be performed by the systematic reviewer. Quality control will be performed by the senior systematic reviewer. Dual sifting will be performed on at least 10% of records and where possible all records. Dual quality assessment and data extraction will be performed when capacity allows.
Equalities	No equalities issues identified for this question.
Notes	• see Nicolas Pettrelli
Key Papers	M. R. Stephens, W. G. Lewis, A. E. Brewster et al., "Multidisciplinary team management is associated with improved outcomes after surgery for esophageal cancer," Diseases of the Esophagus, vol. 19, no. 3, pp. 164–171, 2006. A. R. Davies, D. A. C. Deans, I. Penman et al., "The multidisciplinary team meeting improves staging accuracy and treatment selection for gastro-esophageal cancer," Diseases of the Esophagus, vol. 19, no. 6, pp. 496–503, 2006 Kersten C, Cvancarova M, Mjåland S, Mjåland O. Does in-house availability of multidisciplinary teams increase survival in upper gastrointestinal-cancer? World J Gastrointest Oncol. 2013 Mar 15;5(3):60-7. doi: 10.4251/wjgo.v5.i3.60. National Oesophago-gastric cancer audit 2015: http://www.hscic.gov.uk/catalogue/PUB19627/clin-audi-supp-prog-oeso-gast-2015-rep.pdf

D.5 Staging investigations

What are the optimal staging investigations to determine suitability for curative treatment of oesophageal or gastro-oesophageal junctional cancer after diagnosis with endoscopy and whole-body CT scan?

Item	Details
Area in scope	Assessment of oesophago-gastric cancer
Review question in the scope	What is the optimal choice and sequence of staging investigations to identify metastatic disease and determine suitability for curative treatment of oesophageal and gastro-oesophageal junctional cancer after diagnosis with endoscopy and whole-body CT scan (for example, endoscopic ultrasound, PET-CT, staging laparoscopy)?
Review question in guideline	What are the optimal staging investigations to determine suitability for curative treatment of oesophageal or gastro-oesophageal junctional cancer after diagnosis with endoscopy and whole-body CT scan?
Objective	The staging of oesophageal and oesophago-gastric cancer can help determine whether disease is suitable for radical treatment with curative intent, or whether the disease is too advanced for such treatment. Advances in imaging modalities and techniques have facilitated more accurate staging and thus more appropriate referral of patients for curative interventions. British consensus guidelines recommend that diagnosis is made by visualising a mass on endoscopy and by histological diagnosis based on at least six biopsy

Item	Details
	samples from the mass and adjacent tissue. Endoscopic ultrasound is routinely used to characterise tumour size and stage, but it is not helpful for the detailed staging of mucosal disease and nodal staging. Endoscopic ultrasound has been reported to have a sensitivity and specificity of 86% and 91% for tumours without nodal involvement; and 69% and 84% for tumours with nodal involvement (1). PET-CT can be used to detect distant metastases, but its role in assessing the primary tumour and nodal disease remains unclear. Staging laparoscopy enables peritoneal cytology and biopsies of suspicious lesions to be obtained and is seen as a safe and effective staging tool used to detect small peritoneal and liver metastases missed by imaging techniques when determining resectability of tumours. Currently it is well established which staging investigations should be used to assess local tumour stage, nodal or distant metastatic spread (TNM staging) in oesophageal and oesophago-gastric junctional cancer. The order, timing and selection of tests could, however be improved and tailored to individual people. This review aims to explore the optimal choice of diagnostic technologies to identify cases of oesophageal/ junctional cancer suitable for curative treatment. In order to establish the optimal order and timing of tests, this review aims to explore the choice and sequence of staging investigations for curative treatment of oesophageal and oesophago-gastric junctional cancer.
Population	People with newly diagnosed oesophageal or oesophago-gastric junctional cancer who have been found at endoscopy and whole body CT to be potentially suitable for curative treatment. If there is a large amount of evidence could prioritise T2 and T3 disease Some studies may combine T1 and T2 disease
Subgroups and sensitivity analyses	Oesophageal cancer (upper third, middle-third and lower third) Oesophago-gastric junctional cancer (I, II and III) TNM classification 5 vs 6 vs 7 used/reported in studies T1, T2, T3 and T4a disease
Index test: Severity assessment tools/clinical markers	Endoscopic ultrasound (T,N and M or all three) Endoscopic ultrasound can help with M stage eg cervical nodes, coeliac nodes, adrenal etc Staging laparoscopy (M stage for lower third oesophageal and junctional tumours) PET-CT (for M and N stage) Allow combinations of above tests and assess outcomes according to combinations/strategies of investigations
Reference standard or target condition/patient outcomes	Final TNM stage (using TNM Staging number 7) or suitability for curative treatment based on: cytological/histopathological/clinical imaging/laparotomy and follow-up
Outcomes	Critical outcomes Diagnostic accuracy: sensitivity specificity positive predictive value negative predictive values positive likelihood ratios negative likelihood ratios change in management plan Important but not critical outcomes: Time to decision to treat Test-related morbidity (e.g. oesophageal perforation.)

Item	Details
Study design	Studies of diagnostic accuracy: Systematic reviews Cross sectional diagnostic accuracy studies
Setting	Settings in which people with oesophageal and oesophago-gastric junctional tumours are offered secondary investigations to determine suitability for curative treatment. All geographic locations of studies will be considered Secondary and tertiary care only
Search strategy	Sources to be searched: Medline, Medline In-Process, CENTRAL, CDSR, DARE, HTA, Embase, Web of Science Date limit: 1990 for EUS 2000 for PET-CT Supplementary search techniques: Snowballing techniques will be used to ensure a thorough representation of the published literature. This will involve exploration of reference lists from key narrative and systematic reviews where appropriate or necessary.
Review strategy	Appraisal of methodological quality: The methodological quality of each study will be assessed using an appropriate checklist: ROBIS for systematic reviews QUADAS-2 for the quality assessment of diagnostic accuracy studies Synthesis of data: Meta-analysis will be conducted where appropriate. Minimum important differences Unless more appropriate values are identified in the literature the guideline committee will decide minimally important differences in test accuracy using their experience and the likely consequences of correct and incorrect test results for the patient. Double sifting, data extraction and methodological quality assessment Sifting, data extraction and appraisal of methodological quality will be performed by the systematic reviewer. Quality control will be performed by the senior systematic reviewer. Dual sifting will be performed on at least 10% of records and where possible all records. Dual quality assessment and data extraction will be performed when capacity allows.
Equalities	No equalities issues identified for this question.
Key Papers	1. Mocellin S, Marchet A, Nitti D. EUS for the staging of gastric cancer: a meta-analysis. Gastrointestinal endoscopy. 2011;73(6):1122-34. 2. Allum WH, Blazeby JM, Griffin SM, Cunningham D, Jankowski JA, Wong R, et al. Guidelines for the management of oesophageal and gastric cancer. Gut. 2011;60(11):1449-72. de Graaf GW, Ayantunde AA, Parsons SL, Duffy JP, Welch NT. The role of staging laparoscopy in oesophagogastric cancers. European journal of surgical oncology : the journal of the European Society of Surgical Oncology and the British Association of Surgical Oncology. 2007;33(8):988-92. Initial Staging of Esophageal Cancer: Systematic Review of the Performance of Diagnostic Methods prepared for AETMIS by Julie Tranchemontagne. Agence d'évaluation des technologies et des modes d'intervention en santé (AETMIS). 2009;5(6): 1-113. van Vliet E P, Heijenbrok-Kal M H, Hunink M G, Kuipers E J, Siersema P D. Staging investigations for oesophageal cancer: a meta-analysis. British Journal of Cancer 2008; 98(3): 547-557

Item	Details
	Shi W, Wang W, Wang J, Cheng H, Huo X. Meta-analysis of 18FDG PET-CT for nodal staging in patients with esophageal cancer. Surg Oncol. 2013 Jun;22(2):112-6. doi: 10.1016/j.suronc.2013.02.003

D.6 Staging investigations

What are the optimal staging investigations to determine suitability for curative treatment of gastric cancer after diagnosis with endoscopy and whole-body CT scan?

Item	Details
Area in scope	Assessment of oesophago-gastric cancer
Review question in the scope	What is the optimal choice and sequence of staging investigations to identify metastatic disease and determine suitability for curative treatment of gastric cancer after diagnosis with endoscopy and whole-body CT scan (for example, endoscopic ultrasound, PET-CT, staging laparoscopy)?
Review question in guideline	What are the optimal staging investigations to determine suitability for curative treatment of gastric cancer after diagnosis with endoscopy and whole-body CT scan?
Objective	Gastric adenocarcinoma arises from the gastric mucosa of the stomach and account for 90% of all gastric cancers. Early diagnosis is often challenging because clinical presentation is often with vague non-specific symptoms. British consensus guidelines recommend that diagnosis is made on endoscopy and histological diagnosis based on at least six biopsy samples. Advances in imaging modalities and techniques have facilitated more accurate staging and thus more appropriate referral of patients for curative interventions. Endoscopic ultrasound has been reported to have a sensitivity and specificity of 86% and 91% for tumours without nodal involvement; and 69% and 84% for tumours with nodal involvement (1). British Society of Gastroenterology's guidelines recommend its use selectively for gastric cancers (2). PET-CT has been found to detect metastases with a sensitivity of 35% (range: 19%-55%) and specificity of 99% (93%-100%) in a prospective cohort study of 113 patients (3). Staging laparoscopy enables peritoneal lavage for cytology and biopsies of suspicious lesions to be obtained and is seen as a safe and effective staging tool used to detect small peritoneal and liver metastases missed by imaging techniques when determining resectability of tumours. A retrospective review of 511 patients found that staging laparoscopy found nodal or distant metastatic disease in 20.2% of the study population and thus avoided laparotomy with curative intent in these patients. The authors estimated a sensitivity of 88% for curative resection. Of those found to be resectable by staging laparoscopy, 8.1% were found to be unresectable at laparotomy (4). Currently the place of laparoscopy is established but the role of PET-CT and EUS is uncertain. This review aims to explore the optimal choice of diagnostic technologies to identify cases of gastric cancer suitable for curative treatment. Furthermore the sequence in which tests are offered varies. This review thus aims to inform recommendations on the sequence of staging investigations for curative treatment of gastric cancer.
Population	People with newly diagnosed gastric cancer who have been found at endoscopy and whole body CT to be suitable for potentially curative treatment.
Subgroups and sensitivity analyses	

Item	Details
Index test: Severity assessment tools/clinical markers	Endoscopic ultrasound (T and N, potentially/rarely M stage) Staging laparoscopy (T and M) PET-CT (for M and N stage)
Reference standard or target condition/patient outcomes	Final TNM stage or suitability for curative treatment based on: cytological/histopathological/clinical imaging/laparotomy and follow-up
Outcomes see 3.1 for priority	Critical outcomes Diagnostic accuracy: sensitivity specificity positive predictive value negative predictive values positive likelihood ratios negative likelihood ratios change in management plan Important but not critical outcomes Time to decision to treat Test-related morbidity (e.g. oesophageal perforation...)
Study design	Studies of diagnostic accuracy Systematic reviews Cross sectional diagnostic accuracy studies
Setting	Settings in which people with gastric tumours are offered secondary investigations to determine suitability for curative treatment. All geographic locations of studies will be considered Secondary and tertiary care only
Search strategy	Sources to be searched: Medline, Medline In-Process, CENTRAL, CDSR, DARE, HTA, Embase, Web of Science Date limit: 1990 for EUS and 2000 for PET-CT Supplementary search techniques: Snowballing techniques will be used to ensure a thorough representation of the published literature this will involve exploration of reference lists from key narrative and systematic reviews where appropriate or necessary.
Review strategy	Appraisal of methodological quality: The methodological quality of each study will be assessed using an appropriate checklist: ROBIS for systematic reviews QUADAS-2 for the quality assessment of diagnostic accuracy studies Synthesis of data: Meta-analysis will be conducted where appropriate. Minimum important differences Unless more appropriate values are identified in the literature the guideline committee will decide minimally important differences in test accuracy using their experience and the likely consequences of correct and incorrect test results for the patient. Double sifting, data extraction and methodological quality assessment Sifting, data extraction and appraisal of methodological quality will be performed by the systematic reviewer. Quality control will be performed by the senior systematic reviewer. Dual sifting will be performed on at least 10% of records and

