National Institute for Health and Care Excellence

V1.0 Pre-consultation

Oesophago-gastric cancer

Assessment and management in adults

NICE Guideline

Methods, evidence and recommendations

15 June 2017

Draft for Consultation

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

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

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

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Contents

1 Introduction

1.1 Foreword

Oesophago-gastric cancer presents patients, carers and healthcare professionals alike with a range of difficult management decisions. Those affected by the disease often undergo a complex investigative pathway as a prelude to a variety of treatments with wide ranging short- and long-term effects that require continued support throughout the initial period of care and beyond. We hope that this document will provide helpful and appropriate guidance to both patients and professionals alike on the diagnosis and subsequent management of early and locally advanced oesophago-gastric cancers.

It has been impossible to cover every aspect of the patient pathway but instead as a group we have concentrated on those areas where it was felt uncertainty or variation in practice currently exists. As such the guideline is not intended as an exhaustive textbook on the management of oesophago-gastric cancer. The guideline sets out recommendations that will hopefully be helpful and informative in decision-making and management of a variety of situations but cannot be a substitute for clinical judgement in a specific case. We were aided and supported in our goal by a diverse and engaged Guideline Committee and are grateful for all the hard work, commitment and common sense demonstrated by them throughout the two-year process. Their complementary skills and perspectives have inspired this guideline. We would also like to thank the staff at the National Guideline Alliance for their considerable support during the development of this guideline.

Cyrus Kerawala, Chair, Guideline Committee

Mark Harrison, Topic Expert, Guideline Committee

1.2 Epidemiology and current management

This guideline focuses on the assessment and management of oesophago-gastric cancer in adults. This includes oesophageal cancer, gastric cancer, and cancer occurring at the oesophageal-gastric junction.

Oesophageal cancer is the 13th most common cancer in the UK. In 2011, 8,300 people were diagnosed with the disease. The prevalence of the disease varies significantly around the world, and is more common in men than women. There are two common histological subtypes: squamous cell carcinoma and adenocarcinoma.

Most oesophageal cancers are linked to lifestyle and other risk factors, mainly tobacco smoking, obesity and alcohol. Oesophageal cancer rates have increased by 56% in men and 14% in women since the mid-1970s. Oesophageal cancer is the 6th most common cause of cancer deaths in the UK, accounting for about 5% of all cancer deaths. In 2012, 7700 people died of oesophageal cancer in the UK, and there were twice as many men than women. Almost half of those who died of oesophageal cancer were aged over 75. The UK mortality rate is the highest in Europe for both men and women.

Gastric cancer is the 11th most common cancer in men and the 15th most common cancer in women in the UK, with 7,100 people diagnosed with the disease in 2011. The incidence has halved in the UK since the late 1980s. It is the 10th most common cause of cancer death in the UK, with 4800 deaths in 2012. Approximately a third of gastric cancers are linked to *H. pylori* infection, an avoidable risk factor.

Survival rates for both oesophageal and gastric cancers are improving and have tripled in the UK in the last 40 years. But survival remains poor, with only 3 in 20 (15%) of people diagnosed with oesophageal cancer and around a fifth (19%) of people diagnosed with

stomach cancer in 2010-11 in England and Wales expected to survive their disease for 5 years or more.

Over the past few years there has been a rapid increase in incidence of tumours at the junction of the oesophagus and stomach. These are called ‘junctional’ tumours. These tend to come from changes in the lining of the oesophagus in turn leading to adenocarcinoma of the lowest part of the oesophagus, which goes across the gastro-oeosphageal junction. Tumours of the middle of the oesophagus have decreased in incidence over the past few years.

Current UK practice for managing oesophago-gastric cancers follows a relatively straightforward pathway after diagnosis. When appropriate, people with oesophago-gastric cancer have their disease staged and discussed within an oeosphago-gastric multidisciplinary team (MDT). For those people whose disease is thought suitable for treatment with curative intent, further staging investigations and fitness assessments are made, usually within the context of a specialist MDT, and radical surgery is conducted within a specialist surgical unit.

However, for many people, curative surgery or chemoradiotherapy is not possible and appropriate palliative care is needed. This may include palliative radiotherapy or chemotherapy, inserting an oesophageal stent or simply appropriate supportive care.

As such, managing people's disease may be complex and needs collaboration and discussion between the person, their family and the medical teams involved.

2 Guideline Summary

2.1 Committee membership and National Guideline Alliance (NGA) staff

Table 1: Guideline Committee

Name	Job Title, Organisation
Chair	
Mr Cyrus Kerawala	Consultant Head & Neck Surgeon, The Royal Marsden NHS Foundation Trust
Topic expert	
Mr Mark Harrison	Consultant Oncologist, Mount Vernon Cancer Centre
Members	
Mr David Exon	Consultant Upper GI Surgeon, University Hospital of Leicester NHS Trust
Mr Nick Maynard	Consultant Upper GI Surgeon, Oxford University Hospitals NHS Foundation Trust
Dr Hugh Burnett	Consultant Radiologist, Christie Hospital, Manchester
Ms Venetia Wynter-Blyth	UGI Clinical Nurse Specialist, Imperial College NHS Trust
Miss Orla Hynes	Prinicipal Dietitian, Guy's & St Thomas' NHS Foundation Trust
Dr Robert Willert	Consultant Gastroenterologist, Manchester Royal Infirmary (Central Manchester University Hospitals NHS Foundation Trust)
Dr Andrew Bateman	Consultant Clinical Oncologist, Honorary Senior Lecturer Cancer Care, University Hospital Southampton NHS Foundation Trust
Dr Naureen Starling	Consultant Medical Oncologist in GI Cancers & Associate Director of Clinical Research, The Royal Marsden
Dr David Brooks	Macmillan Consultant in Palliative Medicine at the Chesterfield and North Derbyshire Hospital NHS Trust
Mr David Simpson	Patient/Carer Member
Mrs Mimi McCord	Patient/Carer Member

Table 2: NGA staff

Name	Role
John Graham	Clinical Adviser
Matthew Prettyjohns	Guideline Lead (until Jan 2017)
Hilary Eadon	Guideline Lead (from Feb 2017))
Lianne Gwillim	Project Manager (until September 2016)
Katrina Blears	Project Manager (until February 2017)
Victoria Titshall	Project Manager (until May 2017)
Nathan Broman	Senior Systematic Reviewer
Natasha Pillai	Systematic Reviewer (until October 2016)
Abigail Moore	Systematic Reviewer (until February 2017)
Amy Burt	Systematic Reviewer (until March 2017)
May Oo Khin	Systematic Reviewer
Matthew Prettyjohns	Senior Health Economist

Name	Role
Sabine Berendse	Information Scientist

2.2 Recommendations

1. Provide information about planned surgery, radiotherapy or chemotherapy in all discussions with people with oesophago-gastric cancer who are going to have radical treatment. Make sure the information is consistent and covers:
    - treatment outcomes (prognosis and future treatments)
    - recovery, including the consequences of treatment and how to manage them
    - nutrition and lifestyle changes.

   Follow the recommendations in NICE's guideline on patient experience in adult NHS services.
2. Make sure the person has information to take away and review in their own time after you have spoken to them about their cancer and care.
3. Consider access to an oesophago-gastric clinical nurse specialist and a specialist oesophago-gastric cancer dietitian (through the person's multidisciplinary team).
4. Inform people about peer-to-peer local or national support groups for them to join if they wish.
5. Provide psychosocial support to the person with oesophago-gastric cancer and those important to them (as appropriate). Inform them where they can get further support. Include psychosocial support relating to:
    - potential impact on family life, changing roles and relationships
    - uncertainty about the disease course and prognosis
    - concerns over heredity of cancer, recovery and recurrence.
6. For people with oesophago-gastric cancer who can only have palliative management, offer personalised information and support to them and the people who are important to them (as appropriate), at a pace that is suitable for them. Include information on:
    - life expectancy
    - the treatment and care available, and how to access this both now and for future symptoms
    - holistic issues (such as physical, emotional, social, financial and spiritual issues), and how they can get support and help
    - dietary changes, and how to manage these and access specialist dietetic support
    - which sources of information in the public domain give good advice about the issues listed above.

   Follow the recommendations in NICE's guideline on patient experience in adult NHS services.
7. Make sure the person has information to take away and review in their own time after you have spoken to them about their cancer and care. Consider providing support from:

- a specialist cancer care dietitian
- a specialist palliative care team
- a peer support group, if available.

8. Follow the recommendations in the NICE guideline on improving supportive and palliative care for adults with cancer
9. Review the treatment of people with confirmed oesophago-gastric cancer in a multidisciplinary meeting that includes an oncologist and specialist radiologist with an interest in oesophago-gastric cancer.
10. Review the treatment of people with confirmed localised, non-metastatic oesophago-gastric cancer in a specialist oesophago-gastric cancer multidisciplinary meeting.
11. Ensure curative oesophago-gastric resections are performed in a specialist surgical unit by specialist oesophago-gastric surgeons.
12. Offer PET-CT to people with oesophageal and gastro-oesophageal junctional tumours that are suitable for radical treatment (except for T1a tumours).
13. Do not offer endoscopic ultrasound only to distinguish between T2–T3 tumours in people with oesophageal and gastro-oesophageal junctional tumours.
14. Offer endoscopic ultrasound only when it will help guide ongoing management.
15. Consider staging laparoscopy only when it will help guide ongoing management.
16. Offer staging laparoscopy to all people with potentially curable gastric cancer.
17. Consider endoscopic ultrasound only if it will help guide ongoing management.
18. Consider PET-CT only if metastatic disease is suspected and it will help guide ongoing management.
19. Offer HER2 testing to people with metastatic oesophago-gastric adenocarcinoma (see the NICE technology appraisal guidance on trastuzumab for HER2-positive metastatic gastric cancer).
20. Offer endoscopic mucosal resection for staging for people with suspected T1 oesophageal cancer.
21. Offer endoscopic eradication of remaining Barrett's mucosa for people with T1aN0 oesophageal cancer.
22. Offer radical resection for people with T1bN0 oesophageal adenocarcinoma if they are fit enough to have surgery.
23. Offer people with T1bN0 squamous cell carcinoma of the oesophagus the choice of:
    - definitive chemoradiotherapy or
    - surgical resection.

    Make the choice after discussing the benefits, risks and treatment consequences of each option with the person and those who are important to them (as appropriate).
24. Consider an open or hybrid oesophagectomy for surgical treatment of oesophageal cancer.

25. When performing a curative gastrectomy for people with gastric cancer, consider a D2 lymph node dissection.
26. When performing a curative oesophagectomy for people with oesophageal cancer, consider two-field lymph node dissection.
27. For people with localised oesophageal and gastro-oesophageal junctional adenocarcinoma (excluding T1N0 tumours) who are going to have surgical resection, offer a choice of:
    - chemotherapy, before or before and after surgery or
    - chemoradiotherapy, before surgery.

    Make the choice after discussing the benefits, risks and treatment consequences of each option with the person and those important to them (as appropriate).
28. Offer chemotherapy before and after surgery to people with gastric cancer who are having radical surgical resection.
29. Consider chemotherapy or chemoradiotherapy after surgery for people with gastric cancer who did not have chemotherapy before surgery with curative intent.
30. Offer people with resectable non-metastatic squamous cell carcinoma of the oesophagus the choice of:
    - radical chemoradiotherapy **or**
    - chemoradiotherapy before surgical resection.

    Discuss the benefits, risks and treatment consequences of each option with the person and those who are important to them (as appropriate).
31. Consider chemoradiotherapy for people with non-metastatic oesophageal cancer that can be encompassed within a radiotherapy field.
32. When the cancer cannot be encompassed within a high-dose radiotherapy field, consider one or more of:
    - chemotherapy
    - local tumour treatment, including stenting or palliative radiotherapy
    - best supportive care.

    Discuss the benefits, risks and treatment consequences of each option with the person and those who are important to them (as appropriate).
33. After treatment, assess the tumour's response to chemotherapy or chemoradiotherapy and reconsider if surgery is an option.
34. Offer trastuzumab (in combination with cisplatin[1] and capecitabine or 5-fluorouracil) as a treatment option to people with HER2-positive metastatic adenocarcinoma of the stomach or gastro-oesophageal junction (also see the NICE technology appraisal guidance on trastuzumab for the treatment of HER2-positive metastatic gastric cancer).
35. Offer first-line palliative combination chemotherapy to people with advanced oesophago-gastric cancer who have a performance status 0 to 2 and no significant comorbidities. Possible drug combinations include:
    - doublet treatment: 5-fluorouracil or capecitabine[2] in combination with cisplatin[1] or oxaliplatin[3]

- triplet treatment: 5-fluorouracil or capecitabine in combination with cisplatin or oxaliplatin plus epirubicin[4].

Discuss the benefits, risks and treatment consequences of each option with the person and those important to them (as appropriate).

36. Consider second-line palliative chemotherapy for people with oesophago-gastric cancer.
37. Discuss the risks, benefits and treatment consequences of second-line palliative chemotherapy for oesophago-gastric cancer with the person and those who are important to them (as appropriate). Cover:
    - how different treatments can have similar effectiveness but different side effects
    - how the treatments are given
    - if the person has any preference for one treatment over another.
38. Consider a clinical trial (if a suitable one is available) as an alternative to second-line chemotherapy.
39. Offer self-expanding stents to people who need immediate relief of dysphagia.
40. Offer self-expanding stents or radiotherapy as primary treatment, depending on the degree of dysphagia and its impact on nutrition and quality of life, performance status and prognosis.
41. Consider external beam radiotherapy after stenting, for long-term disease control.
42. Offer uncovered self-expanding metal stents or palliative surgery, depending on fitness to undergo surgery, prognosis and extent of disease.
43. Consider nutritional assessment and tailored support from a specialist oesophago-gastric dietitian to people with oesophago-gastric cancer before, during and after radical treatments.
44. Offer immediate enteral or parenteral nutrition after surgery to people who are having radical surgery for oesophageal and oesophago-gastric junction cancers.
45. Follow the recommendations in the NICE guideline on nutrition support for adults
46. Consider support from a specialist cancer-specific dietitian for people with oesophago-gastric cancer receiving palliative care.
47. Together with members of the multidisciplinary team and the hospital and community palliative care teams, tailor dietetic support to the person with oesophago-gastric cancer and their clinical situation.
48. Follow the recommendations in the NICE guidelines on improving supportive and palliative care for adults with cancer.
49. For people who have no symptoms or evidence of residual disease after treatment for oesophago-gastric cancer with curative intent:
    - provide information about the symptoms of recurrent disease, and what to do if they develop these symptoms
    - offer rapid access to the oesophago-gastric multidisciplinary team for review, if symptoms develop.

50. For people who have no symptoms or evidence of residual disease after treatment for oesophago-gastric cancer with curative intent, do not offer:
    - routine clinical follow-up solely for the detection of recurrent disease
    - routine radiological surveillance solely for the detection of recurrent disease.

[1]Although this use is common in UK clinical practice, at the time of publication ([month year]), cisplatin did not have a UK marketing authorisation for oesophageal or gastric cancer. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.
[2]Although this use is common in UK clinical practice, at the time of publication ([month year]), capecitabine did not have a UK marketing authorisation for oesophageal cancer. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.
[3]Although this use is common in UK clinical practice, at the time of publication ([month year]), oxaliplatin did not have a UK marketing authorisation for oesophageal or gastric cancer. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.
[4]Although this use is common in UK clinical practice, at the time of publication ([month year]), epirubicin did not have a UK marketing authorisation for oesophageal cancer. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information

2.3 Research Recommendations

1. What are the specific information and support needs before, during and after treatment for adults with oesophago-gastric cancer who are suitable for radical treatment, and their carers?
2. What is the optimal treatment for T1bN0 adenocarcinoma of the oesophagus?
3. What is the role of intraperitoneal chemotherapy following surgical resection for gastric cancer?
4. Does the addition of surgery to chemoradiotherapy improve disease-free and overall survival in people with squamous cell carcinoma of the oesophagus?
5. What is the optimal combination and sequence of chemotherapy and radiotherapy, and selection criteria, for patients with non-metastatic oesophageal cancer who are not suitable for surgery?
6. Can palliative treatment for oesophago-gastric cancer be defined along a molecular strategy such as HER2?
7. What is the optimal method of delivering nutritional support to adults after surgery with curative intent for oesophago-gastric cancer?
8. What is the effectiveness of long-term jejunostomy support compared to intensive dietary counselling and support along with symptom management for people having radical surgery for oesophago-gastric cancer?
9. What is the benefit of artificial nutritional support in people undergoing gastrectomy?

10. What is the role of prophylactic gastrostomy placement in people undergoing radical chemoradiotherapy for oesophageal cancer?
11. What is the effectiveness of nutritional interventions in adults with oesophago-gastric cancer being treated palliatively?
12. Is the routine use of CT and tumour markers effective in detecting recurrent disease suitable for radical treatment in asymptomatic people who have had treatment for oesophago-gastric cancer with curative intent?

2.4 Other versions of this guideline

NICE produce a number of versions of this guideline:

- The 'short guideline' lists the recommendations, context and recommendations for research
- NICE Pathways brings together all connected NICE guidance.

2.5 Schedule for updating this guideline

Following publication, NICE will undertake a reviews at specified times to determine whether the evidence base has progressed significantly to alter the guideline recommendations and warrant an update. The review for update process is presented and in accordance with the NICE guidelines manual 2014.

3 Development of the guideline

3.1 What is a NICE guideline?

National Institute for Health and Care Excellence (NICE) guidelines are recommendations for the care of individuals in specific clinical conditions or circumstances within the NHS – from prevention and self-care through primary and secondary care to more specialised services. We base our clinical guidelines on the best available research evidence, with the aim of improving the quality of healthcare. We use predetermined and systematic methods to identify and evaluate the evidence relating to specific review questions.

NICE clinical guidelines can:

- provide recommendations for the treatment and care of people by healthcare professionals
- be used to develop standards to assess the clinical practice of individual healthcare professionals
- be used in the education and training of healthcare professionals
- help patients to make informed decisions
- improve communication between patients and healthcare professionals.

While guidelines assist the practice of healthcare professionals, they do not replace their knowledge and skills.

We produce our guidelines using the following steps:

- the guideline topic is referred to NICE from the Department of Health
- Stakeholders register an interest in the guideline and are consulted throughout the development process
- the scope is prepared by the National Guideline Alliance (NGA)
- the NGA establishes a Guideline Committee
- a draft guideline is produced after the group assesses the available evidence and makes recommendations
- there is a consultation on the draft guideline
- the final guideline is produced.

The NGA and NICE produce a number of versions of this guideline:

- the ‘full guideline’ and its appendices contain all the recommendations, together with details of the methods used and the underpinning evidence
- the ‘short version’ lists the recommendations, context and recommendations for research
- NICE Pathways brings together all connected NICE guidance.

3.2 Remit

NICE received the remit for this guideline from the Department of Health. It commissioned the NGA to produce the guideline.

The remit for this guideline is to develop a clinical guideline on the assessment and management of oesophago-gastric cancer in adults.

The scope for this guideline is provided in Appendix A. Stakeholders were consulted on a draft of the scope (for a list of stakeholders see Appendix B).

3.3 Who developed this guideline?

A multidisciplinary Guideline Committee (hereafter referred to as 'the Committee') comprising healthcare professionals and lay members developed this guideline.

NICE funds the NGA and thus supported the development of this guideline. The Committee was convened by the NGA and chaired by Mr Cyrus Kerawala in accordance with guidance from NICE.

The group met every 4 to 6 weeks during the development of the guideline. At the start of the guideline development process all group members declared interests including consultancies, fee-paid work, shareholdings, fellowships and support from the healthcare industry. At all subsequent group meetings, members declared arising interests.

Members were either required to withdraw completely or for part of the discussion if their declared interest necessitated it appropriate to do so. The details of declared interests and the actions taken are shown in Appendix C.

Staff from the NGA provided methodological support and guidance for the development process. The team working on the guideline included a guideline lead, a project manager, systematic reviewers, health economists, and information scientists. They undertook systematic searches of the literature, appraised the evidence, conducted meta-analysis and cost-effectiveness analysis where appropriate and drafted the guideline in collaboration with the group.

3.4 What this guideline covers

3.4.1 Groups covered by this guideline

This guideline covers the following groups:

- Adults (18 years and over) with newly-diagnosed or recurrent oesophago-gastric cancer.

3.4.2 Key clinical issues covered by this guideline

The following clinical issues are covered in this guideline:

- Information and support needs specific to people with oesophago-gastric cancer and their carers
- Organisation of specialist teams
- Assessment of oesophago-gastric cancer
- Staging before curative treatment
- HER-2 (human epidermal growth factor receptor 2) testing
- Management of oesophago-gastric cancer
- Curative treatment
- Palliative treatment
- Nutritional support
- Follow-up of people with oesophago-gastric cancer.

Note that guideline recommendations relating to pharmacologic treatment normally fall within licensed indications; exceptionally, and only if clearly supported by evidence, use outside a licensed indication is recommended. The guideline assumes that prescribers will use a medicine's summary of product characteristics to inform decisions made with individual patients.

3.5 What this guideline does not cover

3.5.1 Groups not covered by this guideline

This guideline does not cover:

- Adults (18 years and over) in primary care with suspected oesophago-gastric cancer
- Adults (18 years and over) referred to secondary care with suspected oesophago-gastric cancer
- People with gastrointestinal stromal tumours (GIST), neuroendocrine tumours, sarcoma, melanoma or lymphomas in the oesophagus or stomach
- People with familial gastric cancer.

3.5.2 Clinical issues not covered by this guideline

This guideline does not cover:

- Identification in primary care of people with suspected oesophago-gastric cancer and their referral to secondary care
- Initial diagnosis of oesophago-gastric cancer
- Management of Barrett's oesophagus.

3.6 Relationship between the guideline and other NICE guidance

3.6.1 Related NICE guidance

- Capecitabine for the treatment of advanced gastric cancer (2010) NICE technology appraisal guidance 191
- Endoscopic submucosal dissection of oesophageal dysplasia and neoplasia (2010) NICE interventional procedure guidance 355
- Endoscopic submucosal dissection of gastric lesions (2010) NICE interventional procedure guidance 360
- Fluorouracil chemotherapy: the My5-FU assay for guiding dose adjustment (2014) NICE diagnostics guidance 16
- Laparo-endogastric surgery (2003) NICE interventional procedure guidance 25
- Laparoscopic gastrectomy for cancer (2008) NICE interventional procedure guidance 269
- Minimally invasive oesophagectomy (2011) NICE interventional procedure guidance 407
- Palliative photodynamic therapy for advanced oesophageal cancer (2007) NICE interventional procedure guidance 206
- Photodynamic therapy for early oesophageal cancer (2006) NICE interventional procedure guidance 200
- Ramucirumab for treating advanced gastric cancer or gastro-oesophageal junction adenocarcinoma after chemotherapy.(2016) NICE technology appraisal guidance 378
- Trastuzumab for the treatment of HER2-positive metastatic gastric cancer (2010) NICE technology appraisal guidance 208.

4 Guideline development methodology

This chapter sets out in detail the methods used to review the evidence and to generate the recommendations that are presented in subsequent chapters. This guidance was developed in accordance with the methods outlined in the NICE guidelines manual 2014.

4.1 Developing the review questions and protocols

The 20 review questions developed for this guideline were based on the key areas identified in the guideline scope. They were drafted by the NGA and refined and validated by the Committee.

The review questions were based on the following frameworks:

- intervention reviews – using a population, intervention, comparison and outcome (PICO) framework
- reviews of diagnostic test accuracy – using population, diagnostic test (index tests), reference standard and target condition
- qualitative reviews – using population, area of interest and themes of interest
- prognostic reviews – using population, presence or absence of a risk factor, and outcome.

Full literature searches, critical appraisals and evidence reviews were completed for all review questions.

4.2 Searching for evidence

4.2.1 Clinical literature search

Systematic literature searches were undertaken to identify all published clinical evidence relevant to the review questions.

Databases were searched using relevant medical subject headings, free-text terms and study type filters where appropriate. Studies published in languages other than English were not reviewed and where possible, searches were restricted to retrieve only articles published in English. All searches were conducted in MEDLINE, Embase and The Cochrane Library. All searches were updated in May 2017. Any studies added to the databases after this date (even those published prior to this date) were not included unless specifically stated in the text.

Search strategies were quality assured by cross-checking reference lists of highly relevant papers, analysing search strategies in other systematic reviews and asking the group members to highlight any additional studies. The questions, the study types applied, the databases searched and the years covered can be found in Appendix E.

The titles and abstracts of records retrieved by the searches were inspected for relevance, with potentially significant publications obtained in full text. These were assessed against the inclusion criteria.

During the scoping stage, a search was conducted for guidelines and reports on websites of organisations relevant to the topic. Searching for grey literature or unpublished literature was not undertaken. Searches for electronic, ahead-of-print publications were not routinely undertaken unless indicated by the Committee. All references suggested by stakeholders at the scoping consultation were initially considered.

4.2.2 Health economic literature search

A systematic literature search was also undertaken to identify relevant published health economic evidence. A broad search was conducted to identify evidence relating to oesophago-gastric cancer in the following databases: NHS Economic Evaluation Database (NHS EED), Health Technology Assessment (HTA), Medline, Cochrane Central Register of Controlled Trials (CCTR) and Embase with an economic search filter applied. Where possible, the search was restricted to articles published in English and studies published in languages other than English were not eligible for inclusion.

The search strategy for the health economic literature search is included in Appendix E. The literature search was updated in May 2017. Any studies added to the databases after this date (including those published prior to this date but not yet indexed) were not included unless specifically stated in the text.

4.3 Reviewing research evidence

4.3.1 Types of studies and inclusion and exclusion criteria

For most intervention reviews in this guideline, parallel randomised controlled trials (RCTs) were prioritised because they are considered the most robust type of study design that could produce an unbiased estimate of the intervention effects.

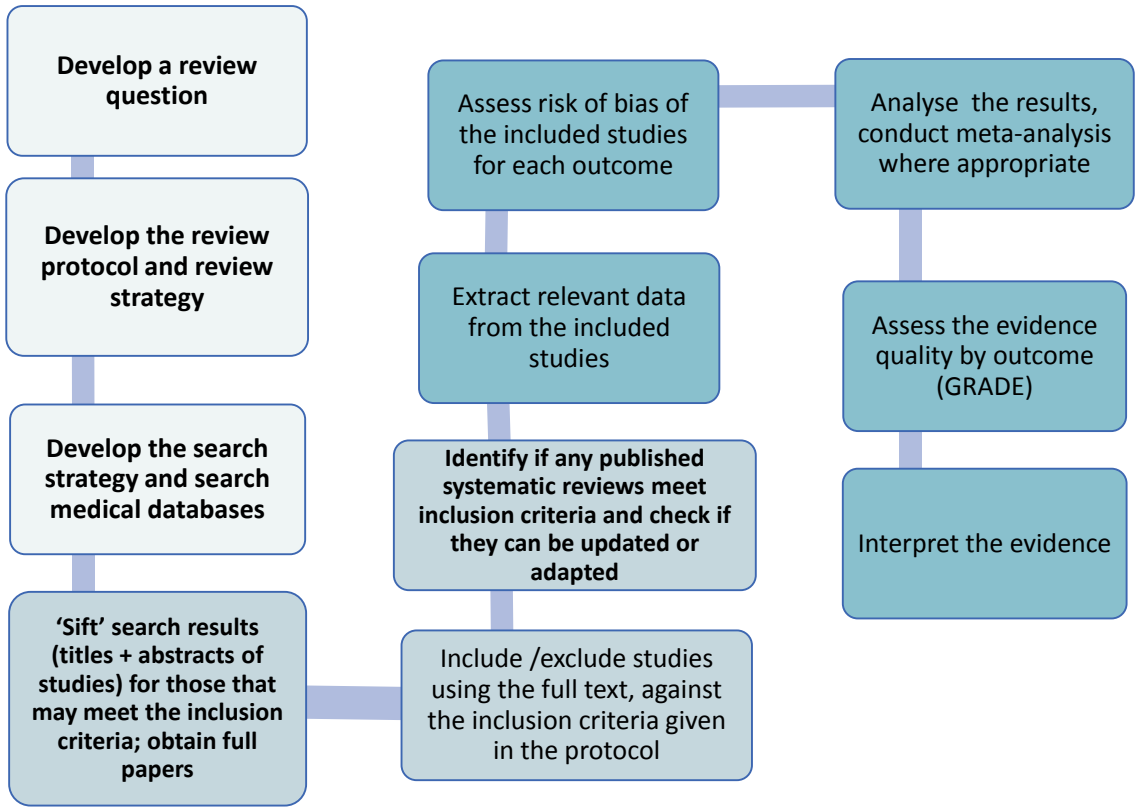
For diagnostic reviews, cross-sectional, retrospective or prospective comparative observational studies were considered for inclusion. For prognostic reviews, prospective and retrospective cohort studies were included. Case-control studies were not considered for inclusion.

In the qualitative review, studies using focus groups, or structured or semi-structured interviews were considered for inclusion. Survey data or other types of questionnaires were only included if they provided analysis from open-ended questions, but not if they reported descriptive quantitative data only.

Where data from observational studies were included, the Committee decided that the results for each outcome should be presented separately for each study and meta-analysis was not conducted.

The evidence was reviewed following the steps shown schematically in Figure 1.

Figure 1: Process used to obtain the evidence used to form recommendations



Potentially relevant studies were identified for each review question from the relevant search results by reviewing titles and abstracts. Full papers were then obtained

- Full papers were reviewed against pre-specified inclusion and exclusion criteria to identify studies that addressed the review question in the appropriate population, as outlined in the review protocols (review protocols are included in Appendix D)
- Relevant studies were critically appraised using the appropriate checklist as specified in the NICE guidelines manual
- Key information was extracted on the study's methods, according to the factors specified in the protocols and results. These were presented in summary tables (in each review chapter) and evidence tables (in Appendix F)
- Summaries of evidence were generated by outcome (included in the relevant review chapters) and were presented in Committee meetings (details of how the evidence was appraised is described in Section 4.5 below):
  - Randomised studies: meta-analysis was carried out where appropriate and results were reported in GRADE profiles (for intervention reviews)
  - Observational studies: data were presented as a range of values in GRADE profiles
  - Prognostic studies: data were presented as a range of values, usually in terms of the relative effect as reported by the authors
  - Diagnostic studies: data were presented as measures of diagnostic test accuracy (sensitivity and specificity) and were presented in modified GRADE profiles.

Qualitative studies: each study was summarised by theme and meta-synthesis was carried out where appropriate to identify an overarching framework of themes and subthemes. These were then presented in modified GRADE-CERQual (Lewin 2015) profile, where CERQual stands for Confidence in the Evidence from Reviews of Qualitative research.

For quality assurance of study identification, 10% of searches for certain review questions of high economic importance or for which network-meta analysis was planned were double

sifted by a second reviewer .These review topics were the extent of radical lymph node dissection, second line chemotherapy for locally advanced and metastatic disease and treatment of squamous cell carcinoma of the oesophagus.

4.4 Method of combining clinical studies

When planning reviews (protocols), the following approaches for data synthesis were discussed and agreed with Committee.

4.4.1 Data synthesis for intervention reviews

It was planned to conduct meta-analyses where possible, to combine the results of studies for each review question using Cochrane Review Manager (RevMan5) software.

Fixed-effect (Mantel–Haenszel) techniques were used to calculate risk ratios (relative risk) for binary outcomes, such as rate of adverse events (Mantel–Haenszel 1959) if statistical heterogeneity (I^2) was < 50%. If I^2 is ≥ 50%, clinical heterogeneity in-between the studies were interrogated and subgroup analyses were performed as appropriate. If there was no clinical heterogeneity, then, random effect model was applied to pool the results.

For continuous outcomes, measures of central tendency (mean) and variation (standard deviation) were pooled for meta-analysis. The choice of fixed and random effect model were determined by statistical and clinical heterogeneity as in binary outcomes. A generic inverse variance option in RevMan5 was used where any studies reported solely the summary statistics and 95% confidence interval (95% CI) or standard error. However, in cases where standard deviations were not reported per intervention group, the standard error (SE) for the mean difference is calculated from other reported statistics (p values or 95% CIs): meta-analysis was then undertaken for the mean difference and SE using the generic inverse variance method in RevMan5. When the only evidence was based on studies summarising results by presenting medians (and interquartile ranges) or only p values were given, this information was assessed in terms of the study's sample size and was included in the GRADE tables without calculating the relative or absolute effects. Consequently, aspects of quality assessment, such as imprecision of effect, could not be assessed for evidence of this type. However, the limited reporting of this outcome was classified as a risk of bias in study limitations.

Stratified analyses were predefined for some review questions at the protocol stage when the Committee identified that these strata are different in terms of biological and clinical characteristics and the interventions were expected to have a different effect. Predefined analyses were performed and the results were interpreted appropriately.

Statistical heterogeneity was assessed by visually examining the forest plots (please see Appendix H) and by considering the chi-squared test for significance at $p<0.1$ or an I-squared inconsistency statistic (with an I-squared value of more than 50% indicating considerable heterogeneity and I-squared of more than 80% very serious heterogeneity). Where considerable statistical heterogeneity was present, reasons for clinical heterogeneity were looked for and appropriate actions (use of subgroup analyses or a random effects model) were taken.

Assessments of potential differences in effect between subgroups were based on the chi-squared tests for heterogeneity statistics between subgroups. If no sensitivity analysis was found to resolve statistical heterogeneity ($I^2<50\%$), then a random-effects (DerSimonian and Laird) model was employed to provide a more conservative estimate of the effect – (DerSimonian and Laird, 1986). In this situation evidence could be downgraded for inconsistency (see Grading the quality of clinical evidence section below).

4.4.1.1 Data synthesis for intervention reviews using Network Meta-Analysis (NMA)

In some circumstances, the results of conventional pairwise meta-analyses of direct evidence does not help assess which intervention is most effective. The challenge of interpretation may arise for two main reasons:

- Relative treatment efficacies based on separate individual pairwise comparisons across multiple treatments are difficult to assess.
- Direct RCT comparison between treatments of clinical interest are not available in published literature.

To overcome these issues, NMA can be performed. Advantages of performing this type of analysis are:

- It allows the synthesis of data from direct and indirect comparisons without breaking randomisation, to produce measures of treatment effect and ranking of different interventions. If treatment A has never been compared against treatment B head to head, but these two interventions have been compared to a common comparator, then an indirect treatment comparison can use the relative effects of the two treatments versus the common comparator. This is also the case whenever there is a path linking two treatments through a set of common comparators. All the randomised evidence is considered within the same model.
- For every intervention in a connected network, a relative effect estimate can be estimated versus any other intervention. These estimates provide a useful clinical summary of the results and facilitate the formation of recommendations based on all of the best available evidence, whilst appropriately accounting for uncertainty. Furthermore, these estimates will be used to parameterise treatment effectiveness in the de novo cost-effectiveness modelling.

The three key assumptions behind an NMA are consistency, similarity and transitivity.

Consistency is the assumption that the direct estimates are equal to the indirect estimates (i.e. that the relative effect of A versus C is equal to the relative effect of A versus B minus B versus C).

Similarity across trials is the critical rationale for the consistency assumption to be valid as, by ensuring the clinical characteristics of the trials are similar, we ensure consistency in the data analysis.

More specifically, randomisation holds only within individual trials, not across the trials. Therefore, if the trials differ in terms of patient characteristics, measurement and/or definition of outcome, length of follow-up across the direct comparisons, the similarity assumption is violated and this can bias the analysis. The methods used for the review in this guideline ensured that randomisation was preserved.

Transitivity is the assumption that an intervention (A) will have the same efficacy in a study comparing A versus B as it will in a study comparing A versus C. Another way of looking at it, in terms of the study participants, is that we assume that it is equally likely that any patient in the network could have been given any of the treatments in the network and would have responded to the treatments in the same way (depending on how efficacious the treatments are). This assumption is closely related to similarity in that if participants in a study comparing A versus B are not the same as those in a study comparing A versus C.

As it is the case for ordinary pairwise meta-analysis, NMA may be conducted using either fixed or random effects models. A fixed effects model typically assumes that there is no variation in relative effects across trials for a particular pairwise comparison and any observed differences are solely due to chance. For a random effects model, it is assumed that the relative effects are different in each trial but that they are from a single common

distribution. The variance reflecting heterogeneity is often assumed to be constant across trials.

Incoherence in NMA between direct and indirect evidence can be assessed in closed treatment loops within the network. These closed treatment loops are regions within a network where direct evidence is available on at least 3 different treatments that form a closed "circuit" of treatment comparisons (for example A versus B, B versus C, C versus A). If closed treatment loops exist then discrepancies between direct and indirect evidence can be assessed for each loop using node-splitting.

NMA was considered particularly important for the review question relating to the choice of second-line palliatice chemotherapy, where it was used because it allows use of indirect evidence to make comparisons between treatments that have not yet been compared in head-to-head RCTs.

The network in that review included a number of trials comparing active treatment to a placebo or best supportive care and therefore NMA allows us to estimate relative effects between all active treatments. NMA also allows all treatments to be compared to a single comparator, which is useful for health economic analysis that takes a fully incremental approach to determine the most cost-effective treatment out of all treatments under consideration.

The outputs of the NMA were:

- Treatment specific RRs and HRs with their 95% CIs for every possible pair of comparisons by combining direct and indirect evidence (where available) in each network.
- The probability that each treatment is ranked as the best treatment.

4.4.2 Data synthesis for diagnostic test accuracy reviews

4.4.2.1 Data and outcomes

There are a number of diagnostic test accuracy measures. Sensitivity, specificity and likelihood ratios were used as outcomes for diagnostic reviews in this guideline.

Sensitivity and specificity are measures of the ability of a test to correctly classify a person as having a disorder or not having a disorder. When sensitivity is high, a **N**egative test result rules out the target disorder. When specificity is high, a **P**ositive test result rules in the target disorder – researchers have created the mnemonic SpPin/SnNout for this (Sackett 1992). An ideal test would be both highly sensitive and highly specific, but this is frequently not possible and typically there is a trade-off.

The positive likelihood ratio expresses the odds of a positive diagnostic test result in a patient with (as opposed to without) the target disorder (Sackett, 1992). Similarly the negative likelihood ratio expresses the odds that a negative diagnostic test result would be expected in a patient with (as opposed to without) the target disorder.

4.4.2.2 Data synthesis

Diagnostic paired sensitivity-specificity forest plots were produced for each diagnostic test using RevMan5 or 'R' softwares. In order to do this, 2×2 tables (the number of true positives, false positives, true negatives and false negatives) were extracted.

4.4.2.3 Diagnostic meta-analysis

When data from 3 or more studies were available, a diagnostic meta-analysis was carried out. To show the differences between study results, pairs of sensitivity and specificity were plotted for each study on one receiver operating characteristics (ROC) curve in RevMan5 (for

plots please see Appendix H). Study results were pooled using the bivariate method for the direct estimation of summary sensitivity and specificity using a random effects approach (using the STATA metan module). Using the output from STATA, we constructed and plotted confidence regions and, where appropriate ROC curves.

4.4.3 Data synthesis for qualitative reviews

Where possible, a meta-synthesis was conducted to combine qualitative study results. The main aim of the synthesis of qualitative data was to produce a description of the topics or themes. Whenever studies identified a qualitative theme, this was extracted and the main characteristics were summarised. When all themes were extracted from studies, common concepts were categorised and tabulated. This included information on how many studies had contributed to an identified overarching theme. In qualitative synthesis, a theme being reported by different studies more often than other themes does not necessarily mean that it would be more important than those other themes. The aim of qualitative research is to identify new perspectives on a particular topic. Study type and population in qualitative research can differ widely, meaning that themes identified by just one or a few studies can provide important new information for a given topic. Therefore, for the purpose of the qualitative reviews in this guideline, we did not add further studies when they reported the same themes that had already been identified from the same perspectives (that is from patients, carers or their families, or healthcare professionals) because the emphasis was on conceptual robustness rather than the quantitative completeness of evidence. This has implications for the types and numbers of studies that are included in the qualitative reviews. Study inclusion continued until no new relevant data could be found regarding a topic that would add to or refute it, a concept referred to in the literature as 'theoretical saturation' (Dixon-Woods 2005).

The most relevant evidence in this respect would originate from studies set in the target context of the UK NHS setting. Themes from individual studies were then integrated into a wider context and, when possible, overarching categories of themes with sub-themes were identified. Themes were derived from data presented in individual studies based directly on quotes from interviewees. When themes were extracted, theme names derived from the studies that provided it were used. The names of overarching themes, however, were named by the systematic reviewers.

Emerging themes were then placed into a thematic map that presents the relationship between themes and subthemes. The purpose of the map was to show relationships between overarching themes and their subthemes. The mapping part of the review was drafted by a member of the technical team, but the final framework of themes was further shaped and, when necessary, re-classified through discussion with at least one other member of the technical team. The Committee could then draw conclusions from each theme and use them in forming recommendations.

4.4.4 Data synthesis for prognostic reviews

For the review on follow up it was important to estimate how disease free and overall survival vary with treatment and disease characteristics. In this respect, odds ratios (ORs), risk ratios (RRs) or hazard ratios (HRs), with their 95% confidence intervals (95% CIs) for the effect of the pre-specified prognostic factors, were extracted from the papers when reported. For this topic, we looked for studies that took into account possible key confounders as reported in multivariable analyses. The reported measures were therefore adjusted to take into account other characteristics.

4.5 Appraising the quality of evidence

For intervention reviews, the evidence for outcomes from the included RCTs and observational studies were evaluated and presented using GRADE, which was developed by the international GRADE working group. Modified GRADE assessments were also carried out for accuracy measures in diagnostic reviews. For the appraisal of the quality of the evidence from qualitative reviews an adapted GRADE-CERQual (Lewin 2015) approach was used, where CERQual stands for Confidence in the Evidence from Reviews of Qualitative research.

The software developed by the GRADE working group (GRADEpro) was used to assess the quality of each outcome, taking into account individual study quality factors and the meta-analysis results. The clinical/economic evidence profile tables include details of the quality assessment and pooled outcome data, where appropriate, an absolute measure of intervention effect and the summary of quality of evidence for that outcome. In this table, the columns for intervention and control indicate summary measures of effect and measures of dispersion (such as mean and standard deviation or median and range) for continuous outcomes and frequency of events (n/N: the sum across studies of the number of patients with events divided by sum of the number of completers) for binary outcomes. Reporting or publication bias was only taken into consideration in the quality assessment and included in the clinical evidence profile tables if it was apparent.

The selection of outcomes for each review question was decided when each review protocol was discussed with the Committee. The outcomes selected for a review question were critical for decision-making in a specific context.

The evidence for each outcome in interventional reviews was examined separately for the quality elements listed and defined in Table 3. Each element was graded using the quality levels listed in Table 4. The main criteria considered in the rating of these elements are discussed below. Footnotes were used to describe reasons for grading a quality element as having serious or very serious limitations. The ratings for each component were summed to obtain an overall assessment for each outcome (Table 5).

Table 3: Description of quality elements in GRADE

Quality element	Description
Risk of bias (study limitations)	Limitations in the study design and implementation may bias the estimates of the treatment effect. High risk of bias for the majority of the evidence decreases confidence in the estimate of the effect.
Inconsistency	Inconsistency refers to an unexplained heterogeneity of results or findings.
Indirectness	Indirectness refers to differences in study population, intervention, comparator and outcomes between the available evidence and the review question, or recommendation made, such that the effect estimate is changed. This is also related to applicability or generalisability of findings.
Imprecision	Results are imprecise when studies include relatively few patients and few events and thus have wide confidence intervals around the estimate of the effect. Imprecision results if the confidence interval includes the clinically important threshold. For qualitative research this can relate to the sufficiency of data within each theme.

Quality element	Description
Publication bias	Publication bias is a systematic underestimate or an overestimate of the underlying beneficial or harmful effect due to the selective publication of studies.

Table 4: Level of quality elements in GRADE level

Levels of quality elements in GRADE level	Description
None	There are no serious issues with the evidence.
Serious	The issues are serious enough to downgrade the outcome evidence by 1 level.
Very serious	The issues are serious enough to downgrade the outcome evidence by 2 levels.

Table 5: Overall quality of outcome evidence in GRADE level

Overall quality of outcome evidence in GRADE level	Description
High	Further research is very unlikely to change our confidence in the estimate of effect.
Moderate	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low	Any estimate of effect is very uncertain.

GRADE is primarily designed for intervention review question, but we adapted the quality assessment elements and outcome presentation for diagnostic accuracy and qualitative studies, subject to data availability. For example, for diagnostic accuracy studies, the GRADE tables were modified to include the most appropriate measures of diagnostic accuracy (sensitivity and specificity) whereas qualitative studies were presented in summary evidence tables around themes identified or direct participants' quotations. Quality of the evidence in the qualitative reviews was assessed per study level.

4.5.1 Grading the quality of clinical evidence

After results were pooled, the overall quality of evidence for each outcome was considered. The following procedure was adopted when using the GRADE approach:

- A quality rating was assigned based on the study design. RCTs start as high, observational studies as low and uncontrolled case series as low.
- The rating was then downgraded for the specified criteria: risk of bias (study limitations); inconsistency; indirectness; imprecision; and publication bias. These criteria are detailed below. Evidence from observational studies (which had not previously been downgraded) was upgraded if there was a large magnitude of effect or a dose-response gradient, and if all plausible confounding would reduce a demonstrated effect, or suggest a spurious effect when results showed no effect.
- Each quality element considered to have 'serious' or 'very serious' issues was rated down by 1 or 2 points respectively. Value based judgements for relevant interpretation of the levels of quality elements were informed by discussion with the Committee for each review to balance consistency of approach across the guideline and clinical relevance within each review.

- The downgraded/upgraded ratings were then summed and the overall quality rating was revised, taking into account the relative contributions from the individual studies within a meta-analyses, where performed. For example, RCTs start as high and the overall quality becomes moderate, low or very low if 1, 2 or 3 points are deducted respectively
- The reasons or criteria used for downgrading were specified in the footnotes.

The details of the criteria used for each of the main quality elements are discussed further in sections 4.5.1.1 to 4.5.1.4 below. Quality statements were informed by assessment of risk of bias.

4.5.1.1 Risk of bias

Intervention studies

Bias can be defined as anything that causes a consistent deviation from the truth. Bias can be perceived as a systematic error.

The magnitude of risk of bias for a given study relevant to its outcome is associated with the risk of over or underestimation of the true effect.

Sources of bias in randomised controlled trials are listed in Table 6. The standard tools used to appraise the risk of bias were Cochrance risks of bias tools for randomised studies and Newcastle Ottowa scales for non-randomised studies.

A study with a poor methodological design does not automatically imply high risk of bias; the bias is considered individually for each outcome and it is assessed whether this poor design will impact on the estimation of the intervention effect.

Table 6: Sources of bias in randomised controlled trials

Risk of bias	Explanation
Allocation concealment	Those enrolling patients are aware of the group to which the next enrolled patient will be allocated (this is a major problem in 'pseudo' or 'quasi' randomised trials with allocation by, for example, day of week, birth date, chart number).
Lack of blinding	Patient, caregivers, those recording outcomes, those adjudicating outcomes or data analysts are aware of the arm to which patients are allocated.
Incomplete accounting of patients and outcome events	Missing data not accounted for and failure of the trialists to adhere to the intention to treat principle when indicated.
Selective outcome reporting	Reporting of some outcomes and not others on the basis of the results.
Other risks of bias	For example: • stopping early for benefit observed in randomised trials, in particular in the absence of adequate stopping rules • use of unvalidated patient-reported outcomes • recruitment bias in cluster randomised trials.

Diagnostic studies

For diagnostic accuracy studies, the Quality Assessment of Diagnostic Accuracy Studies version 2 (QUADAS- 2) checklist was used (http://www.bristol.ac.uk/social-community-

medicine/projects/quadas/quadas-2/). Risk of bias and applicability in primary diagnostic accuracy studies in QUADAS- 2 consists of 4 domains:

- patient selection
- index test
- reference standard
- flow and timing.

Qualitative studies

For qualitative studies, quality was assessed using a checklist for qualitative studies (as suggested in Appendix H in the NICE guidelines manual 2014). This was based on the Critical Appraisal Skills Programme (CASP) checklist for qualitative studies. The quality rating for risk of bias (low, high and unclear) was derived by assessing the risk of bias across 6 domains. The evidence was then assessed by theme using GRADECerqual across studies as described above and labelled (no limitations, minor limitations, major limitations and unclear), see Table 7.

Table 7: Domains for quality assessment of qualitative studies

Risk of bias	Explanation
Aim and appropriateness of qualitative evidence.	This refers to an assessment of whether the aims and relevance of the study were clearly described and whether qualitative research methods were appropriate for investigating the research question.
Rigour in study design or validity of theoretical approach	This domain assesses whether the study approach has been clearly described and is based on a theoretical framework (for example ethnography or grounded theory). This does not necessarily mean that the framework has to be explicitly stated, but that at least a detailed description is provided which makes it transparent and reproducible.
Sample selection	The background, the procedure and reasons for the chosen method of selecting participants should be stated. It should also be assessed whether there was a relationship between the researcher and the informant and if so, how this may have influenced the findings that were described.
Data collection	Consideration was given to how well the method of data collection (in-depth interviews, semi-structured interviews, focus groups or observations) was described, whether details were provided and how the data were collected (who conducted the interviews, how long did they last and where did they take place).
Data analysis	For this criterion it is assessed whether sufficient detail is provided about the analytical process and whether it is in accordance with the theoretical approach. For instance, if a thematic analysis was used, it is assessed whether there was a clear description of how the theme was arrived at. Data saturation is also part of this section. This refers to whether a theoretical point of theme saturation was achieved at which point no further citations or observations would provide more insight or suggest a different interpretation of this theme. This could be explicitly stated, or it may be clear from the citations presented that it may have been possible to find more themes.
Results	In relation to this section the reasoning about the results are important, for instance whether a theoretical proposal or framework is provided rather than being restricted to citations / presentation of data.

Prognostic studies

For prognostic studies, quality was assessed using the checklist for prognostic studies - Hayden 2006 checklist (Appendix H in the NICE guidelines manual 2014).

This risk of bias for each risk factor across studies was derived by assessing the risk of bias across 6 domains for each study – selection bias, attrition bias, prognostic factor bias, outcome measurement bias, control for confounders and appropriate statistical analysis – with the last 4 domains being assessed for each outcome. A summary table on the quality of prognostic studies is presented at the beginning of each review to summarise the risk of bias across the 6 domains. More details about the quality assessment for prognostic studies are shown in Table 8:

Table 8: Sources of bias for prognostic factor studies

Risk of bias	Explanation
Patient selection	Selection bias would occur if the study population is not representative of the population of interest on important charateristics.
Prognostic factor bias (or sign/symptom)	This refers to any biases that could directly be linked to the validity of the prognostic factor under investigation, such as how the signs or symptoms were assessed or measured.
Attrition bias	This is assessed by whether there are similar numbers of people who were followed up in groups who have or have not got the particular sign or symptom.
Outcome measurement bias	This usually refers to whether or not the outcome has been measured on a validated scale or was otherwise reliably assessed.
Control for confounders / statistical analysis	This domain is an assessment of whether confounders have been adequately accounted for. Confounders would be signs and symptoms that may be related to dying but that are not under direct investigation. For instance, age is related to dying, but we would not assess age in general as a sign or symptom of dying. We therefore wanted to assess whether signs and symptoms were independent predictors, regardless of other non-related factors.

4.5.1.2 Inconsistency / coherence of findings

Inconsistency refers to unexplained heterogeneity of results. When estimates of the treatment effect, prognostic risk factor or diagnostic accuracy measures vary widely across studies (that is, there is heterogeneity or variability in results), this suggests true differences in underlying effects.

Heterogeneity in meta-analyses was examined; if present, sensitivity and subgroup analyses were performed as pre-specified in the protocols (Appendix D).

When heterogeneity existed (chi-squared probability less than 0.1, I-squared inconsistency statistic of greater than 50%, or from visually examining forest plots), but no plausible explanation could be found (for example duration of intervention or different follow-up periods), the quality of the evidence was downgraded in GRADE by one or two levels, depending on the extent of inconsistency in the results. For example an I-squared value of 80% or more indicated very serious heterogeneity and evidence was downgraded by two levels in the absence of a plausible explanation. When outcomes are derived from a single trial, inconsistency is not an issue for downgrading the quality of evidence. However, 'no inconsistency' is nevertheless used to describe this quality assessment in the GRADE profiles as this is the default option in the GRADEpro software used.