Item	Details
	where possible all records. Dual quality assessment and data extraction will be performed when capacity allows.
Equalities	No equalities issues identified for this question.
Notes	Notes from committee subgroup during protocol drafting: Comment from HB 12/04/16: Laparoscopy and EUS are widely available while PET-CT is little used in gastric cancer I have found the The Cochrane review "Mocellin_et_al-2015-The_Cochrane_library Diagnostic accuracy of endoscopic ultrasonography (EUS) for the preoperative locoregional staging of primary gastric cancer (Review)" to be of interest when considering the range in accuracy quoted from EUS studies which may be a point of interesting debate Comment from NM 17/04/16: I agree that most would agree that the main staging is CT and laparoscopy with peritoneal lavage (the use of the peritoneal lavage varies widely but should be done), with selective use of EUS, and I agree no proven use for PET CT (although we use it in Oxford!) - we can discuss. Comment from RW 17/04/16: I agree entirely with Nicks comments regarding the limited role of EUS in gastric cancer staging - although it can be helpful in select cases.
Key Papers	1. Mocellin S, Marchet A, Nitti D. EUS for the staging of gastric cancer: a meta-analysis. Gastrointestinal endoscopy. 2011;73(6):1122-34. 2. Allum WH, Blazeby JM, Griffin SM, Cunningham D, Jankowski JA, Wong R, et al. Guidelines for the management of oesophageal and gastric cancer. Gut. 2011;60(11):1449-72. 3. Smyth E, Schoder H, Strong VE, Capanu M, Kelsen DP, Coit DG, et al. A prospective evaluation of the utility of 2-deoxy-2-[(18) F]fluoro-D-glucose positron emission tomography and computed tomography in staging locally advanced gastric cancer. Cancer. 2012;118(22):5481-8. 4. de Graaf GW, Ayantunde AA, Parsons SL, Duffy JP, Welch NT. The role of staging laparoscopy in oesophagogastric cancers. European journal of surgical oncology : the journal of the European Society of Surgical Oncology and the British Association of Surgical Oncology. 2007;33(8):988-92. Mocellin S, Pasquali S. Diagnostic accuracy of endoscopic ultrasonography (EUS) for the preoperative locoregional staging of primary gastric cancer. Cochrane Database Syst Rev. 2015 Feb 6;2:CD009944 Wang M, Ye Y, Yang Q, Li J, Han C, Wang W, Zhao C, Wen J. Pre-operative lymph node status of gastric cancer evaluated by multidetector computed tomography. Int J Clin Exp Med. 2015 Oct 15;8(10):18213-24

D.7 HER2 testing in adenocarcinoma

Should all patients with newly-diagnosed adenocarcinoma of the stomach and oesophagus be HER2 tested?

Item	Details
Area in scope	Assessment of oesophago-gastric cancer
Review question in the scope	Which pathological subtypes of gastric and gastro-oesophageal junctional cancer should be HER-2 tested?
Review question	Which people with adenocarcinoma of the stomach and oesophagus should have their tumours HER2 tested?

Item	Details
Objective(1-4)	Trastuzumab in combination with platinum/fluropyrimidine chemotherapy can be used for the treatment of HER-2 positive (immunohistochemistry 3+ or immunohistochemistry 2+/fluorescence *in situ* hybridization-positive) metastatic adenocarcinoma of the gastro-oesophageal junction and stomach. HER2 amplification is thought to be associated with worse outcomes, although the relationship between HER2 status and prognosis in gastric cancer remains unequivocal in the published literature. Trastuzumab has been used extensively in breast cancer, however HER2 testing differs in gastric and gastro-oesophageal junctional cancer. This is due to tumour cell HER2 expression heterogeneity and focal staining of tumour cells in many HER2 positive cases. This review aims to investigate whether all people with newly diagnosed adenocarcinoma of the stomach or oesophagus should be HER2 tested in order to direct HER2 directed therapy based on these results. This includes people with localised disease at presentation and people with de novo advanced disease.
Population	People with adenocarcinoma of the stomach or oesophagus (localised and advanced).
Subgroups and sensitivity analyses	• Metastatic at presentation vs localised at presentation • Eastern vs Western study location
Intervention	• HER2 testing using immunohistochemistry and/or gene amplification testing (Noreen to give some synonyms) HER2 positivity will be defined as: IHC3+ or 2+ or FISH +
Comparison	No HER2 testing
Outcomes	• Overall survival • Time to treatment initiation from detection of metastatic disease • PROMs and QoL
Importance of outcomes	Critical outcomes: • All outcomes above will be considered critical
Study design	• Systematic reviews of RCTs • RCTs (Blinding will predictably only be possible for patients) • Conference abstracts of RCTs will be considered if adequate useful information is reported and the full text publication is unavailable. • Comparative cohort or observational studies (only if RCTs unavailable or limited data to inform decision making)
Setting	Settings in which people with adenocarcinoma of the stomach or oesophagus are offered HER2 testing. All geographic locations of studies will be considered Secondary and tertiary care only
Search strategy	Sources to be searched: Medline, Medline In-Process, CENTRAL, CDSR, DARE, HTA, Embase, Web of Science Date limit: 2005 (big HER2 screening study) Supplementary search techniques: Snowballing techniques will be used to ensure a thorough representation of the published literature. This will involve exploration of reference lists from key narrative and systematic reviews where appropriate or necessary.
Review strategy	**Appraisal of methodological quality:** The methodological quality of each study will be assessed using an appropriate checklist: • ROBIS for systematic reviews

Item	Details
	• Cochrane risk of bias tool for RCTs • Cochrane risk of bias tool for non-randomised studies The quality of the evidence for an outcome (i.e. across studies) will be assessed using GRADE. **Synthesis of data:** Meta-analysis will be conducted where appropriate. **Minimum important differences** Default values will be used of: 0.80 and 1.25 for dichotomous outcomes; 0.5 times SD for continuous outcomes, unless more appropriate values are identified by the guideline committee or in the literature. **Double sifting, data extraction and methodological quality assessment** Sifting, data extraction and appraisal of methodological quality and GRADE assessment will be performed by the systematic reviewer. Quality control will be performed by the senior systematic reviewer. Dual sifting will be performed on at least 10% of records and where possible all records. Dual quality assessment and data extraction will be performed when capacity allows.
Equalities	• No equalities issues identified for this question.
Notes/additional information	Trastuzumab and ramicurumab are the only targeted agents approved for gastric cancer (some data coming through on apatinib too). Only tools that are externally validated will be assessed Note from NS: this is the key study and conducted a large screening program first and established the scoring system for OG adenoca and variation in HER according to site within the OG tract. • Testing for HER2 status in Gastric Cancer for access to trastuzumab (Structured abstract). Health Technology AssessmentDatabase. 2012(3). • Jorgensen JT. Targeted HER2 treatment in advanced gastric cancer. Oncology. 2010;78(1):26-33 • Jorgensen JT, Hersom M. HER2 as a Prognostic Marker in Gastric Cancer - A Systematic Analysis of Data from the Literature. Journal of Cancer. 2012;3:137-44. • Bang YJ, Van Cutsem E, Feyereislova A, Chung HC, Shen L, Sawaki A, et al. Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial. Lancet. 2010;376(9742):687-97. The following 2 papers helped to benchmark HER2 testing in OG cancer (staining and thresholds): • Hoffman et al, Histopathology 2008 • Ruschoff et al Virchows Arch (2010) 457:299-307 Also ASCO/CAP guidelines for HER2 testing– be aware that draft guidance has been written and is under review (Jan 2016) The following papers looked at heterogeneity and discordance as a prelude to TOGA (there are likely to be more): • Lee et al Histopathology, 2011 Nov;59(5):832-40 • Kim et al, Histopathology, 2011. 59(5): p. 822-831.

D.8 T1N0 oesophageal cancer

What is the optimal management of T1N0 oesophageal cancer?

[Item	Details
Area in the scope	Management of oesophageal cancer

[Item	Details
Review question in the scope	What is the optimal management of T1N0 oesophageal cancer?
Review question for the guideline	What is the optimal management of T1N0 oesophageal cancer?
Objective	The prognosis for those with mucosal (T1a) and submucosal (T1b) oesophageal cancer is favourable compared to those with more advanced disease. Oesophagectomy and other surgical treatments while oncologically effective, carry high morbidity and mortality profiles. Local treatment with endoscopic resection, radiofrequency ablation, (cryotherapy and photodynamic therapy?) could provide curative therapy with favourable treatment-related morbidity and mortality outcomes in appropriate selected cases. This review aims to assess which curative treatments are associated with the best outcomes for adults with T1aN0 and T1bN0 oesophageal cancer.
Population and directness	People with T1aN0 oesophageal cancer and people with T1b N0 oesophageal cancer
Intervention	Endoscopic mucosal resection (EMR) Endoscopic submucosal dissection (ESD) Endoscopic resection with radiofrequency ablation Cryotherapy (not UK licenced but an important experimental technology which may be more routinely used in the near future. Surgical resection of tumour Chemoradiotherapy
Comparison	Each other No combinations of interventions
Outcomes	Overall survival. Disease-free survival. Treatment-related morbidity. Stricture Perforation Bleeding Treatment-related mortality. Health-related quality of life. Patient-reported outcome measures. Nutritional Histopathological Deep margins lateral margins lymphovascular invasion differentiation
Importance of outcomes	Preliminary classification of the outcomes for decision making: Critical outcomes (up to 3 outcomes) Disease-free survival. Treatment-related morbidity: Stricture Perforation Bleeding Histopathological Important but not critical outcomes (up to 3 outcomes) Overall survival.

[Item	Details
	Treatment-related mortality. Health-related quality of life. Of limited importance (1 outcome) Patient-reported outcome measures. Nutritional
Setting	All settings in which T1N0 oesophageal cancer is managed and where treatments used are available and licensed for use in the UK.
Stratified, subgroup and adjusted analyses	In the presence of heterogeneity, the following subgroups will be considered for sensitivity analysis: Population Subgroups Oesophageal cancer (T1a and T1b separately) Endoscopic findings Endoscopic length of abnormal mucosa (Prague classification) Single/Multi focal Visible/No visible lesion Adenocarcinoma vs Squamous Cell Carcinoma
Language	English
Study design	Systematic reviews of RCTs RCTs (Blinding will predictably only be possible for patients) Conference abstracts of RCTs will be considered if adequate useful information is reported and the full text publication is unavailable. Comparative cohort or observational studies (only if RCTs unavailable or limited data to inform decision making)
Search strategy	Synonyms: HALO radiofrequency ablation (RFA) Endoscopic resection (ER) Endoscopic mucosal resection (EMR) Endoscopic submucosal dissection (ESD) Oesophageal / esophageal adenocarcinoma Oesophageal / esophageal squamous cell carcinoma Barrett's Neoplasia Prague classification Mucosal (T1a) / Submucosal (T1b) Oes/Gastric cancer Gastro-oesophageal junctional cancer Cryotherapy Sources to be searched: Medline, Medline In-Process, CENTRAL, CDSR, DARE, HTA, Embase, Web of Science Date limit:1995 Rationale for data limit: Important studies on relevant endoscopic techniques and comparisons published since 1995. English language publications HALO RFA data limited until RCT 2009 No RCT of surgery versus endoscopic therapies in T1 Cryotherapy data is very limited (new technology) Supplementary search techniques: Snowballing techniques will be used to ensure a thorough representation of the published literature this will involve exploration of reference lists from key narrative and systematic reviews where appropriate or necessary.
Review strategy	Appraisal of methodological quality:

[Item	Details
	The methodological quality of each study will be assessed using an appropriate checklist: ROBIS for systematic reviews Cochrane risk of bias tool for RCTs Cochrane risk of bias tool for non-randomised studies The quality of the evidence for an outcome (i.e. across studies) will be assessed using GRADE. Synthesis of data: Meta-analysis will be conducted where appropriate. Minimum important differences Default values will be used of: 0.80 and 1.25 for dichotomous outcomes; 0.5 times SD for continuous outcomes, unless more appropriate values are identified by the guideline committee or in the literature. Double sifting, data extraction and methodological quality assessment Sifting, data extraction and appraisal of methodological quality and GRADE assessment will be performed by the systematic reviewer. Quality control will be performed by the senior systematic reviewer. Dual sifting will be performed on at least 10% of records and where possible all records. Dual quality assessment and data extraction will be performed when capacity allows.
Equalities	No equalities issues identified for this question.
Notes/additional information	The population includes those who may have a surgically resectable tumour but are not fit for surgery. (Endoscopic resection in those patients with T1b oesophageal cancer not fit for surgery is an option but curative rates depend on depth of submucosal invasion, presence or absence of lymphovascular invasion and degree of differentiation histologically). Question also assumes that patients have already undergone EUS. (This is not always done in early oesophageal T1 disease as it cannot accurately differentiate T1a from T1b disease - this is the role of endoscopic resection – but EUS is the most sensitive modality for N staging locally and for differentiating T1 from T2 disease – need to discuss. EUS not used routinely in gastric cancer staging in UK. EUS helpful in junctional OG cancer to determine proximal extent – to discuss). Should radiofrequency ablation alone be included as an intervention option? (This is only appropriate for Oesophageal HGD (Tis) as all patients with T1a will have had endoscopic resection first anyway). Also need to discuss differences between adenocarcinoma and squamous cell carcinoma especially in T1N0 as evidence and management strategies not identical to adenocarcinoma (role of Radiofrequency ablation T1b higher lymph node metastatic rate etc.)
Key papers	1. Berry MF, Zeyer-Brunner J, Castleberry AW, Martin JT, Gloor B, Pietrobon R, et al. Treatment modalities for T1N0 esophageal cancers: a comparative analysis of local therapy versus surgical resection. Journal of thoracic oncology : official publication of the International Association for the Study of Lung Cancer. 2013;8(6):796-802.

D.9 Surgical treatment of oesophageal cancer

What is the most effective operative approach for the surgical treatment of oesophageal cancer?

Item	Details
Area in the scope	Management of oesophago-gastric cancer
Review question for the guideline	What is the most effective operative approach for the surgical treatment of oesophageal cancer?
Objective	Surgery, combined with neo-adjuvant chemotherapy or chemoradiation is often the preferred definitive treatment of oesophageal cancer for adults with acceptable performance status. The type of surgical resection and operative approach used, while based on tumour location can vary between one, two or three-stage procedures; open, laparoscopic, thoracoscopic or a combination of all three. The primary goal of surgery is to achieve a complete resection at all margins (R0), and avoid microscopic (R1) or macroscopic (R2) residual disease. Traditionally, the discussion of technique has mainly focused on a comparison of the transthoracic and transhiatal approach, with particular reference to perioperative morbidity / mortality, disease-free and overall survival. Minimally invasive procedures including laparoscopy and thoracoscopy (video assisted thoracic surgery - VATS) have increased the surgical techniques available. There are perceived advantages to minimally invasive approaches (both partial or complete) such as reduced pain, blood loss and hospital stay, however, there are concerns about the adequacy of resection and extent of nodal harvest to control residual disease. The development of Enhance Recovery following oesophagectomy, may reduce the difference in recovery between open and minimally invasive approaches. The aim of this review is to investigate the most effective operative approach for the surgical treatment of oesophageal cancer.
Population and directness	Adults with oesophageal cancer deemed suitable for surgical treatment.

Intervention	• Open approach.
	  ○ Left thoracoabdominal approach (trans-thoracic approach): single left thoracoabdominal incision
	  ○ Two stage (Ivor Lewis or trans-thoracic approach): laparotomy followed by right thoracotomy and intrathoracic anastomosis
	  ○ Three stage (McKeown): three incision resection with cervical anastomosis
	  ○ Transhiatal approach (incision in abdomen and neck): Allows access to disease in distal oesophagus, which is readily approachable through the diaphragmatic hiatus. A left cervical incision along the anterior border of the sternocleidomastoid muscle provides exposure to the cervical esophagus.
	• Totally minimally invasive approach (MIO)
	  ○ Thoracoscopic and laparoscopic with cervical anastomosis
	  ○ Thoracoscopic and laparoscopic with intrathoracic anastomosis
	• Robotic approach
	  ○ Thoracoscopic and laparoscopic with cervical anastomosis
	  ○ Thoracoscopic and laparoscopic with intrathoracic anastomosis
	• Hybrid approach
	  ○ Thoracoscopic and laparotomy or
	  ○ Laparoscopic (gastric mobilisation) and thoracotomy

Comparison	Comparisons are likely to be • Transthoracic (any of the three approaches above) vs transhiatal

Item	Details
	• Minimally invasive vs open • Hybrid minimally invasive vs open • Robotic vs open

Outcomes	• Overall survival.
	• Disease-free survival.
	• Treatment-related mortality.
	• Health-related quality of life.
	• Patient-reported outcome measures.
	• Length of operation
	• Treatment-related morbidity:
	  ○ Hospital stay
	  ○ Bleeding/units of blood transfusions required
	  ○ Postoperative complications
	  - Anastomotic leak/stenosis
	  - Sarcopenia
	  - Nutritional status/complication
	• Histopathological outcomes:
	  ○ Resection margins
	  ○ Lymph node harvest
	• Recurrence

Importance of outcomes	Preliminary classification of the outcomes for decision making:
	• **Critical (up to 3 outcomes)**
	  ○ Survival (overall survival, disease-free survival)
	  ○ Histopathological outcomes:
	  - Resection margins
	  - Lymph node harvest
	  ○ Treatment-related morbidity
	  - Hospital stay
	  - Bleeding/units of blood transfusions required
	  - Postoperative complications:
	  - Anastomotic leak/stenosis
	  - Sarcopenia
	  - Nutritional status/complication
	Important but not critical (up to 3 outcomes)
	  ○ Recurrence
	  ○ Health related quality of life
	  ○ Length of operation

Setting	All settings in which minimally invasive, open and hybrid approaches to oesophago-gastric surgery are performed.
Stratified, subgroup and adjusted analyses	n/a
Language	English
Study design	Only published full text papers Systematic reviews of RCTs RCTs Cohort studies (only if RCTs unavailable or limited data to inform decision making)

Item	Details
Search strategy	Sources to be searched: Medline, Medline In-Process, CENTRAL, CDSR, DARE, HTA, Embase Search should include oesophago-gastric as a search term Limits (e.g. date, study design): 1980 Rationale for date limit: Important studies on relevant surgical techniques published since 1980. Supplementary search techniques: Snowballing techniques will be used to ensure a thorough representation of the published literature this will involve exploration of reference lists from key narrative and systematic reviews where appropriate or necessary.
Review strategy	**Appraisal of methodological quality:** The methodological quality of each study will be assessed using an appropriate checklist: ROBIS for systematic reviews Cochrane risk of bias tool for RCTs Cochrane risk of bias tool for non-randomised studies The quality of the evidence for an outcome (i.e. across studies) will be assessed using GRADE. **Synthesis of data:** Meta-analysis will be conducted where appropriate. **Minimum important differences** Default values will be used of: 0.80 and 1.25 for dichotomous outcomes; 0.5 times SD for continuous outcomes, unless more appropriate values are identified by the guideline committee or in the literature. **Double sifting, data extraction and methodological quality assessment** Sifting, data extraction, appraisal of methodological quality and GRADE assessment will be performed by the systematic reviewer. Quality control will be performed by the senior systematic reviewer. Dual sifting will be performed on at least 10% of records and where possible all records. Dual quality assessment and data extraction will be performed when capacity allows.
Equalities	No equalities issues identified for this question.
Notes/additional information	Studies may classify junctional cancers as oesophageal cancer (Siewert types I and II) Search should include oesophago-gastric as a search term

D.10 Lymph node dissection in oesophageal and gastric cancer

Does the extent of lymph node dissection influence outcomes in adults with oesophageal and gastric cancer?

Item	Details
Area in the scope	Management of oesophago-gastric cancer
Review question for the guideline	Does the extent of lymph node dissection influence outcomes in people with oesophageal and gastric cancer?
Objective(1)	Surgical resection, with or without perioperative chemotherapy/ radiotherapy, remains the standard of care for oesophago-gastric cancer. The role of surgery is to remove the primary tumour as well as locoregional lymph nodes (the lymph nodes that drain the lymph from the affected organ) that may contain tumour cells. For gastrectomy: **D0 resection** refers to dissection of no lymph nodes.

Item	Details
	D1 dissection refers to a limited dissection of the nodal groups strictly adjacent to the stomach (perigastric lymph node dissection – stations 1-6). **D2 dissection** refers to the removal of nodes along the three branches of the coeliac axis (stations 7-11) in addition to D1 nodes. **D3 dissection** refers to the removal of more distant nodes (stations 12-15) in addition to D1/2 nodes. For oesophagectomy: **1 field lymphadenectomy** refers to removal of the abdominal lymph nodes (stations 1 – 4 and 7 – 9). **2-field lymphadenectomy** refers to removal of the mediastinal lymph nodes (paraoesophageal, para-aortic with thoracic duct, pulmonary hilar, subcarinal, right paratracheal) together with the first field. **3-field lymphadenectomy** refers to a neck lymph node dissection (cervical, brachiocephalic, recurrent laryngeal nodes), together with the first and second fields While it is standard practice in most UK centres to carry out radical lymph node dissections for gastrectomy (D2 dissection) and oesophagectomy (2 field lymphadenectomy), any benefit remains largely unproven. More extended lymph node dissections (D3 and 3 field) remain controversial and are infrequently carried out. Lymphadenectomy gives accurate pathological staging of the tumour (N stage) and thus allows a more accurate identification of patients at risk of recurrence. More extended removal of lymph nodes should increase the likelihood of removing microscopic metastatic disease and thus theoretically should reduce recurrence rates and improve disease-free survival. However, this theoretical improved survival needs to be balanced against the increased post-operative morbidity and mortality associated with more radical lymphadenectomies. This review aims to explore whether the extent of lymph node dissection influences outcomes in people undergoing surgery for oesophageal or gastric cancer.
Population and directness	People undergoing surgery with curative intent for oesophageal and gastric cancer.
Intervention	• Lymphadenectomy: • Gastrectomy • D1 • D2 • D3 • Oesophagectomy • One field • Two field • Three field
Comparison	• No nodal dissection (D0) - D1 - D2 - D3: each other • No nodal dissection - One - two - three field: each other
Outcomes	• Overall survival • Treatment-related morbidity • R0 resection (circumferential and longitudinal) • Short term mortality • Disease-free survival. • Health-related quality of life. • Number of lymph nodes retrieved • Site of recurrence - locoregional or distant metastases • Patient-reported outcome measures

Item	Details
Importance of outcomes	Preliminary classification of the outcomes for decision making: • critical (up to 3 outcomes) • Overall survival • Treatment-related morbidity • R0 resection (circumferential and longitudinal) • important but not critical (up to 3 outcomes) • Short term mortality • Disease-free survival. • Health-related quality of life. • of limited importance (1 outcome) • Number of lymph nodes retrieved
Setting	All settings in which surgical resection of oesophageal and gastric cancer is performed

Stratified, subgroup and adjusted analyses	In the presence of heterogeneity, the following subgroups will be considered for sensitivity analysis:
	Population subgroups
	• Baseline characteristics:
	  ○ age,
	  ○ sex,
	  ○ comorbidities and/or
	  ○ performance status
	• TNM stage
	• Anatomical location
	gastric: cardia, upper body, distal
	oesophageal:upper, middle, lower
	junctional: Siewert type 1 / 2 / 3
	• Gastrectomy type – total or subtotal
	• Tumour histology
	• Tumour site
	Intervention subgroups
	• Surgical approach (e.g. open or laparoscopic or hybrid)
	• Neoadjuvant therapy (chemo- or chemoradiotherapy)
	• Resection margins achieved at surgery
	Important confounders
	The above subgroups will be considered as confounders

Language	English
Study design	Systematic reviews of RCTs RCTs (Blinding will predictably only be possible for patients) Cohort studies (only if RCTs unavailable or limited data to inform decision making)
Search strategy	Sources to be searched: Limits (e.g. date, study design): Only published full text 1980 onwards Supplementary search techniques: None Include Far East studies
Review strategy	**Appraisal of methodological quality:** The methodological quality of each study will be assessed using an appropriate checklist: ROBIS for systematic reviews Cochrane risk of bias tool for RCTs

Item	Details
	Cochrane risk of bias tool for non-randomised studies The quality of the evidence for an outcome (i.e. across studies) will be assessed using GRADE. **Synthesis of data:** Meta-analysis will be conducted where appropriate. **Double sifting** All search records will be double sifted. **Minimum important differences** Default values will be used of: 0.80 and 1.25 for dichotomous outcomes; 0.5 times SD for continuous outcomes, unless more appropriate values are identified by the guideline committee or in the literature.
Equalities	No equalities issues identified for this question.