For diagnostic and prognostic evidence, inconsistency was assessed visually according to the differences in point estimates and overlap in confidence intervals on the sensitivity/ specificity forest plots. In addition to the I-squared and chi-squared values and examination of forest plots, the decision for downgrading was dependent on factors such as whether the uncertainty about the magnitude of benefit (or harm) of the outcome showing heterogeneity would influence the overall judgment about net benefit or harm (across all outcomes).

For qualitative research, a similar concept to inconsistency is coherence, which refers to the way findings within themes are described and whether they make sense. This concept was

used in the quality assessment across studies for individual themes. This does not mean that contradictory data was downgraded automatically, but that it was highlighted and presented, and that reasoning was provided. As long as the themes, or components of themes, from individual studies fit into a theoretical framework, they do not necessarily have to have the same perspective. It should, however, be possible to explain these by differences in context (for example, the views of healthcare professionals might not be the same as those of family members, but they could contribute to the same overarching theme). Coherence was graded across studies with the following labels: coherent, incoherent or unclear.

4.5.1.3 Indirectness / applicability or relevance of findings

For quantitative reviews, directness refers to the extent to which the populations, intervention/risk factor/index test, comparisons and outcome measures are similar to those defined in the inclusion criteria for the reviews. Indirectness is important when these differences are expected to contribute to a difference in effect size, or may affect the balance of harms and benefits considered for an intervention.

Relevance of findings in qualitative research is the equivalent of indirectness for quantitative outcomes and refers to how closely the aims and context of the studies contributing to a theme reflect the objectives outlined in the review protocol of the guideline question.

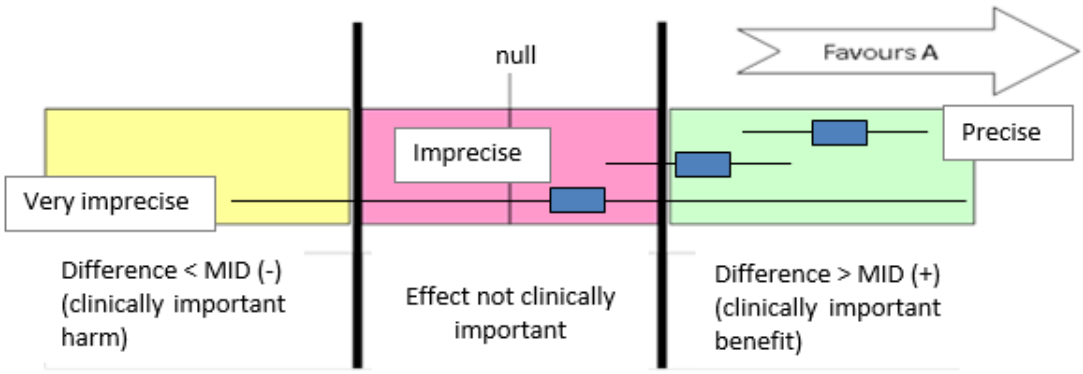
4.5.1.4 Imprecision / theme saturation or sufficiency

For quantitative reviews, imprecision in guidelines concerns whether the uncertainty (confidence interval) around the effect estimate means that it is not clear whether there is a clinically important difference between interventions or not (that is, whether the evidence would clearly support a single recommendation or appear to be consistent with several different types of recommendations). Therefore, imprecision differs from the other aspects of evidence quality because it is not really concerned with whether the point estimate is accurate or correct (has internal or external validity); instead, it is concerned with the uncertainty about what the point estimate actually is. This uncertainty is reflected in the width of the confidence interval.

If a trial were repeated infinitely often, and each time a 95% confidence interval (95% CI) for the effect was calculated, then 95% of these intervals would contain the true effect. Larger trials tend to give more precise estimates with narrower 95% CIs leading to greater certainty in the effect estimate.

Imprecision in the evidence reviews was assessed by considering whether the width of the 95% CI of the effect estimate was relevant to decision-making, considering each outcome in isolation. This is explained in Figure 2 which considers a positive outcome for the comparison of treatment A versus treatment B. Three decision-making zones can be identified, bounded by the thresholds for clinical importance (minimal important difference, MID) for benefit and for harm. The MID for harm for a positive outcome means the threshold at which drug A is less effective than drug B by an amount that is clinically important to patients (favours B).

Figure 2: Illustration of precise, imprecise and very imprecise evidence based on the confidence interval of outcomes in forest plots



When the confidence interval of the effect estimate is wholly contained in 1 of the 3 zones (for example clinically important benefit), we are not uncertain about the size and direction of effect (whether there is a clinically important benefit, or the effect is not clinically important, or there is a clinically important harm), so there is no imprecision.

When a wide confidence interval lies partly in each of 2 zones, it is uncertain in which zone the true value of effect estimate lies and therefore there is uncertainty over which decision to make (based on this outcome alone). The confidence interval is consistent with 2 possible decisions and so this is considered to be imprecise in the GRADE analysis and the evidence is downgraded by 1 level ('serious imprecision').

If the confidence interval of the effect estimate crosses into 3 zones, this is considered to be very imprecise evidence because the confidence interval is consistent with 3 possible clinical decisions and there is therefore a considerable lack of confidence in the results. The evidence is therefore downgraded by 2 levels in the GRADE analysis ('very serious imprecision').

Implicitly, assessing whether the confidence interval is in, or partially in, a clinically important zone, requires the Committee to estimate an MID or to say whether they would make different decisions for the 2 confidence limits.

The literature was searched for established MIDs for the selected outcomes in the evidence reviews. In the absence of published MIDs, the Committee was asked whether they were aware of any acceptable MIDs in the clinical community. Finally, the Committee considered whether it was clinically acceptable to use the GRADE default MID to assess imprecision: for binary outcomes a 25% relative risk increase and the related relative risk reduction was used, which corresponds to clinically important thresholds for a risk ratio of 0.8 and 1.25 respectively (due to the statistical characteristic of this measure which means that this is not a symmetrical interval). This default MID for relative effect was used for relative risk of binary outcomes in intervention reviews unless the Committee suggested a more appropriate value, such as an absolute risk difference criterion. Imprecision was considered 'serious' if 95% confidence interval of effect estimate crossed either 0.8 or 1.25 whereas 'very serious imprecision' was considerd if 95% confidence interval of effect estimate crossed both 0.8 and 1.25.

For continuous outcomes default MIDs were also used as being half of the median standard deviation of the control group if there is odd number of study and mean standard deviation of the control group was used if there is even number of study. As in binary outcomes, the upper and lower boundaries of default MIDs were used to determine level of imprecision.

For diagnostic accuracy measures, it was first considered whether sensitivity or specificity would be given more weight in the decision-making process. If one measure was given more

importance than the other, then imprecision was rated on this statistical measure. The width of the 95% confidence interval of test sensitivity or specificity was used to assess the precision of the estimate. If the Committee could not agree the MID then the following defaults were used: 0 – 20% difference between the upper and lower 95% CI boundaries was defined as precise, 20 – 40% difference as serious imprecision and >40% difference as very serious imprecision.

Theme saturation or sufficiency refers to a similar concept in qualitative research. This refers to whether a theoretical point of theme saturation was achieved, at which point no further citations or observations would provide more insight or suggest a different interpretation of this theme. As already highlighted in a previous section on qualitative reviewing methods, it is not equivalent to the number of studies contributing to a theme, but rather to the depth of data and whether sufficient quotes or observations were provided that could underpin these findings.

4.5.2 Quality assessment of Network Meta-Analysis (NMA)

The use of GRADE to assess the quality of studies addressing a particular review question for pairwise comparisons of interventions is relatively established. However, the use of GRADE to assess the quality of evidence across a NMA is still a developing methodology. While most criteria for pairwise meta-analyses still apply, it is important to adapt some of the criteria to take into consideration additional factors, such as how each 'link' or pairwise comparison within the network applies to the others. As a result, we used the following adapted GRADE approach for appraising the quality of NMA (Table 9).

Table 9: Rationale for downgrading quality of evidence in NMAs

GRADE criteria	Example reasons for downgrading quality
Risk of bias	Risk of bias was assessed in accordance with GRADE, as specified in 'The guidelines manual (2014)'. This includes limitations in the design or execution of the study, including concealment of allocation, blinding, loss to follow up (these can reduce the quality rating).
Inconsistency	Evidence of any inconsistency between the direct and indirect estimates of effect (for example from a Wald test for inconsistency)
Indirectness	The extent to which the available evidence fails to address the specific review question (this can reduce the quality rating). This may be in relation to the setting, population, outcomes, interventions or study designs used in the evidence base. Evidence was only downgraded if this was likely to have an impact on the overall rankings of each treatment's probability of being the best.
Imprecision	This is considered to be present when there is uncertainty around the estimate of effect, and reflects the confidence in the estimate of effect. It is assessed based on the overall distribution of the rankings of each treatment's probability of being the best. For example if the probability being the best treatment was shared equally between the treatments in a network this would indicate imprecision.

4.5.3 Assessing clinical significance (of intervention effects)

The Committee assessed the evidence by outcome in order to determine if there was, or potentially was, a clinically important benefit, a clinically important harm or no clinically important difference between interventions. To facilitate this, where possible, binary outcomes were converted into absolute risk differences (ARDs) using GRADEpro software: the median control group risk across studies was used to calculate the ARD and its 95% confidence interval from the pooled risk ratio. For continuous outcomes, the mean difference between the intervention and control arm of the trail was calculated. This was then assessed in relation to the default MID (0.5 times the median/mean control group standard deviation).

For overall survival, progression free survival and mortality the Committee considered any statistically significant effect to be of clinical significance. For other outcomes the assessment of clinical benefit or harm was based on the MID of the relative risk and the point estimate of the absolute effect, taking into consideration the precision around this estimate.

4.5.4 Assessing clinical significance (of prognostic, diagnostic or qualitative findings)

Absolute risk differences were not calculated for prognostic findings in this guideline. The Committee considered the size of the relative effects and whether this was large enough to constitute a sign or symptom predicting the outcome of interest.

In a similar manner, this was carried out for diagnostic accuracy statistics to interpret how likely the accuracy measures reflect a clinically meaningful association between a positive test result and the condition of interest. If the Committee could not agree clinically relevant thresholds of sensitivity or specificity then default values were used: less than 75% being low, 75% to 90% moderate and above 90% high sensitivity or specificity.

For themes stemming from qualitative findings, clinical importance was decided upon by the Committee taking into account the generalisability of the context from which the theme was derived and whether it was convincing enough to support or warrant a change in current practice, as well as the evidence quality.

4.5.5 Evidence statements

Evidence statements are summary statements that are presented after the GRADE profiles, summarising the key features of the clinical evidence presented. The wording of the evidence statements reflects the certainty or uncertainty in the estimate of effect. The evidence statements are presented by outcome or theme and encompass the following key features of the evidence:

- the quality of the evidence (GRADE rating)
- the number of studies and the number of participants for a particular outcome
- a brief description of the participants
- an indication of the direction of effect (for example, if a treatment has clinically significant benefits or harms compared with another, or whether there is no difference between the tested treatments).

4.6 Evidence of cost effectiveness

The aims of the health economic input to the guideline were to inform the Committee of potential economic issues related to the diagnosis and management of oesophago-gastric cancer to ensure that recommendations represented a cost-effective use of healthcare resources. Health economic evaluations aim to integrate data on healthcare benefits (ideally in terms of quality-adjusted life-years (QALYs)) with the costs of different care options. In addition, the health economic input aimed to identify recommendations which may have a high resource impact.

4.6.1 Literature review

The titles and abstracts of publications identified by the health economic literature searches were assessed against the following pre-defined eligibility criteria:

Inclusion criteria

- Intervention or comparators match those in the scope
- Study population matches that in the scope

- Full economic evaluations that reports both costs and outcomes associated with the interventions of interest (cost-utility, cost-effectiveness, cost-benefit or cost-consequence analyses).

Exclusions criteria

- Abstracts with insufficient methodological details

Once the screening of titles and abstracts was complete, full versions of the selected papers were obtained for assessment. For economic evaluations, no standard system of grading the quality of evidence exists and included papers were assessed using the economic evaluations checklist as specified in the NICE guidelines manual.

4.6.2 De novo economic analysis

As well as reviewing the published economic literature, as described above, new economic analysis was undertaken in selected areas prioritised by the Committee in conjunction with the health economist. Topics were prioritised on the basis of the following criteria, in accordance with the NICE guidelines manual:

- the overall importance of the recommendation, which may be a function of the number of patients affected and the potential impact on costs and health outcomes per patient
- the current extent of uncertainty over cost effectiveness, and the likelihood that economic analysis will reduce this uncertainty
- the feasibility of building an economic model

The following priority areas for de novo economic analysis were agreed by the Committee after formation of the review questions and consideration of the available health economic evidence:

- staging investigations in oesophageal and gastro-oesophageal junctional cancer
- operative approaches for the surgical treatment of oesophageal cancer
- curative treatments for squamous cell carcinoma of the oesophagus

The methods and results of de novo economic analyses are reported in Appendix I. When new economic analysis was not prioritised, the Committee made a qualitative judgement regarding cost effectiveness by considering expected differences in resource and cost use between options, alongside clinical effectiveness evidence identified from the clinical evidence review.

4.6.3 Cost effectiveness criteria

NICE's report Social value judgements: principles for the development of NICE guidance sets out the principles that Committees should consider when judging whether an intervention offers good value for money. In general, an intervention was considered to be cost effective if either of the following criteria applied (given that the estimate was considered plausible):

- the intervention dominated other relevant strategies (that is, it was both less costly in terms of resource use and more clinically effective compared with all the other relevant alternative strategies), or;
- the intervention cost less than £20,000 per QALY gained compared with the next best strategy, or;
- the intervention provided clinically significant benefits at an acceptable additional cost when compared with the next best strategy.

The Committee's considerations of cost-effectiveness are discussed explicitly in the 'Consideration of economic benefits and harms' section for each topic.

4.7 Developing recommendations

Over the course of the guideline development process, the Committee was presented with:

- evidence tables of the clinical and economic evidence reviewed from the literature: all evidence tables are in Appendix F
- summary of clinical and economic evidence and quality assessment (as presented in Chapters 5 to 11)
- forest plots (Appendix H)
- a description of the methods and results of the cost-effectiveness analysis undertaken for the guideline (Appendix I).

Recommendations were drafted on the basis of the group's interpretation of the available evidence, taking into account the balance of benefits, harms and costs between different courses of action. This was either done formally, in an economic model, or informally. Firstly, the net benefit over harm (clinical effectiveness) was considered, focusing on the critical outcomes. When this was done informally, the group took into account the clinical benefits and harms when one intervention was compared with another. The assessment of net benefit was moderated by the importance placed on the outcomes (the group's values and preferences) and the confidence the group had in the evidence (evidence quality). Secondly, the group assessed whether the net benefit justified any differences in costs.

When clinical and economic evidence was of poor quality, conflicting or absent, the group drafted recommendations based on their expert opinion. The considerations for making consensus-based recommendations include the balance between potential harms and benefits, the economic costs or implications compared with the economic benefits, current practices, recommendations made in other relevant guidelines, patient preferences and equality issues. The group also considered whether the uncertainty was sufficient to justify delaying making a recommendation to await further research, taking into account the potential harm of failing to make a clear recommendation.

The wording of recommendations was agreed by the group and focused on the following factors:

- the actions healthcare professionals need to take
- the information readers of the guideline need to know
- the strength of the recommendation (for example the word 'offer' was used for strong recommendations and 'consider' for weak recommendations)
- the involvement of patients (and their carers if needed) in decisions about treatment and care
- consistency with NICE's standard advice on recommendations about drugs, waiting times and ineffective interventions.

The main considerations specific to each recommendation are outlined in the 'Recommendations and link to evidence' sections within each chapter.

4.7.1 Research recommendations

When areas were identified for which good evidence was lacking, the group considered making recommendations for future research in accordance with the NICE Research Recommendations Process and methods guide (2011), available from the NICE website.

4.7.2 Public consultation

This guidance is subject to a 6-week public consultation and feedback as part of the quality assurance and peer review of the document. All comments received from registered stakeholders are responded to in turn and posted on the NICE website at publication.

4.7.3 Updating the guideline

Following publication, and in accordance with the NICE guidelines manual, NICE will undertake a review of whether the evidence base has progressed significantly to alter the guideline recommendations and warrant an update.

4.7.4 Disclaimer

Healthcare providers need to use clinical judgement, knowledge and expertise when deciding whether it is appropriate to apply guidelines. The recommendations cited here are a guide and may not be appropriate for use in all situations. The decision to adopt any of the recommendations cited here must be made by practitioners in light of individual patient circumstances, the wishes of the patient, clinical expertise and resources.

5 Information and support

This chapter covers the information and support needs of people with oesophago-gastric cancer and is divided into two sections: the information and support needs of those people suitable for curative or radical treatment, and the needs of those people who are suitable for palliative management.

For those people in whom radical treatment is planned the potential benefits of therapy must be balanced against the consequences of treatment, which can have a significant impact on health-related quality of life. For people receiving palliative care, being told you have an incurable oesophago-gastric cancer has a devastating and wide ranging impact on the person who receives that diagnosis and those important to them.

It is therefore important for all people diagnosed with oesophago-gastric cancer, at whatever stage of their disease, 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 the cancer and its treatment, available clinical trials and practical issues is vital. People 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.

There is no standard agreement or approach on how best to provide the full array of support and information needed at various times during and after the cancer treatment. However, it is documented that information should be tailored to the individual's needs. It is evident that satisfaction improves and anxiety decreases when information is provided at the right time. There are many approaches to informing people with cancer about their diagnosis, disease and treatment. The key is to ensure that the right information, at the right time and in an accessible format (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 both people with cancer and their carers. A system of providing such information that is up to date, accurate, and reliable and in a language that carers and people with cancer can read and understand needs to be agreed and implemented.

However, as well as generic cancer-related information and support, there are specific needs that are particular to those with oesophago-gastric cancer. This includes treatments specific to oesophago-gastric cancer and also the particular nutritional issues encountered as a result of the disease and the treatments; for example dysphagia, upper gastrointestinal obstruction, reduced appetite, reduced gastric capacity, delayed gastric emptying, gastrointestinal disturbances and malabsorption. 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. In contrast to those with cancers that do not affect the gastro-oesophageal tract people with oesophago-gastric cancers often lose the ability to maintain adequate hydration and nutrition long before this is part of the natural dying phase of advancing cancer. There are also sometimes difficult decisions about what forms of clinically assisted nutrition or hydration should be used, particularly in more advanced disease, which need skilled support.

The reviews in this chapter aim to identify the specific information and support services that are beneficial to adults and their carers before and after radical or palliative treatments for oesophago-gastric cancer, and to provide recommendations to improve provision in this area.

5.1 Radical treatment

Review question: 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?

5.1.1 Description of clinical evidence

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.

We looked for studies that collected data using qualitative methods (such as semi-structured interviews, focus groups and surveys with open-ended questions) in which the authors analysed the data qualitatively (including thematic analysis, framework thematic analysis or content analysis). Survey studies restricted to reporting descriptive data that were analysed quantitatively were excluded.

Given the nature of qualitative reviews, findings/ themes were summarised from the literature and were not restricted to those identified as likely themes by the Guideline Committee at protocol stage.

For full details see review protocol in Appendix D.

Seven studies were included in this review. All the studies were qualitative studies. Five studies used qualitative, semi-structured interviews (Andreassen 2005, Andreassen 2006, Henselmans 2012, McNair 2016, Mills 2000). McNair 2016 also used observation of patient-surgeon consultations in addition to semi-structured interviews. Two studies used a focus group study design (Malmstrom 2013, McCorry 2009).

The size of the studies ranged from 7–31 participants. Two studies included a mixed population of adults and carers of adults undergoing palliative and curative intent treatments (Andreassen 2005, Andreassen 2006). Five studies included adults and families of adults undergoing curative intent surgery (Henselmans 2012, Malmstrom 2013, McCorry 2009, McNair 2016, Mills 2000). All studies focused on oesophageal cancer alone.

Three studies were conducted in the UK (McCorry 2009, McNair 2016, Mills 2000), 3 studies were conducted in Sweden (Andreassen 2005, Andreassen 2006 and Malmstrom 2013) and 1 study was conducted in The Netherlands (Henselmans 2012).

A summary of the included studies is presented in Table 10. See also study selection flow chart in Appendix K, excluded studies list in Appendix J, and study evidence tables in Appendix F.

5.1.2 Summary of included studies

A summary of the studies that were included in this review are presented in Table 10.

Table 10: Summary of included studies

Study	Aim of the Study	Participants	Study Design/ Methods	Comments
Andreassen et al., 2005 Sweden Study dates: December 2003 and	To describe family members' experiences, information needs and information seeking in relation to living with a patient	N=9 The sample consisted of close family members from an ongoing study of 13 patients. One brother, two husbands and six wives were included.	Sample selection: Convenience sampling - family members of study participants	Overall quality: MODERATE Data saturation was not discussed by

Study	Aim of the Study	Participants	Study Design/ Methods	Comments
January 2004	suffering from oesophageal cancer.		Data collection: Qualitative study, semi-structured interviews	the author or used in sampling
Andreassen et al., 2006 Sweden Study dates: December 2003 and March 2004	To describe patients' experiences of living with oesophageal cancer and how they seek information.	N=13 Their ages ranged from 44 to 77 years. The selection criteria for this study were as follows: women and men of different ages who had undergone different treatments for oesophageal cancer, i.e., a total thoracic oesophagectomy, oncological treatment with a curative intent and/or palliative treatment.	Sample selection: Purposive sampling was used. The surgeon in charge of their care identified and constructed a list of potential participants. Data collection: Qualitative study, semi-structured interviews.	Overall quality: HIGH Data saturation was reached Thematic analysis was detailed and carried out by 3 independent researchers.
Henselman, et al., 2012 The Netherlands Study dates: Not Reported	To examine the content and type of patients' information needs and patient perceived facilitators and barriers to patient participation.	N=20 Patients' mean age= 62 years. Fourteen participants were male (70%); Four patients (20%) were interviewed more than half a year after discharge. Most patients either had an open transthoracic (n = 10; 50%) or a thoraco-laporoscopic (n = 8; 40%) esophageal resection; two patients had a transhiatal resection (10%). One patient (5%) had tumour in stage I, 25% in stage II, 50% in stage III and 20% in stage IV. One or more companions were present in 11(55%) interviews.	Sample selection: Purposive sampling: To ensure a diverse sample, patients were selected purposefully based on information in their medical files, i.e., time since discharge, age and sex. Data collection: Qualitative study with semi-structured interviews.	Overall quality: HIGH Sampling was based on reaching data saturation. Data analysis was detailed and carried out
Malmstrom, et al., 2013 Sweden	To illuminate patients' experiences of supportive care from a long-term	N=17 (divided in 4 focus groups)	Sample selection: Purposively sampled from	Overall quality: HIGH

Study	Aim of the Study	Participants	Study Design/ Methods	Comments
Study dates: January and April 2009.	perspective after oesophagectomy or oesophago-gastrectomy for cancer.	Patients that two to five years earlier had been through elective surgery for oesophageal (oesophagectomy) or cardia cancer (oesophago-gastrectomy), had the ability to communicate in Swedish and place of residence in southern Sweden were included in the study.	an oesophageal cancer database at a university hospital Data collection: Four focus group interviews with between three and five respondents in each group were conducted during data collection.	Data saturation was reached. Data analysis was detailed and carried out by multiple researchers.
McCorry, et al., 2009 UK Study dates: Not reported	The current study explored the emotional and cognitive experiences of oesophageal cancer survivors and those of their carers, using focus groups conducted with members of a patient support group.	N= 22 (12 patients, 10 carers) In total, 12 survivors (9 men and 3 women) and 10 carers (8 women and 2 men) participated in the focus group discussions. The relationships between survivor and carer were: seven husband–wife dyads, two wife–husband dyads, and one mother–daughter dyad. Two male survivors were unaccompanied. Six survivors were aged 56 to 65 years, 3 were aged 66 to 75 years, 2 were aged 76 to 85 years, and 1 survivor was aged 46 to 55 years. All patients had undergone surgery as part of their treatment for oesophageal cancer. At the time of participation, time since diagnosis (self-reported) ranged from 14 months to 17 years, and time since surgery ranged from 7 months to 17 years.	Sample selection: Recruited from members of the Oesophageal Patients' Association in Northern Ireland. Data collection: Focus groups groups were separated for carers versus patients	Overall quality: MODERATE Convenience sample of patients who were part of a patient association could have introduced bias. Data saturation not addressed.
McNair, et al., 2016 UK	This study explored information provided by surgeons and patient preferences for information in consultations in which surgery for	N= 31 (25 consultations, 27 interviews) Six consultations were not recorded because of	Sample selection: Eligible participants were posted study information.	Overall quality: HIGH Unclear and limited detail on recruitment strategy.

Study	Aim of the Study	Participants	Study Design/ Methods	Comments
Study dates: Interviews conducted 2010/2011.	oesophageal cancer surgery was discussed.	equipment failure and four patients declined an interview. Characteristics mean age= 67 years (range 55-79) 24 male, 7 female 18 adenocarcinoma/13 squamous cell carcinoma	Data collection: Qualitative study (patient interviews and observation of patient-surgeon consultation).	Data saturation was reached. Multiple researchers carried out thematic analysis.
Mills, and Sullivan, 2000. UK Study dates: Not Reported	To gain an insight into the experiences of patients with operable cancer of the oesophagus and the information they received.	N=7 5 male, 2 female Exclusion criteria: Those over the age of 70 were excluded, as from experience the researcher considered this age group to be less willing to critically evaluate care.	Sample selection: Purposively sampled from list provided by surgeons. Data collection: Qualitative study of semi-structured interviews.	Overall quality: Moderate Concerns over sample selection that excludes those over the age of 70.

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5.1.31 Clinical evidence

5.1.3.12 Theme maps

3 The theme maps are presented in Figure 3 and Figure 4

Figure 3: Theme map: information needs for adults with oesophago-gastric cancer undergoing curative treatment and their carers

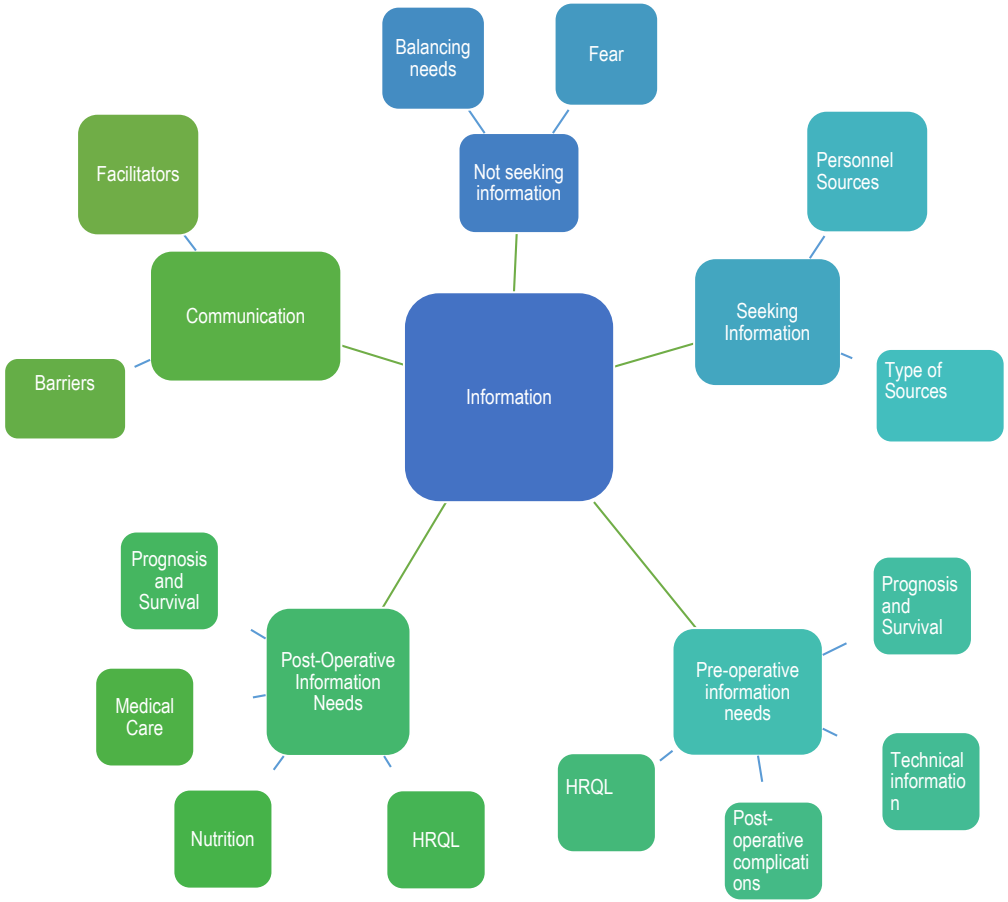

Figure 4: Theme map: support needs for adults undergoing curative treatment for oesophago-gastric cancer and their carers

5.1.4 Clinical evidence profile

The clinical evidence (GRADE-CERQual) for the information and support question is presented in Table 11 to Table 23Table 16.

5.1.4.1 Clinical evidence profile: information needs for adults with oesophago-gastric cancer suitable for curative treatment and their carers.

Table 11: Summary clinical evidence profile (GRADE-CERQual): Theme 1. Seeking information

STUDY information			CERQUAL Quality Assessment				
Number of studies	**Design**	**Description of Theme or Finding**	**Methodological Limitations**	**Relevance**	**Coherence**	**Adequacy of Data**	**Overall Confidence**
Sub-theme 1: Seeking information from consultant doctors							
Andreassen 2005 Andreassen 2006 Mills 2000	3 studies using interviews	Trusting expert opinion. Giving oneself over to the experts. Desire for more open discussion on details of being a person with oesophageal cancer. *The doctor is our lifeline. When you are so close to the experts as we are now, we ought to get the truth directly from the doctor if there is anything we wonder about. We have entrusted ourselves to the experts. (family member comment)* *I thought 'I can't do anything now; I'll just hand myself over to the experts and let them do whatever they want with me'. I've handed my life over to the doctors. (comment)* *The health-care professionals perhaps could have had time to tell me more about how it really is to be a patient. Perhaps they could have devoted a few hours to talk about a number of things concerning this cancer…in another way. (comment)* Generally participants were very positive about the surgeons,	Minor concerns over methodological limitations. CASP ratings: high (2 studies) and moderate (1 study)	Moderate concern over relevance: 2 studies with Swedish setting and mixed population.	Minor concerns over coherence (data reasonably consistent within and across studies).	Minor concerns over adequacy (3 studies that offered moderately rich data).	Moderate.

STUDY information			CERQUAL Quality Assessment				
Number of studies	**Design**	**Description of Theme or Finding**	**Methodological Limitations**	**Relevance**	**Coherence**	**Adequacy of Data**	**Overall Confidence**
		commenting on how `attentive' or `helpful' they were or how they provided `a lot of information' and spoke to their families. (author comment) *I was in awe of the doctor, these guys are God to me, they are life-savers. They are able to cut me in half and take bits out and throw them away. You are in awe! (comment)*					
Sub-theme 2: Information from nurses							
Andreassen 2005 Andreassen 2006 Mills 2000	3 studies using interviews	Nurses more approachable, accessible and trustworthy. Some people expressed discontent at communication with nurses. It's easier to talk with a nurse when it concerns important questions. *You may receive quite good and reassuring answers. / . . . / You get a feeling of trust when you talk with a nurse. (family member comment)* *I've seen a lot less of the doctors in the hospital. I see mostly nurses there. And things are different there; you ask the nurses, rather than the doctors, a lot more often than you do outside the hospital. (comment)* *And she said the doctor sees everybody before they go. She lied (comment)*	Minor concerns over methodological limitations. CASP ratings: high (2 studies) and moderate (1 study)	Moderate concern over relevance: 2 studies with Swedish setting and mixed population.	Minor concerns over coherence (data reasonably consistent within and across studies).	Minor concerns over adequacy (3 studies that offered moderately rich data).	Moderate.

STUDY information			CERQUAL Quality Assessment				
Number of studies	**Design**	**Description of Theme or Finding**	**Methodological Limitations**	**Relevance**	**Coherence**	**Adequacy of Data**	**Overall Confidence**
		But no-one (nursing staff) has time, it took me a while to find out what a TTO was about, actually what the letters stood for. Nobody sat down and actually explained that. (comment)					
Subtheme 3: Seeking information from other medical staff							
Mills 2000	Semi-structured interviews	Importance of being honest with people. Importance of respecting people's privacy and confidentiality. People are aware of different levels of expertise within medical community. On one occasion a participant related how a junior doctor admitted that he could not answer his question. His honesty was appreciated and made the person realise `these guys are only human'. (author comment) *Doctors have to realize that this is a very traumatic time for patients. (comment)* *It doesn't matter how confident you are, and I am normally confident and used to standing up and speaking to people. Yet here I was, petrified. (comment)* *It was just some of the questions that she asked that made me feel that she is treating me in general.*	No concerns over methodological limitations. CASP rating: high.	Minor concerns over relevance. One study from the UK on patients undergoing operative treatment for oesophago-gastric cancer.	Minor concerns over coherence (data reasonably consistent within study).	Major concern over adequacy (only 1 study included, offering thin data).	Low

STUDY information			CERQUAL Quality Assessment				
Number of studies	**Design**	**Description of Theme or Finding**	**Methodological Limitations**	**Relevance**	**Coherence**	**Adequacy of Data**	**Overall Confidence**
		She doesn't specifically know about me. (comment) *Doctors should be very careful what they say within the earshot of patients. Patients at this stage need support and confidence that all will be well. (comment)*					
Subtheme 4: Seeking information form allied health care professionals.							
	1 study using focus group interview.	All members of the health care team can play a role in providing information. *She (physiotherapist) was brilliant, she gave me more information than the doctors and nurses had. She was the only one that actually sat down. (comment)*	No concerns over methodological limitations. CASP rating: high.	Minor concerns over relevance. One study from the UK on patients undergoing operative treatment for oesophago-gastric cancer.	Minor concerns over coherence (data reasonably consistent within study).	Major concern over adequacy (only 1 study included offering thin data).	Low
Subtheme 5: Seeking information from social circles							
Andreassen 2005 Andreassen 2006	2 studies using qualitative interviews	Medical professionals in people's social circles also play a role providing information. Family members help people to gather and understand information. *I trusted the judgements that doctors in our acquaintance circle gave, but not completely, since they are not in the field. They can't be well read in all areas. (family member comment)* *I have experienced it positive that my son has come with me to the doctor. It is good to have another*	Minor concerns over methodological limitations. CASP ratings: high and moderate	Major concern over relevance: 2 studies with Swedish setting and mixed population.	Minor concerns over coherence (data reasonably consistent within and across studies).	Minor concerns over adequacy (3 studies that offered moderately rich data).	Moderate.

STUDY information			CERQUAL Quality Assessment				
Number of studies	**Design**	**Description of Theme or Finding**	**Methodological Limitations**	**Relevance**	**Coherence**	**Adequacy of Data**	**Overall Confidence**
		pair of ears listening. He has asked questions from an outside perspective. (comment) *It is my wife, who gathers the information that is needed. She is often with me when I visit the doctor. (comment)* *'I have a cousin who is a doctor and I also had my brother-in-law who was a doctor. I trust them a little more because they know what information I am capable of understanding'. (comment)*					
Subtheme 6: People with oesophago-gastric cancer as experts in their own right							
Andreassen 2005 Andreassen 2006 Mills 2000	3 studies using interviews	People with oesophago-gastric cancer are information sources for fellow people as well as family members or carers. Interactions with other people with oesophago-gastric cancer are generally positive and allow for positive, open discussions. *I haven't asked anything myself because I knew that my husband would ask everything so minutely himself. I know he would look up everything himself. He has shared his knowledge with me and we have discussed it together. (family member comment)* *It is immensely important that a new patient can talk with a fellow patient. That information is much*	Minor concerns over methodological limitations. CASP ratings: high (2 studies) and moderate (1 study)	Moderate concern over relevance: 2 studies with Swedish setting and mixed population.	Minor concerns over coherence (data reasonably consistent within and across studies).	Minor concerns over adequacy (3 studies that offered moderately rich data).	Moderate.

STUDY information			CERQUAL Quality Assessment				
Number of studies	**Design**	**Description of Theme or Finding**	**Methodological Limitations**	**Relevance**	**Coherence**	**Adequacy of Data**	**Overall Confidence**
		more valuable than the information the doctor gives. You can ask questions you wouldn't dare to pose otherwise. (comment) They used words such as `brilliant' and `terrific' to describe their encounters (author comment) *The main one there for me, which stands out in all of this, was talking to that woman [another patient]. That gave me the greatest hope. (comment)*					
Subtheme 7: Seeking information from TV and newspapers							
Andreassen 2005	1 study using semi-structured interviews	OG cancer may be missing from representation in mass media. TV and newspaper reports can offer positive or success stories. *I hadn't heard about that disease. I think you have heard about most of the variations, but not cancer of the oesophagus. (family member comment)* *I receive most of the information through the mass media. In that way, I get my information and it is sort of positive, since more and more people pull through. (family member comment)*	Minor concerns over methodological limitations. CASP ratings: moderate	Major concern over relevance: study with Swedish setting and mixed population.	Minor concerns over coherence (data reasonably consistent within study).	Major concern over adequacy (only 1 study included offering thin data).	Very low.
Subtheme 8: Seeking information from written material							

STUDY information			CERQUAL Quality Assessment				
Number of studies	**Design**	**Description of Theme or Finding**	**Methodological Limitations**	**Relevance**	**Coherence**	**Adequacy of Data**	**Overall Confidence**
Andreassen 2005 Mills 2000	2 studies with semi-structured interviews	Pamphlets produced vary in their utility to people and their families. The act of seeking information gives a sense of being productive to family members. *We have received books on how you deal with the illness, quite thin pamphlets from the medical authorities both to us and to the children. (family member comment)* *I have an encyclopaedia at home, which certainly is a bit old. I also have a book for quick medical reference, where I can look up different things in order to be able to read briefly about them. (family member comment)* *Seeking information is much more than receiving knowledge, it also includes a feeling of doing something. (family member comment)* All participants also received an information booklet produced by the Oesophageal Patients Association, and six participants spoke positively about this booklet. Some described it as `great' or `a tremendous help', while others just stated that it was useful. It was apparent from the data that participants used the booklet to refresh their memories and clarify any misconceptions. In addition, poor concentration postoperatively was experienced by	Minor concerns over methodological limitations. CASP ratings: moderate and high.	Moderate concern over relevance: 1 study with Swedish setting and mixed population.	Minor concerns over coherence (data reasonably consistent within and across studies).	Minor concerns over adequacy (2 studies that offered moderately rich data).	Moderate.

STUDY information			CERQUAL Quality Assessment				
Number of studies	Design	Description of Theme or Finding	Methodological Limitations	Relevance	Coherence	Adequacy of Data	Overall Confidence
		three participants and this could also explain why they frequently relied on written material. (author comment) One participant was particularly keen on written data and stated that he `knew the booklet inside and out' and that he could easily refer to different sections when he needed to clarify anything. In contrast, two patients described their concentration as being so poor that they could not read the booklet. It was thus less useful to them. (author comment) Three participants also indicated that written information was useful to their families to help them understand what had occurred and what to expect. However, one family did seek additional written information from the charity Cancer BACUP which provides advice, support and literature for cancer patients and their families. This indicates that the current booklet did not satisfy all their information needs. (author comment) One participant was very critical of the information booklet. He described it as being `too optimistic' and of viewing the situation through `rose-coloured glasses'. This patient also contradicted some of the current literature regarding					

STUDY information			CERQUAL Quality Assessment				
Number of studies	**Design**	**Description of Theme or Finding**	**Methodological Limitations**	**Relevance**	**Coherence**	**Adequacy of Data**	**Overall Confidence**
		the usefulness of written information. He stated: *I have read the booklet and what I took out of it, and my wife has read it and what she has taken out of it, we never actually discussed.* (comment)					
Subtheme 9: Seeking information from audio-visual sources							
Mills 2000	1 study with semi-structures interviews	Audio-visual sources of information vary in their utility to people. When asked about audio-visual methods of providing information, participants differed in their responses. Three participants, who highlighted some problems with written information, were in favour of audio-visual information, two were uncertain about the need for it and the remaining two, both from professional occupations, strongly opposed it, stating that training videos were generally of poor educational value and that videos were of little use for quick reference. (author comment)	Minor concerns over methodological limitations. CASP ratings: high.	Minor concerns over relevance. One study from the UK on patients undergoing operative treatment for OG Cancer.	Minor concerns over coherence (data reasonably consistent within study).	Major concern over adequacy (only 1 study included offering thin data).	Low.
Subtheme 10: Seeking information from the internet							
Andreassen 2005 Andreassen 2006	2 studies using semi-structured interviews	Information on the internet is not always applicable to all people. Seeking information on the internet can be upsetting and frightening. *I think that the Internet was a great help, since it is difficult to telephone*	Minor concerns over methodological limitations.	Major concern over relevance: 2 studies with Swedish setting and mixed population.	Minor concerns over coherence (data reasonably consistent	Minor concerns over adequacy (3 studies that	Moderate.

STUDY information			CERQUAL Quality Assessment				
Number of studies	**Design**	**Description of Theme or Finding**	**Methodological Limitations**	**Relevance**	**Coherence**	**Adequacy of Data**	**Overall Confidence**
		someone and pose relevant questions when I hardly know what I want to find out. Then it is possible that if you receive incorrect information, you can form an opinion later. (family member comment) *The prognosis was so bad. It was so depressing and I started to believe that I would find my husband dead in bed. I got terrified and there was nothing positive at all in the information I read. (family member comment)* *I said to the doctor that I had been on the Net and read about a study where it said that there was a terribly poor prognosis. He said that the information was not really current and that the prognosis is better now. I didn't go into greater detail. (family member comment)* *'It became apparent that I could just as well ignore the information since it dealt with men between 60- and 80 years old. You don't put up with this information when you are 44 years old. This information is completely irrelevant' (comment)* *I found a research report, brought it with me and discussed it with the doctor. He took it out of my hand and said, 'It doesn't apply to you'. I experienced it positively that he reacted so because it was a negative report. (comment)*	CASP ratings: high and moderate		within and across studies).	offered moderately rich data).	

STUDY information			CERQUAL Quality Assessment				
Number of studies	Design	Description of Theme or Finding	Methodological Limitations	Relevance	Coherence	Adequacy of Data	Overall Confidence

1 **Table 12: Summary clinical evidence profile (GRADE-CERQual): Theme 2. Not seeking information**

STUDY information			CERQUAL Quality Assessment				
Number of studies	Design	Description of Theme or Finding	Methodological Limitations	Relevance	Coherence	Adequacy of Data	Overall Confidence
Subtheme 1: Balancing needs							
Andreassen 2005	1 study with semi-structured interviews	Family members strive to find balance between receiving necessary information and being overwhelmed and frightened. *I want to know if the prognosis is terribly poor or if it is about one year. I want to know what will happen... Actually, I really don't want to know. (family member comment)* *Perhaps it isn't so terrible. Everything you know something about loses its terribleness. (family member comment)*	Minor concerns over methodological limitations. CASP ratings: moderate	Major concern over relevance: study with Swedish setting and mixed population.	Minor concerns over coherence (data reasonably consistent within study).	Major concern over adequacy (only 1 study included offering thin data).	Very low.
Subtheme 2: Fear							
Andreassen 2005 Andreassen 2006 McNair 2016	3 studies with semi-structured interviews	Fear of receiving upsetting information or bad news. Fear can be a barrier to seeking information on survival and prognosis. *Certainly I can search for information. That isn't the problem but the problem is that it takes time. I shall mobilise the courage,*	Minor concerns over methodological limitations. CASP ratings: high (2 studies) and moderate (1 study)	Moderate concern over relevance: 2 studies with Swedish setting and mixed population.	Minor concerns over coherence (data reasonably consistent within and across studies).	Minor concerns over adequacy (3 studies that offered moderately rich data).	Moderate.

STUDY information			CERQUAL Quality Assessment				
Number of studies	Design	Description of Theme or Finding	Methodological Limitations	Relevance	Coherence	Adequacy of Data	Overall Confidence
		the power, the energy . . . call it whatever you want, to be able to sit down and go through things. I am not sure I am going to like the answers I get. Maybe it is better not to know so very much but to do like the ostrich, to bury your head in the sand and hope for the best and keep your fingers crossed. (family comment) *I don't want to ask the doctor a question, which he has to respond to negatively when my husband is with me. (family member comment)* *I don't pose any questions because I think it is scary. I've left myself in the doctors' hands… they can help me. (comment)* *"I've got to ask the question because clearly those are the answers you want to know, you know. Am I gonna die? Or, you know, how long am I likely to live? You know, these are sort of basic questions that you want answers to but you're scared that someone's gonna say well, actually not very long', you know (laughs) and you can't argue because they're the professional". (comment)*					

1 **Table 13: Summary clinical evidence profile (GRADE-CERQual): Theme 3. Barriers to communication**

STUDY information			CERQUAL Quality Assessment				
Number of studies	**Design**	**Description of Theme or Finding**	**Methodological Limitations**	**Relevance**	**Coherence**	**Adequacy of Data**	**Overall Confidence**
Subtheme 1: Values							
Henselmans 2012	1 study with semi-structured interviews	Not wanting to be bothersome Feeling embarrassed about a subject *R2: (. . .) I think everybody has that in a certain way, you don't want to be too bothersome. You want to pose your question and you hope you will get an answer to that, but bothersome, no. No. You certainly don't want to be bothersome, no. (companion comment)* *I: And is it also because of that, that sometimes you don't ask something or keep your mouth shut?* *R: I think that in general, in that situation, most people are very modest, that is what I think. That is a human thing. You are visiting an expert who operated on you. (interview excerpt)* *R: No. No, in the beginning, I did have certain limits, but I don't have them anymore. [laughter]* *I: Ok, they all disappeared.* *R2: That wasn't [the case in] this conversation, but in the very first conversation with xxx, you were wondering if your breath would smell after the surgery. You didn't dare to ask that then.*	Minor concerns over methodological limitations. CASP ratings: high	Moderate concern over relevance: 1 study from The Netherlands.	Minor concerns over coherence (data reasonably consistent within study).	Moderate concern over adequacy (only 1 study offering results).	Low.

STUDY information			CERQUAL Quality Assessment				
Number of studies	**Design**	**Description of Theme or Finding**	**Methodological Limitations**	**Relevance**	**Coherence**	**Adequacy of Data**	**Overall Confidence**
		R: We did ask that then, didn't we? *R2: I asked that, yes.* *R: Well, I can't remember that I didn't dare to ask that.* *R2: Well, yes, you wanted to know that before, but you didn't ask it in the conversation. And then I asked it and then you downplayed it a little bit. (interview excerpt)*					
Subtheme 2: Beliefs							
Henselmans 2012 Andreassen 2006	2 studies with semi-structured interviews	Belief that it was not part of the surgeon's task or that the surgeon cannot provide an answer or solution anyway Perception there is too little time. Belief that a subject is not important. Expecting consequences of bringing up a subject. *[R and R2 say they had a hard time in the post-operative period]* *I: Do you want to bring up these things the next time you see the surgeon?* *R: Yes, I am not sure if you should speak to the surgeon about that, I personally don't think so. You see, the surgeon conducts the surgery and the follow-up care after surgery and I think for everything else, there*	Minor concerns over methodological limitations. CASP ratings: high	Major concern over relevance: study with Swedish setting and mixed population. 1 study from The Netherlands.	Minor concerns over coherence (data reasonably consistent within and across studies).	Minor concerns over adequacy (2 studies that offered moderately rich data).	Low.

STUDY information			CERQUAL Quality Assessment				
Number of studies	Design	Description of Theme or Finding	Methodological Limitations	Relevance	Coherence	Adequacy of Data	Overall Confidence
		are other people for that, I believe. (interview excerpt) *I: So, you're saying, I'm also a little bit afraid, this issue with eating, that might also be because I don't dare to. Would you like to discuss that with the surgeon?* *R: No, he cannot provide an answer anyway. Probably, this surgeon will probably say, nonsense or it will improve naturally.(interview excerpt)* *R: Well, I do sometimes have the feeling that everything has to take place within a certain time span, and that I find detrimental, that often you have to go over a number of things rather quickly... I think that is the disadvantage that that is hanging over it a little bit. Yes. Especially with the GP, then you have to leave within 10 minutes, back through the door. (interview excerpt)* *R: I am not sure how much time with the surgeon …* *I: I think it is the same… 10, 15 minutes …* *R: So you know that, so you have to more or less... yes, give those answers fast and quickly, or pose those questions.* *Sometimes I have written down a lot of questions, but usually not*					

STUDY information			CERQUAL Quality Assessment				
Number of studies	Design	Description of Theme or Finding	Methodological Limitations	Relevance	Coherence	Adequacy of Data	Overall Confidence
		more than half or in some cases a third part is answered…the doctors are so rushed and suddenly they are gone. (interview excerpt) *R2: Yes, that they should… that the surgeon should realize more that there are lay people in front of him who did not go to college and who are just lay people. And that for them, it is always very terrible, while for a surgeon it might be … like, well, is that all? But for the patient it is really terrible. Cause they know what they are talking about and for us it is something unfamiliar, that suddenly happens to you…* *R2: Yes, so they should think more about the people, realize that for the patient it sometimes does… yes… Cause because of the response, you sometimes don't dare to[speak up] anymore. That's it. (interview excerpt)* *I: And would you like to talk about this kind of thing in the hospital, I mean about anxiety or sadness?* *R: Not really, no. No, because it won't help me… they might talk you into other things…while it is not really an issue for me [negative emotions].*					

STUDY information			CERQUAL Quality Assessment				
Number of studies	**Design**	**Description of Theme or Finding**	**Methodological Limitations**	**Relevance**	**Coherence**	**Adequacy of Data**	**Overall Confidence**
		I: No, cause what doyou mean exactly, if you bring that up, then… *R: Then they might refer you and then you end up with a shrink or something like that… (interview excerpt)*					
Subtheme 3: Skills							
Henselmans 2012 Andreassen 2006 Andreassen 2005 Mills 2000	4 studies with interviews	Uncertainty about own understanding Remembering questions only afterwards Too tired to ask questions Not being able to process information and ask subsequent questions No experience with this type of conversation Not knowing what to ask or how to interrupt the doctor *I: Ok, any other things that makes it difficult to say or to ask what's on your mind?* *R2: That there are things of which we think like well, maybe it has something to do with it. Often you have, how should I say this… you see, that is what I mean…that's what stops you, because you can't say something completely clearly, you don't say it. Cause that's what it is like. That you think, like, I have the*	Minor concerns over methodological limitations. CASP ratings: high (3 studies) and moderate (1 study)	Moderate concern over relevance: 2 studies with Swedish setting and mixed population. 1 study from The Netherlands.	Minor concerns over coherence (data reasonably consistent within and across studies).	Minor concerns over adequacy (4 studies that offered rich data).	Moderate.