D.11 Localised oesophageal and gastro-oesophageal junctional adenocarcinoma

What is the optimal choice of chemotherapy or chemoradiotherapy in relation to surgical treatment for people with localised oesophageal and gastro-oesophageal junctional cancer?

Item	Details
Area in the scope	Management of oesophago-gastric cancer
Review question in scope	What is the optimal choice and timing of chemotherapy or chemo-radiotherapy in relation to surgical treatment for people with localised oesophageal and gastro-oesophageal junctional cancer?
Review question for guideline	What is the optimal choice of chemotherapy or chemoradiotherapy in relation to surgical treatment for people with localised oesophageal and gastro-oesophageal junctional cancer?
Objective(1-3)	For patients on a curative pathway for oesophageal cancer radical surgery is often recommended. Despite. Surgical resection locoregional or metastatic recurrence is unfortunately common..In order to improve disease-free survival and overall survival, patients are often treated with chemotherapy or chemoradiotherapy either before surgery (neoadjuvant), after surgery (adjuvant) or both (perioperative). This review aims to explore the clinical effectiveness of chemotherapy, chemoradiotherapy and surgery alone for people with oesophageal and gastro-oesophageal junctional cancer who are suitable for surgical resection. We aim to explore which intervention is optimal in terms of overall survival, disease-free survival and disease related and treatment related morbidity and mortality. We also aim to explore the optimal timing of therapy in relation to surgery.
Population and directness	People with newly diagnosed oesophageal and gastro-oesophageal junctional cancer who are suitable for surgical treatment. Accept that some papers will include some gastric cancer patients – highlight proportion in review Since definitions of junctional tumours has changed, these might be difficult to easily classify in chemo studies

Item	Details
Intervention	Surgical resection of oesophageal and oesophago-gastric junctional tumours plus: Chemotherapy (systemic) Pre Peri Post Chemoradiotherapy Pre Post **Chemotherapy agents:** • Platinum – Cisplatin, Carboplatin, Oxaliplatin • Taxanes – Docetaxel, Paclitaxel • Fluoropyrimidines – 5FU, capecitabine • Others - Epirubicin, Irinotecan **External beam radiotherapy + Chemotherapy agents:** • Platinum – Cis, Carbo, Oxali • Taxanes - Docetaxel, Paclitaxel • Fluoropyrimidines - 5FU, capecitabine
Comparison	Each other (any combination of the above) Surgery alone Could group choice of chemotherapy by class or doublet vs triplet combinations Dose of radiotherapy: more than or less than 40gy
Outcomes	• **Critical Outcomes** • Overall survival. • Disease-free survival. • Treatment-related morbidity. • **Important but not critical outcomes** • Treatment-related mortality. • Complete resection (R0) at surgery • Tumour regression grade (TRG) • **Of limited importance** • Health-related quality of life/PROMS
Setting	All settings will be considered which consider medications and treatments available in the UK
Stratified, subgroup and adjusted analyses	In the presence of heterogeneity, the following subgroups will be considered for sensitivity analysis: Population subgroups (although likely to be mixed in many trials) Adenocarcinoma Squamous cell carcinoma
Language	English
Study design	Systematic reviews of RCTs RCTs (Blinding will predictably only be possible for patients)

Item	Details
	Conference abstracts of RCTs will be considered if adequate useful information is reported and the full text publication is unavailable. Comparative cohort or observational studies (only if RCTs unavailable or limited data to inform decision making)
Search strategy	Sources to be searched: Medline, Medline In-Process, CENTRAL, CDSR, DARE, HTA, Embase, Web of Science Date limit:1990 (1st trial in the UK) Supplementary search techniques: Snowballing techniques will be used to ensure a thorough representation of the published literature. This will involve exploration of reference lists from key narrative and systematic reviews where appropriate or necessary.
Review strategy	**Appraisal of methodological quality:** The methodological quality of each study will be assessed using an appropriate checklist: ROBIS for systematic reviews Cochrane risk of bias tool for RCTs Cochrane risk of bias tool for non-randomised studies The quality of the evidence for an outcome (i.e. across studies) will be assessed using GRADE. **Synthesis of data:** Meta-analysis will be conducted where appropriate. **Minimum important differences** Default values will be used of: 0.80 and 1.25 for dichotomous outcomes; 0.5 times SD for continuous outcomes, unless more appropriate values are identified by the guideline committee or in the literature. **Double sifting, data extraction and methodological quality assessment** Sifting, data extraction and appraisal of methodological quality and GRADE assessment will be performed by the systematic reviewer. Quality control will be performed by the senior systematic reviewer. Dual quality assessment and data extraction will be performed when capacity allows.
Equalities	No equalities issues identified for this question.
Key papers	1. Ronellenfitsch U, Schwarzbach M, Hofheinz R, Kienle P, Kieser M, Slanger TE, et al. Preoperative chemo(radio)therapy versus primary surgery for gastroesophageal adenocarcinoma: systematic review with meta-analysis combining individual patient and aggregate data (Provisional abstract). Databaseof Abstractsof Reviewsof Effects. 2013(2):3149-58. 2. Arnott SJ, Duncan W, Gignoux M, Girling D, Hansen H, Launois B, et al. Preoperative radiotherapy for esophageal carcinoma. CochraneDatabaseof SystematicReviews. 2005(4). 3. Kidane B, Coughlin S, Vogt K, Malthaner R. Preoperative chemotherapy for resectable thoracic esophageal cancer. CochraneDatabaseof SystematicReviews. 2015(5). 4. van Hagen P, Hulshof MC, van Lanschot JJ, Steyerberg EW, van Berge Henegouwen MI, Wijnhoven BP, et al. Preoperative chemoradiotherapy for esophageal or junctional cancer. The New England journal of medicine. 2012;366(22):2074-84. 5. Gebski et al Lancet Oncol 2007;8:226-34 6. Sjoquist et al Lancet Oncol 2011; 12:681-92 7. Cunningham et al N Eng J Med 2006; 355:11-20

Item	Details
	8. OE02 Lancet 2002 359: 1727-33 + details for OE 05 awaited = UK phase 3 trial showing no benefit of ECX x4 vs CX x2 CROSS trial see 4. and the update Ychou M JCO 2011 Stahl M JCO 2009 Klevebro F Annals of Oncology 2016

D.12 Gastric Cancer

What is the optimal choice of chemotherapy or chemoradiotherapy in relation to surgical treatment for people with localised oesophageal and gastro-oesophageal junctional cancer?

Item	Details
Area in the scope	Management of oesophago-gastric cancer
Review question in scope	What is the optimal choice and timing of chemotherapy or chemo-radiotherapy in relation to surgical treatment for people with localised oesophageal and gastro-oesophageal junctional cancer?
Review question for guideline	What is the optimal choice of chemotherapy or chemoradiotherapy in relation to surgical treatment for people with localised oesophageal and gastro-oesophageal junctional cancer?
Objective(1-3)	For patients on a curative pathway for oesophageal cancer radical surgery is often recommended. Despite. Surgical resection locoregional or metastatic recurrence is unfortunately common..In order to improve disease-free survival and overall survival, patients are often treated with chemotherapy or chemoradiotherapy either before surgery (neoadjuvant), after surgery (adjuvant) or both (perioperative). This review aims to explore the clinical effectiveness of chemotherapy, chemoradiotherapy and surgery alone for people with oesophageal and gastro-oesophageal junctional cancer who are suitable for surgical resection. We aim to explore which intervention is optimal in terms of overall survival, disease-free survival and disease related and treatment related morbidity and mortality. We also aim to explore the optimal timing of therapy in relation to surgery.
Population and directness	People with newly diagnosed oesophageal and gastro-oesophageal junctional cancer who are suitable for surgical treatment. Accept that some papers will include some gastric cancer patients – highlight proportion in review Since definitions of junctional tumours has changed, these might be difficult to easily classify in chemo studies
Intervention	Surgical resection of oesophageal and oesophago-gastric junctional tumours plus: Chemotherapy (systemic) Pre Peri Post Chemoradiotherapy Pre

Item	Details
	Post **Chemotherapy agents:** • Platinum – Cisplatin, Carboplatin, Oxaliplatin • Taxanes – Docetaxel, Paclitaxel • Fluoropyrimidines – 5FU, capecitabine • Others - Epirubicin, Irinotecan **External beam radiotherapy + Chemotherapy agents:** • Platinum – Cis, Carbo, Oxali • Taxanes - Docetaxel, Paclitaxel • Fluoropyrimidines - 5FU, capecitabine
Comparison	Each other (any combination of the above) Surgery alone Could group choice of chemotherapy by class or doublet vs triplet combinations Dose of radiotherapy: more than or less than 40gy
Outcomes	• **Critical Outcomes** • Overall survival. • Disease-free survival. • Treatment-related morbidity. • **Important but not critical outcomes** • Treatment-related mortality. • Complete resection (R0) at surgery • Tumour regression grade (TRG) • **Of limited importance** • Health-related quality of life/PROMS
Setting	All settings will be considered which consider medications and treatments available in the UK
Stratified, subgroup and adjusted analyses	In the presence of heterogeneity, the following subgroups will be considered for sensitivity analysis: Population subgroups (although likely to be mixed in many trials) Adenocarcinoma Squamous cell carcinoma
Language	English
Study design	Systematic reviews of RCTs RCTs (Blinding will predictably only be possible for patients) Conference abstracts of RCTs will be considered if adequate useful information is reported and the full text publication is unavailable. Comparative cohort or observational studies (only if RCTs unavailable or limited data to inform decision making)
Search strategy	Sources to be searched: Medline, Medline In-Process, CENTRAL, CDSR, DARE, HTA, Embase, Web of Science

Item	Details
	Date limit:1990 (1st trial in the UK) Supplementary search techniques: Snowballing techniques will be used to ensure a thorough representation of the published literature. This will involve exploration of reference lists from key narrative and systematic reviews where appropriate or necessary.
Review strategy	**Appraisal of methodological quality:** The methodological quality of each study will be assessed using an appropriate checklist: ROBIS for systematic reviews Cochrane risk of bias tool for RCTs Cochrane risk of bias tool for non-randomised studies The quality of the evidence for an outcome (i.e. across studies) will be assessed using GRADE. **Synthesis of data:** Meta-analysis will be conducted where appropriate. **Minimum important differences** Default values will be used of: 0.80 and 1.25 for dichotomous outcomes; 0.5 times SD for continuous outcomes, unless more appropriate values are identified by the guideline committee or in the literature. **Double sifting, data extraction and methodological quality assessment** Sifting, data extraction and appraisal of methodological quality and GRADE assessment will be performed by the systematic reviewer. Quality control will be performed by the senior systematic reviewer. Dual sifting will be performed on at least 10% of records and where possible all records. Dual quality assessment and data extraction will be performed when capacity allows.
Equalities	No equalities issues identified for this question.
Notes/additional information	Important trial presented at ASCO in conference abstract – contact Mark/Noreen if we would like more information because this has not been published fully yet
Key papers	1. Ronellenfitsch U, Schwarzbach M, Hofheinz R, Kienle P, Kieser M, Slanger TE, et al. Preoperative chemo(radio)therapy versus primary surgery for gastroesophageal adenocarcinoma: systematic review with meta-analysis combining individual patient and aggregate data (Provisional abstract). Databaseof Abstractsof Reviewsof Effects. 2013(2):3149-58. 2. Arnott SJ, Duncan W, Gignoux M, Girling D, Hansen H, Launois B, et al. Preoperative radiotherapy for esophageal carcinoma. CochraneDatabaseof SystematicReviews. 2005(4). 3. Kidane B, Coughlin S, Vogt K, Malthaner R. Preoperative chemotherapy for resectable thoracic esophageal cancer. CochraneDatabaseof SystematicReviews. 2015(5). 4. van Hagen P, Hulshof MC, van Lanschot JJ, Steyerberg EW, van Berge Henegouwen MI, Wijnhoven BP, et al. Preoperative chemoradiotherapy for esophageal or junctional cancer. The New England journal of medicine. 2012;366(22):2074-84. 5. Gebski et al Lancet Oncol 2007;8:226-34 6. Sjoquist et al Lancet Oncol 2011; 12:681-92 7. Cunningham et al N Eng J Med 2006; 355:11-20 8. OE02 Lancet 2002 359: 1727-33

Item	Details
	+ details for OE 05 awaited = UK phase 3 trial showing no benefit of ECX x4 vs CX x2 CROSS trial see 4. and the update Ychou M JCO 2011 Stahl M JCO 2009 Klevebro F Annals of Oncology 2016

D.13 Squamous cell carcinoma of the oesophagus

What is the most effective curative treatment of squamous cell carcinoma of the oesophagus?

Item	Details
Area in the scope	Management of oesophago-gastric cancer
Review question in scope	What is the most effective curative treatment (chemoradiotherapy with or without surgery) of squamous cell carcinoma of the oesophagus?
Review question for the guideline	What is the most effective curative treatment of squamous cell carcinoma of the oesophagus?
Objective(1-4)	Squamous cell carcinoma of the oesophagus is an important health issue in the UK. The incidence of SCC is declining but still accounts for a substantial proportion of cases. Major predisposing factors to the development of SCC oesophageal cancer are alcohol and cigarette smoking. Treatment options for patients with SCC Oesophagus include surgery, radiotherapy and chemotherapy; either as single modalities, or in combination (multi-modality). The aim of this review is to explore the most effective treatment options available. This will involve evaluating in particular whether non-operative treatment is as effective as surgery based treatment, and whether multimodal is superior to unimodal treatment.
Population and directness	Adults with squamous cell oesophageal cancer suitable for radical treatment (T1b and above).
Intervention	Surgery Chemoradiotherapy without surgery Chemoradiotherapy followed by surgery Chemotherapy followed by surgery Radiotherapy alone Surgery followed by adjuvant chemoradiotherapy
Comparison	Each other
Outcomes	Overall Survival (30 day, 90 days, 1 year 5 years) Disease-free survival Treatment-related mortality Treatment-related morbidity Intra-operative Bleeding/unit of blood transfused Post-operative complications Infection Anastomotic leak or stenosis Health-related quality of life/Patient-reported outcome measures Number going on to curative resection (for initial non operative management

Item	Details
Importance of outcomes	Preliminary classification of the outcomes for decision making: Critical outcomes (up to 3 outcomes) Overall Survival (30 day, 90 day, 1 year, 5 year) Disease-free survival Treatment-related mortality Important but not critical outcomes (up to 3 outcomes) Treatment-related morbidity Intra-operative Bleeding/unit of blood transfused Post-operative complications Infection Anastomotic leak or stenosis Health-related quality of life/Patient-reported outcome measures Number going on to salvage resection (for initial non operative management)
Setting	Settings in which people with squamous cell carcinoma of the oesophagus are offered curative treatment. All geographic locations of studies will be considered Secondary and tertiary care only
Stratified, subgroup and adjusted analyses	Population subgroups: Baseline characteristics: age, gender Stage of disease: Surgically resectable tumours T1-T4a Surgically unresectable tumours T4b+ Performance status Intervention subgroups: Adjuvant vs neoadjuvant chemoradiotherapy Different therapeutic regimens and doses Surgical approach Lymph node dissection When comparative observational studies are included the above subgroups will be considered as confounders
Language	English
Study design	Systematic reviews of RCTs RCTs (Blinding will predictably only be possible for patients) Conference abstracts of RCTs will be considered if adequate useful information is reported and the full text publication is unavailable. Comparative cohort or observational studies (only if RCTs unavailable or limited data to inform decision making)
Search strategy	Sources to be searched: Medline, Medline In-Process, CENTRAL, CDSR, DARE, HTA, Embase, Web of Science Search should include oesophago-gastric as a search term Date limit:1990 Rationale for date limit: Changes in clinical practice since this date. Important studies on relevant interventions published since 1990. Supplementary search techniques: Snowballing techniques will be used to ensure a thorough representation of the published literature this will involve exploration of reference lists from key narrative and systematic reviews where appropriate or necessary.
Review strategy	Appraisal of methodological quality:

Item	Details
	The methodological quality of each study will be assessed using an appropriate checklist: ROBIS for systematic reviews Cochrane risk of bias tool for RCTs Cochrane risk of bias tool for non-randomised studies The quality of the evidence for an outcome (i.e. across studies) will be assessed using GRADE. Synthesis of data: Meta-analysis will be conducted where appropriate. Minimum important differences Default values will be used of: 0.80 and 1.25 for dichotomous outcomes; 0.5 times SD for continuous outcomes, unless more appropriate values are identified by the guideline committee or in the literature. Double sifting, data extraction and methodological quality assessment: Sifting, data extraction and appraisal of methodological quality and GRADE assessment will be performed by the systematic reviewer. Quality control will be performed by the senior systematic reviewer. Dual sifting was performed for 10% of records and 98% agreement was obtained between the reviewers. Dual quality assessment and data extraction were not performed due to limited resources. Dual quality assessment and data extraction will be performed when capacity allows.
Equalities	No equalities issues identified for this question.
Key papers	1. Allum WH, Blazeby JM, Griffin SM, Cunningham D, Jankowski JA, Wong R, et al. Guidelines for the management of oesophageal and gastric cancer. Gut. 2011;60(11):1449-72. 2. Kranzfelder M, Schuster T, Geinitz H, Friess H, Buchler P. Meta-analysis of neoadjuvant treatment modalities and definitive non-surgical therapy for oesophageal squamous cell cancer (Structured abstract). British Journal of Surgery. 2011;98(6):768-83. 3. Greer SE, Goodney PP, Sutton JE, Birkmeyer JD. Neoadjuvant chemoradiotherapy for esophageal carcinoma: a meta-analysis (Structured abstract). Surgery. 2005;137(2):172-7. 4. Sjoquist KM, Burmeister BH, Smithers BM, Zalcberg JR, Simes RJ, Barbour A, et al. Survival after neoadjuvant chemotherapy or chemoradiotherapy for resectable oesophageal carcinoma: an updated meta-analysis (Structured abstract). Lancet Oncology. 2011;12(7):681-92. 5. Best LM et Al Non-surgical vs surgical treatment for oesophageal cancer Cochrane Database Syst Rev 2016 Mar 29:3 6. Cross Trial (- multimodal vs surgery alone) 7. Scope -1 trial – as contemporary definitive CRT trial in UK 8. OE02 – old now but included SCC, And for definitive chemoradiation: Stahl et al JCO 2005 Bedenne et al JCO 2007 And an older meta-analysis; Gebski et al 2007

D.14 Non-metastatic oesophageal cancer not suitable for surgery

What is the optimal treatment for adults with non-metastatic disease in the oesophagus who are not suitable for surgery?

Item	Details
Area in the scope	Management of oesophago-gastric cancer
Review question in the scope	What is the optimal treatment for people with local disease in the oesophagus or stomach that is not suitable for surgery?
Review question for guideline	What is the optimal treatment for adults with non-metastatic disease in the oesophagus who are not suitable for surgery? This question includes those who have tumours not suitable for surgery and those who are considered not suitable for surgery due to comorbidity, performance status or personal choice
Objective	Curative intent surgical resection of oesophago-gastric cancer is major surgery and not without risk. Therefore before embarking on surgery a careful evaluation of risk:benefit takes place. There will be people with non-metastatic OG cancer where the risk outweighs the benefit; due to patient (comorbidity/fitness) or tumour (locally advanced T4) factors, or the person may prefer to avoid surgery. For people with well differentiated, localised tumours that have not progressed beyond the submucosa endoscopic treatment is offered. For the remainder with more advanced non-metastatic oesophago-gastric cancer non-surgical treatment options may include systemic treatment, radiotherapy or chemoradiotherapy This review aims to investigate the effective non-surgical treatments for people with non-metastatic oesophageal cancer disease and identify patient groups most likely to benefit from these treatments.
Population and directness	Adults with non-metastatic oesophageal cancer (≥T2, any N [including T1N+], M0) who are not suitable for surgical treatment as a result of either comorbidities or tumour characteristics.
Intervention	Chemotherapy: Monotherapy Fluoropyrimidine Combination therapy Taxane combination Irinotecan combination FOLFIRI (Irinotecan, 5FU bolus, 5Fu infusion) Platinum combination PFp (Platinum: Oxaliplatin or cisplatin, Fluoropyrimidine: 5FU or Capecitabine) +/- Anthracycline +/- Taxane Fluoropyrimidine combination (e.g.S1 plus Oxaliplatin) Radiotherapy: Brachytherapy External beam therapy Combination of chemotherapy and radiotherapy (as defined above) Stent procedures (e.g. luminal stents) Best supportive care (e.g. similar frequency of clinic follow-up as active treatment arm and symptomatic support as required)
Comparison	Each Other
Outcomes	Overall survival. Disease-free survival.

Item	Details
	Secondary resectability Disease-related morbidity. Dysphagia Treatment-related morbidity. Treatment-related mortality. Health-related quality of life/Patient-reported outcome measures.
Importance of outcomes	Preliminary classification of the outcomes for decision making: Critical outcomes (up to 3 outcomes) Overall survival. Disease-free survival. Health-related quality of life/Patient-reported outcome measures. Important but not critical outcomes (up to 3 outcomes) Disease-related morbidity. Dysphagia Treatment-related morbidity. Treatment-related mortality. Of limited importance (1 outcome) Secondary resectability
Setting	All settings in which people with non-metastatic oesophageal cancer are offered non-surgical treatment. All geographic locations of studies will be considered Secondary and tertiary care only
Stratified, subgroup and adjusted analyses	Adenocarcinoma versus squamous cell carcinoma Stomach versus oesophagus Performance status/Co-morbidities
Language	English
Study design	Systematic reviews of RCTs RCTs (Blinding will predictably only be possible for patients) Conference abstracts of RCTs will be considered if adequate useful information is reported and the full text publication is unavailable. Comparative cohort or observational studies (only if RCTs unavailable or limited data to inform decision making)
Search strategy	Sources to be searched: Medline, Medline In-Process, CENTRAL, CDSR, DARE, HTA, Embase, Web of Science Date limit:2000 Rationale for date limit: Important studies on relevant interventions published since 2000. Supplementary search techniques: Snowballing techniques will be used to ensure a thorough representation of the published literature this will involve exploration of reference lists from key narrative and systematic reviews where appropriate or necessary.
Review strategy	Appraisal of methodological quality: The methodological quality of each study will be assessed using an appropriate checklist: ROBIS for systematic reviews Cochrane risk of bias tool for RCTs Cochrane risk of bias tool for non-randomised studies The quality of the evidence for an outcome (i.e. across studies) will be assessed using GRADE. Synthesis of data:

Item	Details
	Meta-analysis will be conducted where appropriate. Minimum important differences Default values will be used of: 0.80 and 1.25 for dichotomous outcomes; 0.5 times SD for continuous outcomes, unless more appropriate values are identified by the guideline committee or in the literature. Double sifting, data extraction and methodological quality assessment Sifting, data extraction and appraisal of methodological quality and GRADE assessment will be performed by the systematic reviewer. Quality control will be performed by the senior systematic reviewer. Dual sifting will be performed on at least 10% of records and where possible all records. Dual quality assessment and data extraction will be performed when capacity allows.
Equalities	No equalities issues identified for this question.
Notes/additional information	Adults with non-resectable locally advanced tumours are likely to have been included in trials of palliative chemotherapy with metastatic patients Comment from AB 04/09/2016: This is an extremely heterogeneous group, with (as far as I can tell) no straight forward literature review process. I think we had excluded the 'early' endoscopically treatable tumours by making the population T2 or above, or any N1 - and therefore is only about chemo/RT or CRT. For oesophagus - all the studies of definitive chemoradiation e.g. Scope 1 will in the main part include patients 'not suitable' for surgery. However what I am sure of is there are not studies of comparison between chemo vs CRT. So it may be a distillation of some studies looking to inform guidance? Try looking at Crosby T et al, Br J Cancer 2004 Jan 12;90:70-75 for a flavour.
Key Papers	Crosby T et al, Br J Cancer 2004 Jan 12;90:70-75

D.15 First-line palliative chemotherapy

What is the optimal palliative first-line systemic chemotherapy for locally advanced and/or metastatic oesophago-gastric cancer?