STUDY information			CERQUAL Quality Assessment				
Number of studies	Design	Description of Theme or Finding	Methodological Limitations	Relevance	Coherence	Adequacy of Data	Overall Confidence
		idea it might have something to do with it, but you don't want to raise it, because then you might stray off… Yes, I am not sure how to say this right. But that is also what stops you often [referring to husband]. *(R2 says he would have liked to know about the possibility of recurrence)* *R2: Yes, the chance of… that is something I would like to know. Yes. That question I already wanted to pose, by the way, when we were there the last time, but then it did not happen.* *R: Yes, simply forgotten I think. . .* *R2: Yes, forgotten (interview excerpt)* *There is a great deal I should have asked the doctor about, but I was so tired of everything that I got to the point that I didn't feel like doing it. I became worn out over everything and had enough. (comment)* I*: You say, because you have little experience with having such conversations, and you noticed that in…?* *R: Well yes, you are the subject of the conversation and everything is new and, yes, for some time that has… yes that*					

STUDY information			CERQUAL Quality Assessment				
Number of studies	Design	Description of Theme or Finding	Methodological Limitations	Relevance	Coherence	Adequacy of Data	Overall Confidence
		has an impact, it's about you, and not about your work. *I: Yes, so do you then succeed in getting attention for what you personally want to say? Did you succeed at that time?* *R2: You are actually waiting for what she is going to say, cause otherwise you don't know any questions at all, while she is talking… then you think, that is what I am going to ask in a moment, but then she is actually already so far, before you get to ask that question….* *I:...then the moment is gone….* *R2: Then the moment is gone.* *(interview excerpt)* *R: Maybe this kind of things, these questions here [referring to the preformatted lists used in the interview], and maybe even the largest part of the items where the question was, like, do you want to discuss that with the surgeon', this question could come from the surgeon, when you are visiting.* *I: Yes, that is a possibility, that he asks you, do you want to talk about that?* *R: Yes, cause you can't think of it yourself. (interview excerpt)* *You are not enough medically knowledgeable. Therefore, you*					

STUDY information			CERQUAL Quality Assessment				
Number of studies	Design	Description of Theme or Finding	Methodological Limitations	Relevance	Coherence	Adequacy of Data	Overall Confidence
		don't know what to ask. (family member comment) *If you ask you will be told, but if you don't know what to ask, then your questions will never be answered. (comment)* *What you could say related to that, is that, you know, because it is a whole new area and because it is about you personally, that the pace might be too high. That was not really a big issue in this conversation, I believe, but that could play a part. You always come home and then you think like, ah yes, maybe I should have enquired a bit further on that subject. (comment)*					

1 **Table 14: Summary clinical evidence profile (GRADE-CERQual): Theme 4. Facilitators to Communication**

STUDY information			CERQUAL Quality Assessment				
Number of studies	Design	Description of Theme or Finding	Methodological Limitations	Relevance	Coherence	Adequacy of Data	Overall Confidence
Subtheme 1: Personality or attitude of the surgeon							
Henselmans 2012	Semi-structured interviews	Personality characteristics of the surgeon may help or hinder interactions. Consistent consultant surgeon interactions help facilitate communication with people *R: It also depends a lot on the person, I believe. Yes, cause I know*	Minor concerns over methodological limitations. CASP ratings: high	Moderate concern over relevance: 1 study from The Netherlands.	Minor concerns over coherence (data reasonably consistent within study).	Moderate concern over adequacy (only 1 study offering results).	Low.

STUDY information			CERQUAL Quality Assessment				
Number of studies	**Design**	**Description of Theme or Finding**	**Methodological Limitations**	**Relevance**	**Coherence**	**Adequacy of Data**	**Overall Confidence**
		that with that other surgeon it was much more difficult. *I: With doctor xxx.* *R: That is a totally different person. And maybe that is also a different type of conversation that I don't know. But there it was more difficult, cause he was more in a hurry. (interview excerpt)* *R: I think is a pity…well yes, it is a holiday season, that you didn't see the surgeon that operated on you. Cause yes, that makes the conversation difficult. Although…well, yes, doctor xxx did…yes, we were out of there in no time. Well, I think we weren't in there for more than ten minutes, very short. Yes, I thought that was a pity. And for Wednesday, will I have more…yes, I expect that doctor xxx will be back. (interview excerpt)*					
Subtheme 2: Pre-visit preparatory interventions							
Henselmans 2012	Semi-structured interviews	Many people endorsed some sort of pre-visit preparatory intervention. Many patients saw merit in the suggested types of pre-visit preparatory interventions - 13 endorsed a written question prompt sheet, 9 a preparatory website (including example questions) and 8 a preparatory conversation with a nurse prior to the consultation with the physician. Some patients would	Minor concerns over methodological limitations. CASP ratings: high	Moderate concern over relevance: 1 study from The Netherlands.	Minor concerns over coherence (data reasonably consistent within study).	Moderate concern over adequacy (only 1 study offering results).	Low.

STUDY information			CERQUAL Quality Assessment				
Number of studies	**Design**	**Description of Theme or Finding**	**Methodological Limitations**	**Relevance**	**Coherence**	**Adequacy of Data**	**Overall Confidence**
		appreciate example questions (independent of the medium), because these show them the range and type of questions appropriate to ask a physician. A few patients compared example questions with the preformatted topic list used in the interview, to illustrate how this helped them think about their needs. A few patients warned that example questions might prevent patients from coming up with their own questions. Moreover, a few patients did not endorse internet-based preparation, as they did not have internet access, were not frequent users or disliked searching the internet for information. A few patients mentioned additional benefits of preparing for the consultation with a nurse, i.e., a nurse has more time to 'pull things out of you' and can already deal with some questions. (author comment)					
Subtheme 3: Skill building intervention							
Henselmans 2012	Semi-structured interviews	Few patients endorsed the suggested skill-building interventions - 5 endorsed a brochure on how to talk to your doctor, while none endorsed videos modelling doctor-patient communication or a workshop in communication skills. A few patients mentioned that such interventions are 'too far-fetched' and some considered every	Minor concerns over methodological limitations. CASP ratings: high	Moderate concern over relevance: 1 study from The Netherlands.	Minor concerns over coherence (data reasonably consistent within study).	Moderate concern over adequacy (only 1 study offering results).	Low.

STUDY information			CERQUAL Quality Assessment				
Number of studies	Design	Description of Theme or Finding	Methodological Limitations	Relevance	Coherence	Adequacy of Data	Overall Confidence
		conversation to be unique, so 'examples won't help'. A few thought it might help other (older, less assertive) patients, but would not benefit them. (author comment)					

1 **Table 15: Summary clinical evidence profile (GRADE-CERQual): Theme 5. Pre-operative information needs.**

STUDY information			CERQUAL Quality Assessment				
Number of studies	Design	Description of Theme or Finding	Methodological Limitations	Relevance	Coherence	Adequacy of Data	Overall Confidence
Subtheme 1: Technical Information							
McNair 2016 Mills 2000	2 studies of semi-structured interviews	Emphasis on surgical techniques and in-hospital risks by surgeons. People accepting the necessity of technical information. Some people did not want technical information and some found it overwhelming. *Now, the operation is a very big operation. It's a very serious operation and there are risks involved, ok? It is one of the biggest operations a human being can actually undergo. (consultant comment)* *The overall mortality rate with a major operation like this, in our hands, is less than two percent, so it's a ninety-eight percent chance of getting through it. (consultant comment).* *I think it's, erm- 'cause of litigation, isn't it these days–they have to tell you everything. (comment)*	Minor concerns over methodological limitations. CASP ratings: high	Minor concerns over relevance. Two studies from the UK on patients undergoing operative treatment for oesophago-gastric cancer.	Minor concerns over coherence (data reasonably consistent within study).	Minor concerns over adequacy (2 studies that offered moderately rich data).	High.

STUDY information			CERQUAL Quality Assessment				
Number of studies	Design	Description of Theme or Finding	Methodological Limitations	Relevance	Coherence	Adequacy of Data	Overall Confidence
		I did have the fleeting thought going through my mind, 'For goodness sake, why are you telling me all this. I'm confident, you're confident. Let's get on with it (comment) *I don't think I was as interested in that sort of detail. I know that there are risks, I don't want to dwell on it. It's always near the front of your mind at this particular time - and you're trying to get away from that as much as possible (comment)* *I must confess it came as rather a blow and what I what I didn't like really were the statistics that he went into - I would have liked to have heard more about the sort of positive side of it. (comment)* *Surgeons see it every day. They're quite happy to talk about it. A lot of people seen somebody run over in the road and their insides hanging out, they'd be on the side of the road throwing up. You know, and if they tell you they're gonna do something similar to you, you don't wanna know about it. (comment)* *Obviously one needs some idea of the process but not necessarily every gory detail. (comment)* *Assumptions were made that people know what procedures are all about So a number of assumptions were made, are made, that people know*					

STUDY information			CERQUAL Quality Assessment				
Number of studies	**Design**	**Description of Theme or Finding**	**Methodological Limitations**	**Relevance**	**Coherence**	**Adequacy of Data**	**Overall Confidence**
		about these things, and people don't. (comment) Likewise, one woman stated that she had no idea what to expect about hospitalisation in general as neither she nor any of her family had ever been in hospital. (author comment)					
Subtheme 2: Health-related quality of life							
McNair 2016	Semi-structured interviews	Recovery, long-term quality of life information was desired by most but not all people Long-term effects of surgery were minimised by surgeons *I was trying to gauge what the time would be before I could begin to embark upon relatively normal activities. (comment)* *Will I not be able to work any more? (comment)* *I wanted to know basically what you're like. Can you, erm, do the things that I now do? Bearing in mind I'm seventy-six years old and I can't run about like I used to …after six months, erm, how - what will it do? Can I - will I be able to stretch? Will I be able to paint the ceiling? Will I be able to run about? What I'll be like - I'll be able to drive a car, I guess but- you know, so those are the things.(comment)* *I don't think that I would really want to know what would be the long-term problems if any. I want to stay on top– I want to keep on top of it… I don't*	Minor concerns over methodological limitations. CASP ratings: high	Minor concerns over relevance. One study from the UK on patients undergoing operative treatment for oesophago-gastric cancer.	Minor concerns over coherence (data reasonably consistent within study).	Moderate concern over adequacy (only 1 study offering thin results).	Moderate.

STUDY information			CERQUAL Quality Assessment				
Number of studies	**Design**	**Description of Theme or Finding**	**Methodological Limitations**	**Relevance**	**Coherence**	**Adequacy of Data**	**Overall Confidence**
		really want to think too far ahead, there is probably enough to think about, y'know, at the moment. (comment) *It can take six months or so before you are back to where you were, maybe longer—six to nine months to how you're feeling now. (consultant comment)* *He said, 'six months.' But that's to full fitness, you should be feeling a lot better a lot sooner. (comment)*					
Subtheme 3: Prognosis and survival							
McNair 2016 Mills 2000	2 studies of semi-structured interviews	Survival information was desired by people. Importance of honesty of physicians was emphasized by people. *I'd like to know is- is your thoughts on, erm- on whether you'd like to know the- the chances of a successful cure and these kinds of things. (patient)* *But, you know, as- as I tell people, you know, if- say there was a percentage cure rate, you're not gonna be percentage cured, you're either gonna be cured or not cured and that's a problem – that's when we just don't know anything. (consultant)*	Minor concerns over methodological limitations. CASP ratings: high	Minor concerns over relevance. Two studies from the UK on patients undergoing operative treatment for oesophago-gastric cancer.	Minor concerns over coherence (data reasonably consistent within study).	Minor concerns over adequacy (2 studies that offered moderately rich data).	High.

STUDY information			CERQUAL Quality Assessment				
Number of studies	**Design**	**Description of Theme or Finding**	**Methodological Limitations**	**Relevance**	**Coherence**	**Adequacy of Data**	**Overall Confidence**
		I thought, it's better that [surgeon] said that than, 'Oh look, we'll cure you. (patient) *He told me that it was localized, and all the good news, that it was in the lower third, which is highly survivable, or less fatal. He said `I don't know whether I can help you or not.' You can't get straighter than that. That was what I liked. I can't stand anybody beating around the bush. (patient comment)*					
Subtheme 4: Post-operative complications							
Mills 2000	Semi-structured interview	Most, but not all, people were well-informed about post-operative complications. In relation to possible side-effects of the operation, participants appeared to be well informed, through both verbal and written means, about the possibility of having swallowing difficulties. Some other side-effects were also included in the information booklet, such as dietary problems, changes in gastric emptying and altered bowel habit. However, one participant felt that she did not receive satisfactory advice on discharge about postoperative complications and it was this woman's family that contacted the Cancer BACUP help-line to clarify some issues. Another stated `all the little set-backs made me	Minor concerns over methodological limitations. CASP ratings: high	Minor concerns over relevance. One study from the UK on patients undergoing operative treatment for oesophago-gastric cancer	Minor concerns over coherence (data reasonably consistent within study).	Major concern over adequacy (only 1 study offering thin results with limited qualitative detail).	Low.

STUDY information		Description of Theme or Finding	CERQUAL Quality Assessment				
Number of studies	Design		Methodological Limitations	Relevance	Coherence	Adequacy of Data	Overall Confidence
		feel that they were lying'. (author comment)					

1 **Table 16: Summary clinical evidence profile (GRADE-CERQual): Theme 6. Post-operative information needs**

STUDY information		Description of Theme or Finding	CERQUAL Quality Assessment				
Number of studies	Design		Methodological Limitations	Relevance	Coherence	Adequacy of Data	Overall Confidence
Subtheme 1: Nutrition							
Henselmans 2012	Semi-structured interviews	Almost all people desired information on nutrition. Almost all patients had questions related to nutrition. In the top three were meal size, enteral nutrition (providing food through a stomach tube) and dysphagia. (author comment)	Minor concerns over methodological limitations. CASP ratings: high	Moderate concern over relevance: 1 study from The Netherlands.	Minor concerns over coherence (data reasonably consistent within study).	Moderate concern over adequacy (only 1 study offering results).	Low.
Subtheme 2: Health-related quality of life							
Henselmans 2012 Mills 2000	2 studies of semi-structured interviews,	People desired information on when they could expect a return to normality as well as the likely course of symptoms and limitations. One quarter of patients' information needs (26%) within the HRQL domain reflected a need for information about the likely course of symptoms or limitations. In addition, patients' information needs often reflected a need to understand the cause of symptoms and limitations and	Minor concerns over methodological limitations. CASP ratings: high	Moderate concern over relevance: 1 study from The Netherlands.	Minor concerns over coherence (data reasonably consistent within study).	Moderate concern over adequacy (2 studies offered limited qualitative details).	Low.

STUDY information			CERQUAL Quality Assessment				
Number of studies	**Design**	**Description of Theme or Finding**	**Methodological Limitations**	**Relevance**	**Coherence**	**Adequacy of Data**	**Overall Confidence**
		whether or not a symptom was considered 'normal' (22%). Moreover, a number of information needs reflected requests for information about self-management (17%), i.e., how to deal with symptoms or limitations in daily life. Lastly, patients often reported a need to discuss a certain symptom with the physician, without indicating a specific reason or question (31%). (author comment) Six participants indicated that they were given some advice relating to their return to normality and self-care. `I just wanted to get back to my routine.' Four participants indicated that they required more information about convalescence. (author comment)					
Subtheme: 3: Medical care							
Henselmans 2012	1 study of semi-structured interviews	People desired information on medical care including the hospital treatment course and self-management. Many patients had questions about medication (the use of painkillers, antacid), the follow-up procedure and technical aspects of surgery. Patients' questions often reflected a need for explanation (54%), e.g., about how patients will be monitored	Minor concerns over methodological limitations. CASP ratings: high	Moderate concern over relevance: 1 study from The Netherlands.	Minor concerns over coherence (data reasonably consistent within and between studies).	Moderate concern over adequacy (1 study offered limited qualitative details).	Low.

STUDY information			CERQUAL Quality Assessment				
Number of studies	**Design**	**Description of Theme or Finding**	**Methodological Limitations**	**Relevance**	**Coherence**	**Adequacy of Data**	**Overall Confidence**
		and the necessity of tests (e.g., scans), about things that happened during hospital admission or about how surgery changed their body. Other questions within this domain reflected a need for self-management information (33%), often related to medication (about prolongation or how to quit use), wound care and the availability of or referral to other care providers (physiotherapist, family support). (author comment)					
Subtheme 4: Prognosis and Survival							
Henselmans 2012 Malmstrom 2013 Mills 2000	1 study of focus groups, 2 studies of semi-structured interviews	Knowing whether the surgery was successful was important to most people. People highlighted the importance of setting realistic expectations. Some patients emphasized that the outcome of surgery was most important in the first consultation after discharge and many reported a need to be informed about these results (70%). Fewer patients, but still 40%, reported a need to be informed about the likelihood of recurrence. (author comment) *One thing that I miss especially is this: What's the prognosis? Will I be around in five years' time, or three years or will I just kick the*	Minor concerns over methodological limitations. CASP ratings: high	Moderate concern over relevance: 1 study from The Netherlands. 1 study from Sweden.	Minor concerns over coherence (data reasonably consistent within study).	Minor concern over adequacy (3 studies offering moderately rich data).	Moderate.

STUDY information		Description of Theme or Finding	CERQUAL Quality Assessment				
Number of studies	Design		Methodological Limitations	Relevance	Coherence	Adequacy of Data	Overall Confidence
		bucket? I'm not afraid of that//dying. It's just, I wonder about the future, I mean I've got kids and all. (comment) *We have your lab test back and you are completely clear. There is no cancer anywhere. He said it was a great success. (comment)* *He told me, `You had four out of 14 nodes that were positive. The four nodes were small and that is good news. Anything that was left could take years to reoccur, if ever.' (comment)*					

5.1.4.21 Clinical evidence profile: support needs for adults with OG cancer suitable for curative treatment and their carers.

2 **Table 17: Summary clinical evidence profile (GRADE-CERQual): Theme 1. Intrusions on family.**

STUDY information		Description of Theme or Finding	CERQUAL Quality Assessment				
Number of studies	Design		Methodological Limitations	Relevance	Coherence	Adequacy of Data	Overall Confidence
Subtheme 1: Children							
Andreassen 2005 Andreassen 2006	2 studies of semi-structured interviews	Children need support and are affected by parents' diagnosis. *I don't think anyone has ever asked how old our children are, if they visit school or anything like that. They don't seem to care that there is a family around the patient and that we in fact have a sixteen-year-old*	Minor concerns over methodological limitations. CASP rating: moderate and high	Major concern over relevance: Indirect evidence. Uncertain evidence: studies included use a mixed population of people receiving both palliative and curative treatment. Indirect evidence:	Minor concerns over coherence. Data reasonably consistent within and across studies.	Moderate concern over data adequacy due to only 2 linked studies offering moderate data richness.	Very low.

STUDY information			CERQUAL Quality Assessment				
Number of studies	Design	Description of Theme or Finding	Methodological Limitations	Relevance	Coherence	Adequacy of Data	Overall Confidence
		son, who has grown up with this. (family member comment) *Our son had his 18th birthday this year. Although he himself says that his mother's illness doesn't affect him at all, we have noted that his grades dropped disastrously during his first term. (family member comment)* *I think it would be good to receive joint information, to involve the children, since the parent, who comes home is a little foreign. You can say: 'One parent left and another one came home who is also a patient at home.' (family member comment)* *My 18-year-old son was feeling very badly when he got the information that his mother had cancer. From having excellent marks in all his subjects, he started to ignore school completely. He didn't discuss this with my husband or me. He didn't want to make me upset or his father unhappy. He was convinced that I would die. He gave up everything. (comment)* *It's immensely important that he also has a chance to meet someone, who allows him to express himself in his own way. (comment on son with special*		included studies from Sweden.			

STUDY information		Description of Theme or Finding	CERQUAL Quality Assessment				
Number of studies	**Design**		**Methodological Limitations**	**Relevance**	**Coherence**	**Adequacy of Data**	**Overall Confidence**
		needs coping with parent's illness)					
Subtheme 2: Effect on partner role and relationship							
Andreassen 2006	1 study of semi-structured interviews	People need to be supported through changing roles and relationships. *My husband does all the housework; he cooks, he irons, he does laundry, he takes the dog for a walk five times a day and he helps our son iron his clothes. (comment)* *I became somewhat dependent on my wife, who had to help me wash up around the gastrostomy. (comment)* *I feel that the cancer hasn't struck me too hard, but my wife has taken it much worse mentally. (comment)*	Minor concerns over methodological limitations. CASP rating: high	Major concern over relevance: Indirect evidence. Uncertain evidence: study included use a mixed population of people receiving both palliative and curative treatment. Indirect evidence: included study from Sweden.	Minor concerns over coherence. Data reasonably consistent within study.	Major concern over data adequacy due to only 1 study offering relatively thin data.	Very low.

1 **Table 18: Summary clinical evidence profile (GRADE-CERQual): Theme 2. Uncertainty**

STUDY information		Description of Theme or Finding	CERQUAL Quality Assessment				
Number of studies	**Design**		**Methodological Limitations**	**Relevance**	**Coherence**	**Adequacy of Data**	**Overall Confidence**
Subtheme 1: Course and prognosis							
Andreassen 2005 Andreassen 2006	2 studies of semi-structured interviews	Feelings of uncertainty surrounding course and prognosis are constant and can lead to hopelessness.	Minor concerns over methodological limitations.	Major concern over relevance: Indirect evidence. Uncertain evidence: studies	Minor concerns over coherence. Data reasonably consistent within	Moderate concern over data adequacy	Very low.

STUDY information			CERQUAL Quality Assessment				
Number of studies	**Design**	**Description of Theme or Finding**	**Methodological Limitations**	**Relevance**	**Coherence**	**Adequacy of Data**	**Overall Confidence**
		They tell me they don't know why I got it and they can't give me a prognosis. Of course, that's not what you want to hear from your doctor…but if you think about it, they really don't know either. Sometimes it feels so hopeless. (comment) *You know all the time that one day it will get worse. You may receive an answer that it is a metastasis, exactly as we received now. I live constantly with this. (family member comment)* *Since after five years one is considered be out of the danger zone, we can calculate that my husband will in some form be given a clean bill of health, but perhaps not quite be declared healthy.(family comment)*	CASP rating: moderate and high	included use a mixed population of people receiving both palliative and curative treatment. Indirect evidence: included studies from Sweden.	and across studies.	due to only 2 linked studies offering moderate data richness.	
Subtheme 2: Future							
Andreassen 2005 Andreassen 2006	2 studies of semi-structured interviews	Uncertainty around the future affects planning and behaviour. *Shall we sell the house or shall we not? Shall we renovate our house or shall we not. Shall I work full time or shall I not? Will my husband die tomorrow,*	Minor concerns over methodological limitations. CASP rating: moderate and high	Major concern over relevance: Indirect evidence. Uncertain evidence: studies included use a mixed population of people receiving both palliative and curative treatment.	Minor concerns over coherence. Data reasonably consistent within and across studies.	Moderate concern over data adequacy due to only 2 linked studies offering moderate	Very low.

STUDY information			CERQUAL Quality Assessment				
Number of studies	**Design**	**Description of Theme or Finding**	**Methodological Limitations**	**Relevance**	**Coherence**	**Adequacy of Data**	**Overall Confidence**
		or what? (family member comment) *When I heard that I didn't have any metastases, I thought that perhaps this is only a respite and therefore I have been terribly active. I work frantically. I think that time is very valuable, something I never bothered about before. (comment)* *We have a son who will graduate this summer. The whole time I've set up a goal to take part in his graduation day. (comment)* *I think that as long as I want to live, I will fight to be healthy (comment)*		Indirect evidence: included studies from Sweden.		data richness.	
Subtheme 3: Hereditary							
Andreassen 2005 Andreassen 2006	2 studies of semi-structured interviews	People were concerned with the heredity of the cancer and uncertain whether their children would be affected. *What worries me most is that the illness will affect the children. If they will get this… whether it is hereditary. (family member comment)* *Since my brother now has cancer of the oesophagus and all my other siblings and my mother and father also had cancer, I want to know if I am*	Minor concerns over methodological limitations. CASP rating: moderate and high	Major concern over relevance: Indirect evidence. Uncertain evidence: studies included use a mixed population of people receiving both palliative and curative treatment. Indirect evidence: included studies from Sweden.	Minor concerns over coherence. Data reasonably consistent within and across studies.	Moderate concern over data adequacy due to only 2 linked studies offering moderate data richness.	Very low.

STUDY information			CERQUAL Quality Assessment				
Number of studies	**Design**	**Description of Theme or Finding**	**Methodological Limitations**	**Relevance**	**Coherence**	**Adequacy of Data**	**Overall Confidence**
		exposed to cancer and have it in my genes, so I can take some special tests. (family member comment) *My Dad and his brother died of cancer (comment)*					
Subtheme 4: Existential concerns							
Andreassen 2006 McCorry 2009	1 focus group study, 1 study of semi-structured interviews	People need support adjusting to the emotional changes of receiving a diagnosis of and living with a life-threatening illness. *What will happen? Will I survive? Will I die? Will I only be lying in bed and die/ (comment)* *Haven't I taken care of myself well enough? (comment)* *When you have the operation it changes your life. . . . It changes you mentally and I feel that eh . . . somewhere along the line I think a psychologist could talk to you and ease your worries, because we all know doubt…. You don't know when you'll be getting measured for the coffin. (comment)* *It's the fear of the unknown. If I get it again there's nowhere else to go, but…there's more chance of getting knocked down by a bus…I had my*	Minor concerns over methodological limitations. CASP rating: high	Moderate concern over relevance: 1 study from Sweden with a mixed population.	Minor concerns over coherence. Data reasonably consistent within and across studies.	Moderate concern over data adequacy due to 2 studies offering moderate data richness	Low.

STUDY information		Description of Theme or Finding	CERQUAL Quality Assessment				
Number of studies	Design		Methodological Limitations	Relevance	Coherence	Adequacy of Data	Overall Confidence
		surgery five and a half years ago and I keep very active, and eh, I think it's part of the cure. (comment)					

1 **Table 19: Summary clinical evidence profile (GRADE-CERQual): Theme 3. Receiving a diagnosis of OG cancer**

STUDY information		Description of Theme or Finding	CERQUAL Quality Assessment				
Number of studies	Design		Methodological Limitations	Relevance	Coherence	Adequacy of Data	Overall Confidence
Subtheme 1: Unprepared without prior knowledge							
Andreassen 2006	Semi-structured interviews	People found receiving a diagnosis of oesophago-gastric cancer particularly hard as they had no previous knowledge of the disease. *I knew nothing about my condition before I got the diagnosis. I was completely dumbfounded. My wife said when the doctor discussed it, I looked like a little child. (comment)* *If the doctors had told me it was breast cancer, uterine cancer, gastric cancer or intestinal cancer, I would have understood. But I had never expected this. (comment)*	Minor concerns over methodological limitations. CASP rating: high	Major concern over relevance: Indirect evidence. Uncertain evidence: study included use a mixed population of people receiving both palliative and curative treatment. Indirect evidence: included study from Sweden.	Minor concerns over coherence. Data reasonably consistent within study.	Major concern over data adequacy due to only 1 study offering relatively thin data.	Very low.
Subtheme 2: Coping with a death sentence							
McCorry 2009	Focus group	People experience a loss of control when receiving a	Minor concerns over	Minor concerns over relevance.	Minor concerns over coherence.	Major concern	Low.

STUDY information			CERQUAL Quality Assessment				
Number of studies	Design	Description of Theme or Finding	Methodological Limitations	Relevance	Coherence	Adequacy of Data	Overall Confidence
		diagnosis of oesophago-gastric cancer. *When you are first diagnosed it hits you like a 10-ton hammer hitting you in the chest, but when you think about it, okay, you've got cancer, what can I do about it? Nothing. And that's what I said to my cancer specialist. "I don't have the problem, you have the problem, so I'm not going to worry about it. I'm giving it to you, you worry about it." And exactly the same thing with the surgeon. (comment)*	methodological limitations. CASP rating: moderate	One study from the UK on patients undergoing operative treatment for oesophago-gastric cancer.	Data reasonably consistent within study.	over data adequacy due to only 1 study offering relatively thin data.	

1 **Table 20: Summary clinical evidence profile (GRADE-CERQual): Theme 4. Adjusting to and accepting an altered self.**

STUDY information			CERQUAL Quality Assessment				
Number of studies	Design	Description of Theme or Finding	Methodological Limitations	Relevance	Coherence	Adequacy of Data	Overall Confidence
Subtheme 1: Adjusting to physical changes							
Andreassen 2006	1 study of semi-structured interviews	People experience physical changes with affect daily-life activities. The experience of undergoing treatments and investigation is extremely tiring. *The cancer itself hasn't given me any concerns, but it is the treatment that takes away my strength. When I finished the radiotherapy, I was so exhausted that I couldn't walk. The*	Minor concerns over methodological limitations. CASP rating: moderate and high	Major concern over relevance: 1 study from Sweden with a mixed population.	Minor concerns over coherence. Data reasonably consistent within study.	Minor concern over data adequacy (1 study offering moderate data richness).	Low.

STUDY information			CERQUAL Quality Assessment				
Number of studies	**Design**	**Description of Theme or Finding**	**Methodological Limitations**	**Relevance**	**Coherence**	**Adequacy of Data**	**Overall Confidence**
		first week I rested at home. (comment) *The doctor said that after the treatment I would be very, very tired. I thought that this tumour was so small and that I could fix it in a month or two. But oh, how I deceived myself. I am terribly, terribly tired. (comment)* *I really don't understand why I'm still so tired after 6 months…but I am. (comment)* *I am terribly, terribly tired. Certainly, I am out walking every day, but not very long stretches. I must stop quite often to breathe and to rest a little while. (comment)*					
Subtheme 2: Adjusting to role changes							
McCorry 2009	Focus groups	People must accept and adjust to role changes. *You get up some mornings and you don't feel like doing anything. Those are the mornings that you really say to yourself, "Right—start such and such, because if you get started you keep going." . . . Having something to do and something to think about is the best medicine of the whole lot. (comment)*	Minor concerns over methodological limitations. CASP rating: moderate	Minor concerns over relevance. One study from the UK on patients undergoing operative treatment for oesophago-gastric cancer.	Minor concerns over coherence. Data reasonably consistent within study.	Major concern over data adequacy due to only 1 study offering relatively thin data.	Low.

STUDY information			CERQUAL Quality Assessment				
Number of studies	**Design**	**Description of Theme or Finding**	**Methodological Limitations**	**Relevance**	**Coherence**	**Adequacy of Data**	**Overall Confidence**
Subtheme 3: Dietary habits changed							
McCorry 2009 Andreassen 2006	1 focus group, 1 semi-structured interview	Dietary habit changes are an intrusion into daily-life. Dietary changes are also linked to changes and adjustments to social life. *You feel so embarrassed and you are eating a wee corner of your meal, and the waiter says, 'Is there something wrong with that?'* *I can't eat the same food as I used to eat and I have no appetite right now. Cooking is no fun. Nothing tastes good anymore. I try to eat sour milk, but I keep vomiting. I have an enormous amount of phlegm and it really bothers me. (comment)* *I have no energy…and it is really hard for me to eat anything. Where I used to eat two potatoes, I can only eat one now and even that can be too much. Eating makes me so tired that I have to lie down, even though I haven't eaten a whole lot. (comment)* *The PEG is an obstacle when I shower and when I travel. It has to be washed. I can't go to a public sauna and places like that. (comment)* *Every day there was something else that you couldn't get down. Even different liquids. Suddenly I found even the tea couldn't go*	Minor concerns over methodological limitations. CASP rating: moderate and high	Moderate concern over relevance: 1 study from Sweden with a mixed population.	Minor concerns over coherence. Data reasonably consistent within study.	Minor concern over data adequacy (2 studies offering data richness).	Moderate.

STUDY information			CERQUAL Quality Assessment				
Number of studies	Design	Description of Theme or Finding	Methodological Limitations	Relevance	Coherence	Adequacy of Data	Overall Confidence
		down. Then the coffee wouldn't go down and some solids as well… I would suddenly have to disappear because maybe a wee sandwich that I knew I could eat the previous day, I just couldn't get it down that day. You had to disappear to get rid of it. It was awkward and I stopped eating in front of anybody, even my wife. So before the surgery, every day there was something else you couldn't get down, and after the surgery, every day, there was something that you could get down. (comment) *You can't really eat a lot, but I don't find something telling me that I'm full and if I enjoy something I would say, "Is there any more?" But after it is down, that extra [food] I feel as if I want to be sick then, but it's only after I've eaten it . . . I just find that you have to accept it, and this is how life is going to be from now on. That's the way I look at it. (comment)* *Well I've got to the stage now where I cut off [eating] at a certain level, because you can find yourself in the bathroom or you find it coming up again, so you try and measure your meal as you go and stop at the right time. It is hard to do. (comment)*					

1 **Table 21: Summary clinical evidence profile (GRADE-CERQual): Theme 5. Hospital-based support**

STUDY information			CERQUAL Quality Assessment				
Number of studies	**Design**	**Description of Theme or Finding**	**Methodological Limitations**	**Relevance**	**Coherence**	**Adequacy of Data**	**Overall Confidence**
Subtheme 1: Importance of future planning							
Malmstrom 2013	Focus group	Hospital-based support is needed to plan for discharge from hospital services. *Up until then (discharge) we'd received all the information we needed. But afterwards I thought of it today, when am I going to the doctor the next time? They told me it was the last time what did they mean by that? (comment)*	Minor concerns over methodological limitations. CASP rating: high	Moderate concern over relevance: 1 study from Sweden	Minor concerns over coherence. Data reasonably consistent within study.	Major concern over data adequacy due to only 1 study offering relatively thin data.	Very low.
Subtheme 2: Need for support in a complex healthcare system							
Malmstrom 2013	Focus group	People need support navigating the complex healthcare system in the hospital. *There's no-one who gets in touch with me from healthcare now. And then, when I phone they say that: You can't be under our care any longer; you have to be well now. You'll have to phone another doctor. What do they mean, ".phone another doctor"? Who am I supposed to phone? (comment)* *She's a clinical nurse specialist; she takes care of everyone. It was to her I phoned on the Friday. The doctor wasn't there, she said, but he would be coming on the Monday. "So I'll speak to him and then we'll get in touch with you." She phoned on*	Minor concerns over methodological limitations. CASP rating: high	Moderate concern over relevance: 1 study from Sweden	Minor concerns over coherence. Data reasonably consistent within study.	Major concern over data adequacy due to only 1 study offering relatively thin data.	Very low.

STUDY information			CERQUAL Quality Assessment				
Number of studies	**Design**	**Description of Theme or Finding**	**Methodological Limitations**	**Relevance**	**Coherence**	**Adequacy of Data**	**Overall Confidence**
		Tuesday morning and said that I could come the next day. (comment)					
Subtheme 3: Need for a nurse specialist							
Mills 2000	Semi-structured interview	Some people suggest a nurse specialist could help in providing hospital-based support. Another significant finding relating to the sources of information was that six participants expressed the need for a nurse specialist in thoracic surgery. Four participants proposed that such a nurse would have been useful during the postoperative period, when they needed information and advice about matters such as returning to work. A nurse with counselling skills, who would have time to `sit down and talk' to the patient, was specifically identified by two participants. Another two participants suggested that such a nurse could have provided support and reassurance for families. (author comment)	Minor concerns over methodological limitations. CASP rating: high	Minor concerns over relevance. One study from the UK on patients undergoing operative treatment for oesophago-gastric cancer.	Minor concerns over coherence. Data reasonably consistent within study.	Major concern over data adequacy due to only 1 study offering relatively thin data.	Low.
Subtheme 4: Being transferred from specialist to general care							
Malmstrom 2013	Focus group	People need support during and after the transfer from specialist to general care. *They [the municipal nurses] didn't really know what it was all about, many of them felt insecure. Maybe someone came who'd seen this sort*	Minor concerns over methodological limitations. CASP rating: high	Moderate concern over relevance: 1 study from Sweden	Minor concerns over coherence. Data reasonably consistent within study.	Major concern over data adequacy due to only 1 study offering	Very low.

STUDY information		Description of Theme or Finding	CERQUAL Quality Assessment				
Number of studies	Design		Methodological Limitations	Relevance	Coherence	Adequacy of Data	Overall Confidence
		of thing before and knew exactly what to do but then the next day someone else would come. I think they came about five times and it was a different person every time. So, I thought on the Sunday evening, no, now I've had enough. They can't come anymore. (comment) *General physicians in healthcare, they're supposed to know about everything, but they're not specialists. Maybe they can't intervene in cases like yours and mine. They listen and all and maybe give you certification of illness or something. But they can't help you in the way that specialists can. (comment)*				relatively thin data.	

1 **Table 22: Summary clinical evidence profile (GRADE-CERQual): Theme 6. Support in daily life**

STUDY information		Description of Theme or Finding	CERQUAL Quality Assessment				
Number of studies	Design		Methodological Limitations	Relevance	Coherence	Adequacy of Data	Overall Confidence
Subtheme 1: Importance of support from one's social network							
Malmstom 2013	Focus group	People receive support in daily life from their social network. *I had my wife with me from beginning to end. Every single visit to the doctor, everything. Very good I advise everyone to do the same because she gets to know exactly the same things as I do. I don't make anything look better than it is for her. I can't do anything. She's heard the*	Minor concerns over methodological limitations. CASP rating: high	Moderate concern over relevance: 1 study from Sweden	Minor concerns over coherence. Data reasonably consistent within study.	Major concern over data adequacy due to only 1 study offering relatively thin data.	Very low.

STUDY information			CERQUAL Quality Assessment				
Number of studies	**Design**	**Description of Theme or Finding**	**Methodological Limitations**	**Relevance**	**Coherence**	**Adequacy of Data**	**Overall Confidence**
		same things as I have, and that feels good. (comment) *But there's one thing that I find enormously irritating and that is that previous friends who I used to hang out with before the sickness. I haven't heard from them the last three years, that's irritating. (comment)*					
Subtheme 2: Need for support meeting the demands of society							
Malmstrom 2013	Focus group	People need support coping with the demands of society along with being ill. *It's a slap in the face for someone who's sick. It's not only that you're sick; the sicker you are the more rotten it is. So, it's not only the sickness that you need to have treated but you also have to be on the alert about what's going to happen. It means that a person who's sick hardly gets better psychologically of something like that, rather that they [the social insurance office] add to the psychological thing you're already carrying around when it comes to cancer, relapse and all that. (comment)*	Minor concerns over methodological limitations. CASP rating: high	Moderate concern over relevance: 1 study from Sweden	Minor concerns over coherence. Data reasonably consistent within study.	Major concern over data adequacy due to only 1 study offering relatively thin data.	Very low.
Subtheme 3: peer-to-peer support							
Malmstrom 2013 McCorry 2009	2 studies of focus groups	People and their carers alike receive support through peer-to-peer interaction or groups. *I thought I was alone with this. When it's good to hear that there are others going through the same thing. I feel exactly the same way and then you know that you're*	Minor concerns over methodological limitations. CASP rating: high and moderate.	Moderate concern over relevance: 1 study from Sweden	Minor concerns over coherence. Data reasonably consistent within study.	Minor concern over data adequacy due to 2 studies offering	Moderate.

STUDY information			CERQUAL Quality Assessment				
Number of studies	Design	Description of Theme or Finding	Methodological Limitations	Relevance	Coherence	Adequacy of Data	Overall Confidence
		not alone with the disease you've been through. (comment) *I think that one of the things that helped me was whenever I was in touch with Ben [member of support group] after the operation… and he wasn't there because he was on holiday in Australia, and I thought, "Oh, there is life after this." And that actually helped me a lot. (comment)* *The day I was actually diagnosed and they told me I needed to have an operation. And there was a lady in that day who had come in to get a check-up and she had had the operation . . . six weeks ago. And me meeting that woman made my mind up for me—I'm going for the operation straight away. (comment)* *Carers are supposed to forage for information, you know: "Am I doing the right thing?" You know he's not eating right, I can't get him to eat and it was only when I came here that I started talking to people… the first lifeline we had was here [the support group]… it was just like a breath of fresh air…and things that Brian had, this dumping syndrome, he wasn't the only on. My friends were good but I think they cared about us so much, they couldn't ask, they didn't want to, they just wanted life to go on. (carer comment)*				moderate data richness.	

1 **Table 23: Summary clinical evidence profile (GRADE-CERQual): Theme 7. Support for carers**

STUDY information			CERQUAL Quality Assessment				
Number of studies	**Design**	**Description of Theme or Finding**	**Methodological Limitations**	**Relevance**	**Coherence**	**Adequacy of Data**	**Overall Confidence**
Subtheme 1: Concern and uncertainty over patient's wellbeing							
McCorry 2009	Focus group	The carer as the buffer for the family and patient. Carers continually look for representations of recovery and recurrence. *He [the patient] wasn't aware of the severity of the operation. And also, he doesn't know himself that he haemorrhaged after the operation and that night they had to bring him back to stop the haemorrhage, they opened him, I think they said his lungs were full of blood. They also told me that if he hadn't had the operation, if they hadn't got him back to surgery that night it would have been too late. He is not aware of that; as a matter of fact nobody else in the family is aware of that, because I think a secret's best kept if you really keep it to yourself. (carer comment)* *I felt, em, I had to be strong for the whole family because I would be a strong person anyway, but they were all looking to me and I couldn't let the side down. And I had nobody to talk to. I was nursing my father with cancer, my sister had just died, I had cancer, John had cancer. There was just nobody. I couldn't let myself down, my guard down, and I found the isolation terrible. (carer comment)* *You were trying to get him to eat, trying to get him to take his tablets and I was*	Minor concerns over methodological limitations. CASP rating: moderate.	Minor concerns over relevance. One study from the UK on patients undergoing operative treatment for oesophago-gastric cancer.	Minor concerns over coherence. Data reasonably consistent within study.	Moderate concern over data adequacy due to only 1 study offering moderate data richness.	Moderate.

STUDY information			CERQUAL Quality Assessment				
Number of studies	Design	Description of Theme or Finding	Methodological Limitations	Relevance	Coherence	Adequacy of Data	Overall Confidence
		getting the brunt of everything. And that was the worst… and it was so hard you know, and I used to have to go out of the room because I started crying. (carer comment) *I had to take the guy away to the side, and I says, "Look, would you mind coming back and removing the plate and not saying anything, because"—well, I told him the situation. (carer comment)* *I continually worry about him, he's never out of my mind. He's the first thing on my mind in the morning and the last thing at night—"Have you got pain? Where's the pain?" . . . I used to just look for a reaction from their faces, just to see is he doing a bit better, is he not? . . . If there's a slight smile it gave you hope. You know, I was very aware of people's reactions in the hospital around me. (carer comment)*					

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5.1.5 Economic evidence

A systematic review of the economic literature was conducted but no relevant studies were identified which were applicable to this review question. Economic modelling was not undertaken for this question because other topics were agreed as higher priorities for economic evaluation.

5.1.6 Evidence statements

5.1.6.1 Information needs for adults suitable for curative treatment and their carers

5.1.6.1.1 Theme 1: Seeking information

Very low to moderate quality evidence from 3 qualitative studies conducted with adults undergoing surgery for oesophageal cancer, a mixed group of adults diagnosed with oesophageal cancer and their carers reported on sources of information. Adults and their carers sought information in person with consultant doctors, nurses, other medical staff, allied healthcare professionals and their own social circles. Adults with oesophageal cancer were considered to be an important information source for other adults with oesophago-gastric cancer and their carers. Sources of information for adults with oesophago-gastric cancer and their carers include written material, TV and newspapers, audio-visual sources and the internet. Written material varied in its utility to adults with oesophago-gastric cancer and their carers. Oesophago-gastric cancer was often missing from representation in mass media and information on the internet did not apply to all adults with oesophago-gastric cancer.

5.1.6.1.2 Theme 2: Not seeking information

Very low to moderate quality evidence from 3 qualitative studies conducted with adults undergoing surgery for oesophageal cancer, a mixed group of adults diagnosed with oesophageal cancer and their carers reported on potential reasons for not seeking information. Family members strive to find balance between receiving necessary information and being overwhelmed and frightened. Adults with oesophago-gastric cancer and their carers fear receiving upsetting information or bad news. Fear can be a barrier to seeking information on survival and prognosis.

5.1.6.1.3 Theme 3: Barriers to communication

Low to moderate quality evidence from 4 qualitative studies reported on barriers to communication. Two studies were conducted with adults undergoing surgery for oesophageal cancer, 1 was a mixed group of adults diagnosed with oesophageal cancer and one was their carers. These studies reported on the values, beliefs and skills of adults with oesophago-gastric cancer and their carers that could be a barrier to communication. People may not seek information if they do not want to be bothersome or feel embarrassed about a subject. Many people had the perception that there was not enough time to seek information. Others held the belief that it was not part of the surgeon's task to provide information, the subject was not important or they expected consequences of bringing up a certain subject.

5.1.6.1.4 Theme 4: Facilitators to communication

Low quality evidence from 1 qualitative study conducted with adults undergoing surgery for oesophageal cancer reported on potential facilitators to communication. Individual personality and attitude of the consultant surgeon as well as consistent consultant interactions helped facilitate communication with people. Pre-visit preparatory interventions or skill building interventions were suggested to facilitate communication.

5.1.6.1.5 Theme 5: Pre-operative information needs

Low to high quality evidence from 2 qualitative studies conducted with adults undergoing surgery for oesophageal cancer reported on technical information, health-related quality of life and prognosis and survival. Technical information was emphasized by the surgeons. Most people accepted the necessity of this information, however some people did not want to receive this information and found it overwhelming. Recovery and long-term quality of life information was desired by most, but not all, people. Prognosis and survival information was desired by people. The importance of honesty of physicians when providing this information was emphasized by people.

5.1.6.1.6 Theme 6: Post-operative information needs

Low to moderate quality evidence from 3 qualitative studies conducted with adults undergoing surgery for oesophageal cancer reported on nutrition, health-related quality of life, medical care and prognosis and survival. Almost all people desired information on nutrition including meal size, enteral nutrition and dysphagia. People desired information on health-related quality of life including when they could expect a return to normality as well as the likely course of symptoms and limitations. People desired information on medical care including the hospital treatment course and self-management. Knowing whether the surgery was successful was important to most people. People highlighted the importance of setting realistic expectations when providing this sort of information.

5.1.6.2 Support needs for adults suitable for curative treatment and their carers

5.1.6.2.1 Theme 1: Intrusions on family

Very low quality evidence from 2 qualitative studies conducted with a mixed group of adults diagnosed with oesophageal cancer and their carers reported on intrusions on children and partners. Children need support and are affected by parents' diagnosis. People with oesophageal cancer need to be supported through changing roles and relationships.

5.1.6.2.2 Theme 2: Uncertainty

Very low to low quality evidence from 3 qualitative studies conducted with adults undergoing surgery for oesophageal cancer, a mixed group of adults diagnosed with oesophageal cancer and their carers reported on uncertainty surrounding course and prognosis, future, hereditary and existential concerns. People's feelings of uncertainty surrounding course and prognosis are constant and can lead to hopelessness. Additionally, uncertainty around the future affects people and their family's planning and behaviour. People and family members were concerned with the heredity of the cancer and uncertain whether their children would be affected. People need support adjusting to the emotional changes of receiving a diagnosis of and living with a life-threatening illness.

5.1.6.2.3 Theme 3: Receiving a diagnosis of oesophageal cancer

Very low to low quality evidence from 2 qualitative studies conducted with adults undergoing surgery for oesophageal cancer, a mixed group of adults diagnosed with oesophageal cancer reported on support needed surrounding receiving a diagnosis of oesophageal cancer. People found receiving a diagnosis of oesophago-gastric cancer particularly hard as they had no previous knowledge of the disease. Some people describe the experience of a loss of control when receiving a diagnosis of oesophago-gastric cancer.

5.1.6.2.4 Theme 4: Adjusting to and accepting an altered self

Low to moderate quality evidence from 2 qualitative studies conducted with adults undergoing surgery for oesophageal cancer and a mixed group of adults diagnosed with oesophageal cancer reported on physical changes, role changes and changes to dietary habits. People experienced physical changes which affected daily-life activities. In particular,

the experience of undergoing treatments and investigation is extremely tiring. People must accept and adjust to role changes. Changes to dietary habit changes are also an intrusion into daily-life which is linked to changes and adjustments in social life.

5.1.6.2.5 Theme 5: Hospital-based support

Very low to low quality evidence from 2 qualitative studies conducted with adults undergoing surgery for oesophageal cancer reported on support needed for future planning, complex healthcare systems and being transferred to general care. Some people suggest a nurse specialist could help in providing hospital-based support.

5.1.6.2.6 Theme 6: Support in daily life

Very low to moderate quality evidence from 2 qualitative studies conducted with adults undergoing surgery for oesophageal cancer and their carers reported on the need for support meeting the demands of society and the importance of support from social networks as well as peer-to-peer support. Peer-to-peer support and interactions were a positive experience for people and their carers alike.

5.1.6.2.7 Theme 7: Support for carers

Moderate quality evidence from 1 qualitative study conducted with adults undergoing surgery for oesophageal cancer reported on carer concern and uncertainty over people's wellbeing. Carers continually look for representations of recovery and recurrence. Additionally, some carers reported acting as the buffer for the family and person affected by cancer.

5.1.7 Evidence to recommendations

5.1.7.1 Relative value placed on the themes considered

The Committee considered that people with oesophago-gastric cancer would need psychosocial support, counselling and parent/carer information, but that the most important needs of people with oesophago-gastric cancer were not the same as those with other types of cancer and that this group would have specific information and support needs. These specific needs would include:

- Nutrition/artificial feeding
- Dietetic input/advice and counselling
- Oesophago-gastric cancer-specific support groups

The Committee identified other more generic themes (i.e ones which would apply to people with a diagnosis of any cancer) relating to information and support needs and these included:

- Holistic needs assessments
- Financial and benefits advice
- Support available in tertiary, secondary or primary/community care
- Named individual/key-worker or specialist nurse for point of contact
- Use of personalised treatment plans

For all these themes the Committee was interested in the timing of support and information provision (at diagnosis, pre-treatment, during treatment, end of treatment), the format of information (verbal, written, web-based to include videos and social media, electronic data such as mobile phone applications, online support forums).

The provision of information on a number of specific aspects of oesophago-gastric cancer was identified by the Committee as being relevant. These aspects were:

- Availability and format of various tools or aids.

- Enhanced recovery protocols and 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
- Post-operative nutritional complications (immediate and long-term)
- Potential long term consequences of surgery
- Potential long term consequences of chemoradiotherapy
- Symptom management
- Post-operative nutritional needs/supplementation/artificial feeding
- Respite care
- Lifestyle, leisure, work and social issues
- Treatment failure/outcomes

Some of these more generic themes and topics have already been covered in other guidance patient experience in adult NHS services and so the Committee agreed that instead of making individual recommendations the guidelines could cross-refer to this document.

Other themes which the Committee discussed but which were deemed to be of less importance was the use of 'information prescriptions' (a list of potentially useful leaflets as determined by healthcare professional for a particular patient) and patients' understanding of jargon and terminology.

5.1.7.2 Quality of the evidence

The evidence for this review was qualitative so was assessed using the CERQual method.. Of the 7 studies included in the review only 3 were from the UK but the remaining 4 studies were European and the Committee felt that the data from these studies was applicable to the UK population. There was some concern over the sampling methods used in two of the studies, but data saturation was reported in four of the studies.

As the data were qualitative, a number of the outcomes that the Committee had prioritised were not available in the included articles, but other aspects of support and information were included in the themes discussed. Thus while the Committee felt the evidence did provide a good basis for making recommendations, they did identify that additional research in this area would be useful and they made a research recommendation.

Very low to high quality evidence was available to guide the Committee on making recommendations about the type of information that is useful for people undergoing radical treatment for oesophago-gastric cancer, and this included information on recovery, quality of life, prognosis, survival, their medical care, when they could expect a return to normality and aspects of nutrition. There was low to moderate quality evidence relating to concerns people had over the lack of time available to seek and receive information during a consultation with their doctor. In terms of who should deliver the information, there was very low to moderate evidence for the role of doctors, nurses, allied health professionals and social circles, as well as peer groups of people with oesophago-gastric cancer.

As well as information, there was very low to moderate evidence suggesting that people with oesophago-gastric cancer require support relating to the effect of their illness on family life, relationships, prognosis and specific concersn over heredity, recovery and prognosis. There was very low to low quality evidence for the role of clinical nurse specialists in providing this support.

There was no evidence for the role of the dietitian in providing information and support, despite the fact that low to moderate quality evidence had identified that people wished to receive information on nutrition, meal size and dysphagia. However, the Committee agreed that in their clinical experience the person best-placed to provide this information and support was a specialist oesophago-gastric dietitian.

5.1.7.3 Consideration of benefits and harms

The information themes identified that patients seek information from doctors, nurses, other medical staff, allied healthcare professionals, their own social circles and other adults with oesophago-gastric cancer, and that written material, information from the media and from the internet is used. Barriers to information include a fear of being overwhelmed, not wishing to 'bother' others, or not feeling there is enough time. Facilitiators included the attitude and personality of the consultant. Patients' information needs included technical information, but most importantly information on recovery, long-term quality of life, prognosis and survival. In particular patients sought information about nutrition, including meal size and how to deal with dysphagia.

The support themes identified included dealing with changing roles and relationships, uncertainty about the disease course and prognosis, the heredity of oesophago-gastric cancer, and delaing with the emotional changes of receiving a cancer diagnosis. People also sought support around delaing with physical changes, including dietary changes, and thought specialist nurses had a role to play in delivering in-hospital support. Peer-to-peer support was felt to be very valuable, and also support for the careres or realtives of those with the cancer.

The Committee discussed the fact that a diagnosis of oesophago-gastric cancer can have a major impact on the ability of a patient to eat, and this effect is very specific to this type of cancer. While the Committee recognised that all patients with a diagnosis of cancer cope better with their disease if offered appropriate support and advice, they felt that as eating is an activity of daily living, as well as being closely linked with family, social, personal life and sense of self-worth, there is a particular benefit to be gained by people with oesophago-gastric cancer who receive appropriate nutritional advice and support.

The Committee agreed that their recommendations would lead to more consistent and tailored information being provided to people with oesophago-gastric cancer, would ensure improved specialist dietetic advice and would increase the provision or sign-posting to peer to peer support.

The Committee recognised that there may be individuals who do not wish to receive such detailed information, but that the benefit of offering information to the majority of patients outweighed this concern, and that patients would be free to decline support if they wished.

5.1.7.4 Consideration of economic benefits and harms

A systematic review of the economic literature was conducted but no relevant studies were identified which were applicable to this review question.

The economic implications of this topic were considered but not thought to be substantial as the majority of the recommendations reflect current best practice. However, there is a potential cost implication around providing access to a clinical nurse specialist and specialist oesophago-gastric cancer dietitian in centres not currently following the 'Improving Outcomes in Upper Gastro-intestinal Cancers' guidance from the NHS'.

The cost implications associated with providing a dietitian were estimated using 'worst case scenario' assumptions and it was found that the cost was not substantial. Furthermore, the costs of the recommendation will be offset (at least partially) by a reduction in patient visits and more appropriate provision of information and support.

5.1.7.5 Other considerations

As only 3 UK-based studies were identified as part of this review, the Committee made its recommendations based on available outcomes, but data were not available for a number of outcomes. The Committee agreed that the recommendation could be strengthened in the future by additional research and so made a research recommendation.

The Committee recognised that all information and support provided for patients would need to address individual needs in terms of language, readability and applicability to different ethnic origins, religions or dietary requirements.

The Committee discussed the dietitic input that was required when providing information and support to people with oesophago-gastric cancer undergoing radical treatment and agreed that, despite the lack of evidence, specialist input was required. The Committee agreed that in most units this would reflect current practice but that if not, it would be beneficial to encourage this standard of care by making a recommendation to consider this input.

5.1.7.6 Key conclusions

The Committee concluded that although there was limited evidence, it provided support for the value of consistent information on various aspects of treatment. The evidence also indicated that the support from clinical nurse specialists and specialist oesophago-gastric dietitians was particularly valuable to this cohort of patients, that peer-to-peer support is very helpful and that carers, partners and children need to be provided with information and support as well.

5.1.8 Recommendations

Radical treatment

1. **Provide information about planned surgery, radiotherapy or chemotherapy in all discussions with people with oesophago-gastric cancer who are going to have radical treatment. Make sure the information is consistent and covers:**
    - treatment outcomes (prognosis and future treatments)
    - recovery, including the consequences of treatment and how to manage them
    - nutrition and lifestyle changes.

    Follow the recommendations in NICE's guideline on patient experience in adult NHS services.

2. **Make sure the person has information to take away and review in their own time after you have spoken to them about their cancer and care.**

3. **Consider access to an oesophago-gastric clinical nurse specialist and a specialist oesophago-gastric cancer dietitian (through the person's multidisciplinary team).**

4. **Inform people about peer-to-peer local or national support groups for them to join if they wish.**

5. **Provide psychosocial support to the person with oesophago-gastric cancer and those important to them (as appropriate). Inform them where they can get further support. Include psychosocial support relating to:**
    - potential impact on family life, changing roles and relationships

- uncertainty about the disease course and prognosis
- concerns over heredity of cancer, recovery and recurrence.

5.1.9 Research recommendations

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

Why this is important

Oesophago-gastric cancer pathways can be challenging for people with oesophago-gastric cancer to navigate, due to the complexity of the diagnostic and staging pathway, centralisation of services and multi-modality treatment options. There is a high incidence of disease-related and treatment-related morbidity that can impact significantly on health-related quality of life. Provision of support and information to guide people through this pathway is an integral part of the provision of a comprehensive oesophago-gastric cancer service. In addition, over recent years the importance of personalised support has gathered momentum as part of the paradigm shift towards patient empowerment and shared-decision making.

Support is a broad term that encompasses a range of methods and systems to facilitate patients' engagement in their care, and the provision of information is considered to be one aspect of supporting patients and their carers. However, there is a lack of evidence demonstrating what support and information is most effective at improving outcomes, including quality of life, and research is required to explore the specific concerns and needs of people with oesophago-gastric cancer.

It is anticipated that this research will better enable healthcare professionals to adopt a tailored and proactive approach to care and facilitate supported self-management.

Table 24: Research recommendation rationale

Research question	What are the specific information and support needs before, during and after treatment for adults with oesophago-gastric cancer who are suitable for radical treatment, and their carers?
Why this is needed	
Importance to 'patients' or the population	Identifying the main support needs of patients before, after and during treatment will help alleviate anxiety, promote patient engagement and facilitate supported self-management.
Relevance to NICE guidance	Very few small scale studies have been conducted. This was a challenge to developing the guidance on this topic. Future NICE guidance would benefit from further evidence in this area.
Relevance to the NHS	With more people surviving cancer it is increasingly perceived as a chronic disease. If timely, personalised support is provided throughout the cancer continuum then patients and carers are more likely to be empowered to become active participants in their care. There is a direct correlation between people who are more engaged in their care with better health outcomes, improved patient experience and reduced healthcare costs.
National priorities	Achieving world class cancer outcomes: A strategy for England 2015-2020 Improving outcomes strategy for cancer (2011) Cancer reform strategy (2007) National cancer survivorship initiative (2010)

Research question	What are the specific information and support needs before, during and after treatment for adults with oesophago-gastric cancer who are suitable for radical treatment, and their carers?
Current evidence base	There is currently limited evidence on the specific support and information needs of people with oesophago-gastric cancer.
Equality	Oesophago-gastric cancer affects a wide cross section of the population. The research sample and provision of support and information should reflect this diversity, and be tailored to meet individual needs.
Feasibility	The research should be conducted across a number of oesophago-gastric centres and local units. This will provide an opportunity to examine the efficacy of different information and support systems.

Table 25: Research recommendation statements

Criterion	Explanation
Population	Adults, and carers, who are candidates for or have undergone radical treatment for oesophago-gastric cancer, and their carers
Intervention	Directed assessment of informational and support needs and appropriate individualised intervention
Comparators	Standard care with no directed assessment and individualised intervention.
Outcome	Patient-reported outcome measures, including patient satisfaction and quality of life
Study design	Multi-centre Qualitative, longitudinal evaluation
Timeframe	2-3 years

5.2 Palliative management

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

5.2.1 Description of clinical evidence

This review aims to identify the specific information and support services that are beneficial to adults and their carers suitable for palliative management for oesophago-gastric cancer.

We looked for studies that collected data using qualitative methods (such as semi-structured interviews, focus groups and surveys with open-ended questions) in which the authors analysed the data qualitatively (including thematic analysis, framework thematic analysis or content analysis). Survey studies restricted to reporting descriptive data that were analysed quantitatively were excluded.

Given the nature of qualitative reviews, findings/ themes were summarised from the literature and were not restricted to those identified as likely themes by the Guideline Committee at protocol stage.

For full details see review protocol in Appendix D.

2 studies were included in this review. Both the studies were qualitative studies and used qualitative, semi-structured interviews (Andreassen 2005, Andreassen 2006).

The size of the studies ranged from 9 to 13 participants. The 2 included studies included a mixed population of adults and carers of adults undergoing palliative and curative intent treatments (Andreassen 2005, Andreassen 2006). All studies focused on oesophageal cancer alone.

Both studies were conducted in Sweden (Andreassen 2005, Andreassen 2006).

A summary of the included studies is presented in Table 10. See also study evidence tables in Appendix F, excluded studies list in Appendix J, and study selection flow chart in Appendix K.

5.2.2 Summary of included studies

A summary of the studies that were included in this review are presented in Table 26.

Table 26: Summary of included studies

Study	Aim of the Study	Participants	Study Design/Methods	Comments
Andreassen et al., 2005 Sweden Study dates: December 2003 and January 2004	To describe family members' experiences, information needs and information seeking in relation to living with a patient suffering from oesophageal cancer.	N=9 The sample consisted of close family members from an ongoing study of 13 patients. One brother, two husbands and six wives were included.	Sample selection: Convenience sampling-family members of study participants Data Collection: Qualitative study-semi-structured interviews	Overall quality: MODERATE Data saturation was not discussed by the author or used in sampling
Andreassen et al., 2006 Sweden Study dates: December 2003 and March 2004	To describe patients' experiences of living with oesophageal cancer and how they seek information.	N=13 Their ages ranged from 44 to 77 years. The selection criteria for this study were as follows: women and men of different ages who had undergone different treatments for oesophageal cancer, i.e., a total thoracic oesophagectomy, oncological treatment with a curative intent and/or palliative treatment.	Sample Selection: Purposive sampling was used. The surgeon in charge of their care identified and constructed a list of potential participants. Data Collection: Qualitative study, semi-structured interviews.	Overall quality: HIGH Data saturation was reached Thematic analysis was detailed and carried out by three independent researchers.

5.2.31 Clinical evidence

5.2.3.12 Theme maps

3 The theme maps are presented in Figure 5 and Figure 6.

Figure 5: Theme map: information needs for adults with oesophago-gastric cancer undergoing palliative treatment and their carers

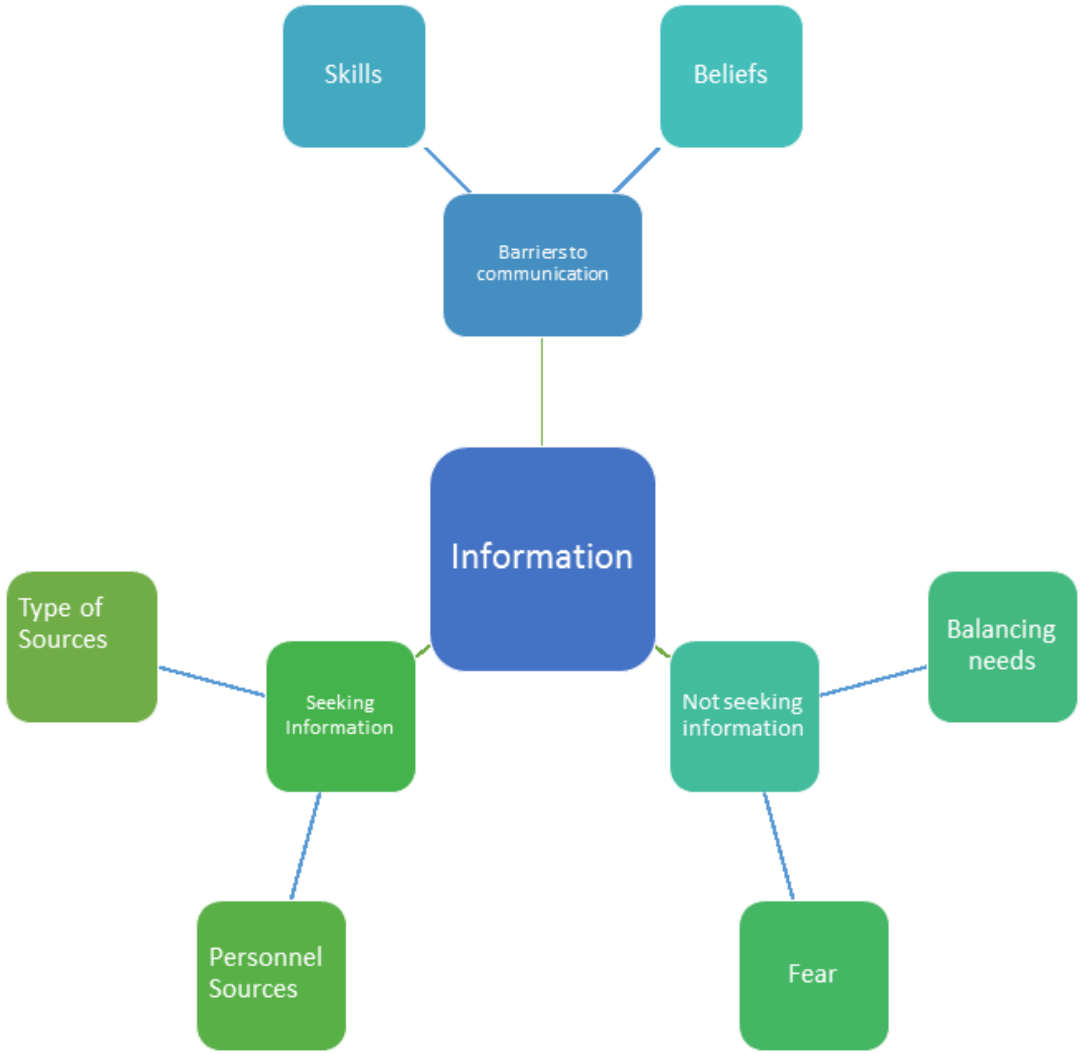
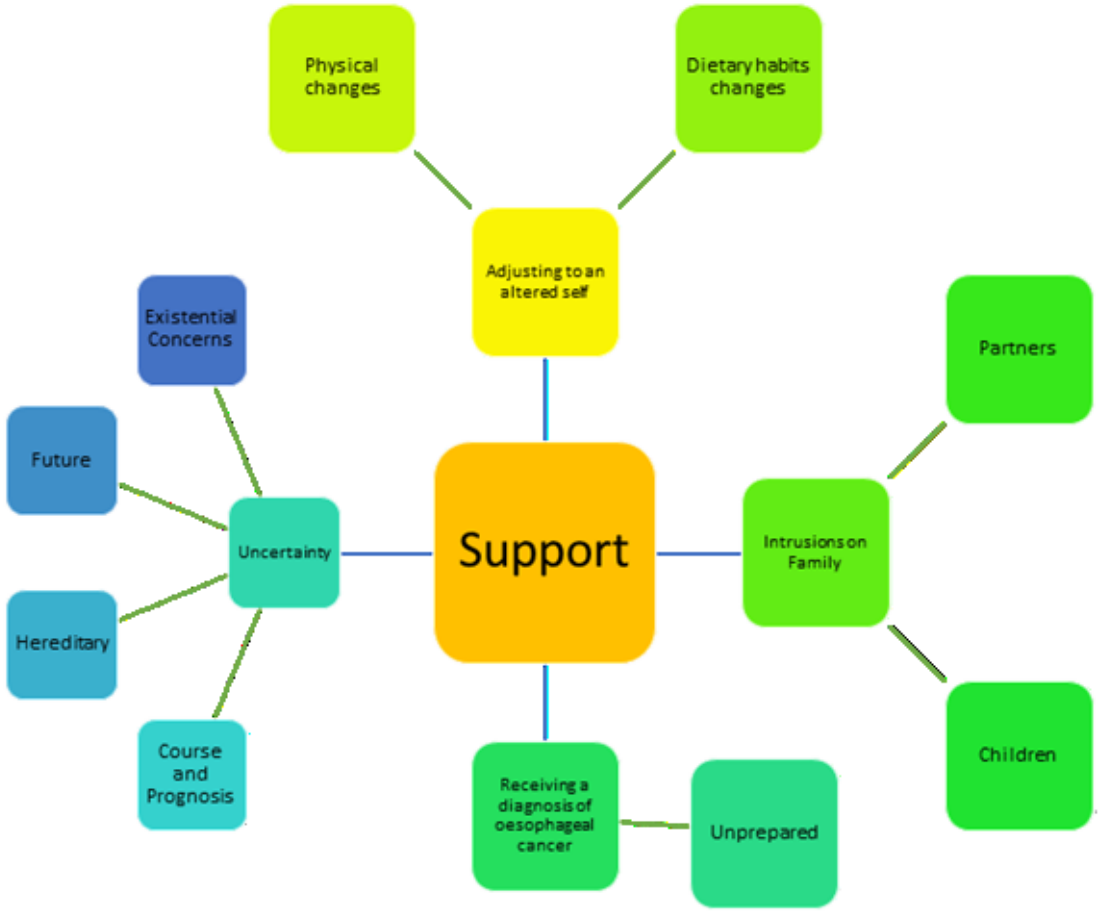


Figure 6: Theme map: support needs for adults undergoing palliative treatment for oesophago-gastric cancer and their carers



5.2.4 Clinical evidence profile

The clinical evidence (GRADE-CERQual) for the information and support question is presented in Table 27 to Table 33

5.2.4.1 Clinical evidence profile: information needs for adults suitable for palliative treatment and their carers

Table 27: Summary clinical evidence profile (GRADE-CERQual): Theme 1. Seeking information

STUDY information		Description of Theme or Finding	CERQUAL Quality Assessment				
Number of studies	**Design**		**Methodological Limitations**	**Relevance**	**Coherence**	**Adequacy of Data**	**Overall Confidence**
Sub-theme 1: Seeking information from consultant doctors							
Andreassen 2005 Andreassen 2006	2 studies using interviews	Trusting expert opinion. Giving oneself over to the experts. Desire for more open discussion on details of being a person affected by oesophageal cancer. *The doctor is our lifeline. When you are so close to the experts as we are now, we ought to get the truth directly from the doctor if there is anything we wonder about. We have entrusted ourselves to the experts. (family member comment)* *I thought 'I can't do anything now; I'll just hand myself over to the experts and let them do whatever they want with me'. I've handed my life over to the doctors. (comment)* *The health-care professionals perhaps could have had time to tell me more about how it*	Minor concerns over methodological limitations. CASP rating: moderate and high.	Major concern over relevance: indirect evidence. Uncertain evidence: studies included use a mixed population of people receiving both palliative and curative treatment. Indirect evidence: included studies from Sweden.	Minor concerns over coherence. Data reasonably consistent within and across studies.	Moderate concern over data adequacy due to only 2 linked studies offering moderate data richness.	Very low.

STUDY information			CERQUAL Quality Assessment				
Number of studies	**Design**	**Description of Theme or Finding**	**Methodological Limitations**	**Relevance**	**Coherence**	**Adequacy of Data**	**Overall Confidence**
		really is to be a patient. Perhaps they could have devoted a few hours to talk about a number of things concerning this cancer…in another way. (patient `comment)					
Sub-theme 2: Information from nurses							
Andreassen 2005 Andreassen 2006	2 studies using interviews	Nurses may be more approachable, accessible and trustworthy. *It's easier to talk with a nurse when it concerns important questions. You may receive quite good and reassuring answers. / . . . / You get a feeling of trust when you talk with a nurse. (family member comment)* *I've seen a lot less of the doctors in the hospital. I see mostly nurses there. And things are different there; you ask the nurses, rather than the doctors, a lot more often than you do outside the hospital. (comment)*	Minor concerns over methodological limitations. CASP rating: moderate and high	Major concern over relevance: Indirect evidence. Uncertain evidence: studies included use a mixed population of people receiving both palliative and curative treatment. Indirect evidence: included studies from Sweden.	Minor concerns over coherence. Data reasonably consistent within and across studies.	Moderate concern over data adequacy due to only 2 linked studies offering moderate data richness.	Very low.
Subtheme 3: Seeking information from social circles							
Andreassen 2005 Andreassen 2006	2 studies using qualitative interviews	Medical professionals in patient's social circles also play a role providing information.	Minor concerns over methodological limitations.	Major concern over relevance: Indirect evidence. Uncertain evidence: studies	Minor concerns over coherence. Data	Moderate concern over data adequacy	Very low.

STUDY information			CERQUAL Quality Assessment				
Number of studies	**Design**	**Description of Theme or Finding**	**Methodological Limitations**	**Relevance**	**Coherence**	**Adequacy of Data**	**Overall Confidence**
		Family members help people to gather and understand information. *I trusted the judgements that doctors in our acquaintance circle gave, but not completely, since they are not in the field. They can't be well read in all areas. (family member comment)* *I have experienced it positive that my son has come with me to the doctor. It is good to have another pair of ears listening. He has asked questions from an outside perspective. (comment)* *It is my wife, who gathers the information that is needed. She is often with me when I visit the doctor. (comment)* *I have a cousin who is a doctor and I also had my brother-in-law who was a doctor. I trust them a little more because they know what information I am capable of understanding.. (comment)*	CASP rating: moderate and high	included use a mixed population of people receiving both palliative and curative treatment. Indirect evidence: included studies from Sweden.	reasonably consistent within and across studies.	due to only 2 linked studies offering moderate data richness.	
Subtheme 4: People with oesophago-gastric cancer as experts in their own right							
Andreassen 2005 Andreassen 2006	2 studies using interviews	People with oesophago-gastric cancer are information sources for fellow patients as well as family members or carers.	Minor concerns over methodological limitations.	Major concern over relevance: Indirect evidence. Uncertain evidence: studies included use a mixed	Minor concerns over coherence. Data reasonably	Moderate concern over data adequacy due to only	Very low.

STUDY information			CERQUAL Quality Assessment				
Number of studies	**Design**	**Description of Theme or Finding**	**Methodological Limitations**	**Relevance**	**Coherence**	**Adequacy of Data**	**Overall Confidence**
		I haven't asked anything myself because I knew that my husband would ask everything so minutely himself. I know he would look up everything himself. He has shared his knowledge with me and we have discussed it together. (family member comment) *It is immensely important that a new patient can talk with a fellow patient. That information is much more valuable than the information the doctor gives. You can ask questions you wouldn't dare to pose otherwise. (comment)*	CASP rating: moderate and high	population of people receiving both palliative and curative treatment. Indirect evidence: included studies from Sweden.	consistent within and across studies.	2 linked studies offering moderate data richness.	
Subtheme 5: Seeking information from TV and newspapers							
Andreassen 2005	1 study using semi-structured interviews	OG cancer may be missing from representation in mass media. TV and newspaper reports can offer positive or success stories. *I hadn't heard about that disease. I think you have heard about most of the variations, but not cancer of the oesophagus. (family member comment)* *I receive most of the information through the mass*	Minor concerns over methodological limitations. CASP ratings: moderate	Major concern over relevance: study with Swedish setting and mixed population.	Minor concerns over coherence (data reasonably consistent within study).	Major concern over adequacy due to only 1 study included offering thin data.	Very low.

STUDY information			CERQUAL Quality Assessment				
Number of studies	**Design**	**Description of Theme or Finding**	**Methodological Limitations**	**Relevance**	**Coherence**	**Adequacy of Data**	**Overall Confidence**
		media. In that way, I get my information and it is sort of positive, since more and more people pull through. (family member comment)					
Subtheme 6: Seeking information from written material							
Andreassen 2005	1 study with semi-structure interviews	Written information is used by patients and families. The act of seeking information gives a sense of being productive to family members. *We have received books on how you deal with the illness, quite thin pamphlets from the medical authorities both to us and to the children. (family member comment)* *I have an encyclopaedia at home, which certainly is a bit old. I also have a book for quick medical reference, where I can look up different things in order to be able to read briefly about them. (family member comment)* *Seeking information is much more than receiving knowledge, it also includes a feeling of doing something. (family member comment)*	Minor concerns over methodological limitations. CASP rating: moderate	Major concern over relevance: Indirect evidence. Uncertain evidence: study included use a mixed population of people receiving both palliative and curative treatment. Indirect evidence: included study from Sweden.	Minor concerns over coherence. Data reasonably consistent within study.	Major concern over data adequacy due to only 1 study offering relatively thin data.	Very low.
Subtheme 7: Seeking information from the internet							

STUDY information			CERQUAL Quality Assessment				
Number of studies	**Design**	**Description of Theme or Finding**	**Methodological Limitations**	**Relevance**	**Coherence**	**Adequacy of Data**	**Overall Confidence**
Andreassen 2005 Andreassen 2006	2 studies using semi-structured interviews	Information on the internet is not always applicable to all people. Seeking information on the internet can be upsetting and frightening. *I think that the Internet was a great help, since it is difficult to telephone someone and pose relevant questions when I hardly know what I want to find out. Then it is possible that if you receive incorrect information, you can form an opinion later. (family member comment)* *The prognosis was so bad. It was so depressing and I started to believe that I would find my husband dead in bed. I got terrified and there was nothing positive at all in the information I read. (family member comment)* *I said to the doctor that I had been on the Net and read about a study where it said that there was a terribly poor prognosis. He said that the information was not really current and that the prognosis is better now. I didn't go into greater detail. (family member comment)*	Minor concerns over methodological limitations. CASP rating: moderate and high	Major concern over relevance: Indirect evidence. Uncertain evidence: studies included use a mixed population of people receiving both palliative and curative treatment. Indirect evidence: included studies from Sweden.	Minor concerns over coherence. Data reasonably consistent within and across studies.	Moderate concern over data adequacy due to only 2 linked studies offering moderate data richness.	Very low.

STUDY information		Description of Theme or Finding	CERQUAL Quality Assessment				
Number of studies	Design		Methodological Limitations	Relevance	Coherence	Adequacy of Data	Overall Confidence
		'It became apparent that I could just as well ignore the information since it dealt with men between 60- and 80 years old. You don't put up with this information when you are 44 years old. This information is completely irrelevant'. (comment) *I found a research report, brought it with me and discussed it with the doctor. He took it out of my hand and said, 'It doesn't apply to you'. I experienced it positively that he reacted so because it was a negative report. (comment)*					

1 **Table 28: Summary clinical evidence profile (GRADE-CERQual): Theme 2. Not seeking information**

STUDY information		Description of Theme or Finding	CERQUAL Quality Assessment				
Number of studies	Design		Methodological Limitations	Relevance	Coherence	Adequacy of Data	Overall Confidence
Subtheme 1: Balancing needs							
Andreassen 2005	1 study with semi-structured interviews	Family members strive to find balance between receiving necessary information and being overwhelmed and frightened. *I want to know if the prognosis is terribly poor or if it is about one year. I want to know what will happen... Actually, I really*	Minor concerns over methodological limitations. CASP ratings: moderate	Major concern over relevance: study with Swedish setting and mixed population.	Minor concerns over coherence: data reasonably consistent within study.	Major concern over adequacy due to only 1 study included offering thin data.	Very low.

STUDY information			CERQUAL Quality Assessment				
Number of studies	**Design**	**Description of Theme or Finding**	**Methodological Limitations**	**Relevance**	**Coherence**	**Adequacy of Data**	**Overall Confidence**
		don't want to know. (family member comment) *Perhaps it isn't so terrible. Everything you know something about loses its terribleness. (family member comment)*					
Subtheme 2: Fear							
Andreassen 2005 Andreassen 2006	2 studies with semi-structured interviews	Fear of receiving upsetting information or bad news. Fear can be a barrier to seeking information on survival and prognosis. *Certainly I can search for information. That isn't the problem but the problem is that it takes time. I shall mobilise the courage, the power, the energy . . . call it whatever you want, to be able to sit down and go through things. I am not sure I am going to like the answers I get. Maybe it is better not to know so very much but to do like the ostrich, to bury your head in the sand and hope for the best and keep your fingers crossed. (family comment)* *I don't want to ask the doctor a question, which he has to respond to negatively when my husband is with me. (family member comment)*	Minor concerns over methodological limitations. CASP rating: moderate and high.	Major concern over relevance: Indirect evidence. Uncertain evidence: studies included use a mixed population of people receiving both palliative and curative treatment. Indirect evidence: included studies from Sweden.	Minor concerns over coherence. Data reasonably consistent within and across studies.	Moderate concern over data adequacy due to only 2 linked studies offering moderate data richness.	Very low.

STUDY information			CERQUAL Quality Assessment				
Number of studies	Design	Description of Theme or Finding	Methodological Limitations	Relevance	Coherence	Adequacy of Data	Overall Confidence
		I don't pose any questions because I think it is scary. I've left myself in the doctors' hands… they can help me. (comment)					

1 **Table 29: Summary clinical evidence profile (GRADE-CERQual): Theme 3. Barriers to communication**

STUDY information			CERQUAL Quality Assessment				
Number of studies	Design	Description of Theme or Finding	Methodological Limitations	Relevance	Coherence	Adequacy of Data	Overall Confidence
Subtheme 1: Beliefs							
Andreassen 2006	1 study with semi-structured interviews	Perception there is too little time. *Sometimes I have written down a lot of questions, but usually not more than half or in some cases a third part is answered…the doctors are so rushed and suddenly they are gone. (comment)*	Minor concerns over methodological limitations. CASP ratings: high.	Major concern over relevance: Indirect evidence. Uncertain evidence: study included use a mixed population of people receiving both palliative and curative treatment. Indirect evidence: included study from Sweden.	Minor concerns over coherence. Data reasonably consistent within study.	Major concern over data adequacy due to only 1 study offering relatively thin data.	Very low.
Subtheme 2: Skills							
Andreassen 2006 Andreassen 2005	2 studies with interviews	Too tired to ask questions. Not knowing what to ask. *There is a great deal I should have asked the doctor about, but I was so tired of everything that I got to the point that I didn't feel like doing it. I became worn out*	Minor concerns over methodological limitations. CASP ratings: high and moderate.	Major concern over relevance: Indirect evidence. Uncertain evidence: study included use a mixed population of people receiving both palliative and curative treatment. Indirect	Minor concerns over coherence. Data reasonably consistent within study.	Moderate concern over data adequacy due to only 2 studies offering relatively thin data.	Very low.

STUDY information			CERQUAL Quality Assessment				
Number of studies	Design	Description of Theme or Finding	Methodological Limitations	Relevance	Coherence	Adequacy of Data	Overall Confidence
		over everything and had enough. (comment) *You are not enough medically knowledgeable. Therefore, you don't know what to ask. (family member comment)*		evidence: included study from Sweden.			

5.2.4.21 Clinical evidence profile: support needs for adults suitable for palliative care and their carers

2 **Table 30: Summary clinical evidence profile (GRADE-CERQual): Theme 1. Intrusions on family**

STUDY information			CERQUAL Quality Assessment				
Number of studies	Design	Description of Theme or Finding	Methodological Limitations	Relevance	Coherence	Adequacy of Data	Overall Confidence
Subtheme 1: Children							
Andreassen 2005 Andreassen 2006	2 studies of semi-structured interviews	Children need support and are affected by parents' diagnosis. *I don't think anyone has ever asked how old our children are, if they visit school or anything like that. They don't seem to care that there is a family around the patient and that we in fact have a sixteen-year-old son, who has grown up with this. (family member comment)* *Our son had his 18th birthday this year. Although he himself says that his mother's illness doesn't affect him at all, we have noted that his grades*	Minor concerns over methodological limitations. CASP rating: moderate and high	Major concern over relevance: Indirect evidence. Uncertain evidence: studies included use a mixed population of people receiving both palliative and curative treatment. Indirect evidence: included studies from Sweden.	Minor concerns over coherence. Data reasonably consistent within and across studies.	Moderate concern over data adequacy due to only 2 linked studies offering moderate data richness.	Very low.

STUDY information			CERQUAL Quality Assessment				
Number of studies	**Design**	**Description of Theme or Finding**	**Methodological Limitations**	**Relevance**	**Coherence**	**Adequacy of Data**	**Overall Confidence**
		dropped disastrously during his first term. (family member comment) *I think it would be good to receive joint information, to involve the children, since the parent, who comes home is a little foreign. You can say: 'One parent left and another one came home who is also a patient at home.' (family member comment)* *My 18-year-old son was feeling very badly when he got the information that his mother had cancer. From having excellent marks in all his subjects, he started to ignore school completely. He didn't discuss this with my husband or me. He didn't want to make me upset or his father unhappy. He was convinced that I would die. He gave up everything. (comment)* *It's immensely important that he also has a chance to meet someone, who allows him to express himself in his own way. (comment on son with special needs coping with parent's illness)*					
Subtheme 2: Effect on partner role and relationship							
Andreassen 2006	1 study of semi-	People need to be supported through changing roles and	Minor concerns over	Major concern over relevance: Indirect	Minor concerns over	Major concern	Very low.

STUDY information		Description of Theme or Finding	CERQUAL Quality Assessment				
Number of studies	Design		Methodological Limitations	Relevance	Coherence	Adequacy of Data	Overall Confidence
	structured interviews	relationships. *My husband does all the housework; he cooks, he irons, he does laundry, he takes the dog for a walk five times a day and he helps our son iron his clothes. (comment)* *I became somewhat dependent on my wife, who had to help me wash up around the gastrostomy. (comment)* *'I feel that the cancer hasn't struck me too hard, but my wife has taken it much worse mentally'. (comment)*	methodological limitations. CASP rating: high	evidence. Uncertain evidence: study included use a mixed population of people receiving both palliative and curative treatment. Indirect evidence: included study from Sweden.	coherence. Data reasonably consistent within study.	over data adequacy due to only 1 study offering relatively thin data.	

1 **Table 31: Summary clinical evidence profile (GRADE-CERQual): Theme 2. Uncertainty**

STUDY information		Description of Theme or Finding	CERQUAL Quality Assessment				
Number of studies	Design		Methodological Limitations	Relevance	Coherence	Adequacy of Data	Overall Confidence
Subtheme 1: Course and prognosis							
Andreassen 2005 Andreassen 2006	2 studies of semi-structured interviews	Feelings of uncertainty surrounding course and prognosis are constant and can lead to hopelessness. *They tell me they don't know why I got it and they can't give me a prognosis. Of course, that's not what you want to hear from your doctor…but if you think about it, they really don't know*	Minor concerns over methodological limitations. CASP rating: moderate and high.	Major concern over relevance: Indirect evidence. Uncertain evidence: studies included use a mixed population of people receiving both palliative and curative treatment. Indirect evidence: included studies from Sweden.	Minor concerns over coherence. Data reasonably consistent within and across studies.	Moderate concern over data adequacy due to only 2 linked studies offering moderate data richness.	Very low.

STUDY information			CERQUAL Quality Assessment				
Number of studies	**Design**	**Description of Theme or Finding**	**Methodological Limitations**	**Relevance**	**Coherence**	**Adequacy of Data**	**Overall Confidence**
		either. Sometimes it feels so hopeless. (comment) *You know all the time that one day it will get worse. You may receive an answer that it is a metastasis, exactly as we received now. I live constantly with this. (family member comment)* *Since after five years one is considered be out of the danger zone, we can calculate that my husband will in some form be given a clean bill of health, but perhaps not quite be declared healthy. (family comment)*					
Subtheme 2: Future							
Andreassen 2005 Andreassen 2006	2 studies of semi-structured interviews	Uncertainty around the future affects planning and behaviour. *Shall we sell the house or shall we not? Shall we renovate our house or shall we not. Shall I work full time or shall I not? Will my husband die tomorrow, or what? (family member comment)* *When I heard that I didn't have any metastases, I thought that perhaps this is only a respite and therefore I*	Minor concerns over methodological limitations. CASP rating: moderate and high.	Major concern over relevance: Indirect evidence. Uncertain evidence: studies included use a mixed population of people receiving both palliative and curative treatment. Indirect evidence: included studies from Sweden.	Minor concerns over coherence. Data reasonably consistent within and across studies.	Moderate concern over data adequacy due to only 2 linked studies offering moderate data richness.	Very low.

STUDY information			CERQUAL Quality Assessment				
Number of studies	**Design**	**Description of Theme or Finding**	**Methodological Limitations**	**Relevance**	**Coherence**	**Adequacy of Data**	**Overall Confidence**
		have been terribly active. I work frantically. I think that time is very valuable, something I never bothered about before. (comment) *We have a son who will graduate this summer. The whole time I've set up a goal to take part in his graduation day.. (comment)* *I think that as long as I want to live, I will fight to be healthy. (comment)*					
Subtheme 3: Hereditary							
Andreassen 2005 Andreassen 2006	2 studies of semi-structured interviews	People were concerned with the heredity of the cancer and uncertain whether their children would be affected. *What worries me most is that the illness will affect the children. If they will get this . . . whether it is hereditary. (family member comment)* *Since my brother now has cancer of the oesophagus and all my other siblings and my mother and father also had cancer, I want to know if I am exposed to cancer and have it in my genes, so I can take some special tests. (family member comment)* *My Dad and his brother died of cancer (comment)*	Minor concerns over methodological limitations. CASP rating: moderate and high.	Major concern over relevance: Indirect evidence. Uncertain evidence: studies included use a mixed population of people receiving both palliative and curative treatment. Indirect evidence: included studies from Sweden.	Minor concerns over coherence. Data reasonably consistent within and across studies.	Moderate concern over data adequacy due to only 2 linked studies offering moderate data richness.	Very low.

STUDY information		Description of Theme or Finding	CERQUAL Quality Assessment				
Number of studies	Design		Methodological Limitations	Relevance	Coherence	Adequacy of Data	Overall Confidence
Subtheme 4: Existential concerns							
Andreassen 2006	1 study of semi-structured interviews	People need support adjusting to the emotional changes of receiving a diagnosis of a life-threatening illness. *'What will happen? 'Will I survive? 'Will I die? Will I only be lying in bed and die? (comment)* *Haven't I taken care of myself well enough? (comment)*	Minor concerns over methodological limitations. CASP rating: high	Major concern over relevance: Indirect evidence. Uncertain evidence: study included use a mixed population of people receiving both palliative and curative treatment. Indirect evidence: included study from Sweden.	Minor concerns over coherence. Data reasonably consistent within study.	Major concern over data adequacy due to only 1 study offering relatively thin data.	Very low.

1 **Table 32: Summary clinical evidence profile (GRADE-CERQual): Theme 3. Receiving a diagnosis of oesophageal cancer**

STUDY information		Description of Theme or Finding	CERQUAL Quality Assessment				
Number of studies	Design		Methodological Limitations	Relevance	Coherence	Adequacy of Data	Overall Confidence
Subtheme 1: Unprepared without prior knowledge							
Andreassen 2006	1 study of semi-structured interviews	People found receiving a diagnosis of OG cancer particularly hard as they had no previous knowledge of the disease. *I knew nothing about my condition before I got the diagnosis. I was completely dumbfounded. My wife said when the doctor discussed it, I looked like a little child. (comment)*	Minor concerns over methodological limitations. CASP rating: high	Major concern over relevance: Indirect evidence. Uncertain evidence: study included use a mixed population of people receiving both palliative and curative treatment. Indirect evidence: included study from Sweden.	Minor concerns over coherence. Data reasonably consistent within study.	Major concern over data adequacy due to only 1 study offering relatively thin data.	Very low.

STUDY information			CERQUAL Quality Assessment				
Number of studies	Design	Description of Theme or Finding	Methodological Limitations	Relevance	Coherence	Adequacy of Data	Overall Confidence
		If the doctors had told me it was breast cancer, uterine cancer, gastric cancer or intestinal cancer, I would have understood. But I had never expected this. (comment)					

1 **Table 33: Summary clinical evidence profile (GRADE-CERQual): Theme 4. Adjusting to and accepting an altered self**

STUDY information			CERQUAL Quality Assessment				
Number of studies	Design	Description of Theme or Finding	Methodological Limitations	Relevance	Coherence	Adequacy of Data	Overall Confidence
Subtheme 1: Adjusting to physical changes							
Andreassen 2006	1 study of semi-structured interviews	People experience physical changes with affect daily-life activities. *The experience of undergoing treatments and investigation is extremely tiring. The cancer itself hasn't given me any concerns, but it is the treatment that takes away my strength. When I finished the radiotherapy, I was so exhausted that I couldn't walk. The first week I rested at home. (comment)* *The doctor said that after the treatment I would be very, very tired. I thought that this tumour was so small and that I could fix it in a month or two.*	Minor concerns over methodological limitations. CASP rating: moderate and high.	Major concern over relevance: 1 study from Sweden with a mixed population.	Minor concerns over coherence. Data reasonably consistent within study.	Minor concern over data adequacy due to only 1 study offering moderate data richness.	Low.

STUDY information			CERQUAL Quality Assessment				
Number of studies	**Design**	**Description of Theme or Finding**	**Methodological Limitations**	**Relevance**	**Coherence**	**Adequacy of Data**	**Overall Confidence**
		But oh, how I deceived myself. I am terribly, terribly tired. (comment) *I really don't understand why I'm still so tired after 6 months…but I am.. (comment)* *I am terribly, terribly tired. Certainly, I am out walking every day, but not very long stretches. I must stop quite often to breathe and to rest a little while. (comment)*					
Subtheme 2: Dietary habits changed							
Andreassen 2006	1 semi-structured interview	Dietary habit changes are an intrusion into daily-life. Dietary changes are also linked to changes and adjustments to social life. *I can't eat the same food as I used to eat and I have no appetite right now. Cooking is no fun. Nothing tastes good anymore. I try to eat sour milk, but I keep vomiting. I have an enormous amount of phlegm and it really bothers me. (comment)* *I have no energy…and it is really hard for me to eat anything. Where I used to eat*	Minor concerns over methodological limitations. CASP rating: high.	Major concern over relevance: Indirect evidence. Uncertain evidence: study included use a mixed population of people receiving both palliative and curative treatment. Indirect evidence: included study from Sweden.	Minor concerns over coherence. Data reasonably consistent within study.	Major concern over data adequacy due to only 1 study offering relatively thin data.	Very low.

STUDY information			CERQUAL Quality Assessment				
Number of studies	Design	Description of Theme or Finding	Methodological Limitations	Relevance	Coherence	Adequacy of Data	Overall Confidence
		two potatoes, I can only eat one now and even that can be too much. Eating makes me so tired that I have to lie down, even though I haven't eaten a whole lot. (comment) *The PEG is an obstacle when I shower and when I travel. It has to be washed. I can't go to a public sauna and places like that. (comment)*					

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5.2.5 Economic evidence

A systematic review of the economic literature was conducted but no relevant studies were identified which were applicable to this review question. Economic modelling was not undertaken for this question because other topics were agreed as higher priorities for economic evaluation.

5.2.6 Evidence statements

5.2.6.1 Information needs for adults suitable for palliative treatment and their carers

5.2.6.1.1 Theme 1: Seeking information

Very low evidence from 2 qualitative studies of a mixed group of adults diagnosed with oesophageal cancer and their carers reported on sources of information. Adults and their carers sought information in person with consultant doctors, nurses, and their own social circles. People with oesophageal cancer were considered to be an important information source for other adults with oesophago-gastric cancer and their carers alike. Sources of information for adults with oesophago-gastric cancer and their carers include written material, TV and newspapers, and the internet. Written material varied in its utility to adults with oesophago-gastric cancer and their carers. Oesophago-gastric cancer was often missing from representation in mass media and information on the internet did not apply to all adults with oesophago-gastric cancer.

5.2.6.1.2 Theme 2: Not seeking information

Very low evidence from 2 qualitative studies of a mixed group of adults diagnosed with oesophageal cancer and their carers reported on potential reasons for not seeking information. Family members strive to find balance between receiving necessary information and being overwhelmed and frightened. Adults with oesophago-gastric cancer and their carers fear receiving upsetting information or bad news. Fear can be a barrier to seeking information on survival and prognosis.

5.2.6.1.3 Theme 3: Barriers to communication

Very low evidence from 2 qualitative studies of a mixed group of adults diagnosed with oesophageal cancer and their carers reported on the beliefs and skills of adults with OG cancer and their carers that could be a barrier to communication. Many people had the perception that there was not enough time to seek information. Others were too tired to seek information or did not know what to ask.

5.2.6.2 Support needs for adults suitable for palliative care and their carers

5.2.6.2.1 Theme 1: Intrusions on family

Very low evidence from 2 qualitative studies of a mixed group of adults diagnosed with oesophageal cancer and their carers reported on intrusions on children and partners. Children need support and are affected by parents' diagnosis. People need to be supported through changing roles and relationships.

5.2.6.2.2 Theme 2: Uncertainty

Very low evidence from 2 qualitative studies of a mixed group of adults diagnosed with oesophageal cancer and their carers reported on uncertainty surrounding course and prognosis, future, hereditary and existential concerns. People's feelings of uncertainty surrounding course and prognosis are constant and can lead to hopelessness. Additionally, uncertainty around the future affects patient and family member's planning and behaviour.

People and family members were concerned with the heredity of the cancer and uncertain whether their children would be affected. Adults with oesophageal cancer need support adjusting to the emotional changes of receiving a diagnosis of and living with a life-threatening illness.

5.2.6.2.3 Theme 3: Receiving a diagnosis of oesophageal cancer

Very low evidence from 1 qualitative study of a mixed group of adults diagnosed with oesophageal cancer reported on support needed surrounding receiving a diagnosis of oesophageal cancer. People found receiving a diagnosis of oesophago-gastric cancer particularly hard as they had no previous knowledge of the disease.

5.2.6.2.4 Theme 4: Adjusting to and accepting an altered self

Very low to low evidence from 1 qualitative study of a mixed group of adults diagnosed with oesophageal cancer reported on physical changes and changes to dietary habits. People experience physical changes with affect daily-life activities. In particular, the experience of undergoing treatments and investigation is extremely tiring. Changes to dietary habit changes are also an intrusion into daily-life which is linked to changes and adjustments in social life.

5.2.7 Evidence to recommendations

5.2.7.1 Relative value placed on the themes considered

The Committee considered that people with oesophago-gastric cancer who were suitable for palliative treatment only would need psychosocial support, counselling and parent/carer information. Many of these needs would be the same as those with other life-limiting conditions, including other cancers, but people with oesophago-gastric cancer would have specific information and support needs. These would include:

- Nutrition/artificial feeding (including nutrition/clinically assisted nutrition and hydration, and the use of supplements)
- Dietetic input/advice and counselling
- Oesophago-gastric cancer-specific support groups
- The Committee identified other more generic themes relating to information and support needs and these included:
- Holistic needs assessments
- Financial and benefits advice
- Support available in tertiary, secondary or primary/community care
- Named individual/key-worker or specialist nurse for point of contact
- Use of personalised treatment plans

For all these themes the Committee was interested in the timing of support and information provision (pre-treatment, during treatment, end of treatment), the format of information (verbal, written, web-based to include videos and social media, electronic data such as mobile phone applications, online support forums).

The provision of information and support on a number of specific aspects of oesophago-gastric cancer that was only suitable for palliative treatment was identified by the Committee as being relevant. These aspects were:

- Support groups and organisations
- Respite care
- Information about palliative treatments (both chemotherapy and radiotherapy)
- Information about palliative interventions including stenting

- Specific information about diet for patients who have stents
- Timing of referral to specialist palliative care services
- Treatment failure/outcomes
- Prognosis of disease
- Psychological difficulties
- End of life care planning
- Advance care planning

Some of the more generic themes and topics have already been covered in other guidance on patient experience in adult NHS services and so the Committee agreed that instead of making individual recommendations the guidelines could cross-refer to this document.

5.2.7.2 Quality of the evidence

The evidence for this review was qualitative so was assessed using the CERQual method.. Two Swedish studies were included in the review and contained small numbers of participants (nine and 13 respectively). The Committee agreed that the data from these studies were applicable to the UK population. Data saturation was reported in one of the studies. The small size of the studies was noted by the Committee when making their recommendations, but sample size alone does not drive the quality assessment of the study based on the NICE pre-defined checklist. It was also noted by the Committee that the populations in the studies were mixed and that not all patients were undergoing palliative treatment.

As the data were qualitative, a number of the outcomes that the Committee had prioritised were not available in the included articles, but other aspects of support and information were included in the themes discussed.

The evidence for the various themes identified was of low or very low quality, and covered a number of areas including effects on family life, uncertainty around prognosis, the difficulty of receiving the diagnosis, and physical changes including changes to diet. The Committee therefore used these themes as a basis for making recommendations but as the evidence was low quality they also used their clinical experience and knowledge of what information and support was likely to be of benfit to people, as well as cross-referncing to the NICE guildeines on patient experience and palliative care.

5.2.7.3 There was some low quality evidence available to guide the Committee when making recommendations about who should provide support for this group of people, and this included doctors, nurses, their own social circles and peer groups of other people with oesophago-gastric cancer. In addition to this evidence, the Committee used their clinical experience of the composition of palliative care teams (which will include doctors and nurses) and the role of of dietitians. Consideration of benefits and harms

The information themes identified that patients seek information from doctors, nurses, other medical staff, allied healthcare professionals, their own social circles and other adults with oesophago-gastric cancer, and that written material, information from the media and from the internet is used. Barriers to information include a fear of being overwhelmed and the fear of receiving upsetting information, as well lack of time or tiredness.

The support themes identified that partners, careres and children require support too, and that support is required to deal with the diagnosis, prognosis, future and existential concerns. It was also identified that people require support to dela with the invetigations and treatmetns which can be exhausting.

The Commmittee discussed the fact that a diagnosis of oesophago-gastric cancer which is suitable only for palliative treatment can be devastating and the Committee recognised that, while all patients with a diagnosis of cancer cope better with their disease if offered appropriate support and advice, people with oesophago-gastric cancer may need specific advice relating to nutrition and the impact of their disease on swallowing and eating. Eating is an activity of daily living, as well as being closely linked with family, social, personal life and sense of self-worth, there is a particular benefit to be gained by people with oesophago-gastric cancer who receive appropriate nutritional advice and support.

The Committee agreed that their recommendations would lead to more consistent and tailored information being provided to people with oesophago-gastric cancer suitable only for palliative care, would ensure improved specialist dietetic advice and would increase the provision of and information about peer to peer support and palliative care services.

The Committee recognised that there may be individuals who do not wish to receive such detailed information, but that the benefit of offering information to the majority of patients outweighed this concern, and that patients would be free to decline support if they wished.

5.2.7.4 Consideration of economic benefits and harms

A systematic review of the economic literature was conducted but no relevant studies were identified which were applicable to this review question.

The economic implications of this topic were considered but not thought to be substantial as the majority of the recommendations reflect current best practice. For those centres not following current best practice there are potential cost implications around making support available from a clinical nurse specialist, specialist dietitian and palliative care team.

However, these costs will be offset (at least partially) by the provision of more appropriate care which should lead to a reduction in unscheduled care and emergency admissions.

5.2.7.5 Other considerations

The Committee noted that there was a lack of evidence for a specific palliative care population with oesophago-gastric cancer. Thus their recommendations to refer to and inform people about palliative care services were made based on their clinical experience, and the knowledge that studies in groups of patients with other cancers had provided evidence that early referral to palliative care was beneficial. The Committee also included a recommendation relating to the use of ‘patient-identified’ sources of information, based on their own clinical experience, that such information can be unreliable or irrelevant and cause undue concern.

The Committee agreed that for people with oesophago-gastric cancer, although there was no evidence for the role of dietitians, they did have a role to play in helping patients with their specific needs relating to food intake, the social issues of potentially not being able to eat, and the most appropriate timing and frequency of meals. However, the Committee agreed that this support could be delivered by a specialist cancer-care dietitian and did not require the input of a specialist oesophago-gastric dietitian. The Committee agreed that in most centres dietitians were available to all cancer patients and that therefore this would reflect a minimal change in practice.

The Committee recognised that all information and support provided for patients would need to address individual needs in terms of language, readability and applicability to different ethnic origins, religions or dietary requirements.

5.2.7.6 Key conclusions

The Committee concluded that although there was very little evidence available for the information and support needs of this palliative population of people with oesophago-gastric cancer, the evidence was in-line with their clinical experience and current clinical practice. Their recommendations were therefore primarily 'generic' recommendations which would be suitable for people with a life-limiting cancer diagnosis, with additional recommendations relating to the specific nutritional needs of those with oesophago-gastric cancer.

5.2.8 Recommendations

Palliative management

6. **For people with oesophago-gastric cancer who can only have palliative management, offer personalised information and support to them and the people who are important to them (as appropriate), at a pace that is suitable for them. Include information on:**
    - life expectancy
    - the treatment and care available, and how to access this both now and for future symptoms
    - holistic issues (such as physical, emotional, social, financial and spiritual issues), and how they can get support and help
    - dietary changes, and how to manage these and access specialist dietetic support
    - which sources of information in the public domain give good advice about the issues listed above.

    Follow the recommendations in NICE's guideline on patient experience in adult NHS services.

7. **Make sure the person has information to take away and review in their own time after you have spoken to them about their cancer and care. Consider providing support from:**
    - a specialist cancer care dietitian
    - a specialist palliative care team
    - a peer support group, if available.

8. **Follow the recommendations in the NICE guideline on improving supportive and palliative care for adults with cancer**

6 Organisation of services

This chapter looks at the organisation of services for people with oesophago-gastric cancer and is divided into two sections – one focussing on the organisation of multi-disciplinary teams, and one focussing on the organisation of surgical services.