Item	Details
Area in the scope	Management of oesophago-gastric cancer
Review question in the scope	What is the optimal first-line chemotherapy for locally advanced and metastatic oesophago-gastric cancer?
Review question for the guideline	What is the optimal palliative first-line systemic chemotherapy for locally advanced and/or metastatic oesophago-gastric cancer?
Objective	The majority of patients diagnosed with oesophago-gastric cancer will present with non-operable or metastatic disease. In addition a significant proportion of those patients able to undergo potentially curative treatment at initial presentation will unfortunately relapse with inoperable or metastatic disease. For these groups of patients there is evidence to support the use of systemic chemotherapy in palliating the disease. A number of chemotherapy drugs and combinations of drugs have been investigated in this setting with varying degrees of response and toxicity identified. This review aims to explore and make recommendations on the optimal first-line palliative chemotherapy used to treat locally advanced and metastatic oesophago-gastric cancer. In addition we aim to indentify subgroups of patients who are most likely to benefit from chemotherapy.

Item	Details
Population and directness	Adults with locally advanced and/or metastatic oesophago-gastric cancer suitable for palliative systemic chemotherapy.
Intervention	Monotherapy Fluoropyrimidine Combination therapy Taxane combination Irinotecan combination FOLFIRI (Irinotecan, 5FU bolus, 5Fu infusion) Platinum combination PFp (Platinum: Oxaliplatin or cisplatin, Fluoropyrimidine: 5-FU or Capecitabine) +/- Anthracycline +/- taxane Fluoropyrimidine combination (e.g.S1 plus Oxailplatin)
Comparison	Each other
Outcomes	Overall survival. Progression-free survival Disease-related morbidity. Treatment-related toxicity. Treatment-related mortality. Health-related quality of life/Patient-reported outcome measures.
Importance of outcomes	Preliminary classification of the outcomes for decision making: Critical outcomes (up to 3 outcomes) Overall survival. Progression-free survival Treatment-related toxicity. Important but not critical outcomes (up to 3 outcomes) Treatment-related mortality. Health-related quality of life/Patient-reported outcome measures. Of limited importance (1 outcome) Disease-related morbidity.
Setting	All settings in which chemotherapies are used that are offered or licensed for use in the UK.
Stratified, subgroup and adjusted analyses	Adenocarcinoma vs SCC Stomach vs oesophagus Performance status/Co-morbidities
Language	English
Study design	Systematic reviews of RCTs RCTs (Blinding will predictably only be possible for patients) Conference abstracts of RCTs will be considered if adequate useful information is reported and the full text publication is unavailable. Comparative cohort or observational studies (only if RCTs unavailable or limited data to inform decision making)
Search strategy	Sources to be searched: Medline, Medline In-Process, CENTRAL, CDSR, DARE, HTA, Embase, Web of Science Date limit:1990 Rationale for data limit : Important studies on relevant chemotherapies and their comparisons published in 1990.

Item	Details
	Supplementary search techniques: Snowballing techniques will be used to ensure a thorough representation of the published literature this will involve exploration of reference lists from key narrative and systematic reviews where appropriate or necessary.
Review strategy	Appraisal of methodological quality: The methodological quality of each study will be assessed using an appropriate checklist: ROBIS for systematic reviews Cochrane risk of bias tool for RCTs Cochrane risk of bias tool for non-randomised studies The quality of the evidence for an outcome (i.e. across studies) will be assessed using GRADE. Synthesis of data: Meta-analysis will be conducted where appropriate. Minimum important differences Default values will be used of: 0.80 and 1.25 for dichotomous outcomes; 0.5 times SD for continuous outcomes, unless more appropriate values are identified by the guideline committee or in the literature. Double sifting, data extraction and methodological quality assessment Sifting, data extraction and appraisal of methodological quality and GRADE assessment will be performed by the systematic reviewer. Quality control will be performed by the senior systematic reviewer. Dual sifting will be performed on at least 10% of records and where possible all records. Dual quality assessment and data extraction will be performed when capacity allows.
Equalities	No equalities issues identified for this question.
Notes/additional information	Exclude peritoneal chemotherapy as an intervention Check if S1: Japanese chemotherapy licensed for use in UK Locally advanced refers to tumours that are not surgically resectable: T1N3 or higher e.g.: T4
Key papers	Cochrane Database Syst Rev. 2010 Mar 17;(3) Chemotherapy for advanced gastric cancer. Wagner AD1, Unverzagt S, Grothe W, Kleber G,Grothey A, Haerting J, Fleig WE.

D.16 Second-line palliative chemotherapy

What is the optimal palliative second-line chemotherapy for locally-advanced or metastatic oesophago-gastric cancer?

Item	Details
Area in the scope	Management of oesophago-gastric cancer
Review question in the scope	What is the optimal second-line chemotherapy for locally advanced and metastatic oesophago-gastric cancer?
Review question for the guideline	What is the optimal palliative second-line chemotherapy for locally advanced and metastatic oesophago-gastric cancer?

Item	Details
Objective	Following first-line platinum/fluoropyrimidine based chemotherapy for advanced oesophago-gastric cancer, a proportion of patients may be suitable for and wish to be considered for second-line chemotherapy. Randomised trials have demonstrated a small but significant survival benefit for second-line chemotherapy as compared to best-supportive care. The modest survival benefit needs to be considered alongside potential treatment-related morbidity, impact of on quality of life and patients' wishes for treatment. This review aims to investigate the optimal second-line palliative approaches for locally advanced and metastatic oesophago-gastric cancer. In addition we aim to identify subgroups of patients most likely to benefit from second-line chemotherapy.
Population and directness	Adults with locally advanced and metastatic oesophago-gastric cancer who have received one prior schedule of chemotherapy for locally advanced and metastatic disease.
Intervention	First order comparisons: Monotherapy • Irinotecan alone • Taxane alone (Paclitaxel or Docetaxel) Combination therapy • Taxane combination • Docetaxel/Irinotecan +/- fluoropyrimidine (5FU/capecitabine) Irinotecan combination • FOLFIRI: Irinotecan, leucovorin (folinic acid), 5FU bolus and 5Fu infusion • IFL: irinotecan, fluorouracil bolus and leucovorin (folinic acid) Platinum combination • EOFp: Epirubicin, Platinum (Oxaliplatin or cisplatin), Fluoropyrimidine (5FU or Capecitabine) • MMC/Capecitabine: Mitomycin C, Capecitabine +/- platinum Best supportive care (e.g. similar frequency of clinic follow-up as active treatment arm and symptomatic support as required)
Comparison	Each other Comparisons between combinations Second order comparisons For statistical validity we will include treatment comparisons where the above interventions are compared to interventions not list above. This is likely to involve comparisons with Ramucirumab, an intervention that has been rejected by a NICE HTA. This drug will therefore be included but the results of this comparisons and effect estimates will not be used in the decision making process.
Outcomes	Overall survival. Progression-free survival Disease-related morbidity. Treatment-related toxicity. Treatment-related mortality. Health-related quality of life. Patient-reported outcome measures.
Importance of outcomes	Preliminary classification of the outcomes for decision making: Critical outcomes (up to 3 outcomes) • Overall survival. • Treatment-related >Grade 3 toxicity ○ nausea,

Item	Details
	○ neutropaenic fever/sepsis, ○ diarrhoea, ○ thrombocytopaenia • Health-related quality of life. Important but not critical outcomes (up to 3 outcomes) • Progression-free survival • Disease-related morbidity. • Treatment-related mortality. Of limited importance (1 outcome) • Patient-reported outcome measures.
Setting	All settings in which chemotherapies are used that are offered or licensed for use in the UK.
Stratified, subgroup and adjusted analyses	In the presence of heterogeneity, the following subgroups will be considered for sensitivity analysis: Patients who received first-line platinum/fluoropyrimidine based chemotherapy agents
Language	English
Search strategy	Sources to be searched: Medline, Medline In-Process, CENTRAL, CDSR, DARE, HTA, Embase, Web of Science Date limit: 2000 Rationale for data limit: Important studies on relevant chemotherapies and comparisons published in 2000. Supplementary search techniques: Snowballing techniques will be used to ensure a thorough representation of the published literature this will involve exploration of reference lists from key narrative and systematic reviews where appropriate or necessary. See appendix for full strategies (add link)
Review strategy	Appraisal of methodological quality: The methodological quality of each study will be assessed using an appropriate checklist: ROBIS for systematic reviews Cochrane risk of bias tool for RCTs Cochrane risk of bias tool for non-randomised studies The quality of the evidence for an outcome (i.e. across studies) will be assessed using GRADE. Minimum important differences Default values will be used of: 0.80 and 1.25 for dichotomous outcomes; 0.5 times SD for continuous outcomes, unless more appropriate values are identified by the guideline committee or in the literature. Double sifting, data extraction and methodological quality assessment Sifting, data extraction and appraisal of methodological quality and GRADE assessment will be performed by the systematic reviewer. Quality control will be performed by the senior systematic reviewer. Dual sifting will be performed on at least 10% of records and where possible all records. Dual quality assessment and data extraction will be performed when capacity allows. Synthesis of data: Network meta-analysis will be conducted using STATA/or Winbugs codes We will use mean differences for reporting the results of continuous outcomes We will use the RRs (95% confidence interval) for reporting the results of dichotomous outcomes We will use rate ratios or HRs for reporting the results of rate outcomes.

Item	Details
	We will impute SD (accounting for uncertainty in SD imputation) where it has not been reported and assess impact of this in a sensitivity analysis
Study design	Systematic reviews of RCTs RCTs and conference abstracts of RCTs For the purposes of the network meta-analysis, only RCTS will be considered for inclusion.
Covariates	Covariates can sometimes be included to reduce heterogeneity instead of running subgroup analyses, where data is available. In order of importance (where data are available): Prior chemotherapy Time since first-line chemotherapy Age Baseline Eastern Cooperative Oncology Group performance status
Model Structure	Class effect model to allow borrowing of evidence from other treatments if network is too sparse. The following investigations into which class effect model fits the data best will be performed. Classes of drug treatments grouped according to monotherapy or combination therapy as listed above (see interventions). We will test for exchangeability of within-class treatments to assess if a class model is appropriate
Assumptions	Classic NMA assumptions Means are normally distributed (Central Limit Theorem) If covariates are included we assume that there is no multiplicative effect of this with the different hormonal therapies
Sensitivity Analyses	Treatment characteristics that have not been stratified/subgrouped (e.g. dose – high/low, if there is not enough data for subgroup analysis) Imputed SDs Priors
Equalities	No equalities issues identified for this question.
Notes/additional information	Include psychosocial outcomes for treatment related morbidity

D.17 Luminal obstruction

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

Item	Details
Area in the scope	Management of oesophago-gastric cancer
Review question in the scope	What is the optimal treatment of dysphagia for people with oesophago-gastric cancer receiving palliative treatment?
Review question for the guideline	What is the optimal management of luminal obstruction for adults with oesophago-gastric cancer not amenable to treatment with curative intent?
Objective	Many patients with oesophago-gastric cancer present with dysphagia or gastric outlet obstruction and are subsequently diagnosed with advanced disease. Although many interventions to treat luminal obstruction exist, the optimal treatment for the palliation of luminal obstruction remains unclear. 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 treatment for palliation of luminal obstruction when considering important outcomes such as

Item	Details
	treatment-related and disease-related morbidity and mortality and patient reported health outcomes (1, 2).
Population and directness	Adults with oesophago-gastric cancer who have luminal obstruction and require palliation:
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 o Intraluminal brachytherapy o External beam radiotherapy Surgery Laser therapy Chemotherapy
Comparison	• Each other • Combinations considered - temporary stent and radiotherapy - biodegradable stent and radiotherapy
Outcomes	• Symptom improvement (including time from intervention to improvement of symptoms and dysphagia score) • Symptom recurrence Time from intervention to recurrence of symptoms Symptoms are defined as follows: • Weight change o Vomiting o Nausea o Resumption of eating o Swallowing (dysphagia score) • Overall survival • Re-intervention • Technical success • Procedure-related mortality • Procedure-related morbidity • Health-related quality of life • PROMS o Chest pain o Gastro-oesophageal reflux
Importance of outcomes	Preliminary classification of the outcomes for decision making: • **Critical outcomes (up to 3 outcomes)** • Procedure-related morbidity • Symptom improvement (including time from intervention to improvement of symptoms and dysphagia score) • Symptom recurrence Time from intervention to recurrence of symptoms • **Important but not critical outcomes (up to 3 outcomes)** • Overall survival • Re-intervention

Item	Details
	• PROMS • **Of limited importance (1 outcome)** • Procedure-related mortality
Setting	Settings in which people with dysphagia are treated with palliative intent and dysphagia improvement is the primary outcome of interest.
Stratified, subgroup and adjusted analyses	In the presence of heterogeneity, the following subgroups will be considered for sensitivity analysis: Groups that will be reviewed and analysed separately: **Population subgroups** • Oesophageal tumour • Gastric tumour **Important confounders** • Age, • gender, • stage of disease, • performance status or comorbidities • degree of obstruction • Site of obstruction • Type of stent used
Language	English
Study design	• Systematic reviews of RCTs • RCTs (Blinding will predictably only be possible for patients) • Conference abstracts of RCTs will be considered if adequate useful information is reported and the full text publication is unavailable. • Comparative cohort or observational studies (only if RCTs unavailable or limited data to inform decision making)
Search strategy	Sources to be searched: Medline, Medline In-Process, CENTRAL, CDSR, DARE, HTA, Embase, Web of Science Date limit:1990 Rationale for date limit: Important studies on relevant therapies published in 1990. Supplementary search techniques: Snowballing techniques will be used to ensure a thorough representation of the published literature this will involve exploration of reference lists from key narrative and systematic reviews where appropriate or necessary.
Review strategy	**Appraisal of methodological quality:** The methodological quality of each study will be assessed using an appropriate checklist: ROBIS for systematic reviews Cochrane risk of bias tool for RCTs Cochrane risk of bias tool for non-randomised studies The quality of the evidence for an outcome (i.e. across studies) will be assessed using GRADE. **Synthesis of data:** Meta-analysis will be conducted where appropriate. **Minimum important differences** Default values will be used of: 0.80 and 1.25 for dichotomous outcomes; 0.5 times SD for continuous outcomes, unless more appropriate values are identified by the guideline committee or in the literature.

Item	Details
	Double sifting, data extraction and methodological quality assessment Sifting, data extraction and appraisal of methodological quality and GRADE assessment will be performed by the systematic reviewer. Quality control will be performed by the senior systematic reviewer. Dual sifting will be performed on at least 10% of records and where possible all records. Dual quality assessment and data extraction will be performed when capacity allows.
Equalities	No equalities issues identified for this question.
Key papers	1. Yakoub D, Fahmy R, Athanasiou T, Alijani A, Rao C, Darzi A, et al. Evidence-based choice of esophageal stent for the palliative management of malignant dysphagia (Structured abstract). World Journal of Surgery. 2008;32(9):1996-2009. 2. Dai Y, Li C, Xie Y, Liu X, Zhang J, Zhou J, et al. Interventions for dysphagia in oesophageal cancer. Cochrane Database of SystematicReviews. 2014(10).

D.18 Curative treatment

What is the effectiveness of nutritional support interventions for adults undergoing curative treatment for oesophago-gastric cancer?

Table 1: Clinical review protocol

Item	Details
Area in the scope	Management of oesophago-gastric cancer
Review question in the scope	What nutritional interventions improve outcomes for people with oesophago-gastric cancer receiving curative treatment (for example, during chemoradiotherapy, or before and after surgery)?
Review question for the guideline	What is the effectiveness of nutritional support interventions for adults undergoing curative treatment for oesophago-gastric cancer?
Objective(1, 2)	Nutrition plays an important role in the management of patients with oesophago-gastric cancer. Weight loss and poor nutritional status is associated with increased post-operative morbidity, mortality and longer hospital stays, and reduced overall 5 year survival. Weight loss is a common presenting symptom, with a reported incidence of 57-83% at diagnosis. Dysphagia, reduced oral intake, symptom burden and the altered metabolism associated with systemic inflammation induced by the tumour, can contribute to weight loss and malnutrition. The treatment pathway for oesophago-gastric cancer has a prolonged course and is usually multimodal. Treatments also can adversely impact nutritional status. Resection of the oesophago-gastric cancer results is associated with postoperative nutritional impairment, weight loss, malabsorption, malnutrition and a significantly reduced quality of life. Dietetic support can improve nutritional status and thus reduce the risk of treatment and disease related morbidity and mortality and help restore quality of life. Oral and artificial nutrition support strategies are regularly used in conjunction with symptom management in this patient group. This review aims to evaluate which nutritional interventions improve outcomes for adults with oesophago-gastric cancer undergoing curative surgical treatment. Since nutritional needs depend on tumour site, symptoms and previous or planned treatments, we aim to investigate the patient groups most likely to benefit from nutritional interventions.

Item	Details
Population and directness	Adults with oesophago-gastric cancer treated with curative intent.
Intervention	Oral nutritional support Oral nutritional supplements Food fortification Immunonutrition/Immunomodulating nutrition Enteral Feeding Gastrostomy Jejunostomy feeding Nasojejunal feeding Nasogastric feeding Parenteral nutrition/ IV nutrition IV hydration Dietary counselling/advice Dietetic review Stent
Comparison	Each other Comparison between interventions or to no nutritional support interventions Combinations of interventions possible
Outcomes	Treatment-related morbidity. Post-operative complications (including those related to route of feeding) Infections Leaks Need for hospital admission/readmission Treatment-related mortality. Sarcopenia Nutritional status (Weight change, various assessments may be used) Health-related quality of life/ Patient-reported outcome measures. Length of hospital stay Survival
Importance of outcomes	Preliminary classification of the outcomes for decision making: Critical outcomes (up to 3 outcomes) Survival Health-related quality of life/ Patient-reported outcome measures. Treatment-related morbidity. Important but not critical outcomes (up to 3 outcomes) Length of hospital stay Treatment-related mortality. Sarcopenia Of limited importance (1 outcome) Nutritional status (Weight change, various assessments may be used)
Setting	Settings in which people with oesophago-gastric cancer who are treated with curative intent are offered nutritional support
Stratified, subgroup and adjusted analyses	In the presence of heterogeneity, the following subgroups will be considered for sensitivity analysis: Oesophagectomy Gastrectomy Total

Item	Details
	Partial Oesophageal cancer Gastro-oesophageal junction cancer Gastric cancer Chemo-radiotherapy Surgical Primary chemotherapy
Language	English
Study design	Systematic reviews of RCTs RCTs (Blinding will predictably only be possible for patients) Conference abstracts of RCTs will be considered if adequate useful information is reported and the full text publication is unavailable. Comparative cohort or observational studies (only if RCTs unavailable or limited data to inform decision making)
Search strategy	Sources to be searched: Medline, Medline In-Process, CENTRAL, CDSR, DARE, HTA, Embase, Web of Science Date limit: 1990 (important studies on relevant nutritional therapies published in 1990) Supplementary search techniques: Snowballing techniques will be used to ensure a thorough representation of the published literature this will involve exploration of reference lists from key narrative and systematic reviews where appropriate or necessary.
Review strategy	Appraisal of methodological quality: The methodological quality of each study will be assessed using an appropriate checklist: ROBIS for systematic reviews Cochrane risk of bias tool for RCTs Cochrane risk of bias tool for non-randomised studies The quality of the evidence for an outcome (i.e. across studies) will be assessed using GRADE. Synthesis of data: Meta-analysis will be conducted where appropriate. Minimum important differences Default values will be used of: 0.80 and 1.25 for dichotomous outcomes; 0.5 times SD for continuous outcomes, unless more appropriate values are identified by the guideline committee or in the literature. Double sifting, data extraction and methodological quality assessment Sifting, data extraction and appraisal of methodological quality and GRADE assessment will be performed by the systematic reviewer. Quality control will be performed by the senior systematic reviewer. Dual sifting will be performed on at least 10% of records and where possible all records. Dual quality assessment and data extraction will be performed when capacity allows.
Equalities	No equalities issues identified for this question.
Key papers	

D.19 Palliative care

What is the effectiveness of nutritional interventions in adults with oesophago-gastric cancer receiving palliative care?

Item	Details
Area in the scope	Management of oesophago-gastric cancer
Review question for the guideline	What is the effectiveness of nutritional interventions in adults with oesophago-gastric cancer receiving palliative care?
Objective(1, 2)	Advanced oesophago-gastric cancer is complicated by a higher incidence of symptoms and morbidity. The side effects of chemotherapy can increase the symptom burden. This and altered metabolism associated with systemic inflammation induced by the tumour, can contribute to weight loss and malnutrition. The aims of nutritional intervention in patients being treated with palliative intent are to minimise deterioration in weight and nutritional status in order to preserve quality of life and to reduce the risk of disease (and treatment) related morbidity associated with poor nutrition. Nutrition is often a cause of emotional distress to patients and carers and therefore supportive advice around these issues and expectations, is an important consideration. As is the case with palliative care interventions, any nutritional intervention needs to be considered in the context of patient's wishes, relative's wishes and the patient's quality of life. This review aims to evaluate which nutritional interventions improve outcomes for adults with oesophago-gastric cancer who are being managed with palliative intent. Since nutritional support needs vary according to oesophago-gastric tumour location as well as symptoms experienced, we aim to investigate the patient groups most likely to benefit from nutritional interventions.
Population and directness	Adults with oesophago-gastric cancer receiving palliative care.

Intervention	• Oral nutrition support
	  ○ Oral nutrition supplements
	  ○ Dietary counselling
	  ○ Dietary advice
	  ○ Food fortification
	• Enteral Feeding
	  ○ Gastrostomy
	  ○ Jejunostomy feeding
	  ○ Nasojejunal feeding
	  ○ Nasogastric feeding
	• Parenteral nutrition/ IV nutrition
	• Clinically assisted hydration

Comparison	• No nutritional intervention • Any combination of the above. • Each other
Outcomes	• Treatment-related morbidity. • Treatment-related mortality. • Health-related quality of life.