Currently, people with newly diagnosed oesophago-gastric cancer are discussed in a formal multidisciplinary team (MDT) meeting in order to plan the most appropriate ongoing management. By virtue of their referral patterns (usually for endoscopy and imaging) most centres have a regular MDT meeting to discuss the management of people with a diagnosis of oesophago-gastric cancer, and in general people found to have localised, potentially radically treatable disease are then referred on to a specialist centre. Some specialist oesophago-gastric cancer centres have regular specialist MDTs to discuss people who are being considered for radical (usually multimodal) treatment, however this is not the case for all specialist MDTs across the UK. People suitable for palliative treatment may be managed either in the local unit or in the specialist centre, and so would be discussed at either type of MDT.

In order to identify the most effective organisation and delivery of MDT services for those with oesophago-gastric cancer this review aimed to explore the outcomes associated with the management of people within local and specialist MDTs. In addition, it aimed to identify which subgroups of people might benefit the most by referral from local to specialist MDTs.

There is a clear relationship between numbers of resections of oesophago-gastric cancer carried out by an individual unit and outcomes, and this has been the main driver of centralisation of specialist oesophago-gastric cancer surgical services. The first major centralization occurred in 2001 with the publication by the NHS Executive of the Improving Outcomes Guidance (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 oesophago-gastric 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. Furthermore, whilst all surgery with curative intent should be carried out in a specialist centre, it may be appropriate for some palliative (especially emergency) surgery to take place in the local units.

This review aimed to explore and make recommendations for the optimal provision and organisation of surgical services for people with oesophago-gastric cancer.

6.1 Multidisciplinary teams

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

6.1.1 Description of clinical evidence

No relevant clinical studies comparing the outcomes for patients managed by local or specialist multi-disciplinary teams were identified.

6.1.2 Summary of included studies

No studies were included for this review.

6.1.3 Clinical evidence

No clinical evidence was available for this review.

6.1.4 Economic evidence

A systematic review of the economic literature was conducted but no relevant studies were identified which were applicable to this review question. Economic modelling was not undertaken for this question because other topics were agreed as higher priorities for economic evaluation.

6.1.5 Evidence statements

No evidence statements are available for this review.

6.1.6 Evidence to recommendations

6.1.6.1 Relative value placed on outcomes considered

Patients with oesophago-gastric cancer are currently discussed in local or specialist multidisciplinary team (MDT) meetings to plan their appropriate management. The outcome considered most important by the Committee when developing recommendations for this question was therefore the 'time to decision to treat'. NHS England has a target of 85% of patients to start their cancer treatment within 62 days following an urgent GP referral for suspected cancer, and a maximum 31-day wait from the date a decision to treat is made to the first definitive treatment. This was considered important due to the difficulty in assembling necessary specialist multidisciplinary team members and the time sensitive and critical nature of oesophago-gastric cancer treatment. However, neither this outcome nor any of the other outcomes the Committee had specified in the protocol were reported in the evidence.

6.1.6.2 Quality of evidence

There was no evidence available for this review question. The Committee therefore made their recommendations based on clinical experience and using the current standard of practice which is defined in the Improving Outcomes in Upper-Gastrointestinal Cancers guidance, published by the NHS Executive in 2001. This document set out the organisation of specialist centres which should cover a population of at least 1 million and defines the organisation of services, including the function and composition of MDTs. This guidance defines two levels of MDT, and these are therefore reflected in the recommendations made.

6.1.6.3 Consideration of clinical benefits and harms

The Committee agreed that reviewing the treatment of all people with a diagnosis of oesophago-gastric cancer in a multidisciplinary team (MDT) meeting was likely to lead to equity of care, improve time to treatment and effective, appropriate decision making, because decisions about individual patients would be made following a discussion about their clinical presentation and the most suitable treatment option. The Committee recognised that in some cases the difficulty of assembling the appropriate personnel for the MDT meeting might lead to delayed decision making. However, the Committee agreed that using an MDT to ensure correct decision making for individual people was more important than a possible (but unlikely) treatment delay.

6.1.6.4 Consideration of economic benefits and harms

A systematic review of the economic literature was conducted but no relevant studies were identified which were applicable to this review question.

The economic implications of this topic were considered, but not thought to be substantial, as the recommendations reflect peer review guidance and current best practice.

The recommendations offer flexibility in the personnel involved in the MDT. In some centres there may be additional resources required for a specialist radiologist and an oncologist to be present at the meetings. However, it is anticipated that there will be cost savings resulting from discussing some people with oesophago-gastric cancer at a local MDT only (avoiding the duplication of process which sometimes occurs if people are discussed at a local MDT but then also at a specialist MDT).

6.1.6.5 Other considerations

6.1.6.6 The Committee used their own clinical experiences to develop the recommendations but also considered the 'Improving Outcomes in Upper Gastro-intestinal Cancers' guidance from the NHS on multidisciplinary teams and their membership. The specialist centres and organisation of service defined in this guidance are now established nationally so implementing these recommendations should not require a change of practice in the majority of centres.Key conclusions

The Committee concluded that people with confirmed oesophago-gastric cancer should be reviewed at a MDT meeting that should include an oncologist and specialist radiologist with an interest in oesophago-gastric cancer. By specifying that an oncologist and a specialist radiologist are included, the Committee aimed to improve time to treatment and reduce the need for people to be referred to a specialist MDT where local MDTs are adequately configured. However, people with localised, non-metastatic oesophago-gastric cancer (i.e. those who were most likely to benefit from radical/curative treatment) should be reviewed in a specialist oesophago-gastric cancer MDT meeting.

6.1.7 Recommendations

9. **Review the treatment of people with confirmed oesophago-gastric cancer in a multidisciplinary meeting that includes an oncologist and specialist radiologist with an interest in oesophago-gastric cancer.**

10. **Review the treatment of people with confirmed localised, non-metastatic oesophago-gastric cancer in a specialist oesophago-gastric cancer multidisciplinary meeting.**

6.2 Surgical services

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

6.2.1 Description of clinical evidence

Nine studies were identified (N=43882). All studies were conducted in Europe. 2 were conducted in the Netherlands (Dikken 2009, Henneman 2014), 4 were conducted in Sweden (Viklund 2006, Derogar 2013, Rouvelas 2007 and Rutegard 2008), 2 in the UK (Anderson 2011, Migliore 2007) and 1 was multicentre (Markar 2015).

6.2.1.1 High vs. low hospital volume

Six studies identified reported on a comparison of high versus low surgical volume at the hospital level (Dikken 2009, Henneman 2014, Derogar 2013, Rutegard 2008, Anderson 2011, and Markar 2015). Two studies were with patients with oesophageal and gastric cancer (Anderson 2011, Dikken 2009). Two studies were with patients with oesophageal or cardia cancer (Henneman 2014, Rutegard 2008). Two studies were with oesophageal cancer only (Derogar 2013, Markar 2015). The definition of high volume hospitals ranged from 8–21 surgeries performed per year.

6.2.1.2 High vs. low surgeon volume

Five studies identified reported on a comparison of high versus. low surgical volume at the surgeon level (Migliore 2007, Rutegard 2008, Rouvelas 2007 Derogar 2013 and Viklund 2006). Three studies were with people with oesophageal or cardia cancer (Viklund 2006, Rouvelas 2007, Rutegard 2008). Two studies had people with oesophageal cancer only (Derogar 2013, Migliore 2007). The definition of high volume surgeons ranged from 5–6 surgeries performed per year.

6.2.2 Summary of included studies

A summary of the studies that were included in this review are presented in Table 34.

Table 34: Summary of included studies

Study	Population	Comparison	Outcomes	Notes
Dikken, 2009 Design: retrospective Dates: 1989-2009 Setting: The Netherlands	N=24,246 Patients with resectable, non-metastatic oesophageal and gastric cancer	Very low vs. low vs. medium vs. high hospital volumes	6-month mortality 3-year mortality	Hospital volumes per year: Very low: 1-5 Low: 6-10 Medium: 11-20 High ≥21/year
Anderson, 2011 Design: retrospective Dates: 1998-2008 Setting: UK	N=3870 Patients diagnosed with oesophageal or gastric cancer and treated operatively	Very low vs. low vs. medium vs. high hospital volumes	30-day mortality 1-year mortality	Hospital volumes per year: Very low:1-10 Low: 11-20 Medium: 21-30 High >30
Viklund, 2006 Design: prospective Dates: 2001-2003 Setting: Sweden	N=275 (147 oesophageal) Patients with a newly diagnosed adenocarcinoma or squamous cell carcinoma of the oesophagus or cardia who underwent tumour resection	Low vs. high surgeon volume	Surgical complications Anastomotic leakage	Low surgeon volume <5/ year High surgeon volume >=5/ year
Derogar, 2013 Design: retrospective Dates: 1998-2005 Setting: Sweden	N= 1355 Patients who underwent oesophagectomy for oesophageal cancer	Low vs. medium vs. high hospital volumes Low vs. medium vs. high surgeon volumes	Short-term mortality (=< 3 months) Long-term mortality (>3 months)	Type according to hospital volume Low: 1-8 surgeries/ year Medium: 9-16 surgeries/ year

Study	Population	Comparison	Outcomes	Notes
				High: ≥17 surgeries/ year Type according to surgeon volume Low: 1-4 surgeries/year Medium: 5-9 surgeries/year High: ≥10 surgeries/year
Henneman, 2014 Design: retrospective Dates: 1989-2009 Setting: The Netherlands	N= 10025 Patients who had under gone surgery for oesophageal or gastric cardia cancer	Hospital volumes (by 10 surgery per year increments)	6 month mortality 2 year mortality	Range: 10-80 surgeries per year per hospital
Markar, 2015 Design: Retrospective Dates: 2000-2010 Setting: Europe (multicentre)	N= 2944 Adult patients undergoing surgical resection for esophageal cancer (including Siewert type I and II junctional tumors) with curative intent.	Hospital volume high vs low	30-day mortality Anastomotic leak Surgical site infection Pulmonary complication Reoperation	Volume over entire 10 year period: Low =<80 High > 80
Rouvelas, 2007 Design: prospective Dates: 2001-2005 Setting: Sweden	N=607 People diagnosed with oesophageal or cardia cancer who were treated with oesophagectomy	High vs. medium vs. low volume surgeon	30-day mortality 90-day mortality	Low-volume surgeons performed <2, medium-volume surgeons performed 2-6, and high-volume surgeons performed >6 per year.
Rutegard, 2008 Design: prospective Dates: 2001-2005 Setting: Sweden	N=355 Patients newly diagnosed with oesophageal or cardia cancer who underwent macroscopically and microscopically radical resection.	High vs. low volume hospital High vs. low volume surgeons	Health-related quality of life (EORTC QLQ-C30 and EORTC QLQ-OES18)	Low volume hospitals conducted 0–9 operations annually and high volume hospitals conducted more than 9 operations/year. Low-volume surgeons carried out 0–6 operations/year, and high volume surgeons carried out more than six procedures annually.

Study	Population	Comparison	Outcomes	Notes
Migliore 2007 Design: retrospective Dates: 1994-2005 Setting: United Kingdom	N=205 Patients who underwent oesophagectomy for malignant disease with palliative or curative intent	High vs. low surgeon volume	In-hospital mortality Overall survival	High volume surgeon: mean of >6 cases per year

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6.2.31 Clinical evidence profile

2 The summary clinical evidence profiles are given in Table 35 to Table 36.

3 **Table 35: Summary clinical evidence profile: High vs. low hospital volume**

Study	n	Risk of Bias[a]	Indirectness[b]	Other considerations[e]	Results[d]	Quality[c]
Short-term mortality (30-day or in-hospital)						
Anderson 2011[1]	3870	Serious risk of bias[5]	No serious risk of indirectness		HR at 30 days: 1-10 cases/year: 1.000 (reference) 11-20 cases/year: 0.974 21-30 cases/year: 0.865 >30 cases/year: 0.660 P trend = 0.001	VERY LOW
Markar 2015[1]	2944	No serious risk of bias	No serious risk of indirectness	Large effect size[8]	RR (95% CI) at 30 days: Centre volume <= 80 resections: 1.00 (reference) Centre volume > 80 resections: 0.29(0.21, 0.39) p<0.001	MODERATE
90-day mortality						
Derogar 2013	1355	No serious risk of bias	Serious risk of indirectness[6]		HR (95%CI): 1-8 surgeries/year: 1.00 (ref) 9-16 surgeries/year: 0.57 (0.38-0.85) >= 17 surgeries/year: 0.47 (0.31-0.71) P trend <0.01	VERY LOW
6-month mortality						
Dikken 2009	24246	No serious risk of bias	No serious risk of indirectness		Post-oesophagectomy HR (95% CI): Very low (1-5/ year): 1.00 (reference)	LOW

Study	n	Risk of Bias[a]	Indirectness[b]	Other considerations[e]	Results[d]	Quality[c]
					Low (6-10/ year): 0.90 (0.78-1.03) Medium (11-20/ year): 0.78 (0.62-0.97) High (≥21/ year): 0.48 (0.38-0.61) Post-gastrectomy HR (95% CI): Very low (1-5/ year): 1.00 (reference) Low (6-10/ year): 0.95 (0.84-1.07) Medium (11-20/ year): 0.95 (0.83-1.08) High (≥21/ year): 1.10 (0.82-1.49)	
Henneman 2014	10025	No serious risk of bias	No serious risk of indirectness		HR (95% CI) at 6 months: 20 surgeries/year: 1.00 (ref) 30 surgeries/year: 0.83 (0.76-0.91) 40 surgeries/year: 0.73 (0.65-0.83) 50 surgeries/year: 0.68 (0.6-0.78) 60 surgeries/year: 0.67 (0.58-0.77) 70 surgeries/year: 0.67 (0.54-0.83) 80 surgeries/year: 0.68 (0.49-0.94)	LOW
Long-term mortality (=> 1 year)						
Anderson 2011	3870	Serious risk of bias[5]	No serious risk of indirectness		HR at 1-year[4] 1-10 cases/year: 1.000 (reference) 11-20 cases/year: 0.947 21-30 cases/year: 1.002 >30 cases/year: 0.705 P trend= 0.215	VERY LOW
Henneman 2014	10025	No serious risk of bias	No serious risk of indirectness		HR (95% CI) at 2 years[7]: 20 surgeries/year 1.00 (ref) 30 surgeries/year 0.92 (0.89-0.96) 40 surgeries/year 0.88 (0.83-0.93) 50 surgeries/year 0.86 (0.79-0.93) 60 surgeries/year 0.85 (0.75-0.97)	LOW

Study	n	Risk of Bias[a]	Indirectness[b]	Other considerations[e]	Results[d]	Quality[c]
					70 surgeries/year 0.86 (0.71-1.05) 80 surgeries/year 0.88 (0.66-1.16)	
Dikken 2009	24246	No serious risk of bias	No serious risk of indirectness		3-year survival[3] Post-oesophagectomy HR (95% CI): Very low (1-5/ year): 1.00 (reference) Low (6-10/ year): 1.01 (0.94-1.10) Medium (11-20/ year): 0.90 (0.81-0.99) High (≥21/ year): 0.77 (0.70-0.85) Post-gastrectomy HR (95% CI): Very low (1-5/ year): 1.00 (reference) Low (6-10/ year): 0.99 (0.91-1.07) Medium (11-20/ year): 0.99 (0.90-1.08) High (≥21/ year): 0.98 (0.86-1.12)	LOW
Overall mortality						
Derogar 2013	1355	No serious risk of bias	Serious risk of indirectness[6]		Overall mortality HR (95% CI): 1-8 surgeries/year: 1.00 (ref) 9-16 surgeries/year: 0.96 (0.82-1.11) >= 17 surgeries/year: 0.84 (0.72-0.98) P trend= 0.03	VERY LOW
Anastomotic leak						
Markar 2015	2944	No serious risk of bias	No serious risk of indirectness		RR (95% CI): Centre volume <= 80 resections: 1.00 (reference) Centre volume > 80 resections: 0.26 (0.14, 0.47), p<0.001	LOW
Surgical site infection						

Study	n	Risk of Bias[a]	Indirectness[b]	Other considerations[e]	Results[d]	Quality[c]
Markar 2015	2944	No serious risk of bias	No serious risk of indirectness		RR (95% CI): Centre volume <= 80 resections : 1.00 (reference) Centre volume >80 resections: 0.65 (0.55 –0.77) p<0.001	LOW
Pulmonary complication						
Markar 2015	2944	No serious risk of bias	No serious risk of indirectness	Large effect size[8]	RR (95% CI): Centre volume <= 80 resections: 1.00 (reference) Centre volume >80 resections: 0.42 (0.30–0.61) p<0.001	MODERATE
Reoperation						
Markar 2015	2944	No serious risk of bias	No serious risk of indirectness		RR (95% CI): Centre volume <= 80 resections: 1.00 (reference) Centre volume >80 resections: 0.59 (0.49–0.70), p<0.001	LOW
Health-related quality of life (EORTC QLQ-C30)						
Rutegard 2008[10]	355 (200 oesophageal cancer only)	No serious risk of bias	No serious risk of indirectness	20% of those eligible did not enrol	Mean score (95% CI) at 6 months post-surgery for oesophageal cancer: Low hospital volume: Appetite loss: 35 (28-42) Dyspnoea: 32 (26-39) Fatigue: 42 (37-47) Nausea and vomiting: 18 (13-22) Pain: 24 (19-31) Physical functioning: 78 (74–83) Global QoL: 60 (56–65) Role functioning: 66 (59–73)	LOW

Study	n	Risk of Bias[a]	Indirectness[b]	Other considerations[e]	Results[d]	Quality[c]
					High hospital volume: Appetite loss: 35 (28–43) Dyspnoea: 37 (30–43) Fatigue: 44 (39–50) Nausea and vomiting: 20 (15–25) Pain: 26 (21–32) Physical functioning: 74 (70–78) Global QoL: 59 (55–64) Role functioning: 61 (54–68)	
Health-related quality of life (EORTC QLQ-OES18)						
Rutegard 2008[10]	355 (200 oesophageal cancer only)	No serious risk of bias	No serious risk of indirectness	20% of those eligible did not enrol	Mean score (95% CI) at 6 months post-surgery: Low hospital volume: Dry mouth: 22 (16–29) Choking with swallowing: 21 (16–26) Trouble with coughing: 28 (21–35) Dysphagia: 23 (17–29) Trouble with eating: 33 (28–38) Oesophageal pain: 27 (22–32) Reflux: 29 (23–35) Speech difficulties: 13 (8–19) Trouble swallowing saliva: 10 (5–15) High hospital volume: Dry mouth: 27 (21–33) Choking with swallowing: 23 (18–29) Trouble with coughing: 36 (30–43) Dysphagia: 21 (17–26) Trouble with eating: 36 (30–41) Oesophageal pain: 23 (19–27)	LOW

Study	n	Risk of Bias[a]	Indirectness[b]	Other considerations[e]	Results[d]	Quality[c]
					Reflux: 26 (20–31) Speech difficulties: 14 (9–19) Trouble swallowing saliva: 16 (10–21)	

Abbreviations: RR=risk ratio; HR= hazard ratio; NR= not reported by the study
[a] Assessed using Cochrane risk of bias tool for non-randomised studies
[b] Assessed using GRADE principle for assessing indirectness
[c] Based on GRADE methodology- observational studies start as low quality. Quality assessed using risk of bias and indirectness and imprecision where applicable (Inconsistency not applicable).
[d] Multivariate model reported. For basic/unadjusted model see full evidence table Appendix F.
[e] Including potential upgrading for large effect, dose-response or residual confounding
[1] 30-day mortality
[2] in hospital mortality
[3] inclusion in 3-year survival was contingent on surviving the first 6 months
[4] inclusion in 1-year survival contingent on surviving the first 3 months
[5] Anderson 2011: Confidence intervals not reported for HR, catchment area of Thames registry not reported
[6] Majority of patient data is pre-2002 (outside protocol time frame)
[7] 2-year mortality conditional on surviving first 6 months
[8] Quality upgraded by 2 level due to very large effect size RR>8 or RR <0.2
[9] Quality upgraded by 1 level due to large effect size RR >2 or RR<0.5
[10] Linear regression and multivariate analysis not conducted as authors did not detect significant difference between groups.

Table 36: Summary clinical evidence profile: High vs. low surgeon volume

Study	n	Risk of Bias[a]	Indirectness[b]	Other considerations[e]	Results[d]	Quality[c]
Short-term mortality (30-day or in-hospital)						
Migliore 2007[1]	205	No serious risk of bias	No serious risk of indirectness		In-hospital mortality : High surgical volume: 1.00 (reference) Low surgical volume Crude RR (95%CI)=3.98 (1.48, 10.73) Crude OR (95%CI) = 4.59 (1.57, 13.46) p=0.006 Adjusted OR for type of tumour= 2.26 (0.48, 10.52), p= 0.30	LOW

Study	n	Risk of Bias[a]	Indirectness[b]	Other considerations[e]	Results[d]	Quality[c]
					Adjusted OR for 10-year changes in age= 1.63 (0.93, 2.84) 0.087	
Rouvelas 2007[2]	607 (320 Oesophageal cancer only)	No serious risk of bias	No serious risk of indirectness		Oesophageal cancer only: OR (95% CI): Low-volume surgeon group: 1.00 (ref) Medium-volume surgeon group: 0.12 (0.01-1.58) High-volume surgeon group: 0.29 (0.02 -3.28)	LOW
90-day survival						
Rouvelas 2007	607 (320 Oesophageal cancer only)	No serious risk of bias	No serious risk of indirectness		Oesophageal cancer only: OR (95% CI): Low-volume surgeon group: 1.00 (ref) Medium-volume surgeon group: 0.40 (0.05 - 3.38) High-volume surgeon group: 2.16 (0.22-20.90)	LOW
Derogar 2013	1355	No serious risk of bias	Serious risk of indirectness[4]		HR (95%CI): 1-4 surgeries/year: 1.00 (ref) 5-9 surgeries/year: 0.91 (0.63-1.31) >= 10 surgeries/year: 0.48 (0.29-0.80) P trend= 0.01	VERY LOW
Overall survival						
Migliore 2007	205	No serious risk of bias	No serious risk of indirectness		Overall survival HR (95% CI): 0.89 (0.64-1.23)	LOW

Study	n	Risk of Bias[a]	Indirectness[b]	Other considerations[e]	Results[d]	Quality[c]
					P log rank test= 0.476.	
Derogar 2013	1355	No serious risk of bias	Serious risk of indirectness[4]		Overall mortality HR (95% CI): 1-4 surgeries/year: 1.00 (ref) 5-9 surgeries/year: 0.82 (0.70-0.96) >= 10 surgeries/year: 0.82 (0.69-0.99) P trend= 0.02	VERY LOW
Surgical complication						
Viklund 2006	275	No serious risk of bias	Serious indirectness[3]		RR (95%CI) at least 1 severe complication: High surgeon volume 1.00 (ref) Low surgeon volume 1.18(0.90, 1.53) OR (95%CI) at least 2 severe complications: High surgeon volume 1.00 (ref) Low surgeon volume 1.38(0.86, 1.56)	VERY LOW
Anastomotic leak						
Viklund 2006	275	No serious risk of bias	Serious indirectness[3]		RR (95%CI): High surgeon volume: 1.00 (ref) Low surgeon volume: 4.62 (1.70, 12.58) (p<0.01)	VERY LOW
Health-related quality of life (EORTC QLQ-C30)						
Rutegard 2008[5]	355 (200 oesophageal	No serious risk of bias	No serious risk of indirectness	20% of those eligible did not enrol	Mean score (95% CI) at 6 months post-surgery for oesophageal cancer: Low surgeon volume:	LOW

Study	n	Risk of Bias[a]	Indirectness[b]	Other considerations[e]	Results[d]	Quality[c]
	cancer only)				Appetite loss: 33 (25–41) Dyspnoea: 30 (23–38) Fatigue: 41 (35–47) Nausea and vomiting: 18 (13–23) Pain: 25 (18–31) Physical functioning: 80 (75–85) Global QoL: 61 (56–66) Role functioning: 70 (62–77) High surgeon volume: Appetite loss: 37 (30–43) Dyspnoea: 37 (32–43) Fatigue: 44 (39–49) Nausea and vomiting: 20 (16–24) Pain: 26 (21–31) Physical functioning: 74 (70–78) Global QoL: 59 (55–63) Role funcitioning: 59 (53–65)	
Health-related quality of life (EORTC QLQ-OES18)						
Rutegard 2008[5]	355 (200 oesophageal cancer only)	No serious risk of bias	No serious risk of indirectness	20% of those eligible did not enrol	Mean score (95% CI) at 6 months post-surgery: Low surgeon volume: Dry mouth: 24 (16-31) Choking with swallowing: 22 (15-28) Trouble with coughing: 24 (18-31) Dysphagia: 26 (19-33) Trouble with eating: 31 (26-37) Oesophageal pain: 28 (23-34)	LOW

Study	n	Risk of Bias[a]	Indirectness[b]	Other considerations[e]	Results[d]	Quality[c]
					Reflux: 28 (23-34) Speech difficulties: 10 (4-15) Trouble swallowing saliva: 11 (5-18) High surgeon volume: Dry mouth: 24 (16-31) Choking with swallowing: 22 (15-28) Trouble with coughing: 38 (32-44) Dysphagia: 20 (16-24) Trouble with eating: 36 (31-41) Oesophageal pain: 22 (19-26) Reflux: 27 (22-32) Speech difficulties: 16 (11-21) Trouble swallowing saliva: 14 (9-19)	

Abbreviations: OR= odds ratio; HR= hazard ratio; NR= not reported by the study; RR=relative risk
a Assessed using Cochrane risk of bias tool for non-randomised studies
b Assessed using GRADE principle for assessing indirectness
c Based on GRADE methodology- observational studies start as low quality. Quality assessed using risk of bias and indirectness and imprecision where applicable (Inconsistency not applicable).
d Multivariate model reported. For basic/unadjusted model see full evidence table Appendix F.
e Including potential upgrading for large effect, dose-response or residual confounding
1 30-day mortality
2 in hospital mortality
3 gastric cardia included in the population (Viklund 2006: 54% oesophageal cancer; Rouvelas 2007: 53% oesophageal cancer)
4 Majority of patient data is pre-2002 (outside protocol time frame)
5 Linear regression and multivariate analysis not conducted as authors did not detect significant difference between groups.

6.2.4 Economic evidence

A systematic review of the economic literature was conducted but no relevant studies were identified which were applicable to this review question. Economic modelling was not undertaken for this question because other topics were agreed as higher priorities for economic evaluation.

6.2.5 Evidence statements

6.2.5.1 High vs. low hospital volume

Survival:

Two studies reported on 30-day mortality. Moderate quality evidence from 1 study with 2944 people indicated a benefit of high volume hospitals compared to low volume hospitals. Very low quality evidence from 1 study with 3870 people with oesophago-gastric reported a trend of lower 30-day mortality in high volume hospitals compared to low volume hospitals, however, uncertainty was not reported.

Very low quality evidence from 1 study with 1355 people with oesophageal cancer indicated a clinically significant benefit to 90-day survival of high volume hospitals compared to low volume hospitals.

Two studies reported 6-month mortality. Low quality evidence from 1 study with 10 205 people with oesophageal cancer indicated a clinically significant benefit to 6-month survival of medium and high volume hospitals compared to very low volume hospitals. Low quality evidence from 1 study with 14 221 people with gastric cancer indicated no clinically significant difference in 6-month survival between high, medium, low and very low volume hospitals. Low quality evidence from 1 study with 10 025 people with oesophageal and cardia cancer reported a trend of lower 6-month mortality in higher volume hospitals compared to lower volume hospitals.

Very low quality evidence from 1 study with 3870 people with oesophago-gastric indicate no clinically significant difference in 1-year survival between higher and lower volume hospitals.

Low quality evidence from 1 study with 10 025 people with oesophago-gastric indicate no clinically significant difference in 2-year survival between higher and lower volume hospitals.

Low quality evidence from 1 study with 10 205 people with oesophageal cancer indicate no clinically significant difference to 3-year survival between high, medium, low and very low hospitals. Low quality evidence from 1 study with 14 221 people with gastric cancer indicate no clinically significant difference in 3-year survival between high, medium, low and very low volume hospitals.

Very low quality evidence from 1 study with 1355 people with oesophageal cancer indicate no clinically significant difference to overall survival of high volume hospitals compared to low volume hospitals.

Post-operative complications:

Low quality evidence from 1 study with 2944 people with oesophageal cancer indicate a lower risk of anastomotic leak in high volume hospitals compared with low volume hospitals.

Moderate quality evidence from 1 study with 2944 people with oesophageal cancer indicate a lower risk of pulmonary complications in high volume hospitals compared with low volume hospitals.

Low quality evidence from 1 study with 2944 people with oesophageal cancer indicate a lower risk of reoperation in high volume hospitals compared with low volume hospitals. Reoperation is lower in high volume hospitals.

Adequacy of surgery:

No studies reported on this outcome.

Health-related quality of life:

Low quality evidence from 1 study with 200 people with oesophageal cancer indicate no difference in health-related quality of life between higher and lower volume hospitals (measured using the EORTC QLQ-C30 and EORTC QLQ-OES18).

Length of hospital stay:

No studies reported on this outcome.

Disease-free survival:

No studies reported on this outcome.

Tumour deemed inoperable/unresectable at surgery:

No studies reported on this outcome.

6.2.5.2 High vs. low surgeon volume

Survival:

Low quality evidence from 1 study with 205 people with oesophageal cancer indicate no clinically significant difference in 30-day mortality between high and low volume surgeons. Low quality evidence from 1 study with 320 people with oesophageal cancer indicate no clinically significant difference in in-hospital mortality between higher and lower volume surgeons.

Low quality evidence from 1 study with 320 people with oesophageal cancer indicate no clinically significant difference in 90-day mortality between higher and lower volume surgeons. Very low quality from 1 study with 1355 people with oesophageal cancer indicate a clinically significant benefit in 90-day mortality of highest volume surgeons compared to lowest volume surgeons.

Very low quality evidence from 2 studies with 205 and 1355 people each indicate no clinically significant difference in overall survival between high volume surgeons and low volume surgeons.

Post-operative complications:

Very low quality evidence from 1 study with 275 people with oesophageal or cardia cancer indicate a lower risk of severe complications between high volume surgeons and low volume surgeons.

Very low quality evidence from 1 study with 275 people with oesophageal or cardia cancer indicate a lower risk of anastomotic leak in high volume surgeons compared to low volume surgeons.

Adequacy of surgery:

No studies reported on this outcome.

Health-related quality of life:

Low quality evidence from 1 study with 200 people with oesophageal cancer indicate no difference in health-related quality of life between higher and lower volume surgeons (measured using the EORTC QLQ-C30 and EORTC QLQ-OES18).

Length of hospital stay:

No studies reported on this outcome.

Disease-free survival:

No studies reported on this outcome.

Tumour deemed inoperable/unresectable at surgery:

No studies reported on this outcome.

6.2.6 Evidence to recommendations

6.2.6.1 Relative value placed on the outcomes considered

As the aim of this review was to determine how organisation of services led to improved surgical outcomes, the outcomes that the Committee considered critical were 30-day survival, post-operative complications (including reoperation or return to theatre) and health-related quality of life. A number of other outcomes included in the review protocol such as adequacy of surgery, time to recurrences, disease-free survival, patient satisfaction and length of hospital stay were not reported in the evidence.

6.2.6.2 Quality of the evidence

All 9 studies included in the evidence review were prospective or retrospective cohort studies, and no randomised controlled trials were identified. The included studies were assessed using the Cochrane risk of bias tool for non-randomised studies and were found to be of moderate to very low quality. All studies were conducted in Europe, but only 1 study was conducted in the UK. The studies were conducted in a variety of settings, and in many the start of the data collection series was over 10 years ago. There was also variability in the way ‘high-volume’ and ‘low-volume’ surgery was defined which meant the Committee was unable to make definitive recommendations on the volumes of surgery required for optimal outcomes to be achieved.

6.2.6.3 Considerations of the benefits and harms

For the comparison of high versus low hospital volumes, 30 day mortality, 90-day survival and 6-month mortality were all better with high volume, although longer term survival measures (1-, 2 and 3-year survival and overall survival) did not differ between the groups. There were also fewer complications with the high volumes groups, including reduced rates of anastamotic leaks, pulmonary complications and reoperations rates. The Committee therefore agreed that there werepossible benefits of high volume hospitals, and no apparent harms.

For the comparions of high versus low surgeon volume, there were no difference in survival or complication outcomes, except for anastamotic leak which was less frequent with higher surgical volumes. This lack of differenc between the groups made it difficult for the Committee to make specific recommendations.

As there was limited evidence, the Committee also based their recommendations on maintaining the currently agreed standard of practice, and therefore considered that their recommendations would reinforce this standard.

6.2.6.4 Consideration of economic benefits and harms

A systematic review of the economic literature was conducted but no relevant studies were identified which were applicable to this review question.

The Committee considered the economic implications of the recommendation to be negligible as it reinforces current practice.

6.2.6.5 Other considerations

Although the evidence did not allow for minimum surgery volumes to be defined, the Committee agreed that there was also no clinical evidence to support further centralisation of oesophago-gastric cancer services. The evidence did show a clear outcome-volume relationship, but this was more at the lower end of the surgical volume (by hospitals) spectrum than the higher end (i.e. those hospitals performing very low numbers of resections had poorer outcomes, but once a threshold had been reached there was little further improvement in outcomes despite increasing surgical volumes).

The Committee was also aware of the improvements in surgical outcomes over the last 15 years, as documented by the National Oesophago-Gastric Cancer Audit results. The Committee agreed that the current service configuration in the UK already demonstrates the improved outcomes that would be expected by moving to ‘high-volume’ surgery.

6.2.6.6 Key conclusions

Due to the poor quality and lack of evidence available for this review the Committee based their recommendation on the current UK practice and current UK service configuration (as defined by the ‘Improving Outcomes in Upper Gastro-intestinal Cancers’ guidance from the NHS, 2001).

6.2.7 Recommendations

11. Ensure curative oesophago-gastric resections are performed in a specialist surgical unit by specialist oesophago-gastric surgeons.

7 Assessment after diagnosis

7.1 Staging investigations

Review question: 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?

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

7.1.1 Introduction

This section reviews the staging investigations appropriate for use in oesophageal, oesophago-gastric and gastric cancer. Such staging investigations 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 people for curative interventions.

Following initial diagnosis of oesophageal cancer or cancer involving the junction between the oesophagus and stomach (usually by endoscopy and biopsy) it is routine practice to proceed to investigation with multi-slice computed tomography (CT) to a protocol including the thorax, abdomen and pelvis. Endoscopic ultrasound (EUS) is routinely used to characterise tumour size and stage, but it is not helpful for the detailed staging of mucosal disease and nodal staging. Positron Emission Tomography combined with multi-slice computed tomography (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.

The staging process is similar for gastric cancer. Following initial diagnosis of gastric cancer (usually by endoscopy and biopsy) it is routine practise to proceed to investigation with multi-slice computed tomography (CT) to a protocol including the thorax, abdomen and pelvis. Positron Emission Tomography combined with multi-slice computed tomography (PET-CT) can be used to detect distant metastases, but its role in assessing the primary tumour and nodal disease remains unclear. It is also recognised to carry limitations in the investigation of gastric cancer on account of its low yield in people with mucinous glandular histological subtypes of the disease but its place and contribution is not standardised or established in practice. 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, oesophago-gastric and gastric cancer. The order, timing and selection of tests could, however be improved and tailored to individual people, and this review aims to explore the optimal choice and order of diagnostic technologies to identify cases of oesophageal, oesophago-gastric and gastric cancer suitable for curative treatment.

7.1.21 Description of clinical evidence

Fifty-one studies (n=17264) were included in the review (Berrisford 2008; Bonavina 1997; Burke 1997; Chemaly 2008; Clements 2004; Convie 2015; de Graaf 2007; Dhupar 2015; Fujimura 2002; Grotehhuis 2013; Heath 2000; Hsu 2011; Kaiser 2007; Krasna 2002; Lee 2012; Lee 2013; Lowe 2005; Liu 2016; Little 2007; Lowy 1996; Luo 2016; Meister 2013; Menningen 2008; Menon 2003; Mirza 2016; Mitsunaga 2011; Mocellin 2015; Molloy 1995; Munasinghe 2013; Nguyen 2001; Nieveen an Dijkum 1999; O'Brien 1995; Pech 2006; Pech 2010; Ramos 2016; Roedl 2008; Roedl 2009; Romijn 1998; Salahudeen 2008; Salminen 1999; Sarela 2006; Shen 2012; Shi 2013; Smyth 2012; Staiger 2010; Strandby 2016; Vilgrain 1990; Wiliams 2009; Wilkiemeyer 2004; Yang 2008; Yau 2006). Evidence from these are summarised in the clinical modified GRADE evidence profile below. See also the study selection flow chart in Appendix K, forest plots in Appendix H, study evidence tables in Appendix F and exclusion list in Appendix J.

Where relevant and up-to-date systematic reviews exist, the data from these have been used as the basis for this review. This includes endoscopic ultrasound for oesophageal and gastric cancer, laparoscopy for gastric cancer and PET-CT for oesophageal cancer. Primary literature was used for the reports on PET-CT for gastric cancer, and staging laparoscopy for oesophageal and junctional cancers, as no existing systematic reviews were found in these areas.

Gastric cancer

Endoscopic ultrasonography

One systematic review article (including data from a total of 7747 participants) (Mocellin 2015) and 2 cohort studies (Lee 2012 and Mitsunaga 2011) were included. The review incorporated data from a total of 66 individual studies, conducted in 16 different countries, and assessed the diagnostic accuracy of endoscopic ultrasound for T and N staging of gastric cancer. Mitsunaga 2011 was done in Japan and a threshold of submucosal thickness 2.2 mm was used to distinguish between mucosal and submucosal lesion whereas Lee 2012 was done in China and miniprobe was used in some cases.

PET-CT

Four studies were identified which reported on the diagnostic accuracy of PET-CT for gastric cancer (Lee 2013; Roedl 2009(i); Smyth 2012; Yang 2008). Two of these studies considered the identification of nodal metastasis (Lee 2013; Yang 2008). The studies were conducted in Korea and Japan, and a total of 122 participants were included. Two other studies (Rodel 2009(i); Smyth 2012) considered the identification of metastatic disease. Both studies were conducted in the USA and included 172 participants.

Staging laparoscopy

One systematic review including 5 studies (n=240) (Ramos 2014) and 5 cohort studies (Burke 1997; Fujimura 2002; Lowy 1996; Sarela 2006; Strandby 2016) were included in the review. The systematic review was done in Brazil and reported staging accuracy for peritoneal metastasis. Burke 1997; Fujimura 2002; Lowy 1996 also reported staging accuracy for peritoneal metastasis. One study reported on the change in management and diagnostic accuracy of laparoscopy in gastric cancer (Sarela 2006). A total of 657 participants were included. The study was conducted in USA.

One study reported on change of management only in patients with gastric cancer (Strandby 2016). 48 participants were included and the study was conducted in Denmark.

Oesophageal cancer

Endoscopic ultrasonography

One systematic review (including data from a total of 2880 participants) was included in the report. This incorporated data from 44 different studies, conducted in a total of 13 countries (Luo 2016).

Nine cohort studies (Chemaly 2008; Lowe 2005; Meister 2013; Menningen 2008; Pech 2006; Pech 2010; Salminen 1999; Staigner 2010; Vilgrain 1990) (n=796) were also included, and their results combined with those from the Luo 2016 systematic review in meta-analysis. Two studies were conducted in France (Chemaly 2008; Vilgrain 1990) and Chemaly 2008 was performed to distinguish mucosal and submucosal staging whereas Vilgrain 1990 was done for diagnostic accuracy of nodal (N) staging. Two studies conducted in USA (Lowe 2005; Mennigen 2008) reported tumour and nodal staging and Lowe 2005 also reported on metastatic staging. Four studies done in Germany (Meister 2013; Pech 2006; Pech 2010; Staigner 2010) reported on tumour and nodal diagnostic accuracy. One study done in Finland (Salminen 1999) reported on tumour and nodal diagnostic staging.

PET-CT

One systematic review (including data from a total of 245 participants) was included in the review (Shi 2013). This incorporated data from 6 studies assessing the diagnostic accuracy of PET-CT for identification of lymph node metastasis.

Eight cohort studies also reported nodal diagnostic staging of PET-CT in oesophageal cancers. Three studies were conducted in USA (Little 2007; Roedl 2008; Roedl 2009(ii). Two studies were done in UK (Berrisford 2008; Salahudeen 2008); another 2 studies in China (Liu 2016; Shen 2012) and 1 other study (Hsu 2011) was done in Taiwan.

One cohort study (Williams 2009) was done in UK and reported data on change in management plan.

Staging laparoscopy

Six studies reported on the change in management (and procedure related complications) following diagnostic laparoscopy for patients with oesophageal cancer (Heath 2000, Nguyen 2001; Nieveen an Dijkum 1999; Romijn 1998; Strandby 2016; Yau 2006). 476 participants in total were included; 2 studies were conducted in the USA, 2 in the Netherlands, 1 in Denmark and 1 in Hong Kong.

Three studies reported on the diagnostic accuracy of staging laparoscopy for detection of metastasis (Krasna 2002; Menon 2003; O'Brien 1995).These included 333 participants; 1 study was done in UK, 1 in USA and the other in Ireland.

Two studies reported on diagnostic accuracy and change in management (Bonavina 1997; Molloy 1995). 294 participants were included. One study was conducted in Italy and 1 in the UK.

Oesophago-gastric cancer (combined)

Endoscopic ultrasound

One cohort study performed in Netherlands (n=50) reported on diagnostic accuracy of tumour staging among oesophago-gastric or junctional cancer participants (Grotenhuis 2013).

Staging laparoscopy

Four studies reported on the effect of staging laparoscopy on changing management for oesophagogastric cancer (Clements 2004; Convie 2015; Kaiser 2007; Munasinghe 2013). 385 participants were included. Three studies were conducted in the UK and 1 in Germany.

Two studies reported on the diagnostic accuracy of staging laparoscopy for oesophageal and gastric cancers (Grotenhuis 2013; Wilkiemeyer 2004). 221 participants were included and the studies were conducted in in the USA.

7.1.31 Summary of clinical studies

2 A summary of the studies that were included in this review are presented in Table 37.

3 **Table 37: Summary of included studies**

Study and country	Cancer	Index test	Reference standard	Sample size	Preliminary staging	Reported outcomes	Notes
Berrisford 2008 (UK)	Oesophageal	PET-CT	Pathological staging of resected nodes	n=37	CT Endoluminal ultrasound	Diagnostic accuracy of N staging	
Bonavina 1997 (Italy)	Oesophageal	Laparoscopy	Final surgical/ histological staging	n = 50	Transabdominal USS and CT chest and abdomen.	Change in treatment plan Procedure related morbidity Diagnostic accuracy (liver metastasis, nodal metastasis, peritoneal carcinosis)	
Burke 1997 (USA)	Gastric	Laparoscopy	Final surgical/ histological staging	n=111	Physical examination, lab values, and CT abdomen and pelvis.	Diagnostic accuracy for intra-abdominal metastases (mostly peritoneal)	
Chemaly 2008 (France)	Oesophageal	Endoscopic ultrasound	Postoperative histological examination	n=91	Not reported	Diagnostic accuracy of T1a and T1b staging	
Clements 2004 (UK)	Oesophago-gastric	Laparoscopy	(n/a)	n = 90	CT for all participants and EUS for those with lower oesophageal or GOJ carcinoma.	Change in treatment plan	n = 98 oesophageal cancer n = 89 GOJ cancer n = 68 gastric cancer
Convie 2015 (UK)	Oesophago-gastric	Laparoscopy	(n/a)	n = 295	CT and PET-CT	Change in treatment plan Procedure related morbidity	n = 136 oesophageal or GOJ cancer

Study and country	Cancer	Index test	Reference standard	Sample size	Preliminary staging	Reported outcomes	Notes
							n = 159 gastric cancer (squamous cell carcinoma of distal oesophagus excluded)
de Graaf 2007 (UK)	Oesophago-gastric	Laparoscopy	Surgical and histological	n = 416	Majority had CT scan alone (n = 337). Remaining participants had CT and EUS (n = 48) or transabdominal USS only (n = 31)	Change in treatment plan Procedure related morbidity Diagnostic accuracy (for unresectable disease)	
Dhupar 2015 (USA)	Oesohagogastric (junctional)	Laparoscopy	Pathological examination	n=181	Not reported	Diagnostic accuracy of T staging	
Fujimura 2002 (Japan)	Gastric	Laparoscopy	Pathological confirmation of findings at laparoscopy or laparotomy.	n=31	Ultrasound and CT.	Diagnostic accuracy for peritoneal metastases	
Grotenhuis 2013 (Netherlands)	Oesohagogastric (junctional)	Endoscopic ultrasound	Postoperative surgical resection of tumour	n=50	CT of the chest and abdomen and external ultrasound of neck	Diagnostic accuracy of T staging	
Heath 2000 (USA)	Oesophageal	Laparoscopy	(n/a)	n = 59	Endoscopic ultrasound and CT scan	Change in treatment plan Procedure related morbidity	6 patients subsequently diagnosed with gastric cancer following laparoscopy (originally

Study and country	Cancer	Index test	Reference standard	Sample size	Preliminary staging	Reported outcomes	Notes
							misdiagnosed as oesophageal).
Hsu 2011 (Taiwan)	Oesophageal	PET-CT	Pathological examination	N=77	Endoscopy, Flexible bronchoscopy, Barium oesohgaography, CT scan from the neck to upper abdomen	Diagnostic accuracy of N staging	PET abnormalities were defined as number of all FDG-avid abnormalities
Kaiser 2007 (Germany)	Oesophago-gastric	Laparoscopy	(n/a)	n = 125	Abdominal USS, CT, gastroscopy and EUS.	Change in treatment plan Procedure related morbidity	
Krasna 2002 (USA)	Oesophageal	Laparoscopy	Surgical and histological	n = 55	Endoscopy with biopsy, CT of chest and abdomen, MRI and EUS. Bronchoscopy was performed for lesions close to the carina or main stem bronchi.	Diagnostic accuracy (for nodal metastasis)	Sample represents subgroup of a larger study which included thoracoscopic staging.
Lee 2012 (China)	Gastric	Endoscopic ultrasound	Pathological	N=309	Not reported	Diagnostic accuracy for T and N staging	In some cases, miniprobe (20 MHz) was also used.
Lee 2013 (Korea)	Gastric	PET-CT	Surgical and histological	n = 44	Not reported	Diagnostic accuracy (for nodal metastasis)	
Little 2007 (USA)	Oesophageal	PET-CT	Pathological examination	n=58	Not reported	Diagnostic accuracy of N staging	5 patients had PET without CT
Liu 2016 (China)	Oesophageal	PET-CT	Pathological examination	n=54	Not reported	Diagnostic accuracy of N staging	

Study and country	Cancer	Index test	Reference standard	Sample size	Preliminary staging	Reported outcomes	Notes
Lowe 2005 (USA)	Oesophageal	Endoscopic ultrasound	Histopathological examination	n=75	PET and CT within 1 month prior	Diagnostic accuracy of T, N and M staging	EUS-guided needle aspiration was done for nonperitumoural needle aspiration
Lowy 1997 (USA)	Gastric	Laparoscopy	pathological confirmation of findings at laparoscopy or laparotomy.	n=71	abdominal CT and physical examination.	Diagnostic accuracy for peritoneal metastases	
Luo 2016 (China)	Oesophageal	Endoscopic ultrasound	Pathological staging from surgical or endoscopic resection/ dissection.	n = 2880	Not reported	Diagnostic accuracy T stage N stage	Systematic review including 44 studies
Meister 2013 (Germany)	Oesophageal	Endoscopic ultrasound	Surgical and histological staging	n=143	Not reported	Diagnostic accuracy T stage N stage	
Menon 2002 (UK)	Oesophageal	Laparoscopy (results of visual inspection)	Surgical and histological staging	n = 133	CT scan	Diagnostic accuracy Liver metastasis Nodal metastasis Peritoneal metastasis	Detection of metastasis at laparoscopy was defined by visual inspection, rather than histology
Mennnigen 2008 (USA)	Oesophageal	Endoscopic ultrasound	Histopathological examination	n=97	Endoscopy	Diagnostic accuracy of T and N staging	EUS miniprobe was used for stenotic tumour
Mirza 2016 (UK)	Oesophago-gastric	Laparoscopy	Surgical and histological staging	n = 387	CT scan. FDG-PET was also performed in 21% oesophageal and 56% gastric cancer patients.	Change in treatment plan Diagnostic accuracy T stage N stage M stage	

Study and country	Cancer	Index test	Reference standard	Sample size	Preliminary staging	Reported outcomes	Notes
Mitsunaga 2011 (Japan)	Gastric	Endoscopic ultrasound	Pathological depth	N=92	Not reported	Diagnostic accuracy for T1a and T1b staging	Submucosal thickness of 2.2 mm threshold was used to distinguish mucosal-submucosal (M-SM1) cancers from submucosal2/3 (SM2/3) cancers
Mocellin 2015 (Italy)	Gastric	Endoscopic ultrasound	Surgical and histological staging	n = 7747	Not reported.	Diagnostic accuracy T stage N stage	Systematic review including 66 studies.
Molloy 1995 (UK)	Oesophageal	Laparoscopy	Surgical and histological staging	n = 244	USS and CT scan. Rigid bronchoscopy in patients with tumours of the upper or middle third.	Change in treatment plan Procedure related morbidity Diagnostic accuracy (hepatic metastasis)	
Munasinghe 2013 (UK)	Oesophago-gastric	Laparoscopy	(n/a)	n = 316	Endoscopy, CT, PET-CT and EUS.	Change in treatment plan Procedure related morbidity	
Nguyen 2001 (USA)	Oesophageal	Laparoscopy	(n/a)	n = 33	CT scan. 82% also had EUS.	Change in treatment plan Procedure related morbidity	Article reports on the use of minimally invasive staging (includes bronchoscopy, oesophagoscopy and laparoscopic ultrasound in addition to laparoscopy). Reported results are findings from

Study and country	Cancer	Index test	Reference standard	Sample size	Preliminary staging	Reported outcomes	Notes
							the laparoscopy procedure only.
Nieveen an Dijkum 1999 (The Netherlands)	Oesophageal	Laparoscopy	(n/a)	n = 87	USS (neck and abdomen), chest X-ray, EUS, bronchoscopy and indirect laryngoscopy	Change in treatment plan	
O'Brien 1995 (Ireland)	Oesophageal	Laparoscopy	Histology of peritoneal resection	n=145	Upper GI endoscopy; CT chest and abdomen; abdominal ultrasound	Diagnostic accuracy of peritoneal metastasis staging	
Pech 2006 (Germany)	Oesophageal	Endoscopic ultrasound	Histological/Pathological examination	n=100	CT of chest and upper abdominal organs; abdominal ultrasound	Diagnostic accuracy of T and N staging	
Pech 2010 (Germany)	Oesophageal	Endoscopic ultrasound	Histological/Pathological examination	n=179	Oesophagogastroscopy; abdominal and thoracic CT and abdominal ultrasound	Diagnostic accuracy of T and N staging	
Ramos 2016 (Brazil)	Gastric	Laparoscopy	Histopathological examination	n=240	Not reported	Diagnostic accuracy of peritoneal metastasis	
Romijn 1998 (The Netherlands)	Oesophageal	Laparoscopy	(n/a)	n = 60	CT scan, EUS, gastroscopy and USS (neck and abdomen)	Change in treatment plan	Study also includes laparoscopic ultrasound, but results reported for the review include only laparoscopy outcomes.
Roedl 2008	Oesophageal	PET-CT	Histopathological examination	N=82	Not reported	Diagnostic accuracy of M staging	

Study and country	Cancer	Index test	Reference standard	Sample size	Preliminary staging	Reported outcomes	Notes
Roedl 2009(ii) (USA)	Oesophageal	PET-CT	Pathological examination of resected tumour	N=81	Not reported	Diagnostic accuracy of N staging	
Roedl 2009(i) (USA)	Gastric	PET-CT	MRI, biopsy or post surgical pathology	n=59	Not reported	Diagnostic accuracy of distant metastasis	
Salminen 1999 (Finland)	Oesophageal	Endoscopic ultrasound	Postoperative pathologic staging	n=32	Not reported	Diagnostic accuracy of T and N staging	
Salahudeen 2008 (UK)	Oesophageal	PET-CT	Histology of resected tumour	N=25	Conventional imaging	Diagnostic accuracy of N staging	Surgical resection was carried out in only 15 patients
Sarela 2006 (USA)	Oesophago-gastric	Laparoscopy	Surgical and pathological staging	n = 657	CT scan abdomen and pelvis. Chest CT, EUS and MRI were used in some patients.	Change in management plan Diagnostic accuracy (metastasis)	
Shen 2012 (China)	Oesophageal	PET-CT	Pathological staging	n=80	CT	Diagnostic accuracy of N staging	
Shi 2013 (China)	Oesophageal	PET-CT	Surgical and histological staging	n = 245	Not reported.	Diagnostic accuracy (nodal metastasis)	Systematic review including 6 studies
Smyth 2012 (USA)	Gastric	PET-CT	Histological staging (by fine needle aspiration or surgery) or further radiological imaging (MRI or radionucleotide bone scan)	n = 113	CT scan and EUS	Diagnostic accuracy (metastatic disease)	

Study and country	Cancer	Index test	Reference standard	Sample size	Preliminary staging	Reported outcomes	Notes
Staiger 2010 (Germany)	Oesophageal	Endoscopic ultrasound	Histopathological staging	n=47	Not reported	Diagnostic accuracy of T and N staging	
Strandby 2016 (Denmark)	Oesophageal and gastric (results presented separately)	Laparoscopy	(n/a)	n = 174 GOJ cancer n = 48 gastric	Endoscopy with biopsy, CT of the chest and abdomen and neck USS. 20 participants had PET-CT.	Change of management plan	
Vilgrain 1990 (France)	Oesophageal	Endoscopic ultrasound	Pathologic examination	n=32	Not reported	Diagnostic accuracy of N staging	
Wilkiemeyer 2004 (USA)	Oesophago-gastric	Laparoscopy	Surgical and histological staging	n = 40	Not reported	Diagnostic accuracy M stage	
Williams 2009 (UK)	Oesophageal	PET-CT	n/a	N=38	Not reported	Change in management plan	Uptake value of 2.5 FDG was consided as test positive
Yang 2008 (Japan)	Gastric	PET-CT	Surgical and histological staging	n = 78	CT scan in 87%	Diagnostic accuracy N stage	
Yau 2006 (Hong Kong)	Oesophageal	Laparoscopy	Surgical and histological staging	n = 63	Endoscopy, barium swallow, CT chest and abdomen, bronchoscopy and EUS	Change in management plan	Only includes squamous cell carcinoma

1 *CT-computed tomography; EUS-endoscopic ultrasonography; FDG-fludeoxyglucose; GOJ-gastroesophageal junction; MRI-magnetic resonance imaging; PET-CT-positron*
2 *emission tomography- computed tomography; USS-ultrasound scan*

7.1.43 Clinical evidence profile

4 The clinical evidence profiles for this review question are presented in Table 38 to Table 45.

Table 38: Summary clinical evidence profile: Endoscopic ultrasound in gastric cancer

Number of studies (Reference)	n	Risk of bias[a]	Inconsistency[b]	Indirectness[c]	Imprecision[d]	Sensitivity % (95% CI)	Specificity % (95% CI)	LR+ (95% CI)	LR- (95% CI)	Quality
To distinguish T1-2 from T3-4 disease										
51 (Mocellin 2015 systematic review, Lee 2012 cohort study)	4706	No serious risk[1]	Serious inconsistency[2]	No serious indirectness	No serious imprecision	86 (81-90)	90 (87-93)	8.73(6.74-11.29)	0.16(0.12-0.21)	Moderate
To distinguish T1 from T2 disease										
47 (Mocellin 2015 systematic review, Lee 2012 cohort study)	3004	No serious risk[1]	Very serious inconsistency[2]	No serious indirectness	No serious imprecision	84 (78-89)	90 (85-93)	8.4(5.9-11.9)	0.17(0.12-0.25)	Low
To distinguish T1a from T1b disease										
22 (Mocellin 2015 systematic review, Lee 2012 cohort study, Mitsunaga 2012 cohort study)	3605	No serious risk[1]	Very serious inconsistency[2]	No serious indirectness	No serious imprecision	87 (79-92)	75 (64-83)	3.43(2.44-4.83)	0.18(0.12-0.27)	Low
To distinguish N+ from N0 disease										
45 (Mocellin 2015 systematic review, Lee 2012 cohort study)	3882	No serious risk[1]	Very serious inconsistency[2]	No serious indirectness	No serious imprecision	83 (78-86)	67 (62-73)	2.5(2.15-2.97)	0.26(0.21-0.32)	Low

The assessment of the evidence quality was conducted with emphasis on test sensitivity
a Risk of bias was assessed using the CASP checklist for systematic reviews and QUADAS-2 for cohort studies
b Inconsistency was assessed by inspection of the 95% prediction region in a HSROC plot if a diagnostic meta-analysis was conducted.
c Indirectness was assessed using the CASP checklist for systematic reviews and QUADAS-2 for cohort studies
d The judgement of precision was based on the confidence interval of test sensitivity as this was considered to be the primary measure of interest. A range of 0-20% of differences in 95% confidence interval of sensitivity was considered not imprecise, 20-40% serious imprecision and >40% very serious imprecision.
1 Only 7/66 studies deemed to be at high risk of bias by the review authors
2 95% prediction region was very wide.