Item	Details
	• Patient-reported outcome measures. • Weight changes • Nutritional status (as mentioned before, a number of assessment tools could be used)
Importance of outcomes	Preliminary classification of the outcomes for decision making: • critical (up to 3 outcomes) • Treatment-related morbidity. • Health-related quality of life. • Patient-reported outcome measures. • important but not critical (up to 3 outcomes) • Treatment-related mortality. • Weight changes • Nutritional status (as mentioned before, a number of assessment tools could be used) • of limited importance (1 outcome) •
Setting	Adults (aged 18 years and older) with oesophago-gastric cancer treated with palliative intent.
Stratified, subgroup and adjusted analyses	n/a
Language	English
Study design	Systematic reviews of RCTs RCTs Cohort studies (only if RCTs unavailable or limited data to inform decision making)
Search strategy	Sources to be searched: Limits (e.g. date, study design): 1990 (important studies on relevant nutritional therapies published in 1990) Only published full text papers Supplementary search techniques: No supplementary search techniques were used.
Review strategy	**Appraisal of methodological quality:** The methodological quality of each study will be assessed using an appropriate checklist: • ROBIS for systematic reviews • Cochrane risk of bias tool for RCTs • Cochrane risk of bias tool for non-randomised studies The quality of the evidence for an outcome (i.e. across studies) will be assessed using GRADE. **Synthesis of data:** Meta-analysis will be conducted where appropriate. **Minimum important differences** Default values will be used of: 0.80 and 1.25 for dichotomous outcomes; 0.5 times SD for continuous outcomes, unless more appropriate values are identified by the guideline committee or in the literature. **Double sifting, data extraction and methodological quality assessment** Sifting, data extraction, appraisal of methodological quality and GRADE assessment will be performed by the systematic reviewer. Quality control will be

Item	Details
	performed by the senior systematic reviewer. Dual sifting will be performed on at least 10% of records and where possible all records. Dual quality assessment and data extraction will be performed when capacity allows.
Equalities	No equalities issues identified for this question.
Notes/additional information	Include those for palliative chemotherapy and palliative chemoradiotherapy. No need to conduct subgroup analyses.
Key papers	1. Stojcev Z, Matysiak K, Duszewski M, Banasiewicz T. The role of dietary nutrition in stomach cancer. Contemporary oncology. 2013;17(4):343-5. 2. Gullett NP, Mazurak VC, Hebbar G, Ziegler TR. Nutritional interventions for cancer-induced cachexia. Current problems in cancer. 2011;35(2):58-90. Additional resources: Nutritional cancer care for health professionals. National Cancer Institute: http://www.cancer.gov/about-cancer/treatment/side-effects/appetite-loss/nutrition-hp-pdq/#link/_50 Andreyev, H.J.N., Norman, A.R., Oates, J., et al. (1998) Why do Patients with Weight Loss have a Worse Outcome when Undergoing Chemotherapy for Gastrointestinal Malignancies? *European Journal of Cancer*, 34 (4), 503-509. Arends, J., Bodoky, G., Bozzetti, F., et al. (2006) ESPEN Guidelines on Enteral Nutrition: Non-surgical oncology. *Clinical Nutrition*. 25 (2), 245–259. Cappell, M.S. (2007) Risk factors and risk reduction of malignant seeding of the percutaneous endoscopic gastrostomy track from pharynoesophageal malignancy: a review of all 44 known case reports. *American Journal of Gastroenterology*. 102 (6), 1307-1311 Shaw, J., Harrison, J., Young, J. et al. (2013) Coping with newly diagnosed upper gastrointestinal cancer: a longitudinal qualitative study of family caregivers' role perception and supportive care needs. Support Care Cancer (2013) 21:749–756 Siddiqui, A.A., Loren, D., Dudnick, R., et al. (2007) Expandable polyester silicon-covered stent for malignant esophageal strictures before neoadjuvant chemoradiation: A pilot study. *Digestive Diseases and Sciences*, 52 (3), 823–829.

D.20 Routine follow-up

In adults who have undergone treatment for oesophago-gastric cancer with curative intent, with no symptoms or evidence of residual disease, what is the optimal method(s), frequency, and duration of routine follow-up for the detection of concurrent disease?

Item	Details
Area in the scope	Follow-up of people with oesophago-gastric cancer
Review question in the scope	What is the most effective follow-up protocol for people with oesophago-gastric cancer?
Review question for guideline	In adults who have undergone treatment for oesophago-gastric cancer with curative intent, with no symptoms or evidence of residual disease, what is the optimal method(s), frequency, and duration of routine follow-up for the detection of recurrent disease?
Objective	There is no consensus on the protocol for follow-up of oesophago-gastric cancer and importantly whether follow-up improves survival and quality of life (1-3).

Item	Details
	The complexity of oesophago-gastric cancer and its treatment often cause symptoms which can adversely affect quality of life. Regular review of patients following assessment and management aims to: Identify and manage disease recurrence Identify and manage treatment-related symptoms Provide supportive care for adults and their carers Facilitate surveillance of management outcome. Regular review may detect recurrence, however, endoscopy, cross-sectional imaging and tumour markers that have been evaluated have imperfect sensitivity and specificity. The evidence for the benefit such investigations have on long-term prognosis and morbidity is unknown. Patients may gain psychological support from regular follow-up but some authors highlight the anxiety caused by planned hospital visits and few studies have formally evaluated this. Regular access to and support from cancer nurse specialists/ dietician or other professional or patient-led self-referral are promising alternatives for follow-up. This review aims to identify the most clinically effective follow-up options for adults who have completed treatment for oesophago-gastric cancer with curative intent and to identify a protocol for following these patients up and the length of follow-up necessary.
Population	Adults who have undergone treatment for oesophago-gastric cancer with curative intent with no symptoms or evidence of residual disease
Index test: Severity assessment tools/clinical markers	History, examination and routine blood tests (type, setting, duration, frequency) Radiological imaging PET-CT CT Endoscopic surveillance Tumour markers Carcinoembryonic antigen (CEA) Carbohydrate antigen 19-9(CA19-9) No active surveillance tests (symptom based)
Reference standard or target condition/patient outcomes	Clinician (surgeon and/or oncologist) or nurse or other professional-led follow-up
Subgroups and sensitivity analyses	The following groups will be assessed separately: Endoscopic resection Surgery Chemoradiotherapy
Outcomes	We aim to extract data on the following outcomes from test and treat studies. If test and treat studies are not available, we aim to extract the following outcomes from each study type. Outcomes to be extracted from diagnostic accuracy studies: Test accuracy according to distant, regional or local recurrence: sensitivity specificity positive predictive value negative predictive values positive likelihood ratios negative likelihood ratios Patient anxiety

Item	Details
	Outcomes to be extracted from prognostic review studies Stage of disease at recurrence Overall survival progression free survival Disease-specific survival Process related complications Additional tests consequential to results of the follow up programme. Health-related quality of life Symptom control
Importance of outcomes	Critical outcomes: Stage of disease at recurrence Overall survival progression free survival Important but not critical outcomes Additional tests consequential to results of the follow up programme. Test accuracy according to distant, regional or local recurrence: sensitivity specificity positive predictive value negative predictive values positive likelihood ratios negative likelihood ratios Patient anxiety Of limited importance Health-related quality of life
Study design	Test and treat studies If test and treat studies not available we will aim to use both diagnostic accuracy and prognostic studies. Studies of diagnostic accuracy: • systematic reviews • Cross sectional diagnostic accuracy studies Studies of prognostic factors • Systematic reviews • Prognostic cohort studies
Setting	Settings in which people with oesophago-gastric cancer undergo follow-up for the detection of recurrent disease.
Search strategy	Sources to be searched: Medline, Medline In-Process, CENTRAL, CDSR, DARE, HTA, Embase, Web of Science, Cinahl Date limit:1990 Rationale for date limit: Important studies on relevant prospective trials on chemoradiotherapy published since 1990. Supplementary search techniques: Snowballing techniques will be used to ensure a thorough representation of the published literature this will involve exploration of reference lists from key narrative and systematic reviews where appropriate or necessary.
Review strategy	Appraisal of methodological quality: The methodological quality of each study will be assessed using an appropriate checklist: ROBIS for systematic reviews

Item	Details
	QUADAS-2 for the quality assessment of diagnostic accuracy studies NICE guidelines manual methodology checklist for prognostic studies Synthesis of data: Meta-analysis will be conducted where appropriate. Minimum important differences Prognostic reviews Default values will be used of: 0.80 and 1.25 for dichotomous outcomes; 0.5 times SD for continuous outcomes, unless more appropriate values are identified by the guideline committee or in the literature. Diagnostic accuracy Unless more appropriate values are identified in the literature the guideline committee will decide minimally important differences in test accuracy using their experience and the likely consequences of correct and incorrect test results for the patient. Double sifting, data extraction and methodological quality assessment Sifting, data extraction and appraisal of methodological quality and GRADE assessment will be performed by the systematic reviewer. Quality control will be performed by the senior systematic reviewer. Dual sifting will be performed on at least 10% of records and where possible all records. Dual quality assessment and data extraction will be performed when capacity allows.
Equalities	No equalities issues identified for this question.
Notes/additional information	Patterns of recurrence in early-stage oesophageal cancer after chemoradiotherapy and surgery compared with surgery alone. Sometimes we find no comparative studies of follow up protocols. One option in this case is to summarise the risk of recurrence following various treatment in the various TNM subgroups using studies like: Robb WB et al. Br J Surg. 2016 Jan;103(1):117-25. http://www.bjs.co.uk/details/article/8684711/Patterns-of-recurrence-in-earlystage-oesophageal-cancer-after-chemoradiotherapy-.html
Key Papers	1. Whiting J, Sano T, Saka M, Fukagawa T, Katai H, Sasako M. Follow-up of gastric cancer: a review. Gastric cancer : official journal of the International Gastric Cancer Association and the Japanese Gastric Cancer Association. 2006;9(2):74-81. 2. Okines A, Verheij M, Allum W, Cunningham D, Cervantes A, Group EGW. Gastric cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Annals of oncology : official journal of the European Society for Medical Oncology / ESMO. 2010;21 Suppl 5:v50-4. 3. Allum WH, Blazeby JM, Griffin SM, Cunningham D, Jankowski JA, Wong R, et al. Guidelines for the management of oesophageal and gastric cancer. Gut. 2011;60(11):1449-72. 1. Armes J et al. Patients' Supportive Care Needs Beyond the End of Cancer Treatment: A Prospective, Longitudinal Survey. Journal of Clinical Oncology. 2009. Vol 27; No 36. 2. Lewis R et al, Nurse-led Vs Conventional physician-led follow up for patients with cancer: systematic review. Journal of Advanced Nursing. 2009. Vol 65; 706-723 3. Improving Outcomes: A Strategy for Cancer. 2011. Department of Health. 4. Hodkinson K et al. Breast cancer survivors supportive care needs 2–10 years after diagnosis. Supportive Care Cancer. 2007. 15: 515–523. 6. Moore et al. Nurse led follow up and conventional follow up in management of patients with lung cancer: randomized trial. BMJ. 2002 7. Foster, C. & Fenlon, D. Recovery and self-management support following primary cancer treatment. Br. J. Cancer 105 (Suppl. 1), S21–28 (2011). 9. Davies, N. J. & Batehup, L. Towards a personalised approach to aftercare: a review of cancer follow-up in the UK. J. Cancer Surviv. 5, 142–151 (2011).

Item	Details
	10. Khan NF, Evans J, Rose PW (2011b) A qualitative study of unmet needs and interactions with primary care among cancer survivors. Br J Cancer 105(Suppl 1): S46–S51 11. Richardson A, Addington-Hall J, Amir Z, Foster C, Stark D, Armes J, Brearley SG, Hodges L, Hook J, Jarret N, Stamataki Z, Scott I, Walker J, Ziegler L, Sharpe M (2011) Knowledge, ignorance and priorities for research in key areas of cancer survivorship: findings from a scoping review. Br J Cancer 105(Suppl 1): S82–S94 12. Tritter JQ, Calnan M (2002) Cancer as a chronic illness? Recondsidering categorization and exploring experience. Eur J Cancer Care 11(3): 161–165 13. Burkett, V.S. and C.S. Cleeland, Symptom burden in cancer survivorship. J Cancer Surviv, 2007. 1(2): p. 167-75. 14. Djarv T, Lagergren J, Blazeby J, Lagergren P. (2008) Long term health related quality of life following surgery for oesophageal cancer. Bristish Journal of Surgery. 95 (9) 1121-1126 15. Andreyev J, Davidson S, Gillespie C, Allum W, Swarbrick E (2011). Practice guidance on the management of acute and chronic gastrointestinal problems arising as a result of treatment for cancer. Gut doi10.1136/gutjnl-2011-300563