Table 39: Summary clinical evidence profile: Endoscopic ultrasound in oesophageal cancer

Number of studies (Reference)	n	Risk of bias[a]	Inconsistency[b]	Indirectness[c]	Imprecision[d]	Sensitivity % (95% CI)	Specificity % (95% CI)	LR+ (95% CI)	LR- (95% CI)	Quality
To distinguish T1 disease										
25 (Luo 2016, systematic review; Pech 2010, cohort study)	2005	No serious risk of bias	No serious inconsistency[6]	No serious indirectness	No serious imprecision	74 (67–80)	97 (94-99)	27.6 (13.3 – 57.0)[3]	0.26 (0.21 – 0.34)[3]	High
To distinguish T1a disease										
12 (Luo 2016, systematic review)	813	No serious risk of bias	Serious inconsistency[2]	No serious indirectness	No serious imprecision	81 (72–88)	93 (84–97)	11.3 (5.0–25.3)[3]	0.20 (0.14–0.31)[3]	Moderate
To distinguish T1b disease										
12 (Luo 2016, systematic review)	813	No serious risk of bias	No serious inconsistency[6]	No serious indirectness	No serious imprecision	79 (72–85)	80 (57–92)	4.0 (1.7–9.4)[3]	0.26 (0.18–0.37)[3]	High
To distinguish T2 disease										
33 (Luo 2016, systematic review; Pech 2010, cohort study)	2629	No serious risk of bias	Serious inconsistency[2]	No serious indirectness	No serious imprecision	67 (60–74)	91 (87–94)	7.9 (5.0–12.5)[3]	0.36 (0.29–0.44)[3]	Moderate
To distinguish T3 disease										
27 (Luo 2016, systematic review; Pech 2010, cohort study)	1998	No serious risk of bias	Serious inconsistency[2]	No serious indirectness	No serious imprecision	89 (85–90)	87 (82-90)	6.6 (4.9–8.9)[3]	0.14 (0.11–0.18)[3]	Moderate
To distinguish T4 disease										
24 (Luo 2016, systematic review)	1722	No serious risk of bias	Serious inconsistency[2]	No serious indirectness	No serious imprecision	84 (74–91)	97 (95–98)	30.4 (17.8–51.9)[3]	0.16 (0.10–0.27)[3]	Moderate
To distinguish N0 from N+ disease										

Number of studies (Reference)	n	Risk of bias[a]	Inconsistency[b]	Indirectness[c]	Imprecision[d]	Sensitivity % (95% CI)	Specificity % (95% CI)	LR+ (95% CI)	LR- (95% CI)	Quality
36 (Luo 2016, systematic review; Lowe 2005, Menningen 2008, Pech 2010, Salminen 1999, Staiger 2010, cohort studies)	3668	No serious risk of bias	Very serious inconsistency[3]	No serious indirectness	No serious imprecision	77 (70–82)	75 (63–84)	3.1 (2.1–4.6)[3]	0.31 (0.24–0.40)[3]	Low
To distinguish M+ from M0 disease										
1 (Lowe 2005, cohort study)	48	Serious risk of bias[5]	No serious inconsistency[6]	No serious indirectness	Serious imprecision[4]	76 (52–88)	86 (65–97)	5.36 (1.82-15.74)	0.31 (0.16-0.60)	Low

The assessment of the evidence quality was conducted with emphasis on test sensitivity
a Risk of bias was assessed using the CASP checklist for systematic reviews and QUADAS-2 for cohort studies
b Inconsistency was assessed by inspection of sensitivity and specificity in forest plot
c Indirectness was assessed using the CASP checklist for systematic reviews and QUADAS-2 for cohort studies
d The judgement of precision was based on the confidence interval of test sensitivity as this was considered to be the primary measure of interest. A range of 0-20% of differences in 95% confidence interval of sensitivity was considered not imprecise, 20-40% serious imprecision and >40% very serious imprecision.
1 The study excluded patients with curative endoscopic therapy, palliative endoscopic therapy and inclusion in other EUS study
2 There was some non-overlapping regions of sensitivities and specificities across the studies.
3 There was a lot of non-overlapping regions of sensitivities and specificities across the studies.
4 The range of 95% confidence interval of sensitivity is 20-40% and downgraded by one level.
3 Likelihood ratio calculated by the NGA technical team from reported sensitivity and specificity. Confidence interval not calculable.
4 2 studies did not include all the patients entered into the study in the analysis.
5 Unclear information on blinding while performing index test or reference tests
6There was few non-overlapping regions of sensitivities and specifities across the studies.

Table 40: Summary clinical evidence profile: Endoscopic ultrasound in oesophagogastric cancer (combined)

Number of studies (Reference)	n	Risk of bias[a]	Inconsistency[b]	Indirectness[c]	Imprecision[d]	Sensitivity % (95% CI)	Specificity % (95% CI)	LR+ (95% CI)	LR- (95% CI)	Quality
To distinguish N+ staging from N0 staging										
1 (Grotenhuis 2013, cohort study)	50	No serious risk	No serious inconsistency	No serious indirectness	Serious imprecison[1]	35 (not reported)	81 (not reported)	Not reported	Not reported	Moderate

The assessment of the evidence quality was conducted with emphasis on test sensitivity

a Risk of bias was assessed using the CASP checklist for systematic reviews and QUADAS-2 for cohort studies
b Inconsistency was assessed by inspection of sensitivity and specificity in forest plot
c Indirectness was assessed using the CASP checklist for systematic reviews and QUADAS-2 for cohort studies
d The judgement of precision was based on the confidence interval of test sensitivity as this was considered to be the primary measure of interest. A range of 0-20% of differences in 95% confidence interval of sensitivity was considered not imprecise, 20-40% serious imprecision and >40% very serious imprecision.
[1]Imprecision was downgraded by one level as 95% confidence interval was unavailable.

Table 41: Summary clinical evidence profile: PET-CT in gastric cancer

Number of studies (Reference)	n	Risk of bias[a]	Inconsistency[b]	Indirectness[c]	Imprecision[d]	Sensitivity % (95% CI)	Specificity % (95% CI)	LR+ (95% CI)	LR- (95% CI)	Quality
To distinguish N+ from N0 disease										
1 (Lee 2013)	44	Serious risk[1]	No serious inconsistency	No serious indirectness	Serious imprecision[4]	50 (29-71)	100 (83-100)	∞ (not calculable)	0.50 (0.34-0.75)	Low
1 (Yang 2008)	78	No serious risk	No serious inconsistency	No serious indirectness	Serious imprecision[4]	31 (18-47)2	97 (85-100)2	11.14 (1.53-81.08)[3]	0.71 (0.58-0.88)[3]	Moderate
To distinguish M1 from M0 disease										
1 (Smyth 2012)	113	No serious risk	Serious inconsitency[7]	No serious indirectness	Very serious imprecision[6]	35 (19-55)	99 (93-100)	29.10 (3.92-216.08)[3]	0.65 (0.50-0.85)[3]	Very low
1(Roedl 2009)	59	Serious risk[5]	Serious inconsistency[7]	No serious indirectness	Very serious imprecision[6]	80 (59-93)	97 (85-100)	27.2(3.91-189.45)[3]	0.21(0.09-0.45)[3]	Very low

The assessment of the evidence quality was conducted with emphasis on test sensitivity
a Risk of bias was assessed using the CASP checklist for systematic reviews and QUADAS-2 for cohort studies
b Inconsistency was assessed by inspection of sensitivity and specificity in forest plot
c Indirectness was assessed using the CASP checklist for systematic reviews and QUADAS-2 for cohort studies
d The judgement of precision was based on the confidence interval of test sensitivity as this was considered to be the primary measure of interest. A range of 0-20% of differences in 95% confidence interval of sensitivity was considered not imprecise, 20-40% serious imprecision and >40% very serious imprecision.
1 Patient selection was neither random nor consecutive. Small proportion of overall population were selected to participate, which may have biased the results.
2 95% confidence interval calculated by the NGA technical team
3 Likelihood ratio and 95% confidence interval calculated by the NGA technical team using data reported in the article

4 The range of 95% confidence interval of sensitivities across 2 studies is 20-40% and downgraded by one level.
5 Unclear risk of patient selection and unclear blinding of index test and reference test
6 The range of 95% confidence interval of sensitivities across 2 studies is >40% and downgraded by two levels.
7 There was some non-overlapping regions of sensitivities and specificities across two studies.

Table 42: Summary clinical evidence profile: PET-CT in oesophageal cancer

Number of studies (Reference)	n	Risk of bias[a]	Inconsistency[b]	Indirectness[c]	Imprecision[d]	Sensitivity % (95% CI)	Specificity % (95% CI)	LR+ (95% CI)	LR- (95% CI)	Quality
To distinguish N+ from N0 disease										
13 (Shi 2013 SR, Berrisford 2008, Hsu 2011, Little 2007; Liu 2016, Roedl 2008, Salahudeen 2008, Shen 2012, cohort studies)	1213	Serious risk of bias[2]	Very serious inconsistency[3]	No serious indirectness	No serious imprecision	60 (41-76)	83 (67-92)	3.51(1.64-7.50)	0.48(0.30-0.77)	Very low

The assessment of the evidence quality was conducted with emphasis on test sensitivity
a Risk of bias was assessed using the CASP checklist for systematic reviews and QUADAS-2 for cohort studies
b Inconsistency was assessed by inspection of sensitivity and specificity in forest plot
c Indirectness was assessed using the CASP checklist for systematic reviews and QUADAS-2 for cohort studies
d The judgement of precision was based on the confidence interval of test sensitivity as this was considered to be the primary measure of interest. A range of 0-20% of differences in 95% confidence interval of sensitivity was considered not imprecise, 20-40% serious imprecision and >40% very serious imprecision.
1 The range of 95% confidence interval of sensitivities across 2 studies is 20-40% and downgraded by one level.
2 three studies did not include all the people entered in the analysis and three studies were unclear of index test and reference tests and the systematic review had low risk of bias
3 There was a lot of non-overlapping regions of sensitivities and specificities across the studies.

Table 43: Summary clinical evidence profile: Staging laparoscopy in gastric cancer

Number of studies (Reference)	n	Risk of bias[a]	Inconsistency[b]	Indirectness[c]	Imprecision[d]	Sensitivity % (95% CI)	Specificity % (95% CI)	LR+ (95% CI)	LR- (95% CI)	Quality
To detect peritoneal metastasis										

Number of studies (Reference)	n	Risk of bias[a]	Inconsistency[b]	Indirectness[c]	Imprecision[d]	Sensitivity % (95% CI)	Specificity % (95% CI)	LR+ (95% CI)	LR- (95% CI)	Quality
9 (Ramos 2016 systematic review, Sarela 2006. Burke 1997, Fujimura 2002, Lowy 1996 cohort studies)	983	No serious inconsistency	No serious inconsistency	No serious indirectness	No serious imprecision	81 (76-84)	100 (99-100)	NC	0.20(0.15-0.25)	High
Change in management plan following laparoscopy										
1 (Strandby 2016)	48	Serious risk[2]	No serious inconsistency	No serious indirectness	No serious imprecision	8/48 (17, 7 to 30)7				Very low

The assessment of the evidence quality was conducted with emphasis on test sensitivity
a Risk of bias was assessed using the CASP checklist for systematic reviews and QUADAS-2 for cohort studies. For change in management outcomes the Newcastle-Ottawa scale was used.
b Inconsistency was assessed by inspection of the 95% prediction region in a HSROC plot if a diagnostic meta-analysis was conducted.
c Indirectness was assessed using the CASP checklist for systematic reviews and QUADAS-2 for cohort studies
d The judgement of precision was based on the confidence interval of test sensitivity as this was considered to be the primary measure of interest. A range of 0-20% of differences in 95% confidence interval of sensitivity was considered not imprecise, 20-40% serious imprecision and >40% very serious imprecision.
[1] The range of 95% confidence interval of sensitivities across 2 studies is >20% but <40% and downgraded by one level
[2] Study was designed to evaluate diagnostic accuracy rather than patient outcome.

Table 44: Summary clinical evidence profile: Staging laparoscopy in oesophageal cancer

Number of studies (Reference)	n	Risk of bias[a]	Inconsistency[b]	Indirectness[c]	Imprecision[d]	Sensitivity % (95% CI)	Specificity % (95% CI)	LR+ (95% CI)	LR- (95% CI)	Quality
To distinguish N+ from N0 disease										
1 (Bonavina 1997)	50	No serious risk	No serious inconsistency	No serious indirectness	Very serious imprecision[1]	77.8 (40 to 97.2)[2]	100 (91.4 to 100)[2]	∞ (not calculable)[3]	0.22 (0.07 to 0.75)[3]	Low
1 (Krasna 2002)	55	Serious risk[4]	No serious inconsistency	No serious indirectness	Serious imprecision[5]	90.9 (70.8 to 98.9)[3]	100 (89.4 to 100)[3]	∞ (not calculable)[3]	0.09 (0.03 to 0.34)[3]	Low

Number of studies (Reference)	n	Risk of bias[a]	Inconsistency[b]	Indirectness[c]	Imprecision[d]	Sensitivity % (95% CI)	Specificity % (95% CI)	LR+ (95% CI)	LR- (95% CI)	Quality
1 (Menon 2002)	108	No serious risk	No serious inconsistency	No serious indirectness	Serious imprecision[5]	82.5 (70.1 to 91.3)[2]	82.4 (69.1 to 91.6)[2]	4.67 (2.55 to 8.56)[3]	0.21 (0.12 to 0.38)[3]	Moderate
1 (O'Brien 1995)	106	No serious risk	No serious inconsistency	No serious indirectness	No serious imprecision	97 (83-100)[2]	95 (87-99)	18.37(7.06-47.78)	0.04(0.01-0.24)	High
To identify liver metastasis										
1 (Bonavina 1997)	50	No serious risk	No serious inconsistency	No serious indirectness	Very serious imprecision[1]	85.7 (42.1 to 99.6)[2]	100 (91.8 to 100)[2]	∞ (not calculable)[3]	0.14 (0.02 to 0.88)[3]	Low
1 (Menon 2002)	110	No serious risk	No serious inconsistency	No serious indirectness	Serious imprecision[5]	100 (69.2 to 100)[2]	99 (94.6 to 100)[2]	100 (14.22to 702.99)[3]	0.00 (not calculable)[3]	Moderate
1 (Molloy 1995)	244	No serious risk	No serious inconsistency	No serious indirectness	No serious imprecision	96.2 (89.2 to 99.2)[2]	100 (97.8 to 100)[2]	∞ (not calculable)[3]	0.04 (0.01 to 0.12)	High
To identify peritoneal metastasis										
1 (Bonavina 1997)	50	No serious risk	No serious inconsistency	No serious indirectness	Very serious imprecision[1]	71.4 (29.0 to 96.3)[2]	100 (91.8 to 100)[2]	∞ (not calculable)[3]	0.29 (0.09 to 0.92)[3]	Low
1 (Menon 2002)	111	No serious risk	No serious inconsistency	No serious indirectness	serious imprecision[5]	100 (73.5 to 100)[2]	100 (96.3 to 100)[2]	∞ (not calculable)[3]	0.00 (not calculable)[3]	Moderate

Number of studies (Reference)	n	Risk of bias[a]	Inconsistency[b]	Indirectness[c]	Imprecision[d]	Sensitivity % (95% CI)	Specificity % (95% CI)	LR+ (95% CI)	LR- (95% CI)	Quality
Change in management										
1 (Bonavina 1997)	50	Serious risk [10]	No serious inconsistency	No serious indirectness	No serious imprecision	5/50 (10, 3 to 22)[6]				Very low
1 (Heath 2000)	59	Serious risk [10]	No serious inconsistency	No serious indirectness	serious imprecision[5]	10/59 (17, 8 to 29)[6]				Very low
1 (Molloy 1995)	244	Serious risk [10]	No serious inconsistency	No serious indirectness	No serious imprecision	103/244 (42, 36 to 49)[6]				Very low
1 (Nguyen 2001)	33	Serious risk [10]	No serious inconsistency	No serious indirectness	serious imprecision[5]	8/33 (24, 11 to 42)[6]				Very low
1 (Nieveen an Dijkum 1999)	87	Serious risk [10]	No serious inconsistency	Serious indirectness[8]	No serious imprecision	10/87 (11, 6 to 20)[6]				Very low
1 (Romijn 1998)	60	Serious risk [10]	No serious inconsistency	No serious indirectness	No serious imprecision	5/60 (8, CI 3 to 18)[6]				Very low
1 (Strandby 2016)	174	Serious risk [10]	No serious inconsistency	No serious indirectness	No serious imprecision	13/174 (7, 4 to 12)[6]				Very low
1 (Yau 2006)	63	Serious risk [10]	No serious inconsistency	No serious indirectness	No serious imprecision	7/63 (11, CI 5 to 22)[6]				Very low
Procedure related morbidity										

Number of studies (Reference)	n	Risk of bias[a]	Inconsistency[b]	Indirectness[c]	Imprecision[d]	Sensitivity % (95% CI)	Specificity % (95% CI)	LR+ (95% CI)	LR- (95% CI)	Quality
1 (Bonavina 1997)	50	Serious risk [10]	No serious inconsistency	No serious indirectness	No serious imprecision	1/50 (2, CI 0 to 11)[6]				Very low
1 (Heath 2000)	59	Serious risk [10]	No serious inconsistency	No serious indirectness	No serious imprecision	2/59 (3, 0 to 12)[6]				Very low
1 (Molloy 1995)	244	Serious risk [10]	No serious inconsistency	No serious indirectness	No serious imprecision	11/244 (5, 2 to 8)[6]				Very low
1 (Nguyen 2001)	33	Serious risk [10]	No serious inconsistency	No serious indirectness	serious imprecision[5]	2/33 (6, 0 to 20)[6]				Very low

The assessment of the evidence quality was conducted with emphasis on test sensitivity
a Risk of bias was assessed using the CASP checklist for systematic reviews and QUADAS-2 for cohort studies. . For change in management and morbidity outcomes the Newcastle-Ottawa scale was used.
b Inconsistency was assessed by inspection of the 95% prediction region in a HSROC plot if a diagnostic meta-analysis was conducted.
c Indirectness was assessed using the CASP checklist for systematic reviews and QUADAS-2 for cohort studies
d The judgement of precision was based on the confidence interval of test sensitivity as this was considered to be the primary measure of interest. A range of 0-20% of differences in 95% confidence interval of sensitivity was considered not imprecise, 20-40% serious imprecision and >40% very serious imprecision.
1 The range of 95% confidence interval of sensitivity is >40% and downgraded by two levels.
2 95% confidence interval calculated by the NGA technical team using https://www.medcalc.org/calc/diagnostic_test.php
3 point estimate and confidence interval calculated by the NGA technical team using https://www.medcalc.org/calc/diagnostic_test.php
4 not all participants were included in final analysis, as some did not undergo laparoscopy and surgical resection.
5 The range of 95% confidence interval of sensitivities is 20-40% and downgraded by one level.
6 calculated by the NGA technical team using http://statpages.info/confint.html
7 index test includes thoracoscopy, bronchoscopy and intraoperative liver ultrasound in addition to laparoscopy
8 population includes participants with mid/upper oesophageal cancer, who were identified as a subgroup in whom laparoscopy was of minimal benefit. Therefore the potential benefit for those with gastroesophageal junction cancer may be underestimated.
9 very wide confidence interval(from negligible effect to more than 50%)
10 Studies were designed to evaluate diagnostic accuracy rather than patient outcome..

Table 45: Summary clinical evidence profile: Staging laparoscopy in oesophago-gastric cancer (combined)

Number of studies (Reference)	n	Risk of bias[a]	Inconsistency[b]	Indirectness[c]	Imprecision[d]	Sensitivity % (95% CI)	Specificity % (95% CI)	LR+ (95% CI)	LR- (95% CI)	Quality
Detection of T1/T2 disease										
1 (Mirza 2016)	387	No serious risk	No serious inconsistency	No serious indirectness	Unable to quantify[1]	85 (not reported)	92 (not reported)	10.63 (not calculable)[2]	0.16 (not calculable)[2]	Moderate
Detection of T3 disease										
1 (Mirza 2016)	387	No serious risk	No serious inconsistency	No serious indirectness	Unable to quantify[1]	82 (not reported)	86 (not reported)	5.86 (not calculable)[2]	0.21 (not calculable)[2]	Moderate
Detection of T4 disease										
1 (Mirza 2016)	387	No serious risk	No serious inconsistency	No serious indirectness	Unable to quantify[1]	84 (not reported)	89 (not reported)	7.64 (not calculable)[2]	0.18 (not calculable)[2]	Moderate
Detection of N0 disease										
1 (Mirza 2016)	387	No serious risk	No serious inconsistency	No serious indirectness	Unable to quantify[1]	82 (not reported)	79 (not reported)	3.90 (not calculable)[2]	0.23 (not calculable)[2]	Moderate
Detection of N1 disease										
1 (Mirza 2016)	387	No serious risk	No serious inconsistency	No serious indirectness	Unable to quantify[1]	66 (not reported)	86 (not reported)	4.71 (not calculable)[2]	0.40 (not calculable)[2]	Moderate
Detection of N2 disease										

Number of studies (Reference)	n	Risk of bias[a]	Inconsistency[b]	Indirectness[c]	Imprecision[d]	Sensitivity % (95% CI)	Specificity % (95% CI)	LR+ (95% CI)	LR- (95% CI)	Quality
1 (Mirza 2016)	387	No serious risk	No serious inconsistency	No serious indirectness	Unable to quantify[1]	89 (not reported)	89 (not reported)	8.09 (not calculable)[2]	0.12 (not calculable)[2]	Moderate
Detection of metastatic disease										
1 (Mirza 2016)	387	No serious risk	No serious inconsistency	No serious indirectness	Unable to quantify[1]	83 (not reported)	92 (not reported)	10.38 (not calculable)[2]	0.18 (not calculable)[2]	Moderate
1 (Sarela 2006)	552	No serious risk	No serious inconsistency	No serious indirectness	No serious imprecision	78.7 (72.2 to 84.2)[4]	100 (99.0 to 100)4	∞ (not calculable)[4]	0.21 (0.16 to 0.28)[4]	High
1 (Wilkiemeyer 2004)	40	No serious risk	No serious inconsistency	No serious indirectness	No serious imprecision	100 (84.6 to 100)[7]	100 (81.5 to 100)[7]	∞ (not calculable)[8]	0.00 (not calculable)[8]	High
Detection of unresectable disease										
1 (de Graaf 2007)	416	No serious risk	No serious inconsistency	No serious indirectness	No serious imprecision	75.7 (66.6 to 83.3)[8]	100 (98.8 to 100)8	∞ (not calculable)[8]	0.24 (0.18 to 0.34)[8]	High
Change in management plan following laparoscopy										
1 (Clements 2004)	90	Serious risk [10]	No serious inconsistency	No serious indirectness	No serious imprecision	16/90 (18, 11 to 27)[9]				Very low
1 (Convie 2015)	295	Serious risk [10]	No serious inconsistency	No serious indirectness	No serious imprecision	63/295 (21, 17 to 26)[9]				Very low

Number of studies (Reference)	n	Risk of bias[a]	Inconsistency[b]	Indirectness[c]	Imprecision[d]	Sensitivity % (95% CI)	Specificity % (95% CI)	LR+ (95% CI)	LR- (95% CI)	Quality
1 (de Graaf 2007)	416	Serious risk [10]	No serious inconsistency	No serious indirectness	No serious imprecision	84/416 (20, 16 to 24)[9]				Very low
1 (Kaiser 2007)	125	Serious risk [10]	No serious inconsistency	No serious indirectness	No serious imprecision	28/125 (22, 15 to 31)[9]				Very low
1 (Mirza 2016)	387	Serious risk [10]	No serious inconsistency	No serious indirectness	No serious imprecision	64/387 (17, 13 to 21)[9]				Very low
1 (Munasinghe 2013)	316	Serious risk [10]	No serious inconsistency	No serious indirectness	No serious imprecision	71/316 (22, 18 to 27)[9]				Very low
1 (Sarela 2006)	657	Serious risk [10]	No serious inconsistency	No serious indirectness	No serious imprecision	151/657 (23, 20 to 26)[9]				Very low
Procedure related morbidity										
1 (de Graaf 2007)	416	Serious risk [10]	No serious inconsistency	No serious indirectness	No serious imprecision	0/416 (0, 0 to 1)[9]				Very low
1 (Kaiser 2007)	125	Serious risk [10]	No serious inconsistency	No serious indirectness	No serious imprecision	0/125 (0, 0 to 3)[9]				Very low
1 (Munasinghe 2013)	316	Serious risk [10]	No serious inconsistency	No serious indirectness	No serious imprecision	1/316 (0.3, 0 to 2)[9]				Very low

1 *The assessment of the evidence quality was conducted with emphasis on test sensitivity*

a Risk of bias was assessed using the CASP checklist for systematic reviews and QUADAS-2 for cohort studies
b Inconsistency was assessed by inspection of the 95% prediction region in a HSROC plot if a diagnostic meta-analysis was conducted.
c Indirectness was assessed using the CASP checklist for systematic reviews and QUADAS-2 for cohort studies
d The judgement of precision was based on the confidence interval of test sensitivity as this was considered to be the primary measure of interest. A range of 0-20% of differences in 95% confidence interval of sensitivity was considered not imprecise, 20-40% serious imprecision and >40% very serious imprecision.
1 insufficent data are reported to enable confidence intervals for the sensitivity and specificity to be calculated and imprecision was downgraded by one level
2 positive and negative likelihood ratios are calculated from reported sensitivity and specificity; insufficient data are reported to allow calculation of a confidence interval
3 confidence interval for sensitivity crosses 75%
4 calculated by the NGA technical team from data reported in the article using https://www.medcalc.org/calc/diagnostic_test.php
5 specific subgroup of oesophago-gastric patients included (n=36 from total population of n=198) – only those who had undergone endoscopic ultrasound, CT and staging laparoscopy were included. Result may not be representative of the value of laparoscopy in the wider population.
6 confidence interval for sensitivity crosses 90%
7 95% confidence interval calculated by the NGA technical team using https://www.medcalc.org/calc/diagnostic_test.php
8 point estimate and 95% confidence interval calculated by the NGA technical team using https://www.medcalc.org/calc/diagnostic_test.php
9 calculated by the NGA technical team using http://statpages.info/confint.html
10 studies were designed to evaluate diagnostic accuracy rather than patient outcomes.

7.1.5 Economic evidence

The staging of patients with oesophageal and oesophageal junctional cancer was identified as an economic priority. The aim of the analysis was to estimate the cost-effectiveness of a strategy of selectively using EUS in the staging of patients with oesophageal cancer.

Note that an economic evaluation was not undertaken on the use of imaging to stage patients with gastric cancer because the committee determined that there wasn't an important economic question to address in these patients.

7.1.5.1 Methods

A systematic literature review was conducted to identify economic evaluations that may be applicable to the current decision problem. No relevant economic studies were identified. However, a non-economic study by Findlay et al. 2015 was identified in which a similar staging algorithm to that suggested by the Committee had been proposed and validated.

Since the current economic literature didn't adequately address the decision problem, a de novo economic evaluation was undertaken to assess cost-effectiveness. The analysis was developed in Microsoft Excel® and was conducted from the perspective of the NHS and Personal Social Services (PSS) as outlined in the NICE Reference Case (The guidelines manual, NICE November 2012).

7.1.5.1.1 Staging strategies

In the modelled staging algorithms it was assumed that EUS would either be used in all patients or in a selected group of patients. In the selective EUS strategy, EUS would only be used in those patients found to have Tx/T1 or T4 disease following a CT scan.

7.1.5.1.2 Clinical data

In the absence of direct data, the individual T stage at presentation was estimated using data on TNM stage groups from Findlay et al. 2015 by making some assumptions about the proportion of patients with each T stage within each stage group. Where multiple T stages occur within a stage group it was assumed that they were equal distributed.

In order to populate the model, data was required on the staging accuracy of EUS, CT and PET-CT. The staging accuracy of CT was not reported in our systematic review since the population of interest specified in our review protocol was "people who have been found at endoscopy and whole body CT to be potentially suitable for curative treatment". In other words, the starting point for the population included in the systematic review was after the initial CT. The staging accuracy of CT was therefore estimated separately for the purposes of the economic evaluation. Data on the sensitivity and specificity of CT were sourced from a subset of studies in a systematic review (Luo et al. 2016), in which CT and EUS were compared. It was assumed that patients without visible tumour on CT (usually noted as "Tx" or "T0" in the studies) would be put forward as part of the T1 stage and proceed to EUS (i.e. they were counted in the sensitivity statistic for the Tx/T1 group). The CT sensitivity and specificity estimates for each T stage are shown in Table 46.

Table 46: Accuracy of CT staging by T stage

T Stage	Sensitivity	Specificity	Reference
T1	82%	97%	Luo et al. 2016
T2	52%	89%	Luo et al. 2016
T3	88%	73%	Luo et al. 2016
T4	59%	94%	Luo et al. 2016

The staging accuracy of EUS was sourced from the meta-analysis conducted as part of the clinical evidence review. The EUS sensitivity and specificity estimates for each of the T stages under consideration are shown in Table 47.

Table 47: Accuracy of EUS staging by T stage

T Stage	Sensitivity	Specificity	Reference
T1	74%	97%	Luo et al. 2016 and Pech et al. 2010
T4	84%	97%	Luo et al. 2016

Data on the accuracy of PET-CT in the detection of distant disease was not identified in the clinical evidence review. It is thought that there is a lack of evidence on this aspect because previous studies, based on PET alone, had already established the clear utility of using this modality to detect distant disease. Therefore, accuracy data from studies using PET alone have been used to approximate the accuracy of using PET-CT to detect distant disease. Based on a meta-analysis by Vliet et al. 2008, the sensitivity and specificity of PET-CT for the detection of distant disease is estimated to be 71% and 93%, respectively.

7.1.5.1.3 Costs

The costs considered in the model reflect the perspective of the analysis, thus only costs that are relevant to the UK NHS & PSS were included. Where possible, all costs were estimated in 2015/16 prices.

The majority of costs were sourced from NHS reference costs 2015/16 by applying tariffs associated with the appropriate HRG code. Drug costs were calculated using unit cost data from the electronic market information tool (eMit) combined with dose information from the British National Formulary (BNF). Other resource use and cost information were sourced from the Personal Social Services Research Unit (PSSRU) and the advice of the Guideline Committee.

The cost associated with EUS was estimated from NHS Reference costs 2015/16 using cost code GB31Z, which relates to an 'Endoscopic Ultrasound Examination, of Hepatobiliary or Pancreatic Duct'. It was assumed that the procedure would be performed as a 'day case' procedure (95% of the procedures in NHS Reference Costs were coded as such) and it was estimated to cost £603.59.

A key aspect of the analysis is capturing the consequences of changes in staging outcomes in terms of changes in patient management. As mentioned above, this applies only to patients with T1 disease and T4 disease as differences in EUS staging only have the potential to change management in these patients (not the case in patients with T2/T3 disease). More specifically, in patients with T1 disease, the value of staging is in identifying or refuting T1a disease whereas in patients with T4 disease, the value of staging is in identifying or refuting T4b disease. Of particular importance to this analysis, are the patients with T1a or T4b disease that have been incorrectly staged by the initial CT as T2/T3 disease. Under the selective EUS strategy, these patients would not go on to receive an EUS and it is therefore possible that these patients may receive suboptimal management.

Patients with T1a disease are typically treated by surgical resection or definitive radiotherapy. For patients with T1a disease that was incorrectly upstaged, it was assumed that the consequence would be that unnecessary neoadjuvant chemotherapy or chemoradiotherapy would be received in addition to surgical resection or definitive radiotherapy. The estimated cost of the unnecessary treatment was £3,934.87, based on a crude average of the cost of neoadjuvant chemotherapy (when used in combination with surgery or radiotherapy) and chemoradiotherapy

It has been assumed that patients with T4b disease are typically treated with systemic chemotherapy. For patients with T4b disease that was incorrectly down-staged, it is assumed that unnecessary radical treatment would be received instead (assumed to be either chemoradiotherapy and surgery or chemoradiotherapy alone). The estimated cost of the unnecessary treatment was £7,444.09, based on a crude average of the cost of chemoradiotherapy and surgery and chemoradiotherapy alone (£12,388.70), minus the cost of systemic chemotherapy (£4,948.09).

7.1.5.1.4 Health related quality of life (QoL) values

As recommended in the NICE reference case, the model estimates effectiveness in terms of quality adjusted life years (QALYs). These are estimated by combining the life year estimates with utility values (or QoL weights) associated with being in a particular health state.

The QALY side of the model was focused on the outcomes that might differ between the two staging strategies. Specifically, we sought to capture the consequences of changes in management as a result of changes in staging outcomes. As mentioned in the above section, this applies only to patients with T1 disease and T4 disease as differences in EUS staging only have the potential to change management in these patients.

For patients with T1a disease that was incorrectly upstaged, it was assumed that there would be a QoL decrement as a result of the unnecessary neoadjuvant chemotherapy or chemoradiotherapy that would be received in addition to surgical resection or definitive radiotherapy. The QoL decrement was estimated using values from a cost-effectiveness analysis of treatments for locally advanced oesophageal cancer by Graham et al. 2007. In the analysis, QoL values of 0.67 and 0.63 were estimated for surgery and multi-modal treatment, respectively at 6 to 12 months after treatment. The difference between these two values (0.04) was used to inform the decrement associated with neoadjuvant chemotherapy or chemoradiotherapy in the analysis,

For patients with T4b disease that was incorrectly down-staged, it is assumed that there would be a QoL decrement associated with the unnecessary radical treatment that would be received instead of systemic chemotherapy. Graham et al. 2007 was again used to inform the QoL decrement. In this analysis, the QoL score in patients treated with surgery was estimated to be 0.63 at 0 to 6 months and 0.70 at 12 to 36 months. The difference between these two values was used to inform the decrement associated with radical treatment in the analysis.

7.1.5.2 Results

7.1.5.2.1 Base case results

The base case results of the analysis are presented in Table 48. It can be seen that the selective use of EUS was found to be less costly (£185) and marginally less effective (0.0024 QALYs) than using EUS for all patients and resulted in an ICER of £77,363 per QALY. This can be interpreted as £77,363 saved for each QALY that is lost. Therefore, the strategy of selectively using EUS was found to be cost-effective as this saving is above the NICE threshold for cost-effectiveness.

Table 48: Base case analysis results

Strategy	Cost		QALYs		ICER (cost per QALY
	Total	Incremental	Total	Incremental	
EUS for all patients	£657	-	-0.0005	-	-
EUS for selected patients	£472	-£185	-0.0029	-0.0024	£77,363

7.1.5.2.2 Sensitivity analysis results

A series of deterministic sensitivity analyses were conducted, whereby an input parameter is changed, the model is re-run and the new cost-effectiveness result is recorded. This analysis is a useful way of estimating uncertainty and determining the key drivers of the model result.

It was found that the conclusion of the analysis remained unchanged in most modelled scenarios. The notable exceptions were decreasing the cost of EUS by 50% or decreasing either the sensitivity or specificity of CT scans to 25%. None of these scenarios were thought likely to be plausible by the Guideline Committee. Therefore the conclusion of the analysis appears to be robust.

Probabilistic sensitivity analysis (PSA) was conducted to assess the combined parameter uncertainty in the model. In this analysis, the mean values that were utilised in the base case are replaced with values drawn from distributions around the mean values. The results of 10,000 runs of the PSA that the likelihood of the selective EUS strategy being deemed cost-effective decreases as the cost-effectiveness threshold increases. At the commonly applied NICE threshold of of £20,000 per QALY, the selective EUS strategy was found to have a 81% probability of being cost-effective, while the strategy of staging all patients was found to have an 19% probability of being cost-effective.

7.1.5.3 Conclusions

The results of the analysis showed that selectively using EUS resulted in substantial savings with a minimal reduction in effectiveness. Overall, the results suggest that the selective EUS strategy was cost-effective, saving £77,363 for each QALY lost. The result was found to be robust in deterministic sensitivity analysis with the conclusion of the analysis remaining unchanged in all plausible scenarios. In probabilistic sensitivity analysis, the strategy of selectively using EUS was found to have a 81% probability of being cost-effective at a threshold of £20,000 per QALY.

7.1.6 Evidence statements

7.1.6.1 Diagnostic accuracy of endoscopic ultrasound for gastric cancer

T-staging

Moderate quality evidence from 1 systematic review (incorporating 66 individual studies) found endoscopic ultrasound to have moderately high sensitivity and specificity for distinguishing superficial (T1-2) from deeper (T3-4) stages of gastric cancer. The test was also moderately useful for ‘ruling in’ and ‘ruling out’ T3-4 disease.

Low quality evidence from 1 systematic review found endoscopic ultrasound to have moderately high sensitivity and specificity to distinguish T1 from T2 disease. The test was also moderately useful for ‘ruling in’ and ‘ruling out’ T2 disease.

High quality evidence from 1 systematic review found endoscopic ultrasound to have moderately high sensitivity and low specificity to distinguish T1a from T1b disease. The test was not useful at ‘ruling in’ but was moderately useful at ‘ruling out’ T1b disease.

Low quality evidence from 1 systematic review found endoscopic ultrasound to have moderately high sensitivity but low specificity to identify lymph node metastasis. The test was not found to be useful for ‘ruling in’ or ‘ruling out’ lymph node metastasis.

7.1.6.2 Diagnostic accuracy of endoscopic ultrasound for oesophageal cancer

High quality evidence from 1 systematic review and 1 cohort study found endoscopic ultrasound to have moderately high sensitivity and high specificity to distinguish T1 disease.

Moderate quality evidence from 1 systematic review found endoscopic ultrasound to have moderately high sensitivity and high specificity to distinguish T1a disease.

High quality evidence from 1 systematic review found endoscopic ultrasound to have moderately high sensitivity and moderately high specificity to distinguish T1b disease.

Moderate quality evidence from 1 systematic review and 1 cohort study found endoscopic ultrasound to have low sensitivity and moderately high specificity to distinguish T2 disease..

Moderate quality evidence from 1 systematic review and 1 cohort study found endoscopic ultrasound to have moderately high sensitivity and moderately high specificity to distinguish T3 disease.

Moderate quality evidence from 1 systematic review found endoscopic ultrasound to have moderately high sensitivity and high specificity to distinguish T4 disease.

Low quality evidence from 1 systematic review and five cohort studies found endoscopic ultrasound to have moderately high sensitivity and moderately high specificity to identify patients without nodal metastasis.

Low quality evidence from 1 cohort study found endoscopic ultrasound to have low sensitivity and moderately high specificity to distinguish distant metastasis. The test was useful for 'ruling in' disease but not 'ruling out' the distant metastasis.

7.1.6.3 Diagnostic accuracy of endoscopic ultrasound for oesophagogastric junctional cancer

High quality evidence from 1 study found that endoscopic ultrasound had a very low sensitivity and moderately high specificity to distinguish nodal metastasis.

7.1.6.4 Diagnostic accuracy of PET-CT for gastric cancer

Low and moderate quality evidence from 2 studies found that PET-CT had a low sensitivity but high specificity for the detection of lymph node metastasis in gastric cancer.

Very low quality evidence from 1 cohort study found that PET-CT had a low sensitivity but a high specificity whereas very low quality evidence from 1 cohort study found that PET CT had a moderately high sensitivity and high specificity for the detection of metastatic disease in gastric cancer. Both studies reported that the test was very useful for 'ruling in' the disease but only one study found moderately useful for 'ruling out' the metastatic disease.

7.1.6.5 Diagnostic accuracy of PET-CT for oesophageal cancer

Nodal metastasis

Very low quality evidence from meta-analysis including 13 studies reported PET-CT to have a low sensitivity and moderate specificity for the diagnosis of positive lymph nodes in oesophageal cancer. The test was also found to be not useful at 'ruling in' but only moderately useful in 'ruling out' the nodal metastasis.

7.1.6.6 Diagnostic accuracy of staging laparoscopy for gastric cancer

Distant metastasis

High quality evidence from 9 studies indicated laparoscopy to have moderately high sensitivity and very high specificity for detection of peritoneal metastasis.

Change of management plan following laparoscopy

Very low quality evidence from 1 study reported on the effect of staging laparoscopy in modifying the management plan for patients with gastric cancer. The median value for change of treatment plan was 17% (range 7 to 30).

7.1.6.7 Diagnostic accuracy of staging laparoscopy for oesophageal cancer

Nodal metastasis

High to low quality evidence from 4 studies (n = 319) found staging laparoscopy to have moderate sensitivity and high specificity for the diagnosis of nodal metastasis.

Distant metastases

Three further studies reported on liver metastasis in particular (low to moderate quality evidence, n = 404), and found moderate to high sensitivity and high specificity to identify hepatic metastasis. Two of these studies also reported on the diagnosis of peritoneal metastasis (low quality evidence, n = 161). The reported sensitivity varied from low in 1 study to high in the second study. Specificity was reported as 100% in both studies.

Change in management

Eight studies (n = 770) reported on the impact of diagnostic laparoscopy on changing management. The quality of the evidence was very low. The median value for change in management was 8.5% (range 3 to 49).

Procedure related morbidity

Four studies (n = 386) reported on morbidity related to staging laparoscopy. The quality of the evidence was very low. The median value for procedure related morbidity was 2% (range 0 to 20).

7.1.6.8 Diagnostic accuracy of staging laparoscopy for oesophago-gastric cancer

T-staging

A single study assessed the diagnostic accuracy of staging laparoscopy for detailed T staging (high quality evidence, n = 387). Moderate sensitivity and high specificity were reported for the detection of T1/2 disease. The test was also found to be useful at ‘ruling in’ and moderately useful at ‘ruling out’ T1/2 disease.

The same study found moderate sensitivity and specificity for the identification of T3 disease. The test was found to be moderately useful at ‘ruling in’ but not useful at ‘ruling out’ disease. For T4 disease, moderate sensitivity and specificity were also found, and the test was moderately useful at ‘ruling in’ or ‘ruling out’ the T3 disease.

Detection of nodal metastasis

One study assessed the diagnostic accuracy of staging laparoscopy for individual nodal stages (N0, 1 and 2). High quality evidence (n = 387) showed moderate sensitivity and specificity for identifying node negative (N0) disease, but the test was not useful to 'rule in' or 'rule out' the nodal metastasis.

The same study showed poor sensitivity and moderate specificity for the identification of N1 disease. Again, staging laparoscopy was not useful to 'rule in' or 'rule out' N1 disease. Results for N2 disease were marginally better, with moderate sensitivity and specificity, and the test was moderately useful to 'rule in' or 'rule out' N2 disease.

Detection of metastatic disease

Three studies (moderate to high quality evidence, n = 979) reported on the ability of staging laparoscopy to detect metastatic disease. Estimates for sensitivity ranged from moderate to high, whilst reported specificity was high. The test was found to be useful at 'ruling in' metastasis but ranged from not useful to very useful at 'ruling out' the metastasis.

Detection of unresectable disease

A single study reported on the ability of staging laparoscopy to detect unresectable disease. Moderate sensitivity but high specificity was identified. The test was found to be useful at 'ruling in' but not useful at 'ruling out' the resectable disease.

Change of management following staging laparoscopy

Seven studies reported on the frequency with which staging laparoscopy altered management in oesophago-gastric cancer (n = 2296, high quality evidence). The median value for a change in management was 21% (range 13 to 31%).

Procedure related morbidity

Three studies reported on the frequency of morbidity associated with staging laparoscopy (n=857, high quality evidence). The median value was 0% (range 0 to 3).

7.1.7 Linking evidence to recommendations: oesophageal and gastro-oesophageal junctional cancer

7.1.7.1 Relative value placed on the outcomes considered

The Committee agreed that the important outcomes to consider when looking at the possible staging investigations were diagnostic accuracy, measured by sensitivity, specificity, positive predictive value, negative predictive value, and positive and negative likelihood ratios. As the aim of this review was to determine the ability of additional diagnostic tests to lead to precise staging, and the best order in which to carry them out, (in addition to whole body CTscans and endoscopy which all patients would have received already) the Committee considered the positive and negative likelihood ratios as the most important in their discussions as it helped define which tests were not useful, moderately useful or very useful. In addition, the Committee were interested in which tests had sensitivity and positive and negative predictive values close to 1, but agreed that high specificity was less important. The Committee agreed that it was also important to look at changes in management plans, since there was no purpose in conducting additional investigations if they did not impact on management, and also test-related morbidity. Time to decision to treat was an outcome that was considered important by the Committee but this outcome was not reported in the evidence.

7.1.7.2 Quality of the evidence

The evidence for this review consisted of data from relevant and up to date systematic reviews and also a number of cohort studies. The quality of evidence for the systematic reviews was assessed using the CASP checklist for systematic reviews, QUADAS-2 for the cohort studies and Newcastle-Ottowa Scale for change in management and morbidity outcomes.

The quality of the evidence varied depending on the investigation and can be summarized as:

- Endoscopic ultrasound (EUS): there was moderate to high quality of evidence from a number of systematic reviews which showed that endoscopic ultrasound was useful in distinguishing T1, T1a, T1b, T2, T3 and T4 disease but only low quality evidence for detecting or ruling out metastatic disease
- PET-CT: there was low quality of evidence from a meta-analysis that reported low sensitivity and moderate specificity for PET-CT for the diagnoisis of nodal metastases
- Staging laparoscopy: there was low to high quality evidence that reported the high specificity of staging laparoscopy in the diagnosis of nodal and distant metastases. There was also very low quality evidence showing that staging laparoscopy was not useful in leading to a change in mamanagement.

Some of the evidence for endoscopic ultrasound and staging laparoscopy was from a mixed population of patients with oesophageal or gastric cancer.

7.1.7.3 Consideration of benefits and harms

The choice of additional diagnostic tests to aid accurate staging and the identification of metastatic disease can lead to more tailored treatment and avoid over- and under-treatment. The Committee agreed that in a population of patients with oesophageal or gastro-oesophageal junctional cancer the identification of metastatic disease is of prime importance (except in those people with very early disease). The Committee therefore agreed that although there was overall less evidence for PET-CT scans compared to endoscopic ultrasound, and it was of a lower quality, PET-CT should be the first-line investigation as this was more likely to detect metastatic disease accurately and so determine if radical treatment was feasible.

If PET-CT scanning ruled out metastatic disease, then endoscopic ultrasound should be used for further staging as the evidence showed that it was effective at staging, and so would allow tailoring of further radical treatment. However, the Committee knew from their clinical experience that treatments would not differ between T2 and T3 tumours and so if the only purpose of further staging investigations was to differentiate between these two stages then it should not be carried out. Similarly, if metastatic disease had been detected by PET-CT scanning then endoscopic ultrasound may not be useful in guiding further management and so should not be offered. Not offering endoscopic ultrasound when it would not lead to changes in management would lead to fewer unnecessary (and upleasant) investigations for patients.

The evidence for staging laparoscopy showed that it may also be useful in staging, but the Committee were aware from their clinical experience that it may lead to greater morbidity, and so recommended this as a third-line investigation only in cases where it would help guide ongoing managmenet.

The Committee agreed that their recommendations would lead to more equitable access to investigations, more standardised use of staging investigations, and more appropriate management decisions based on staging investigations. The recommendation to use PET-CT would increase the use of PET-CT where this had previously not been available, but the

recommendation to use EUS only where it would guide management may reduce the use of EUS.

As with any investigations, there may be false positive results (which could lead to unnecessary further investigations) or false negatives (which would 'under-stage' disease, and so may lead to unnecessary surgery) and this would be the potential harms of these recommendations. The Committee also identified that by not offering routine EUS there was a potential for reducing the accuracy of T-staging, although they did not consider this would lead to any clinically significant under- or over-treatment.

7.1.7.4 Consideration of economic benefits and harms

A systematic review of the economic literature was conducted but no relevant studies were identified which were applicable to this review question.

Since this topic was considered to be a high economic priority, a health economic model was developed. In the committee's view, the key economic question to be addressed was around the use of EUS (specifically, whether it could be used more selectively). There were not thought to be any other resource issues to address since the use of the other modalities is already well established in clinical practice. The model thereforeconsidered the cost-effectiveness of selectively using EUS in the staging of patients with oesophageal or oesophago-gastric cancer. The results of the economic analysis showed that, in comparison to staging all patients with EUS, selectively using EUS resulted in substantial savings with a minimal reduction in effectiveness. Overall, the strategy was found to be cost-effective, saving £77,363 for each QALY lost.

The result was found to be robust in deterministic sensitivity analysis with the conclusion of the analysis remaining unchanged in all plausible scenarios. In probabilistic sensitivity analysis, the strategy of selectively using EUS was found to have a 81% probability of being cost-effective at a threshold of £20,000 per QALY.

In comparison with current practice, it is thought that the recommendations could lead to cost savings through a reduction in the use of EUS. However, in some centres staging is already in line with the recommendations and so no change in costs would be seen. The recommendation to offer PET-CT is not expected to have a substantial resource impact as the use of PET-CT is already well established in current practice and should be offered by the vast majority of centres.

7.1.7.5 Other considerations

The Committee noted that the evidence for the use of PET-CT to detect metastatic disease was based on the use of PET alone, but as 'PET alone' scanning is no longer available, the committee used this evidence to make recommendations for PET-CT scanning. The Committee also acknowledged that they had not sought evidence on the use of other imaging techniques that could be used in staging such as MRI.

PET-CT scanning is already used as standard practice for the assessment of oesophageal cancer after diagnosis and so it was not felt this would lead to a major change in practice in the majority of centres. The main change in practice would be likely to be a reduction in the use of unnecessary endoscopic ultrasound.

7.1.7.6 Key conclusions

The Committee concluded that PET-CT was moderately useful to identify if disease involved regional lymph nodes or not, (N+ or N0 disease), and could also identify the presence or absence of metastases (M+ from M0 disease). PET-CT would therefore be useful in all people with oesophageal cancer, except those with very early stage disease (T1a) who were unlikely to have nodal or metastatic involvement.

The Committee noted that EUS was moderately useful at distinguishing between stages of oesophageal cancer (T1, T1a, T1b, T2, T3 and T4), and was moderately useful at identifying the presence of nodal involvement (N+ from N0 disease) or metastases (M+ from M0 disease). However, the Committee knew from their clinical experience that management strategy would not differ between T2 and T3 disease so there would be no value in using it solely to identify this difference.

The main use of staging laparoscopy is to exclude peritoneal metastases and it leads to a change in the management plan in 7 to 42% of patients, so the Committee recommended its use when it would help guide ongoing management.

7.1.8 Recommendations

Determining suitability for radical treatment of histologically-confirmed oesophageal or gastro-oesophageal cancer after endoscopy and whole-body CT scan diagnosis

12. **Offer PET-CT to people with oesophageal and gastro-oesophageal junctional tumours that are suitable for radical treatment (except for T1a tumours).**

13. **Do not offer endoscopic ultrasound only to distinguish between T2–T3 tumours in people with oesophageal and gastro-oesophageal junctional tumours.**

14. **Offer endoscopic ultrasound only when it will help guide ongoing management.**

15. **Consider staging laparoscopy only when it will help guide ongoing management.**

7.1.9 Linking evidence to recommendations: gastric cancer

7.1.9.1 Relative value placed on the outcomes considered

The Committee agreed that the important outcomes to consider when looking at the possible staging investigations were diagnostic accuracy, measured by sensitivity, specificity, positive predictive value, negative predictive value, and positive and negative likelihood ratios. As the aim of this review was to determine the ability of additional diagnostic tests to lead to precise staging (in addition to whole body CTscans and endoscopy which all patients would have received already) the Committee considered the positive and negative likelihood ratios as the most important in their discussions as it helped define which tests were not useful, moderately useful or very useful. In addition, the Committee were interested in which tests had sensitivity and positive and negative predictive values close to 1, but agreed that high specificity was less important. The Committee agreed that it was also important to look at change in management plan, since there was no purpose in conducting additional investigations if they did not impact on management, and also test-related morbidity. Time to decision to treat was an outcome that was considered important by the Committee but this outcome was not reported in the evidence.

7.1.9.2 Quality of the evidence

The evidence for this review consisted of data from relevant and up to date systematic reviews and also a number of cohort studies. The quality of evidence for the systematic reviews was assessed using the CASP checklist for systematic reviews, QUADAS-2 for the cohort studies and Newcastle-Ottowa Scale for change in management and morbidity outcomes. The quality of the evidence varied depending on the investigation and can be summarized as:

- Endoscopic ultrasound (EUS): there was low to high quality evidence to show that EUS was moderately useful at staging in gastric cancer, particularly T1/2 compared to T3/4, and T1 compared to T2 disease. There was also low quality evidence that showed that EUS was not useful at ruling in or out lymph node metastases.
- PET-CT: there was low to moderate evidence from 2 studies showing that PET-CT had high specificity for lymph node metastases, and very low quality evidence from 2 cohort studies that showed it was useful for ruling in metastatic disease.
- Staging laparoscopy: there was high quality evidence from 9 studies showing that staging laparoscopy had high specificity at detecting peritoneal metastases.

Some of the evidence for endoscopic ultrasound and staging laparoscopy was from a mixed population of patients with oesophageal or gastric cancer.

7.1.9.3 Consideration of benefits and harms

The choice of additional diagnostic tests to aid accurate staging and the identification of metastatic disease can lead to more tailored treatment and avoid over- and under-treatment. The Committee agreed that in a population of patients with gastric cancer the identification of metastatic disease is of prime importance. Staging laparoscopy was shown to be effective a detecting peritoneal metastases and therefore this was recommended as the first-line investigation (after endoscopy and whole-body CT scan for diagnosis).

If metastatic disease is not detected, endoscopic ultrasound may help with further staging of disease but the evidence showed that it may not always be useful at providing accurate staging and so it was recommended only if it would guide ongoing management. PET-CT was also shown to be mainly effective for detecting or ruling out metastatic disease, but as peritoneal metastates will already have been detected by staging laparoscopy its use was only recommended if distant metastases are suspected (which will be detected by PET-CT but not staing laparoscopy) or to guide ongoing management.

The Committee agreed that their recommendations would lead to more standardised use of staging investigations, and more appropriate management decisions based on staging investigations. The recommendation to use staging laparoscopy should lead to more appropriate use of PET-CT and EUS, only in cases where they would lead to a change in the management plan. This should also prevent patients undergoing unnecessary investigations and so avoid the potential morbidities associated with these.

As with any investigations, there may be false positive results (which could lead to unnecessary further investigations) or false negatives (which would ‘under-stage’ disease, and so may lead to unnecessary surgery), and this was a potential harm from these recommendations.

7.1.9.4 Consideration of economic benefits and harms

A systematic review of the economic literature was conducted but no relevant studies were identified which were applicable to this review question.

The recommendations were thought to represent a more structured use of imaging. For the most part, the recommendations reflect current practice although there is some variability in the use of PET-CT scans. Therefore, for some centres the recommendations may lead to a reduction in the use of PET-CT whilst in others there could be an increase in PET-CT use.

For those centres where the recommendations do lead to an increase in PET-CT scans, the additional costs of PET-CT are thought likely to be offset by changes in subsequent management. In particular, it is anticipated that the use of PET-CT would lead to a reduction in surgery.

7.1.9.5 Other considerations

The Committee noted that no evidence was available on the use of EUS in distinguishing between T3 and T4 disease, and that they had therefore been unable to make a more specific recommendation for the use of EUS. The Committee also acknowledged that they had not sought evidence on the use of other imaging techniques that could be used in staging such as MRI.

From their clinical experience the Committee were aware of the fact that PET-CT was not a useful staging investigation for signet ring cell carcinoma or mucinous gastric carcinoma, and this was taken into consideration when agreeing the priority of staging investigations.

7.1.9.6 Key conclusions

The Committee based their recommendation to use staging laparoscopy on high-quality evidence in a gastric cancer population that staging laparoscopy would detect peritoneal metastases. In addition, very low quality evidence showed that it led to a change in management plan in 17-23% of patients, with a low procedure-related morbidity rate of 0 to 0.3%.

The Committee noted the evidence that PET-CT may be useful to distinguish metastatic gastric cancer (M1 from M0) if the primary tumour is FluoroDeoxyGlucose (FDG) avid and therefore recommended its use if distant metastatic disease was suspected.

The Committee agreed that there was evidence that EUS is accurate in T-staging, but it would only need to be carried out if this information would likely alter management.

7.1.10 Recommendations

Determining suitability for radical treatment of histologically-confirmed gastric cancer after endoscopy and whole-body CT scan diagnosis

16. **Offer staging laparoscopy to all people with potentially curable gastric cancer.**

17. **Consider endoscopic ultrasound only if it will help guide ongoing management.**

18. **Consider PET-CT only if metastatic disease is suspected and it will help guide ongoing management.**

7.2 HER2 testing in adenocarcinoma

Which people with adenocarcinoma of the stomach and oesophagus should have their tumours HER2 tested?

7.2.1 Introduction

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 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.

7.2.2 Description of clinical evidence

No relevant clinical studies was found to meet the inclusion criteria for the review.

Full details of the review protocol are reported in Appendix D. Study selection flow chart is reported in Appendix K, and exclusion list in Appendix J.

7.2.3 Summary of included studies

Not applicable as there were no included studies.

7.2.4 Clinical evidence profiles

No clinical evidence was found to meet the inclusion criteria for the review

7.2.5 Economic evidence

A systematic review of the economic literature was conducted but no relevant studies were identified which were applicable to this review question. Economic modelling was not undertaken for this question because other topics were agreed as higher priorities for economic evaluation.

7.2.6 Evidence statements

No clinical evidence was found to meet the inclusion criteria for this review.

7.2.7 Evidence to recommendations

7.2.7.1 Relative value placed on outcomes considered

The Committee wished to identify whether HER2 testing (and subsequent appropriate treatment of HER2 positive disease) led to an improvement in clinical and patient-related outcomes (a ‘test and treat’ strategy). This review was not intended to consider the diagnostic accuracy of the HER2 test. Thus the outcomes the Committee considered important were overall survival, time to initiation of treatment from detection of metastatic disease, patient-reported outcome measures and quality of life.

7.2.7.2 Quality of evidence

No relevant clinical studies were found to meet the inclusion criteria for this review.

7.2.7.3 Consideration of clinical benefits and harms

There was no clinical evidence for this review but the Committee agreed that their recommendation should be in-line with the NICE Technology Appraisal for the use of trastuzumab in metastatic oesophago-gastric adenocarcinoma. This wouldlead to timely testing of the people who were diagnosed with metastatic adenocarcinoma of the stomach and oesophagus. As with all diagnostic tests there are likely to be some level of false positives and false negatives which may lead to inappropriate treatment. There is also additional anxiety for patients undergoing HER2 testing whilst awaiting results. However, the

Committee considered that the benefits of targeted treatment for those patients who tested positive outweighed these concerns.

7.2.7.4 Consideration of economic benefits and harms

A systematic review of the economic literature was conducted but no relevant studies were identified which were applicable to this review question.

Despite the recommendation made by NICE for trastuzumab to be an option in the treatment of metastatic adenocarcinoma of the stomach or gastro-oesophageal junction, there is currently variability in the HER2 testing of patients. Therefore the recommendations may represent a potential increase in HER2 testing in some centres.

It is anticipated that the recommendation should lead to an increase in the number of patients being treated with trastuzumab for HER2 positive disease. Therefore it is possible that the recommendations may require an increase in resources. However, it is not anticipated that there would be a substantial increase in costs (defined as £1 million per year according to NICE methodology).Furthermore, the costs associated with the use of trastuzumab in this setting has previously been deemed cost-effective in a NICE technology appraisal.

7.2.7.5 Other considerations

Due to the lack of evidence available for this review the Committee made their recommendation based on their clinical experience. The Committee were aware that the treatment of HER2 positive metastatic gastric adenocarcinoma with trastuzumab had already been recommended by NICE and so made their recommendation in line with this guidance.

The Committee discussed whether HER2 testing should be offered to people without metastatic disease, but due to the lack of evidence, the large number of people who would then be eligible for testing, and the lack of a NICE-approved treatment for non-metastatic disease, they agreed that they would not make this recommendation.

7.2.7.6 Key conclusions

The Committee agreed that, despite the lack of evidence for a HER2 test and treat strategy, the evidence for the cost-effectiveness of trastuzumab in the treatment of HER2 positive disease enabled them to make a recommendation for HER2 testing in people with metastatic adenocarcinoma of the stomach and oesophagus.

7.2.8 Recommendations

HER2 testing in metastatic oesophago-gastric adenocarcinoma

19. **Offer HER2 testing to people with metastatic oesophago-gastric adenocarcinoma (see the NICE technology appraisal guidance on trastuzumab for HER2-positive metastatic gastric cancer).**

8 Radical treatment

8.1 T1N0 oesophageal cancer

Review question: What is the optimal management of T1N0 oesophageal cancer?

8.1.1 Introduction

The majority of people with both squamous cell and oesophageal adenocarcinoma present symptomatically at an advanced stage with poor long term survival outcomes. In contrast however, there are an increasing number of people who are now diagnosed at an asymptomatic early stage due to improvements in endoscopic training, techniques and surveillance.

Accurate staging of T1 disease can therefore subsequently lead to endoscopic curative therapy by endoscopic mucosal resection (EMR) or endoscopic submucosal dissection (ESD), with excellent long term survival outcomes, thereby preventing the need for oesophagectomy and its associated morbidity and mortality.

The aim of this review was to assess what is the optimal management strategy for those with mucosal (T1aN0) and submucosal (T1bN0) oesophageal cancer to prevent both the under treatment and overtreatment at each stage.

8.1.2 Description of clinical evidence

Two studies (n=370) were included in the review (Takahashi et al 2010; Shimizu et al, 2002) and the evidence is summarised below. See also the study selection flow chart in Appendix K, forest plots in Appendix H, study evidence tables in Appendix F and exclusion list in Appendix J.

No studies of endoscopic resection with radiofrequency ablation, cryotherapy or chemoradiotherapy compared with other treatments in this population were identified.

8.1.3 Summary of included studies

A summary of the studies that were included in this review is presented in Table 49.

Table 49: Summary of included studies

Study	Intervention/Comparison	Population	Outcomes
Shimizu 2002 Country: Japan Comparative observational study Study dates: June 1992 – March 2000	Squamous cell carcinoma (T1, N0) Extended EMR group n=26 Mean age 68.4y (SD 7.8) Inclusion criteria: increased operative risk because of concurrent illness; OR presence of another non-oesophageal advanced cancer; OR age greater than 75 years; OR refusal to undergo open surgery despite explanation of the risk of cancer metastasis Surgical resection group n=44 Mean age 62.9y (SD 7.7)	Extended endoscopic mucosal resection vs surgical resection	Overall survival

Study	Intervention/Comparison	Population	Outcomes
	Inclusion criteria: Invasion of muscularis mucosae/upper third submucosa		
Takahashi 2010 Country: Japan Retrospective cohort study Study dates: March 1994 – July 2007	Squamous cell carcinoma (T1,N0) EMR group n=184 Mean age: 67.1y±8.6 M:F 9.2:1 Mean size of cancer: 20±11 ESD n=116 Mean age: 67.1y±8.6 M:F 7.4:1 Mean size of cancer: 30±16	Endoscopic mucosal resection vs Endoscopic submucosal dissection	Disease-free survival Overall survival Pathological margins free Complications: Perforation Stenosis

Abbreviations: EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection; SD, standard deviation

8.1.4 Clinical evidence profile

The clinical evidence profiles for this review question are presented in Table 50 and Table 51.

Table 50: Summary clinical evidence profile. Comparison 1: Extended endoscopic mucosal resection versus surgical resection

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk with surgical resection	Corresponding risk extended EMR (95% CI)			
Overall survival (OS)	5 year OS 85%	5 year OS 77% (43% to 92%)	HR 1.59 (0.49-5.14)	70 (1 study)	VERY LOW[1]

CI: confidence interval; EMR, endoscopic mucosal resection; HR: hazard ratio;
1 Non randomised study; EMR group were selected due to increased operative risk

Table 51: Summary clinical evidence profile. Comparison 2: Endoscopic submucosal dissection versus endoscopic mucosal resection

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk with ESD	Corresponding risk with EMR (95% CI)			
Disease free survival (DFS)	1 year DFS 99%	1 year DFS 96% (89% to 98%)	HR 4.20 (1.58 to 11.14)	300 (1 study)	VERY LOW[1]
Overall survival (OS)	1 year OS 85%	1 year OS 85%	NR (P=0.40)	300 (1 study)	VERY LOW[1]
Pathological margins free	974 per 1000	779 per 1000 (721 to 848)	RR 0.80 (0.74 to 0.87)	300 (1 study)	VERY LOW[1]
Perforation	26 per 1000	16 per 1000 (3 to 79	RR 0.63 (0.13 to 3.07)	300 (1 study)	VERY LOW[1]
Stenosis	172 per 1000	93 per 100 (50 to 169)	RR 0.54 (0.29 to 0.98)	300 (1 study)	VERY LOW[1]

EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection; HR: hazard ratio; RR: relative risk; NR, not reported
1 Tumours were on average 10mm larger in the ESD group. Only 1 year of follow up available in the ESD group.

8.1.5 Economic evidence

A systematic review of the economic literature was conducted but no relevant studies were identified which were applicable to this review question. Economic modelling was not undertaken for this question because other topics were agreed as higher priorities for economic evaluation.

8.1.6 Evidence statements

Endoscopic mucosal resection versus surgical resection (oesophagectomy)

No evidence was found comparing extended endoscopic mucosal resection and surgical resection in terms of disease-free survival, treatment-related morbidity and histopathological outcomes.

Very low quality evidence from 1 retrospective cohort study (N=70) indicated no clinically important difference in overall survival following extended endoscopic mucosal resection and surgical resection. Five year overall survival was 85% with surgery versus 77% (95% CI 43% to 92%) with EMR.

Endoscopic mucosal resection versus endoscopic submucosal dissection

Very low quality evidence from 1 retrospective cohort study (N=300) indicated a clinically important disease-free survival benefit for patients treated with endoscopic submucosal dissection (ESD) compared to those treated with endoscopic mucosal resection. One year disease free survival were 99% with ESD versus 96% (95%CI 89% to 98%) with EMR.

Very low quality evidence from 1 retrospective cohort study (N=300) indicated a clinically important improvement in the rate of pathological free margins for patients treated with endoscopic submucosal dissection compared to those treated with endoscopic mucosal resection. Free margin rate was 97% with ESD compared to 78% (95%CI 72% to 85%) with EMR.

Very low quality evidence from 1 retrospective cohort study (N=300) indicated no clinically important difference in the risk of perforation following ESD when compared to EMR. Perforation rate with ESD was 2.6% compared with 1.6% (95%CI 0.3% to 7.9%) with EMR

Very low quality evidence from 1 retrospective cohort study (N=300) indicated a clinically important increase in the risk of stenosis (lesions requiring expansion procedures) following ESD when compared to EMR. Stenosis rate following ESD was 17% compared with 9% (95%CI 5% to 17%) following EMR.

8.1.7 Evidence to recommendations

8.1.7.1 Relative value placed on the outcomes considered

As this was an intervention review for treatment at an early disease stage, the outcomes that the Committee considered critical were overall survival and disease-free survival, as the aim of treatment is to achieve cure of the disease and so improve survival. However, treatment-related morbidity (such as stricture, perforation and bleeding) and treatment-related mortality were considered important as these patients may be asymptomatic or only have minor symptoms and consideration of whether the treatment led to worse morbidity than the condition itself may be important in defining the best treatment strategy. Histopathological outcomes (such as deep margins, lateral margins, lymphovascular invasion and differentiation) were also considered but were less important as they would be surrogate markers for overall survival and disease-free survival. Health-related quality of life and

patient-reported outcome measures were considered important by the Committee but none of these outcomes were reported in any of the evidence reviewed.

8.1.7.2 Quality of the evidence

Two studies were identified for inclusion in the evidence review-1 was a comparative observational study and 1 was a prospective cohort study. Both studies were from Japan and the Committee considered the applicability of this population: in Japan, 98% of oesophageal carcinomas are squamous cell carcinomas, and in the UK the majority are adenocarcinomas, so the evidence may not always be directly applicable to the UK population. The quality of the outcomes from these studies was assessed using GRADE and for all outcomes was judged to be very low.

The Committee agreed that the evidence reviewed for 8.6(squamous cell carcinoma) was applicable to this topic because it would have included T1b tumours amongst the cohort of resectable squamous cell carcinomas.

The Committee had hoped to consider the relative efficacy of endoscopic resection, radiofrequency ablation, cryotherapy and photodynamic therapy compared to surgery, but very limited evidence was only available for endoscopic mucosal resection.

Due to the lack of evidence available for this review the Committee agreed that more research was needed in this area and made a research recommendation.

8.1.7.3 Consideration of the benefits and harms

Very low quality evidence from this review showed that endoscopic mucosal resection did not lead to improved survival compared to surgery. The Committee considered however, based on their clinical experience, that endoscopic mucosal resection may have a valuable role in people with very early disease and could potentially lead to a ‘cure’, while it would possibly also lead to a reduction in the morbidity and mortality associated with surgery.

Disease recurrence in people who do not undergo surgery requires long-term endoscopic surveillance and possible re-treatment. However, the Committee agreed that in early stage disease the likely reduction in adverse events from surgery would outweigh these concerns.

Very low quality evidence did show improved disease-free survival and improved disease-free margins with endoscopic submucosal dissection compared to endoscopic mucosal resection, with no increase in the risk of perforation and stenosis. However, in patients with T1bN0 disease, the Committee were primarily interested in comparisons against the current standard of definitive surgery. Therefore this evidence was not compelling enough to deviate from current practice. The committee therefore based the recommendation on their own clinical experience as well as evidence identified in the evidence review for squamous cell carcinoma in 8.6..

In summary the evidence review for squamous cell carcinoma in 8.6 found:

Chemoradiotherapy followed by surgery increased overall survival and disease-free survival compared to surgery alone, but with an increased rate of post-operative mortality.

There was no difference in mortality rates or overall survival between chemoradiotherapy followed by surgery compared to chemoradiotherapy alone, and treatment-related mortality was greater with the combination.

Chemoradiotherapy followed by surgery increased 3-year survival but had no effect on overall survival compared to chemotherapy then surgery, and both treatments led to similar rates of post-operative mortality.

There was no difference in the overall survival rates for surgery followed by chemoradiotherapy compared to surgery alone, but progression-free survival was increased.

Chemoradiotherapy alone had increased rates of 5-year survival and 5-year progression-free survival compared to surgery alone, with similar rates of 30-day mortality.

Surgery led to improved overall survival compared to radiotherapy alone, but treatment-related mortality was similar or increased, depending on the exact procedure.

Chemotherapy then surgery led to similar rates of overall survival and post-operative mortality compared to surgery alone, but disease-free survival was greater with chemotherapy than surgery.

Chemoradiotherapy led to similar rates of overall survival and treatment-related morbidity and mortality compared to radiotherapy, but did lead to increased 5-year survival.

The Committee therefore considered that chemoradiotherapy or surgery could be recommended for the sub-population of people with with T1bN0 squamous cell carcinoma.

8.1.7.4 Consideration of the economic benefits and harms

A systematic review of the economic literature was conducted but no relevant studies were identified which were applicable to this review question.

The economic implications of this topic were thought to be negligible as no change in practice is anticipated as a result of the recommendations. The use of endoscopic mucosal resection is already well established in clinical practice and is a cost-effective way of managing very early stage disease.

8.1.7.5 Other considerations

Due to the limited evidence available for this review the Committee made their recommendations based on their own clinical experience and currently accepted best clinical practice. This included a recommendation to carry our endoscopic eradication of remaining Barrett's mucosa for people with a T1aN0 oesophageal cancer. The Committee had not considered evidence for Barrett's mucosa but considered that this recommendation reflected best clinical practice and should be included, as people with both early oesophageal cancer and Barrett's are not included in exisiting guidance on ablative therapies for Barrett's oesophagus. Endoscopic mucosal resection was also recommended based on current best practice.

8.1.7.6 Key conclusions

The comparisons included in the 2 studies reviewed compared endoscopic mucosal resection with oesophagectomy and endoscopic mucosal resection with endoscopic submucosal dissection.

Although the evidence available was limited the Committee concluded that the evidence from a large cohort did show good outcomes following endoscopic mucosal resection in patients with T1a disease, although this was not different from the overall survival seen with oesophagectomy.

In the comparison with endoscopic submucosal dissection, there was no difference seen in overall survival but endoscopic submucosal dissection did lead to an improvement in disease-free survival and pathological margins at the expense of an increased risk of stenosis.

8.1.8 Recommendations

T1N0 oesophageal cancer

20. Offer endoscopic mucosal resection for staging for people with suspected T1 oesophageal cancer.

21. Offer endoscopic eradication of remaining Barrett's mucosa for people with T1aN0 oesophageal cancer.

22. Offer radical resection for people with T1bN0 oesophageal adenocarcinoma if they are fit enough to have surgery.

23. Offer people with T1bN0 squamous cell carcinoma of the oesophagus the choice of:

- definitive chemoradiotherapy or
- surgical resection.

Make the choice after discussing the benefits, risks and treatment consequences of each option with the person and those who are important to them (as appropriate).

8.1.9 Research recommendations

2. What is the optimal treatment for T1bN0 adenocarcinoma of the oesophagus?

Why this is important?

In patients with submucosal (T1b) N0 oesophageal adenocarcinoma (OAC), the associated risk of lymph node metastases is estimated to be between 4% for submucosal 1 (sm1) and up to 16% for sm3 based on retrospective surgical data. The majority of patients with a submucosal T1bN0 OAC therefore currently have major surgical resection without detecting any cancer cells in the oesophagus or lymph nodes. Oesophagectomy is also a procedure associated with significant morbidity (up to 50%) and mortality (2–4%).

In comparison, endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD) are techniques that can remove the submucosa with less morbidity and mortality than surgery and, providing there is no lymph node involvement, can lead to a cure. However, compared to surgery nodal involvement can only be assessed by PET-CT scanning and endoscopic ultrasound (EUS), which may lead to under-treatment of some patients with T1b disease.

A study to assess which patients should have endoscopic therapy or surgery for T1bN0 OAC would be useful, as this would help prevent both under- and over-treatment of this group of people. This could be a randomised controlled trial comparing surgery and endoscopic treatment.

Table 52: Research recommendation rationale

Research question	What is the optimal treatment for T1bN0 adenocarcinoma of the oesophagus?
Importance to 'patients' or the population	The method of treatment of T1bN0 OAC has a big impact on patient outcomes with possible surgical over-treatment of sm1 disease having high patient morbidity (and associated mortality) whilst the possible under-

Research question	What is the optimal treatment for T1bN0 adenocarcinoma of the oesophagus?
	treatment by endoscopic therapy for sm3 disease may have an impact on overall survival.
Relevance to NICE guidance	No current studies address the optimal management of T1bN0 OAC and thus data in this area would lead to improved NICE guidelines in the future.
Relevance to the NHS	Potential cost saving in reducing the number of surgical resections for T1bN0 (sm1) required but possibly offset by increased surveillance required in this group following endoscopic therapy.
National priorities	NHS Outcomes Framework for 2016-17: Improving 1-year and 5-year survival for all cancers
Current evidence base	There is no current evidence available for OAC. There are some limited poor quality studies in squamous cell carcinoma. Current treatment pathways based on historical surgical literature but were published prior to the development of EMR and ESD.
Equality	Some patients are not suitable for surgery and only endoscopic therapy may be offered in that instance.

Table 53: Research recommendation statements

Criterion	Explanation
Population	Patients with T1bN0 oesophageal cancer following staging investigations with CT, PET-CT and EUS.
Intervention	EMR or ESD for T1bN0 (stratified for degree of submucosal invasion:sm1, sm2, sm3)
Comparator (without the risk factor)	• Oesophagectomy for T1bN0
Outcome	• Disease free survival. • Overall survival. • 30-day mortality. • 30 day and 1 year morbidity • Quality of life • Reintervention rate (radiological, endoscopic and surgical) • Cost effectiveness
Study design	Multicentre randomised controlled trial
Timeframe	3 year study recruitment due to small patient numbers. 5 year follow up

8.2 Surgical treatment of oesophageal cancer

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

8.2.1 Introduction

Surgery, combined with neo-adjuvant chemotherapy or chemoradiotherapy is the preferred definitive treatment of oesophageal cancer for people with acceptable performance status. However the type of resection and operative approach used, while based on tumour position, 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, discussions regarding technique have mainly focused on a comparison of the transthoracic and transhiatal approach, with particular reference to perioperative morbidity and mortality and survival (disease free and overall). With the introduction of laparoscopy and thoracoscopy (video assisted thoracic surgery - VATS) there has been an increase in available techniques. While there are perceived advantages to a minimally invasive operation (both partial or complete) such as reduced pain, less blood loss, shorter hospital stay, there are also concerns about adequacy of resection and extent of nodal harvest. With the development of Enhanced Recovery following oesophagectomy, there may be little 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.

8.2.2 Description of clinical evidence

NOTE: The definitions used in the review of the clinical evidence are as follows:

1-stage: transthoracic

2-stage: transthoracic plus laparotomy

3-stage: transthoracic plus laparotomy plus cervical incision

This review included evidence from 9 studies for three comparisons between surgical approaches to oesophagectomy. The comparisons of interest and trials reporting on these comparisons are summarised below. Please see the clinical evidence tables in Appendix F for further details of the included studies.

- Open approaches:
  - Transhiatal compared to transthoracic plus laparotomy. Three randomised trials that reported on this comparison were included in this review:
    - Chu 1997
    - van Sandick 2003
    - Goldminc 1993
  - Transhiatal compared to transthoracic plus laparotomy plus cervical incision. Four randomised trials that reported on this comparison were included in this review:
    - Chou 2009
    - de Boer 2004
    - Hulscher 2002
    - Jacobi 1997
- Totally minimally invasive approach compared to any open approach. Two randomised controlled trials that reported on this comparison were included in this review:
  - Biere 2012
  - Guo 2013
- Hybrid minimally invasive approach compared to any open approach. One randomised controlled trial that reported on this comparison was included in this review:
  - Mariette 2015
- Robotic approach compared to any open approach. No published evidence was found for this comparison. The trial protocol for an ongoing randomised controlled trial was found and published results are awaited.

Evidence from these studies are summarised below. See also the study selection flow chart in Appendix K, forest plots in Appendix H, clinical evidence tables in Appendix F and exclusion list in Appendix J.

8.2.3 Summary of included studies

A summary of the studies that were included in this review are presented in Table 54 to Table 56.

8.2.3.1 Transhiatal approach versus transthoracic approach

Table 54. Summary of included studies: Transhiatal approach versus transthoracic approach

Study	Population	Intervention/Comparison	Outcomes
Chou 2009 RCT; Taiwan; n=87	Stage II/III resectable cancer; Excluded upper third and T4 cancer Mean age: 57.0 years Male%: 94	Transhiatal approach versus 3-stage transthoracic approach	Postoperative complication, Intraoperative blood loss, Length of operation
Chu 1997 RCT; Hong Kong; n=39	Newly diagnosed OG cancer; Mean age: 62.3 years Male%: 89.7	Open transhiatal approach versus laparotomy plus right thoracic approach	Postoperative complication, Intraoperative blood loss, Length of operation, Recurrence, 30-day mortality
de Boer 2004/Hulscher RCT; Netherlands; n=217	AC (mid to distal oesophagus including gastric) with N0 tumour Mean age: 66.5 years Male %: 85.7	Transhiatal (right-sided oesophagogastrostomy) approach versus 3-stage transthoracic (left-sided oesophagogastrostomy)	Number of lymph node resected, Resection margin, Recurrence, Overall survival, Progression-free survival
Goldminc 1993 RCT; France; n=67	SCC; Excluded cervical cancer Mean age: 57.4 years Male %: 96	Transhiatal approach versus transthoracic approach; All patients had a feeding jejunostomy inserted during the operation.	Treatment-related complication; Length of operating time; Number of transfusion unit; Hospital death; Number of death at follow-up
Jacobi 1997 RCT; Netherlands; n=32	OG cancer suitable for curative resection; Excluded cervical cancer Mean age: 54.5 years	Blunt transhiatal approach versus transthoracic en-bloc resection	Postoperative complication, 30-day mortality
van Sandick 2003 RCT; Germany; n=20	AC suitable for curative resection Mean age: 64 years Male%: 90	Transhiatal approach without thoracotomy versus right thoracotomy followed by laparotomy	Intraoperative blood loss, Length of operation

n=total number of patients
AC=Adenocarcinoma: OG=Oesophageo-gastric; RCT= randomised controlled trials; SCC=Squamous cell carcinoma

Outcomes for disease-free survival, health-related quality of life and recurrence were not able to be extracted.

8.2.3.2 Totally minimally invasive approach versus any open approach

Table 55 Summary of included studies: Minimally invasive approach versus any open approach

Study	Population	Intervention/Comparison	Outcomes
Biere 2012/Maas	Resectable thoracic	Surgery was planned 6 to 8 weeks after CT/CRT.	Postoperative complications, Intraoperative blood loss,

2015 RCT; Netherlands, Spain and Italy; n=115	oesophageal or OGJ cancer; Excluded cervical cancer. Mean age: 62 years Male %: 78.4	Minimally invasive approach versus open approach	Length of operation, Quality of life score, Resection margin, 30-day mortality, Number of lymph node resected
Guo 2013 RCT; China; n=221	Mean age:59.1 years Male %: 43.3	Video-assisted thoracoscopic approach versus traditional open transthoracic approach	Postoperative complication, Intraoperative blood loss, Length of operation, Number of lymph node resected

n=total number of patients
CRT=chemoradiotherapy; CT=chemotherapy; OGJ=Oesophageo-gastric junctional; RCT= randomised controlled trials

Outcomes for overall survival, disease-free survival and recurrence were not able to be extracted.

8.2.3.3 Hybrid minimally invasive versus any open approach

Table 56 Summary of included studies: Hybrid minimally invasive approach versus any open approach

Study	Population	Intervention/Comparison	Outcomes
Mariette 2015 RCT; French; n=207	SCC or AC of middle or lower oesophagus or junctional stage I, II, III before any treatment -Included participants with or without neoadjuvant RT/CT/CRT	Hybrid minimally invasive approach versus open approach	Postoperative complications; 30-day mortality

n=total number of patients
AC=Adenocarcinoma: CRT=chemoradiotherapy; CT=chemotherapy; RCT= randomised controlled trials; RT=radiotherapy; SCC=Squamous cell carcinoma

Outcomes for overall survival, disease-free survival, health-related quality of life, length of operation, histopathological outcomes and recurrence were not able to be extracted.

8.2.4 Clinical evidence profile

The clinical evidence profiles for this review question are presented in Table 57 to Table 59.

8.2.4.1 Transthoracic versus transhiatal oesophagectomy

Table 57: Summary clinical evidence profile. Transhiatal oesophagectomy versus 2-stage or 3-stage open transthoracic oesophagectomy

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)
	Assumed risk Transthoracic approach	Corresponding risk Transhiatal approach			
Post-operative complications: Anastomotic leak - Thoracotomy+Laparotomy	114 per 1000	59 per 1000 (14 to 256)	RR 1.02 (0.45 to 2.29)	73 (2 studies)	very low [1,2]
Post-operative complications: Anastomotic leak - Thoracotomy+Laparotomy+Cervical incision	185 per 1000	89 per 1000 (20 to 397)	RR 0.68 (0.29 to 1.62)	295 (2 studies)	very low [1,2,3]
Overall survival - Thoracotomy+Laparotomy+Cervical incision			HR 1.14 (0.73, 1.79)	217 (1 study)	very low[1,2]
Intraoperative blood loss (ml) - Thoracotomy+Laparotomy		The mean intraoperative blood loss (ml) - thoracotomy+laparotomy in the intervention groups was 8.98 higher (81.33 lower to 99.29 higher)		59 (2 studies)	very low [1,5,6]
Intraoperative blood loss (ml) - Thoracotomy+Laparotomy+Cervical incision		The mean intraoperative blood loss (ml) - thoracotomy+laparotomy+cervical incision in the intervention groups was 16 higher (87.23 lower to 119.23 higher)		80 (1 study)	very low [1,6]
Length of operation (min) - Thoracotomy+Laparotomy		The mean length of operation (min) - thoracotomy+laparotomy in the intervention groups was 30.68 lower (51.82 to 9.55 lower)		93 (3 studies)	very low [1,7,8]
Length of operation (min) -		The mean length of operation (min) -		87 (1 study)	very low [1,9]

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)
	Assumed risk Transthoracic approach	Corresponding risk Transhiatal approach			
Thoracotomy+Laparotomy+Cervical incision		thoracotomy+laparotomy+cervical incision in the intervention groups was 121.1 lower (152.37 to 89.83 lower)			
Post-operative complications: Pneumonia - Thracotomy+Laparotomy	200 per 1000	204 per 1000 (48 to 458)	RR 1.02 (0.45 to 2.29)	73 (2 studies)	very low [1,2]
Post-operative complications: Pneumonia - Thoracotomy+Laparotomy+Cervical incision	193 per 1000	131 per 1000 (56 to 313)	RR 0.68 (0.29 to 1.62)	109 (2 studies)	very low [1,2]
Number of lymph nodes resected - Thoracotomy+Laparotomy+Cervical incision		The mean number of lymph nodes resected - thoracotomy+laparotomy+cervical incision in the intervention groups was 15 lower (18.18 to 11.82 lower)		205 (1 study)	moderate [1,10]
Resection of tumour with marginal clearance - Thoracotomy+Laparotomy+Cervical incision:R0 resection	712 per 1000	726 per 1000 (612 to 861)	RR 1.02 (0.86 to 1.21)	205 (1 study)	moderate [1]
Resection of tumour with marginal clearance - Thoracotomy+Laparotomy+Cervical incision: R1 resection	252 per 1000	245 per 1000 (151 to 394)	RR 0.97 (0.6 to 1.56)	205 (1 study)	very low [1,2]
Resection of tumour with marginal clearance - Thoracotomy+Laparotomy+Cervical incision: R2 resection	36 per 1000	11 per 1000 (1 to 94)	RR 0.3 (0.03 to 2.6)	205 (1 study)	very low [1,2]
Recurrence - Thoracotomy+Laparotomy	316 per 1000	199 per 1000 (66 to 600)	RR 0.63	39 (1 study)	very low [1,2]

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)
	Assumed risk Transthoracic approach	Corresponding risk Transhiatal approach			
			(0.21 to 1.9)		
Recurrence - Thoracotomy+Laparotomy+Cervical incision	536 per 1000	622 per 1000 (493 to 783)	RR 1.16 (0.92 to 1.46)	205 (1 study)	low [1,4]
Mortality - Thoracotomy+Laparotomy			RR 0.73(0.13, 4.09)	106 (2 studies)	very low [1,2]
30-day mortality - Thoracotomy+Laparotomy+Cervical incision	62 per 1000	62 per 1000 (4 to 915)	RR 1 (0.07 to 14.64)	32 (1 study)	very low [1,2]
Progression-free survival - Thoracotomy+Laparotomy+Cervical incision			HR 1.17(0.75, 1.84)	217 (1 study)	very low [1,2]

[1] Poor reporting of random sequence generation and allocation concealment.
[2] 95% CI crosses 2 default MID therefore downgraded by 2 levels
[3] I2 73% therefore downgraded by 1 level
[4] 95% CI crosses 1 default MID therefore downgraded by 1 level
[5] I2 89% therefore downgraded by 2 levels
[6] Default MID: +/-34.25: 95% CI crosses 2 default MIDs therefore downgraded by 2 levels
[7] I2 71% therefore downgraded by 1 level
[8] Default MID: +/-12.53: 95%CI crosses 1 default MID therefore downgraded by 1 level
[9] Default MID +/-12.53: 95%CI crosses 2 default MID therefore downgraded by 2 levels
[10] Default MID: +/-7 therefore not downgraded for imprecision

RR=relative risk; 95% CI=95% confidence interval;min=minutes; ml=millilitres

8.2.4.2 Minimally invasive versus any open oesophagectomy

Table 58: Summary clinical evidence profile. Minimally invasive versus any open oesophagectomy

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk Open oesophagectomy	Corresponding risk Minimally invasive oesophagectomy			
Post-operative complications - Anastomotic leak	36 per 1000	47 per 1000 (16 to 128)	RR 1.28 (0.46 to 3.55)	336 (2 studies)	very low[1,2]

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk Open oesophagectomy	Corresponding risk Minimally invasive oesophagectomy			
Post-operative complications - Pulmonary complications	66 per 1000	30 per 1000 (11 to 82)	RR 0.44 (0.16 to 1.26)	336 (2 studies)	low [2,12]
Intraoperative blood loss (ml)3	The mean intraoperative blood loss (ml) in the control groups was 614.6 ml	The mean intraoperative blood loss (ml) in the intervention groups was	MD 109.43 lower (1061.12 lower to 842.26 higher)	336 (2 studies)	very low [2,4,5]
EORTC Global health score QoL		The mean eortc global health score qol in the intervention groups was 10 higher (2.83 to 17.17 higher)		115 (1 study)	low [2,6]
Length of operation (min)	The mean length of operation (min) in the control groups was 614.6 ml	The mean length of operation (min) in the intervention groups was 48.06 higher (29.56 to 66.56 higher)		336 (2 studies)	low [2,7]
Resection margin - R0	839 per 1000	915 per 1000 (772 to 974)	RR 1.09 (0.95 to 1.25)	115 (1 study)	Low [2,12]
Resection margin - R1	89 per 1000	17 per 1000 (2 to 133)	RR 0.19 (0.02 to 1.57)	115 (1 study)	very low [2]
Number of lymph nodes resected8	The mean number of lymph nodes resected in the control groups was 39.1 lymph nodes	The mean number of lymph nodes resected in the intervention groups was 16.08 lower		336 (2 studies)	very low [2,9,10,11]

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk Open oesophagectomy	Corresponding risk Minimally invasive oesophagectomy			
		(57.55 lower to 25.40 higher)			
30 day mortality	0 per 100	0 per 100 (0 to 0)	RR 2.85 (0.12 to 68.53)	115 (1 study)	very low [1,2]

[1] 95% CI crosses both default MIDs therefore downgraded by 2
[2] Unclear reporting of random sequence generation and allocation concealment.
[3] Mean (standard deviation) intraoperative blood loss in control arm (open oesophagectomy): 614.6 (490.3) ml
[4] I2 98% therefore downgraded by 2
[5] Default MID: +/- 245.15. 95% CI crosses one arm, therefore downgraded by 2
[6] Default MID: +/- 10.5. 95% CI crosses 1 boundary of default MID therefore downgraded by 1
[7] Default MID: +/- 55.9. 95% CI crosses 1 boundary of default MID, therefore downgraded by 1
[8] Mean (standard deviation) number of lymph nodes resected in control arm (open oesophagectomy): 39.1 (11.5)
[9] I2 99% therefore downgraded by 2
[10] Inconsistency could be explained by variation in location of studies (China vs Netherlands), surgical practices and prevalence of oesophageal cancer.
[11] Default MID: +/- 5.75. 95% CI does not cross default MID therefore not downgraded
[12] 95%CI crossed one boundary of default MID, therefore downgraded by 1.
RR=relative risk; 95% CI=95% confidence interval;min=minutes; ml=millilitres

8.2.4.3 Hybrid minimally invasive/open versus any totally open oesophagectomy

Table 59: Summary clinical evidence profile. Hybrid minimally invasive/open versus any totally open oesophagectomy

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk Open oesophagectomy	Corresponding risk Hybrid oesophagectomy			
Major post-operative complications - Pulmonary complication	298 per 1000	176 per 1000 (98 to 289)	RR 0.59 (0.35 to 0.98)	207 (1 study)	moderate [1,2]
Major post-operative complications - Major post-operative complication	644 per 1000	361 per 1000 (245 to 496)	RR 0.56 (0.42 to 0.75)	207 (1 study)	high[1]
30 day mortality	48 per 1000	49 per 1000 (14 to 163)	RR 1.01	207 (1 study)	low [1,3]

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk Open oesophagectomy	Corresponding risk Hybrid oesophagectomy			
			(0.3 to 3.38)		

[1] Risk of bias assessment based on protocol and conference abstract and was considered as 'low risk of bias'. No full publication available.
[2] 95% CI crosses one default MIDs therefore downgraded by 1
[3] 95% CI crosses both default MIDs therefore downgraded by
RR=relative risk; 95% CI=95% confidence interval;min=minutes; ml=millilitres 2

8.2.5 Economic evidence

The surgical approach adopted in the treatment of oesophageal cancer was identified as an economic priority topic. The aim of the analysis was to estimate the cost-effectiveness of operative approaches for the surgical treatment of oesophageal cancer.

8.2.5.1 Methods

A systematic literature review was conducted to identify economic evaluations that may be applicable to the current decision problem. One published cost-utility analysis was identified. Lee et al. 2013 compared the short-term cost and QALY consequences of minimally invasive and open surgical approaches from the Canadian health care perspective (see table 2 in Appendix L). The minimally invasive approach was estimated to be more costly initially due to equipment costs and a longer operative time. However, it was found to be cheaper when incorporating reductions in complications and length of stay. Overall, the minimally invasive approach was found to be less costly and more effective than the open approach (i.e. 'dominant').

While the analysis was thought to be of generally high quality, it was deemed to be only partially applicable to the UK health care system. Therefore it was not considered sufficient to address the decision problem in the UK context. Furthermore some potentially serious limitations were identified with the analysis. Most notably the uncertainty around treatment effects was not fully captured in the probabilistic sensitivity analysis because event probabilities were varied individually rather than using a relative effect estimate (such as a relative risk).

Since the current economic literature didn't adequately address the decision problem, a de novo economic evaluation was undertaken to assess cost-effectiveness. The analysis was developed in Microsoft Excel® and was conducted from the perspective of the NHS and Personal Social Services (PSS) as outlined in the NICE Reference Case (The guidelines manual, NICE November 2012).

8.2.5.1.1 Clinical data and model approach

The clinical evidence review conducted for this topic revealed that there is a lack of clear differences between the various surgical approaches. This is particularly true for the longer term outcomes. Therefore the primary focus of the model is on short term outcomes and in particular differences in complication rates.

However, there is a lack of consistency in the complication outcomes reported for each of the comparisons. Therefore, it was not possible to draw indirect comparisons between the comparators which were not directly compared in any of the studies identified in the evidence

review (such as a comparison between a minimally invasive and hybrid surgical approach). The analysis was therefore restricted to a series of pairwise comparisons for which direct clinical evidence was available. The comparisons considered in the analysis were as follows:

- Minimally invasive in comparison to open surgical approach
- Hybrid in comparison to open surgical approach
- Transhiatal in comparison to two-stage transthoracic approach
- Transhiatal in comparison to three-stage transthoracic approach

Following each surgical approach, patients may die from 30-day mortality (typically used as an estimate of procedure related mortality) or they may experience a major complication (such as anastomotic leak) or they may have survive with no complications. In the comparison of open and minimally invasive or hybrid approaches, patients may convert to the open approach as it is not possible to perform the procedure in all patients.

Data on the differences in complications and 30 day mortality were informed using the data identified in the clinical evidence review conducted for this topic, which showed that there were differences between the approaches. However, it should be noted that there is only evidence of statistically significant differences in the comparison between the hybrid and open approach. Therefore, there is likely to be a high degree of uncertainty around the results from the other comparisons.

Mortality from other causes was captured using 2013-2015 life tables for England and Wales from the office of national statistics (ONS). These life tables give an estimate of the annual probability of death given a person's age and gender. A starting age of 60 and a male proportion of 68.2% were applied in the model based on averages reported in Biere et al. 2012 and Guo et al. 2013.

Mortality from disease specific causes was estimated using data from two studies identified in the clinical evidence review; Hulscher et al. 2002 and Omloo et al. 2007. Recurrence rates were estimated using data from Hulscher et al. 2002.

8.2.5.1.2 Costs

The costs considered in the model reflect the perspective of the analysis, thus only costs that are relevant to the UK NHS & PSS were included. Where possible, all costs were estimated in 2015/16 prices.

The majority of costs were sourced from NHS reference costs 2015/16 by applying tariffs associated with the appropriate HRG code. Drug costs were calculated using unit cost data from the electronic market information tool (eMit) combined with dose information from the British National Formulary (BNF). Other resource use and cost information were sourced from the Personal Social Services Research Unit (PSSRU) and the advice of the Guideline Committee.

One of the key aspects to be captured in the economic analysis is the difference in costs between the various surgical approaches. However, this presents a problem because NHS reference costs have a standard cost for the procedure regardless of the approach taken. Therefore, the analysis used the procedure cost as the starting point for all surgical approaches and then introduced cost variations based on differences in procedure time, equipment costs, complication rates and length of stay.

In the model, a 'base cost' of £8,439.60 was used for the procedure. The cost of complications associated with each surgical technique were then added to this figure. The cost of complications was estimated to be £6,481.20 based on the difference between the weighted average cost of the procedure with complications (£14,920.80) and without complications (£8,439.60).

In the cost-effectiveness analysis by Lee et al. 2013, it was estimated that the additional equipment required to perform the minimally invasive approach was $1,510 (Canadian dollars). This cost has been converted and inflated to UK 2015 prices and has been estimated at £891.30. In the absence of any better alternative data, it was also assumed that the same equipment cost would apply to the hybrid approach too. However, in the opinion of the Guideline Committee, the equipment costs associated with the hybrid approach are likely to be lower than that associated with the minimally invasive approach. Therefore, a conservative approach has been adopted where the cost-effectiveness of the hybrid approach may be underestimated in the analysis.

One of the differences between surgical approaches identified in the clinical evidence review was in the time taken to perform the operation. The costs associated with the additional operation time were captured in the analysis by estimating an average cost per minute of surgical time and multiplying the additional time by this figure. The average minimally invasive and open procedure time (from the evidence review) was estimated to be 256.76 minutes. This figure has been used in conjunction with the procedure cost (£11,057.41) to estimate a cost per minute of operation time (£43.06). This is then used to estimate the additional time costs to perform minimally invasive, hybrid and transthoracic procedures.

One of the reported benefits of the minimally invasive or hybrid surgical procedures is that there is a reduced length of stay after surgery. Based on data reported in Biere et al. 2012 and Guo et al. 2013, it was assumed that the length of stay with minimally invasive or hybrid surgical approaches is reduced by 2.2 days. The cost per additional day (£316.34) was estimated using costs for excess bed days from NHS reference costs.

It was assumed that recurrences would be treated with six cycles of chemotherapy using an average cost of the five chemotherapy regimens that are most likely to be used in clinical practice (as identified by the guideline committee). The chemotherapy delivery costs were sourced from NHS Reference Costs 2015/16 and drug costs were sourced from eMit. The average cost per cycle was estimated to be £824.68 with a cost of £4,948.09 for six cycles.

The cost of palliative care was estimated using estimates from a costing report by the Nuffield Trust (Georghiou et al. 2014, ‘Exploring the cost of care at the end of life’). A cost of £7,287 was applied based on the average resource use of patients with cancer in the last three months of life.

8.2.5.1.3 Health related quality of life (QoL) values

As recommended in the NICE reference case, the model estimates effectiveness in terms of quality adjusted life years (QALYs). These are estimated by combining the life year estimates with utility values (or QoL weights) associated with being in a particular health state.

The QoL values applied in the model were sourced from the cost-effectiveness analysis by Lee et al. 2013 and are shown in the table below. Lee et al. 2013 used data from Biere et al. 2012 to estimate QoL values for various health states in patients treated with open and minimally invasive surgical approaches. The QoL value for the postoperative health state (0.6775) was estimated as the average of the QoL values for the postoperative states following an open or minimally invasive procedure in Lee et al. 2013 (0.649 and 0.706, respectively). As in Lee et al. 2013, a utility decrement of 0.043 was applied for any of the major complications experienced with the surgical approaches.

A QoL increment was applied in the analysis to capture the potential benefits associated with a better postoperative period following a minimally invasive or hybrid surgical procedure. This value was estimated based on the difference between the minimally invasive and open procedure estimated in Lee et al. 2013 (0.057). It was assumed that the QoL benefit would only apply for the first three months after the procedure. A further QoL benefit was applied for the reduced length of stay associated with the minimally invasive and hybrid surgical procedures. A QoL value of 0.0018 was applied based on the QoL value for the in-hospital

postoperative period from Lee et al. 2013 (0.300) estimated per day and multiplied by the reduction in length of stay.

A QoL decrement was estimated for patients experiencing recurrence based on data from Graham et al. 2007, a cost-effectiveness analysis of treatments for locally advanced oesophageal cancer. As part of the analysis, QoL values were estimated for surgical and multi-modal treatments at various time points. For the present analysis it was assumed that the pre-treamtent values would best represent the QoL value with disease while the post-treatment value would best represent the QoL value for patients that are disease-free. A QoL decrement of 0.040 was estimated as the difference between patients with disease (0.63) and without disease (0.67) after surgical treatment.

8.2.5.2 Results

8.2.5.2.1 Base case results

The base case results of each of the pairwise analyses are presented in Table 60 to Table 63. It can be seen that the minimally invasive surgical approach was found to be more costly (£1,002) and less effective (-0.26 QALYs) than the open surgical approach and was therefore dominated

The hybrid surgical approach was found to be more costly (£351) and more effective (0.02 QALYs) than the open surgical approach and resulted in an ICER of £18,036 per QALY. Therefore the hybrid approach can be considered cost-effective in comparison to the open approach as this value is lower than the NICE threshold of £20,000 per QALY.

For the comparisons between the types of open surgical approaches, it can be seen that the transhiatal approach was found to be more costly and less effective than the two-stage transthoracic approach and was therefore dominated. In comparison to the three stage transthoracic approach, the transhiatal approach was found to be less costly and more effective. It was therefore dominant.

Table 60: Base case results for minimally invasive approach in comparison to open approach

Strategy	Cost		QALYs		ICER (cost per QALY
	Total	Incremental	Total	Incremental	
Open approach	£17,373	-	2.71	-	-
Minimally invasive approach	£18,375	*£1,002*	2.45	*-0.26*	**Dominated**

Table 61: Base case results for hybrid approach in comparison to open approach

Strategy	Cost		QALYs		ICER (cost per QALY
	Total	Incremental	Total	Incremental	
Open approach	£20,766	-	2.68	-	-
Hybrid approach	£21,117	*£351*	2.70	*0.02*	**£18,036**

Table 62: Base case results for transhiatal in comparison to two-stage transthoracic approach

Strategy	Cost		QALYs		ICER (cost per QALY
	Total	Incremental	Total	Incremental	
Transthoracic	£17,099	-	2.66	-	-
Transhiatal	£17,523	*£424*	2.66	*-0.00*	**Dominated**

Table 63: Base case results for transhiatal in comparison to three-stage transthoracic approach

Strategy	Cost		QALYs		ICER (cost per QALY
	Total	Incremental	Total	Incremental	
Transthoracic	£18,965	-	2.65	-	-
Transhiatal	£17,975	*-£991*	2.65	*0.01*	**Dominant**

8.2.5.2.2 Sensitivity analysis results

A series of deterministic sensitivity analyses were conducted, whereby an input parameter is changed, the model is re-run and the new cost-effectiveness result is recorded. This analysis is a useful way of estimating uncertainty and determining the key drivers of the model result.

It was found that, for the comparison of the minimally invasive and open surgical open approaches, the conclusion of the analysis remains unchanged in all modelled scenarios (i.e. the open approach is always preferred). For the comparison of the hybrid and open surgical open approaches, the conclusion of the analysis changes in a number of modelled scenarios including a scenario where the upper RR for complications is applied as well as scenarios where QoL assumptions are changed around complications. For the comparisons between the open approaches, the preferred strategy remained the same as in the base case in the majority of modelled scenarios. The only exceptions were the scenarios where the upper RR or lower RR values were used for complications. in which case the strategy with the lower complications was always preferred. This reflects the high degree of uncertainty in the effectiveness estimate for complications.

Probabilistic sensitivity analysis (PSA) was conducted (using 10,000 PSA runs) to assess the combined parameter uncertainty in the model. In this analysis, the mean values that were utilised in the base case are replaced with values drawn from distributions around the mean values. The probability of each treatment being cost-effective was assessed using a NICE threshold of £20,000 per QALY.

For the comparison between the minimally invasive and open surgical approach, it was found that the minimally invasive approach had a 35% probability of being cost-effective while the open approach had a 65% probability of being cost-effective. For the comparison between the hybrid and open surgical approach, it was found that the hybrid approach had a 54% probability of being cost-effective while the open approach had a 46% probability of being cost-effective. For the comparison between the two stage transthoracic and transhiatal approach, it was found that the transhiatal approach had a 76% probability of being cost-effective while the two stage transthoracic approach had a 24% probability of being cost-effective. For the comparison between the three stage transthoracic and transhiatal approach, it was found that the transhiatal approach was found to have a 82% probability of being cost-effective while the three stage transthoracic approach had a 18% probability of being cost-effective.

8.2.5.3 Conclusion

Conducting a robust economic analysis in this area is very difficult due to a lack of high quality clinical evidence showing clear differences between the surgical approaches. The clearest differences in the clinical evidence were observed in the comparison between the hybrid and open surgical approach and this is reflected in the analysis, with the results being more robust for this comparison.

The base case results for the comparison between the hybrid and open surgical approaches showed that the hybrid approach was more costly and more effective with an ICER below the NICE threshold for cost-effectiveness. This suggests that there may be a role for the hybrid surgical approach in the management of these patients. However, it should be noted that the probabilistic sensitivity analysis showed that there was uncertainty over this result.

In all other comparisons, the results were thought to be too uncertain to draw any firm conclusions. This was made clear in the uncertainty observed in the sensitivity analysis. Indeed, when considering the probabilistic results, the conclusions of the analysis were often very different to the conclusion of the deterministic analysis. Overall, it is clear that further research is needed before robust conclusions can be drawn about the cost-effectiveness of the various surgical approaches.

8.2.6 Evidence statements

8.2.6.1 Transhiatal versus transthoracic oesophagectomy for oesophageal cancer

8.2.6.1.1 Post-operative complications – anastomotic leak

Transhiatal oesophagectomy versus 2-stage transthoracic oesophagectomy

Very low quality evidence from 2 RCTs with 73 people with oesophageal cancer showed that there is no clinically significant difference in the groups undergoing transhiatal approach and those undergoing 2-stage transthoracic oesophagectomy for risk of anastomotic leak.

Transhiatal oesophagectomy versus 3-stage transthoracic oesophagectomy

Very low quality evidence from 2 RCTs with 295 people with oesophageal cancer showed uncertainty over whether there is no clinically significant difference in the risk of anastomotic leak between the groups undergoing transhiatal approach and those undergoing 3-stage transthoracic oesophagectomy.

8.2.6.1.2 Post-operative complications – pneumonia

Transhiatal oesophagectomy versus 2-stage transthoracic oesophagectomy

Very low quality evidence from 2 RCTs with 73 people with oesophageal cancer indicated that there is no clinically significant difference in the groups undergoing transhiatal approach and those undergoing 2-stage transthoracic oesophagectomy for risk of pneumonia.

Transhiatal oesophagectomy versus 3-stage transthoracic oesophagectomy

Very low quality evidence from 2 RCTs with 109 people with oesophageal cancer indicated that there is no clinically significant difference in the groups undergoing transhiatal approach and those undergoing 3-stage transthoracic oesophagectomy for risk of pneumonia.

8.2.6.1.3 Intraoperative blood loss

Transhiatal oesophagectomy versus 2-stage transthoracic oesophagectomy

Very low quality evidence from 2 RCTs with 59 people with oesophageal cancer indicated that there is no clinically significant difference in risk of intraoperative blood loss between groups undergoing transhiatal approach and those undergoing 2-stage transthoracic oesophagectomy.

Transhiatal oesophagectomy versus 3-stage transthoracic oesophagectomy

Very low quality evidence from 2 RCTs with 80 people with oesophageal cancer indicated that there is no clinically significant difference in risk of intraoperative blood loss between groups undergoing transhiatal approach and those undergoing 3-stage transthoracic oesophagectomy.

8.2.6.1.4 Length of operation

Transhiatal oesophagectomy versus 2-stage transthoracic oesophagectomy

Very low quality evidence from 3 RCTs with 93 people with oesophageal cancer indicated a clinically significant beneficial effect in groups undergoing transhiatal oesophagectomy in comparison with those undergoing 2-stage transthoracic oesophagectomy for operation time.

Transhiatal oesophagectomy versus 3-stage transthoracic oesophagectomy

Very low quality evidence from 1 RCT with 87 people with oesophageal cancer indicated a clinically significant beneficial effect in groups undergoing transhiatal oesophagectomy in comparison with those undergoing 3-stage transthoracic oesophagectomy for length of operation.

8.2.6.1.5 Number of lymph nodes resected

Transhiatal oesophagectomy versus 3-stage transthoracic oesophagectomy

Moderate quality evidence from 1 RCT with 205 people with oesophageal cancer indicated a clinically significant harmful effect in groups undergoing transhiatal oesophagectomy compared to those undergoing 3-stage transthoracic oesophagectomy for number of lymph node resection.

8.2.6.1.6 Resection margin – R0 resection.

Transhiatal oesophagectomy versus 3-stage transthoracic oesophagectomy

Moderate quality evidence from 1 RCT with 205 people with oesophageal cancer indicated no clinically significant difference in the rate of R0 resection between groups undergoing transhiatal approach and those undergoing 3-stage transthoracic oesophaectomy.

8.2.6.1.7 Resection margin – R1 resection

Transhiatal oesophagectomy versus 3-stage transthoracic oesophagectomy

Very low quality evidence from 1 RCT with 205 people with oesophageal cancer indicated no clinically significant difference in the rate of R1 resection between groups undergoing transhiatal oeosphagectomy and those undergoing 3-stage transthoracic oesophagectomy.

8.2.6.1.8 Resection margin – R2 resection

Transhiatal oesophagectomy versus 3-stage transthoracic oesophagectomy

Very low quality evidence from 1 RCT with 205 people with oesophageal cancer indicated no clinically significant difference in the rate of R2 resection between groups undergoing transhiatal approach and those undergoing 3-stage transthoracic oesophagectomy.

8.2.6.1.9 Recurrence

Transhiatal oesophagectomy versus 2-stage transthoracic oesophagectomy

Very low quality evidence from 1 RCT with 39 people with oesophageal cancer indicated no clinically significant difference in recurrence rate between groups undergoing transhiatal and those undergoing 2-stage transthoracic oesophagectomy.

Transhiatal oesophagectomy versus 3-stage transthoracic oesophagectomy

Low quality evidence from 2 RCTs with 205 people with oesophageal cancer indicated that there is no clinically significant difference in recurrence rate between groups undergoing transhiatal approach and those undergoing 3-stage transthoracic oesophagectomy.

8.2.6.1.10 Mortality

Transhiatal oesophagectomy versus 2-stage transthoracic oesophagectomy

Moderate quality evidence from 2 RCTs with 106 people with oesophageal cancer indicated that there was no clinically significant difference between transhiatal oesophagectomy and 2-stage transthoracic oesophagectomy for any mortality.

Transhiatal oesophagectomy versus 3-stage transthoracic oesophagectomy

Very low quality evidence from 1 RCT with 32 people with oesophageal cancer indicated there is no clinically significant difference in the 30-day mortality between groups undergoing transhiatal approach and those undergoing 3-stage transthoracic oesophaectomy.

8.2.6.1.11 Progression free survival

Transhiatal oesophagectomy versus 3-stage transthoracic oesophagectomy

Very low quality evidence from 1 RCT with 217 people with oesophageal cancer indicated that there is no clinically significant difference in progression-free survival between groups undergoing transhiatal approach and those undergoing 3-stage transthoracic oesophaectomy.

8.2.6.1.12 Overall survival

Transhiatal oesophagectomy versus 3-stage transthoracic oesophagectomy

Moderate quality evidence from 1 RCT with 217 people with oesophageal cancer indicated that there is no clinically significant difference between groups undergoing transhiatal oesophagectomy and those undergoing 3-stage transthoracic oesophaectomy for overall survival.

8.2.6.2 Totally minimally invasive approach versus any open oesophagectomy for oesophageal cancer

8.2.6.2.1 Post-operative complications - anastomotic leak

Very low quality evidence from 2 RCTs with 336 people with oesophageal cancer indicated no clinically significant difference in the risk of anastomotic leak between minimally invasive approach and open oesophagectomy.

8.2.6.2.2 Post-operative complications - pulmonary complications

Low quality evidence from 2 RCTs with 336 people with oesophageal cancer indicated no clinically significant difference in the risk of pulmonary complications between minimally invasive approach and open oesophagectomy.

8.2.6.2.3 Blood loss

Very low quality evidence from 2 RCTs with 336 people with oesophageal cancer indicated conflicting evidence over whether there is a clinically significant difference in the risk of blood loss in groups undergoing totally minimally invasive compared to those undergoing open oesophagectomy. Biere 2012 reported mean blood loss (standard deviation) between 408.5 (313.4) and 1009.4 (786.2) ml for the minimally invasive and open oesophagectomy arms respectively. Conversely Guo 2013 reported mean blood loss (standard deviation) between 590 (324.4) and 219.7 (194.7) ml in the minimally invasive and open oesophagectomy arms respectively.

8.2.6.2.4 Length of operation

Low quality evidence from 2 RCTs with 336 people with oesophageal cancer indicated that there is evidence of a clinically significant harmful effect in those undergoing totally minimally invasive surgery in comparison with those undergoing open oesophagectomy for length of operation.

8.2.6.2.5 Quality of life - EORTC Global health score

Low quality evidence from 1 RCT with 115 people with oesophageal cancer indicated that there is a clinically significant beneficial effect in groups undergoing totally minimally invasive surgery compared to those undergoing any open oesophagectomy for quality of life assessed by EORTC Global health score.

8.2.6.2.6 Resection margin - R0 resection

Moderate quality evidence from 1 RCT with 115 people with oesophageal cancer indicated no clinically significant difference in the rate of R0 resection between groups undergoing totally minimally invasive approach and those undergoing any open oesophagectomy.

8.2.6.2.7 Resection margin - R1 resection

Very low quality evidence from 1 RCT with 115 people with oesophageal cancer indicated no clinically significant difference in the rate of R1 resection between groups undergoing totally minimally invasive approach and those undergoing any open oesophagectomy.

8.2.6.2.8 Mean number of lymph nodes resected

Very low quality evidence from 2 RCTs with 336 people with oesophageal cancer indicated conflicting evidence in the mean number of resected lymph nodes between groups undergoing totally minimally invasive and those undergoing any open oesophagectomy. Biere 2012 reported mean number of resected lymph nodes (standard deviation) between 21.78 (10.77) and 59 (10.55) in the minimally invasive and open oesophagectomy arms respectively. Conversely Guo 2013 reported mean number of resected lymph nodes (standard deviation) between 24.3 (21) and 19.2 (12.5) in the minimally invasive and open oesophagectomy arms respectively.

8.2.6.2.9 30-day mortality

Very low quality evidence from 1 RCT with 115 people with oesophageal cancer indicated no clinically significant difference in the 30-day mortality between groups undergoing totally minimally invasive and those undergoing any open oesophagectomy.

8.2.6.3 Hybrid minimally invasive approach versus any open oesophagectomy for oesophageal cancer

8.2.6.3.1 Post-operative complications - Pulmonary complications

Moderate quality evidence from 1 RCT with 207 people with oesophageal cancer indicated a clinically significant beneficial effect in groups undergoing hybrid minimally invasive/open oesophagectomy in comparison with those undergoing open oesophagectomy for postoperative pulmonary complications.

8.2.6.3.2 Post-operative complications - Major post-operative complication

High quality evidence from 1 RCT with 207 people with oesophageal cancer indicated that there is a clinically significant beneficial effect in groups undergoing hybrid minimally invasive oesophagectomy in comparison with those undergoing any open oesophagectomy for major post-operative complications.

8.2.6.3.3 30-day mortality

Low quality evidence from 1 RCT with 207 people with oesophageal cancer indicated no clinically significant difference between groups undergoing hybrid minimally invasive oesophatectomy and those undergoing open oesophagectomy for 30-day mortality.

8.2.6.4 Robotic versus open oesophagectomy for oesophageal cancer

No evidence was found for the comparison between robotic and open oesophagectomy. A randomised controlled trial is ongoing, however published results are not yet available.

8.2.7 Evidence to recommendations

8.2.7.1 Relative value placed on the outcomes considered

As this was a review looking at a population of patients undergoing radical surgery with the aim of achieving a cure, the critical outcomes for this evidence review were survival (overall and disease-free survival), histopathological outcomes and treatment-related morbidity. Capturing data on both survival and morbidity was important to allow a consideration of the benefits and harms when comparing the surgical approaches. Hisopathological outcomes were considered critical as the primary goal of surgery is to achieve a complete resection at all margins (R0), and avoid microscopic (R1) or macroscopic (R2) residual disease, which in turn can lead to recurrence.

Other outcome measures considered to be important but not critical were recurrence, health-related quality of life and length of operation.

Evidence was found for all critical and important outcomes but not across all of the comparisons.

8.2.7.2 Quality of the evidence

The evidence for this review was based on data from 11 publications. The quality of the evidence for individual outcomes was assessed using GRADE. For the majority of the comparisons and outcomes, the quality of the evidence was rated as low. However, for the study comparing the hybrid and open surgical approaches, the quality of the outcomes were rated as moderate to high.

The main issue with the evidence base is that there is a general absence of high quality randomised controlled trials. Issues with the available evidence were that the surgical techniques used in the studies differed from those used in modern day clinical practice. There were also issues with generalising from the study population to the UK population as there were sometimes significant differences between the two. Furthermore, in many studies the study population was very low making it difficult to draw conclusions with confidence.

Note also that the key evidence for the comparison between the hybrid and open approach was drawn from an abstract rather than a full text publication. However the study was rated as moderate to high quality as details on the study design and approach were available from a published protocol.

The above issues with the evidence base resulted in the Committee making a weaker recommendation than they might have if higher quality evidence had been available.

8.2.7.3 Consideration of benefits and harms

In the comparisons of transhiatal approach with 2-stage or 3-stage thansthoracic oesophagectomy, there was no diffence for most of the outcomes (overall survival, progression-free survival, mortality, recurrence, resection margins, intraoperative blood loss, pneumonia, or anastamotic leak). The only difference was in the length of operation which was better for the transhiatal approach, and the number of lymph nodes resected which was better with 3-stage oesophagectomy.

For the comparison of a minimally invasive approach to any open approach there was no difference or conflicting data for most of the outcomes (30-day mortality, mean number of

lymph nodes resected, blood loss, pulmonary complications, anastamotic leak and resection margins). The only differences were in length of operation which was worse for the minimally invasive procedure, and the quality of life which was better for the minimally invasive approach.

The hybrid minimally invasive procedure led to fewer pulmonary complications and major post-operative complications compared to any open operation, but there was no difference in 30-day mortality.

As there was so little difference seen from evidence between the different procedures, it was difficult for the Committee to balance the benefits and harms of the treatments. However, he Committee agreed that recommendations should improve the consistency of the treatment approaches used in clinical practice.

For the comparison between the open and minimally invasive (MIO) surgical approach, the clinical evidence suggests a high degree of uncertainty over the relative benefits and harms of the approaches in terms of survival or treatment related morbidity, and this mean that the Committee did not feel there was strong enough evidence to recommend this approach, nor to not recommend it.

For the comparison between the open and hybrid surgical approach, the clinical evidence suggests that the benefit of using the hybrid approach is that it reduces treatment related morbidity while maintaining the same effectiveness in survival terms.

8.2.7.4 Consideration of economic benefits and harms

An economic evaluation was identified which considered a similar decision problem to the topic at hand. However, since the analysis considered the Canadian health care system it was considered to be only partially applicable to the UK setting.

A de-novo health economic model was developed which considered the cost-effectiveness of surgical treatments for oesophageal cancer. Due to a lack of evidence it was not possible to directly compare the three strategies against each other. The analysis therefore took the form of four pairwise comparisons.

In the comparison between the minimally invasive and open approach, the base case results suggested that the minimally invasive approach was more costly and less effective than the open approach and was therefore dominated. The result was not found to vary in deterministic sensitivity analysis with the conclusion remaining unchanged in numerous scenarios. In probabilistic sensitivity analysis, the minimally invasive approach was found to have only a 35% probability of being cost-effective at a threshold of £20,000 per QALY. This suggests that there is some uncertainty around whether the minimally invasive or open approach is the best strategy.

In the comparison between the hybrid and open approach, the base case results suggested that the hybrid approach was more costly and more effective than the open approach and resulted in an ICER of £18,036 per QALY. Therefore the hybrid approach can be considered cost-effective in comparison to the open approach as this value is lower than the NICE threshold of £20,000 per QALY. The result was not found to be robust in deterministic sensitivity analysis with the conclusion changing in numerous plausible scenarios. Furthermore, in probabilistic sensitivity analysis, the hybrid approach was found to have a 51% probability of being cost-effective at a threshold of £20,000 per QALY. Therefore, there is uncertainty around whether the hybrid or open approach is the best strategy.

In the comparisons between the types of open surgical approaches, it was found that the transhiatal approach was more costly and less effective than the two-stage transthoracic approach and was therefore dominated. In comparison to the three stage transthoracic

approach, the transhiatal approach was found to be less costly and more effective and was therefore dominant. The result was not found to change in most deterministic sensitivity analysis. However, the conclusion of the analyses was found to change when upper or lower RR estimates were used for complications. In probabilistic sensitivity analysis, the transhiatal approach was found to have a 76% and 82% probability of being cost-effective at a threshold of £20,000 per QALY when compared against the two-stage and three-stage transthoracic approach, respectively.

When discussing the results of the analysis, the committee agreed that the poor quality of the clinical evidence on which the analysis was based limited the conclusions that could be drawn. This was thought to be especially true for the comparison between the minimally invasive and open approach and the comparisons between the types of open approaches where the differences in clinical effectiveness were not found to be statistically significant. Therefore, while all the results were thought to be of some interest by the committee, the focus was primarily on the comparison between the hybrid and open approach where statistically significant differences were observed. The committee agreed that this analysis suggested that there is a role for the hybrid approach but the uncertainty around the result meant that one approach could not be offered in preference to the other.

The committee agreed that there was insufficient evidence to either recommend or not recommend that minimally invasive procedures are performed. The committee further agreed that there was insufficient evidence to recommend a preference for the transhiatal or transthoracic approach,

When discussing the potential resource impact, the committee agreed that the recommendations are unlikely to to have a large cost impact as they reflect current practice.

8.2.7.5 Other considerations

The Committee agreed that their recommendations reflected current clinical practice where both the open approach and minimally invasive approaches (fully minimally invasive or hybrid minimally invasive) are currently used. According to the National Oesophago-Gastric Cancer Audit 2016, 61% of surgeries are currently performed as open procedures while 39% are performed as minimally-invasive or hybrid approaches.

A lack of good quality evidence comparing the two approaches did not allow the Committee to make a recommendation of one of these treatment options over another, and they agreed that the choice would therefore be made in consultation with the patient.

The Committee were aware of the ongoing ‘ROMIO’ trial, which is a randomised controlled trial comparing a minimally invasive, hybrid and open (2- stage) oesophagectomy. A feasibility study has been completed and it is expected that the results from the completed study will provide additional information in this area, when published, and in particular allow a recommendation to be made about the use of a minimally invasive approach..

The Committee noted that although they had considered evidence for the 2-stage and 3-stage operations, the 3-stage approach is used in the Far East but not used in the UK.

8.2.7.6 Key conclusions

From the comparisons included in the evidence review the Committee concluded that there was insufficient evidence on the key outcomes to be able to make a recommendation on the minimally invasive approach (MIO). Essentially the evidence suggested that there was uncertainty around whether the minimally invasive approach was better or worse than the open approach. Therefore the committee did not think that a recommendation could be made for or against minimally invasive surgery. Similarly, the evidence on the comparisons between the open approaches (transhiatal and transthoracic) was also thought to be insufficient to recommend one approach over the other.

For the hybrid and open approaches, the evidence suggests that a hybrid approach may be better in terms of morbidity with survival outcomes that were equivalent to the open approach. However, the evidence base is limited and it was thought that further investigation would be required before making a strong recommendation for the hybrid approach. Therefore the Committee recommended that both approaches should be considered as treatment options for this patient group.

8.2.8 Recommendations

24. Consider an open or hybrid oesophagectomy for surgical treatment of oesophageal cancer.

8.3 Lymph node dissection in oesophageal and gastric cancer

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

8.3.1 Introduction

Surgical resection, with or without perioperative chemotherapy/ radiotherapy, remains the standard of care for oesophageal and gastric cancer. The role of surgery is to remove the primary tumour as well as loco-regional lymph nodes (the lymph nodes that drain the lymph from the affected organ) that may contain tumour cells.

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 adults undergoing surgery for oesophageal or gastric cancer.

8.3.2 Description of clinical evidence

This review involved evaluating the evidence for lymphadenectomy in gastric cancer and oesophageal cancer separately.

The lymphadenectomy in gastric cancer review included 11 randomised controlled trials (RCTs) published in 22 references. Where possible relevant data and risk of bias assessments were extracted from two systematic reviews that included some these studies (Jiang 2014 and the Cochrane review by Mocellin 2015). The Jiang 2014 systematic review reported on mortality and morbidity data while, the Mocellin 2015 Cochrane review reported only on mortality data. Please see clinical evidence table for further details. The 11 randomised controlled trials were:

- British MRC Trial (Cuschieri 1996 and 1999),
- Dutch Gastric Cancer Trial (Bonenkamp 1995, Bonenkamp 1999, Hartgrink 2004, Sasako 1997, Songun 2010, Putter 2005),
- Italian Gastric Cancer Study Group (2x Degiuli),

- Japan Clinical Oncology Group (Kodera 2005, Sasako 2008 and Sano 2004),
- East Asia Surgical Oncology Group (Yonemura 2006 and 2008)
- Polish Gastric Cancer Study Group (Kulig 2007),
- Hong Kong (Robertson 1994),
- Chinese (Wu 2004 and 2006),
- Yonago, Japan (Maeta 1999)
- Li 2007
- South African Study (Dent 1988)

The lymphadenectomy in oesophageal cancer review included 2 RCTs (Nishihara 1998 and Kato 1991) and two observational studies (Kato 1995 and Tabira 1999).

Evidence from these studies are summarised in the clinical GRADE evidence profile below. See also the study selection flow chart in Appendix K, forest plots in Appendix H, study evidence tables in Appendix F and exclusion list in Appendix J.

8.3.3 Summary of included studies

A summary of included studies for this review are presented in **Error! Reference source not ound.** to **Error! Reference source not found.**

Table 64: Summary of included studies: D2 versus D1 lymphadenectomy for people with gastric cancer

Study	Population	Intervention / Comparison	Outcomes
Cuschieri 1999; UK; n=400; RCT	People with resectable primary gastric cancer; Mean age: 66 years Male: 68 % N0: 37%	D2 versus D1 lymphadenectomy	Overall survival; Disease specific survival; Disease free survival; Postoperative mortality; Anastomotic leak; Haemorrhage; Wound infection; Pulmonary complication; Postoperative mortality
Deliuli 2014; Italy; n=267; RCT	People with resectable primary gastric cancer Mean age: 63 years Male: 49% N0: 45%	D2 versus D1 lymphadenectomy	Overall survival; Disease specific survival; Postoperative mortality; Pancreatic leak; Reopearation rate; Anastomotic leak; Haemorrhage; Pulmonary complication; number of resected lymph nodes
Dent 1988; South Africa; n=43; RCT	People with gastric cancer (T1-3, N0-1 and M0) Mean age: 50 years Male: 37%	D1 : N1 nodes on gastric wall removed and staging biopsies taken from abnormal nodes, coeliac, common hepatic and hepatic nodes D2: Lymphadenectomy performed in the infra- and supraduodenal areas along the hepatic, common hepatic, coeliac and splenic arteries	Postoperative mortality; Reopearation rate; Anastomotic leak; Wound infection; Pulmonary complication;
Li 2007*: China; n=217; RCT	People with resectable	D2 versus D1 lymphadenectomy	Postoperative mortality; Pancreatic leak; Reopearation rate; Anastomotic

	primary gastric cancer Median age: 48.1 years		leak; Haemorrhage; Wound infection; Pulmonary complication;
Robertson 1994; Hong Kong; n=54; RCT	People with resectable primary gastric cancer Mean age: 59 years Male %: 78	D2 versus D1 lymphadenectomy	Overall survival; Postoperative mortality; Pancreatic leak; Reopearation rate; Anastomotic leak; Haemorrhage;
Bonekamp 1995/Songun 2010/Hartgrink 2004; Netherlands; n=711; RCT	People with resectable primary gastric cancer Age < 70 years: 33% Male: 56% N0: 44%	D2 versus D1 lymphadenectomy	Overall survival; Disease specific survival; Disease free survival; Postoperative mortality; Pancreatic leak; Reopearation rate; Anastomotic leak; Haemorrhage; Wound infection; Pulmonary complication; R0 resection
Wu 2006; Taiwan; n=221; RCT	People with resectable primary gastric cancer Mean age: 67 years Male: 77% N0: 38%	D2 versus D1 lymphadenectomy	Overall survival; Disease specific survival; Disease free survival; Postoperative mortality; Pancreatic leak; Reopearation rate; Anastomotic leak; Haemorrhage; Wound infection;

n=total number of participants; RCT=randomised controlled trial
**published in Chinese language and data being extracted from Jiang 2014 systematic review*

Outcomes for health-related quality of life was not able to be extracted.

Table 65: Summary of included studies: D3 versus D2 lymphadenectomy for people with gastric cancer

Study	Population	Intervention/Comparison	Outcomes
Kulig 2007; Poland; n=275; RCT	Gastric adenocarcinoma undergoing curative resection; Median age: 65 years Male: 61% N0: 39%	D2: dissection of lymph node groups 1 to 12 D2+/D3: D2+: group 1-12 lymph nodes with additional removal of para-aortic lymph nodes People with positive lymph nodes also received adjuvant chemotherapy	Postoperative mortality; Pancreatic leak; Anastomotic leak; Wound infection; Pulmonary complications;
Maeta 1999; Japan; n=70; RCT	People with resectable primary non-metastatic gastric carcinoma Mean age: 60 years Male%: 59	D2 versus D3 lymph node dissection	Overall survival; Postoperative mortality; Pancreatic leak; Reoperation rate; Anastomotic leak;
Sasako 2008/Sano 2004 Japan; n=523; RCT	Peole with patients with resectable primary non-metastatic gastric carcinoma Mean age: 60 years	D2 versus D3 lymph node dissection	Overall survival; Postoperative mortality; R0 resection; Disease-free survival; Pancreatic leak; Reoperation rate; number of resected lymph nodes

	Male%: 69		
Yonemura 2008; Japan; n=269; RCT	People with resectable primary non-metastatic gastric carcinoma Mean age: 63 years Male%: 67	D2 versus D3 lymph node dissection	Overall survival; Postoperative mortality; Pancreatic leak; Anastomotic leak; Wound infection; Pulmonary complications; Disease free survival; Disease specific survival; Number of resected lymph nodes

n=total number of participants; RCT=randomised controlled trial

Outcomes for R0 resection and health-related quality of life were not able to be extracted.

Table 66: Summary of included studies: 3-field lymphadenectomy versus 2-field lymphadenectomy for people with oesophageal cancers

Study	Population	Intervention/Comparison	Outcomes
Kato 1991; Japan; n=150; RCT	People with oesophageal cancer undergoing right open oesophagectomy and laparotomy Average age: 63 years Male %: 91	2-field dissection: standard radical lymph node dissection without neck lymph node dissection 3-field dissection: standard radical operation with neck lymph node dissection	Overall survival; Postoperative mortality; Any surgical complication; Recurrent nerve palsy; Anastomotic leak; Chylothorax;
Nishihara 1998; Japan; n=62; RCT	People with invasive oesophageal cancer undergoing curative resection who also received either radiochemotherapy or chemotherapy alone as postoperative adjuvant therapy Mean age: 59 years Male: 84% N0: 58%	2-field dissection: abdominal and partial mediastinal lymph node removal only 3-field dissection: mediastinal and cervical lymph node removal	Overall survival; Postoperative mortality; Recurrent nerve palsy; Anastomotic leak; Chylothorax; Pulmonary complication; Phrenic nerve palsy; Tracheostomy

n=total number of participants; RCT=randomised controlled trial;

Outcomes for R0 resection, disease-free survival, health-related quality of life and number of lymph nodes retrieved were not able to be extracted.

Table 67: Summary of included studies: 3-field lymphadenectomy versus 2-field lymphadenectomy for people with oesophageal cancer: observational studies

Study	Population	Intervention	Outcomes
Kato 1995; Japan; n=510; Retrospective observational study	People with thoracic oesophageal cancer undergoing right open oesophagectomy; excluded people with microscopic residual tumour after surgery Mean age: 62 years Male: 85%	2-Field dissection: dissection of lymph nodes in mediastinum and abdomen. 3-Field: dissection of cervical lymph nodes in addition to abdominal and mediastinal nodes	Anastomotic leak, Vocal cord paralysis, Pneumonia, Wound infection, Haemorrhage; Chylothorax; Any postoperative complication; Overall survival

Tabira 1999; Japan; n=152; Prospective observational study	People with T1 to T4 thoracic oesophageal cancer undergoing curative oesophagectomy Mean age: 64 years Male: 84% N0: 66 %	2-Field lymphadenectomy: perigastric and left gastric artery nodes removed. Neck nodes not removed 3-Field lymphadenectomy: bilateral neck dissection, perigastric, left gastric artery nodes removed.	Overall survival

n=total number of participants

Outcomes for R0 resection, short term mortality, disease-free survival, health-related quality of life and number of lymph nodes retrieved were not able to be extracted.

8.3.4 Clinical evidence profile

The clinical evidence profiles for this review question are presented in Table 68 to Table 71.

Table 68: Summary clinical evidence profile: D2 versus D1 lymphadenectomy for people with gastric cancer

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk with D1	Corresponding risk with D2			
Overall survival	5yr OS 49%[24]	5yr OS 52% (43% to 60%)	HR 0.91 (0.71 to 1.17)	1653 (5 studies)	very low[1,3]
Disease free survival	5yr DFS 44%[25]	5yr DFS 46% (42% to 50%)	HR 0.81 (0.71 to 0.92)	1599 (4 studies)	low[1]
Postoperative mortality	34 per 1000	68 per 1000 (45 to 103)	RR 2.02 (1.34 to 3.04)	1913 (7 studies)	low[1,2,3,4]
Pancreatic leak	9 per 1000	27 per 1000 (12 to 60)	RR 2.96 (1.32 to 6.65)	1746 (5 studies)	low[5,6,7,8]
Reoperation rate	46 per 1000	101 per 1000 (61 to 166)	RR 2.18 (1.32 to 3.6)	1513 (6 studies)	very low[9,10,11,12]
Anastomotic leak	35 per 1000	74 per 1000 (49 to 111)	RR 2.12 (1.41 to 3.2)	1808 (7 studies)	low[1,13,14,15]
Haemorrhage	26 per 1000	17 per 1000 (9 to 32)	RR 0.64 (0.34 to 1.2)	1870 (6 studies)	very low[1,2,16,17]
Wound infection	30 per 1000	107 per 1000 (29 to 392)	RR 3.51 (0.96 to 12.86)	1384 (5 studies)	very low[1,7,18,19]
Pulmonary complication	45 per 1000	93 per 1000 (64 to 137)	RR 2.07 (1.41 to 3.03)	1638 (5 studies)	low[1,20,21,22]
R0 resection	892 per 1000	883 per 1000 (839 to 937)	RR 0.99 (0.94 to 1.05)	711 (1 study)	high[23]

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk with D1	Corresponding risk with D2			
Health related quality of life - not reported	-	-	-	-	-

Abbreviations: CI, Confidence interval; DFS, disease free survival; OS, overall survival; RR, risk ratio; HR, hazard ratio;
[1] Risk of bias: Dent 1988 and Robertson 1994 have low sample sizes, Li 2007 and Robertson have unclear risk of bias ratings.
[2] Inconsistency: I-squared=0%
[3] Indirectness: postoperative mortality could be affected by dissection of additional organs such as pancreatectomy and splenectomy, subgroup analyses have not been presented here. Older studies may not be comparable with newer studies where they may be better experience of surgical technique and post-operative care.
[4] Imprecision: 95% confidence interval (1.34-3.04). No imprecision
[5] Risk of bias: Robertson 1994 has low sample size, Li 2007 and Robertson have unclear risk of bias ratings.
[6] Inconsistency: I-squared=0%.
[7] Indirectness: Indirect intervention: patients undergoing pancreatectomy may be more likely to develop post-operative complications. Older studies may not be comparable to more recent studies due to improvements in training and experience with surgical technique and post-operative care.
[8] Imprecision: 95% confidence interval: 1.36-7.41. No MIDs crossed
[9] Risk of bias: Dent 1988 and Robertson 1994 have low sample sizes, Li 2007 and Robertson have unclear risk of bias ratings.
[10] Heterogeneity: I2=7%
[11] Indirectness: reoperation rate could be affected by dissection of additional organs such as pancreatectomy and splenectomy, subgroup analyses have not been presented here. Older studies may not be comparable with newer studies where there may be better experience of surgical technique and post-operative care.
[12] 95% CI: 1.63-3.43. Very wide CI crossing both MIDs
[13] Heterogeneity: I2=0%
[14] No explanation was provided
[15] No imprecision. 95% CI: 1.47-3.29.
[16] Indirectness: Haemorrhage poorly defined or not defined in most studies, therefore unclear of comparability across studies. Haemorrhage could be affected by dissection of additional organs such as pancreatectomy and splenectomy, subgroup analyses have not been presented here. Older studies may not be comparable with newer studies where there may be better experience of surgical technique and post-operative care.
[17] Imprecision: 95% CI: 0.39-1.26. Crosses two MIDs.
[18] Heterogeneity: I2=82%. Very serious imprecision
[19] 95% CI: 1.45-3.61. No imprecision as no MIDs crossed
[20] Heterogeneity: i2=0%
[21] Indirectness: Pulmonary complications poorly define in most studies. Unclear if exclusively refers to pneumonia or includes for instance pleural effusion and pulmonary embolus. Additionally, post-operative complications may have been higher in those who underwent pancreatectomy and splenectomy, older trials might have also been subject to relative inexperience in surgical techniques and post-operative care for D2 resection, thus confounding the results presented here.
[22] 95% CI: 1.44-3.06: No imprecision as no default MIDs crossed.
[23] 95% CI: 0.94-1.05. No imprecision as does not cross default MID
[24] Assumed risk is the median 5yr OS from the trial D1 arms (Mocellin, 2015)
[25] Assumed risk is the median 5yr DFS from the trial D1 arms (Mocellin, 2015).

Table 69: Summary clinical evidence profile: D3 versus D2 lymphadenectomy for gastric cancer

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk with D2	Corresponding risk with D3			
Overall survival	5yr OS 54%[12]	5yr OS 52% (47% to 61%)	HR 1.08 (0.83 to 1.42)	862 (3 studies)	low[1,3]

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk with D2	Corresponding risk with D3			
Disease-free survival	5yr DFS 63%	5yr DFS 60% (51% to 68%)	HR 1.08 (0.83 to 1.42)	523 (1 study)	moderate[1,2]
Postoperative mortality	10 per 1000	21 per 1000 (8 to 56)	RR 2.04 (0.78 to 5.35)	1137 (4 studies)	very low[3,4,5]
Pancreatic leak	53 per 1000	61 per 1000 (38 to 98)	RR 1.15 (0.71 to 1.85)	1124 (4 studies)	very low[3,4,6]
Anastomotic leak	58 per 1000	48 per 1000 (30 to 79)	RR 0.83 (0.51 to 1.36)	1124 (4 studies)	very low[3,4,7]
Wound infection	37 per 1000	40 per 1000 (7 to 240)	RR 1.07 (0.18 to 6.45)	531 (2 studies)	very low[4,8,9]
Pulmonary complications	71 per 1000	54 per 1000 (34 to 86)	RR 0.75 (0.47 to 1.2)	1054 (3 studies)	low[4,10]
Reoperation rate	17 per 1000	30 per 1000 (10 to 90)	RR 1.77 (0.59 to 5.38)	593 (2 studies)	very low[3,4,11]
R0 resection	992 per 1000	1000 per 1000 (982 to 1000)	RR 1.01 (0.99 to 1.02)	523 (1 study)	high
Health related quality of life - not reported	-	-	-	-	-

Abbreviations: CI, Confidence interval; DFS, disease free survival; OS, overall survival; RR, risk ratio; HR, hazard ratio;

[1] *Median follow-up 5.7 years*

[2] *95% CI: 0.83-1.42. One default MID crossed*

[3] *Risk of bias: Maeta 1999: high risk of bias and small sample size.*

[4] *Indirectness: postoperative complications could be affected by dissection of additional organs such as pancreatectomy and splenectomy (Yonemura 2008), subgroup analyses have not been presented here. Older studies may not be comparable with newer studies due to differences in surgical technique and experience and post-operative care. Differences in median follow-up time across included studies.*

[5] *95% CI: 0.78-5.35. Wide CI crosses two default MID therefore downgraded by 2.*

[6] *95% CI: 071-1.83. Two default MIDs crossed; 7 95% CI: 0.51-1.36. Two default MIDs crossed*

[8] *Heterogeneity: i2=40%*

[9] *95% CI: 0.35-2.05. Two default MIDs crossed;*

[10] *95% CI: 0.47-1.21. 1 default MID crossed*

[11] *Heterogeneity: i2=3%; 12 95% CI: 0.69-5.35. Two default MIDs crossed; 13 95% CI: 0.99-1.02*

[12] *Assumed risk is the median 5yr OS from the trial D2 arms (Mocellin, 2015)*

[13] *Downgraded one level for imprecision (one default MID crossed) and one level for risk of bias.*

Table 70: Summary clinical evidence profile: 3-field lymph node resection versus 2-field lymph node resection for oesophageal cancer

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk with 2-field	Corresponding risk with 3-field			
Overall survival	5yr OS 33%13	5yr OS 61% (46% to 72%)	HR 0.46 (0.3 to 0.71)	212 (2 studies)	very low[1,2,3]
Postoperative mortality	107 per 1000	29 per 1000 (9 to 100)	RR 0.26 (0.07 to 0.90)	212 (2 studies)	very low[1,2,4]
Recurrent nerve palsy	194 per 1000	291 per 1000 (62 to 1000)	RR 1.50 (0.32 to 7.08)	212 (2 studies)	very low[1,2,5,6]
Anastomotic leak	223 per 1000	179 per 1000 (40 to 784)	RR 0.80 (0.18 to 3.51)	212 (2 studies)	very low[1,2,7,8]
Pulmonary complication	167 per 1000	188 per 1000 (63 to 550)	RR 1.13 (0.38 to 3.3)	62 (1 study)	very low[1,2,9]
Chylothorax	41 per 1000	6 per 1000 (0 to 106)	RR 0.14 (0.01 to 2.58)	150 (1 study)	very low[1,2,10]
Phrenic nerve palsy	0 per 1000	125 per 1000 (11 to 281)	RR 08.45 (0.47 to 150.66)	62 (1 study)	very low[1,2,11]
Tracheostomy	100 per 1000	531 per 1000 (173 to 1000)	RR 5.31 (1.73 to 16.31)	62 (1 study)	very low[1,2,12]
Any surgical complication	247 per 1000	0 per 1000 (229 to 616)	RR 0 (0.93 to 2.50)	150 (1 study)	Low[1,14]
Health related quality of life - not reported	-	-	-	-	-

Abbreviations: CI, Confidence interval; DFS, disease free survival; OS, overall survival; RR, risk ratio; HR, hazard ratio;

[1] Risk of bias: Kato 1991 provides no details on randomisation method and allocation concealment. Nishihara 1998 also does not report randomisation method and may be subject to small sample size bias (n=62).

[2] Indirectness: Indirect populations. Kato 1991 includes patients with thoracic oesophageal carcinoma and Nishihara 1998 includes those with thoracic oesophageal carcinoma. Indirect interventions: lymphadenectomy described in Nishihara 1998 may not strictly follow definition in protocol and that defined in other included studies. Procedure and approach of lymphadenectomy would also presumably vary depending on site of primary tumour. Thus, downgraded by 2 levels.

[3] 95% CI: 0.30-0.71 and did not downgrade for imprecision

[4] Downgraded one level for imprecision: 95% CI: 0.07-0.90. One default MID crossed.

[5] Heterogeneity: i2=87% therefore very serious inconsistency.

[6] 95% CI: 0.82-2.27. Crosses 1 default MID.

[7] Heterogeneity: i2=72%

[8] Downgraded two levels for imprecision: 95% CI: 0.71-1.86. Crosses 2 boundaries of default MIDs.

[9] Downgraded two levels for imprecision: 95% CI: 0.38-3.30. Crosses 2 boundaries of default MIDs.

[10] Downgraded two levels for imprecision: 95% CI: 0.01-2.58. Crosses 2 boundaries of default MIDs.

[11] Downgraded two levels for imprecision: 95% CI: 0.47-150.66. Crosses 2 boundaries of default MIDs.

[12] 95% CI: 1.71-16.31 and did not downgrade for imprecision

[13] Assumed risk from Kato (1991)

[14]95%CI crossed one default MID

Table 71: Summary clinical evidence profile: 3-field lymphadenectomy vs 2-field lymphadenectomy for oesophageal cancer: observational studies

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk 2-field lymphadenectomy	Corresponding risk 3-field lymphadenectomy			
5 year overall survival (observational studies) death from any cause: Kato 1995, Tabira 1999 Follow-up: 5 years	-	-	Difference in 5 yr OS (%) ranged from 13.6 to 38.2	562 (2 studies)	very low[1]
Anastomotic leak (observational studies) Kato 1995	400 per 1000	428 per 1000 (332 to 556)	RR 1.07 (0.83 to 1.39)	510 (1 study)	very low[1,2]
Vocal cord paralysis (observational studies) Kato 1995	46 per 1000	150 per 1000 (79 to 285)	RR 3.24 (1.71 to 6.14)	510 (1 study)	very low[3]
Wound infection (observational studies) Kato 1995	46 per 1000	60 per 1000 (25 to 146)	RR 1.29 (0.53 to 3.16)	510 (1 study)	very low[1,4]
Haemorrhage (observational studies) Kato 1995	10 per 1000	4 per 1000 (0 to 81)	RR 0.45 (0.02 to 8.33)	510 (1 study)	very low1[,5]
Chylothorax (observational studies) Kato 1995	10 per 1000	4 per 1000 (0 to 81)	RR 0.45 (0.02 to 8.33)	510 (1 study)	very low[5]
Any post operative complication (observational studies)	605 per 1000	708 per 1000 (611 to 823)	RR 1.17 (1.01 to 1.36)	510 (1 study)	very low[1,6]
Pneumonia	102 per 1000	100 per 1000 (52 to 193)	RR 0.98 (0.51 to 1.88)	510 (1 study)	very low[1,7]

[1] Risk of bias: Tabira 1999: moderate overall risk of bias due to critical confounding bias. Kato 1991: serious risk of bias.
[2] 95% CI: 0.83-1.39. Crosses 1 default MID
[3] 95% CI: 1.71-6.14.
[4] 95% CI: 0.53-3.16. Crosses two default MIDs
[5] 95% CI: 0.02-8.33. Crosses two default MIDs
[6] 95% CI: 1.01-1.36. Croses 1 defaul MID
[7] Crosses two default MIDs

8.3.5 Economic evidence

A systematic review of the economic literature was conducted but no relevant studies were identified which were applicable to this review question. Economic modelling was not undertaken for this question because other topics were agreed as higher priorities for economic evaluation.

8.3.6 Evidence statements

8.3.6.1 D2 versus D1 lymphadenectomy for gastric cancer

Very low quality evidence from 5 RCTs with 1653 people with gastric cancer indicates no clinically important difference in the overall survival of groups receiving D2 compared to those receiving D1 lymphadenectomy.

Low quality evidence from 4 RCTs with 1332 people with gastric cancer indicates a clinically important beneficial effect in groups receiving D2 lymphadenectomy compared to those receiving D1 lymphadenectomy for disease free survival.

Low quality evidence from 7 RCTs with 1913 people with gastric cancer showed that there is a clinically significant harmful effect in groups receiving D2 lymphadnectomy in comparison with those receiving D1 lymphadenectomy for postoperative mortality.

Low quality evidence from 5 RCTs with 1746 people with gastric cancer showed that there is a clinically significant harmful effect in groups receiving D2 lymphadnectomy in comparison with those receiving D1 lymphadenectomy for pancreatic leak.

Very low quality evidence from 6 RCTs with 1513 people with gastric cancer showed that there is a clinically significant harmful effect in groups receiving D2 lymphadnectomy in comparison with those receiving D1 lymphadenectomy for reoperation rate.

Low quality evidence from 7 RCTs with 1808 people with gastric cancer showed that there is a clinically significant harmful effect in groups receiving D2 lymphadnectomy in comparison with those receiving D1 lymphadenectomy for anastomotic leak.

Very low quality evidence from 6 RCTs with 1870 people with gastric cancer showed that there is no clinically significant difference between groups receiving D2 and those receiving D1 lymphadenectomy for haemorrhage.

Very low quality evidence from 5 RCTs with 1384 people with gastric cancer showed that there may be a clinically significant harmful effect groups receiving D2 compared to those receiving D1 lymphadenectomy for wound infection, but there is uncertainty around the estimate.

Low quality evidence from 5 RCTs with 1638 people with gastric cancer showed a clinically significant harmful effect in groups receiving D2 lymphadnectomy in comparison with those receiving D1 lymphadenectomy for pulmonary complications.

High quality evidence from 1 RCT with 711 people with gastric cancer showed that there may be a clinically significant beneficial effect in the groups receiving D2 compared to those receiving D1 lymphadenectomy for R0 resection.

8.3.6.2 D3 versus D2 lymphadenectomy for gastric cancer

Low quality evidence from 3 RCTs with 862 people with gastric cancer suggests that there is no clinically important difference between groups receiving D3 lymphadenectomy and those receiving D2 lymphadenectomy for overall survival.

Moderate quality from 1 RCT including 523 people indicates that there is no clinically important difference between groups receiving D3 lymphadenectomy and those receiving D2 lymphadenectomy for disease-free survival.

Very low quality evidence from 4 RCTs with 1137 people with gastric cancer showed that there is no clinically significant difference between groups receiving D3 lymphadenectomy and those receiving D2 lymphadenectomy for postoperative death.

Very low quality evidence from 4 RCTs with 1137 people with gastric cancer indicated that there is no clinically significant difference between groups receiving D3 lymphadenectomy and those receiving D2 lymphadenectomy for pancreatic leak.

Very low quality evidence from 4 RCTs with 1124 people with gastric cancer indicated that there is no clinically significant difference between groups receiving D3 lymphadenectomy and those receiving D2 lymphadenectomy for anastomotic leak.

Very low quality evidence from 2 RCTs with 531 people with gastric cancer showed that there is no clinically significant difference between groups receiving D3 lymphadenectomy and those receiving D2 lymphadenectomy for wound infection.

Low quality evidence from 3 RCTs with 1054 people with gastric cancer showed that there is no clinically significant difference between groups receiving D3 lymphadenectomy and those receiving D2 lymphadenectomy for pulmonary complications.

Very low quality evidence from 2 RCTs with 593 people with gastric cancer showed that there is no clinically significant difference between groups receiving D3 lymphadenectomy and those receiving D2 lymphadenectomy for reoperation rate.

High quality evidence from 1 RCT with 523 people with gastric cancer showed that there may be a clinically significant beneficial effect in the groups receiving D3 compared to those receiving D2 lymphadenectomy for R0 resection, however, there is uncertainty around the estimate.

8.3.6.3 3-field versus 2-field lymphadenectomy for oesophageal cancer

Very low quality evidence from 2 RCTs with 212 people with oesophageal cancer showed a clinically significant beneficial effect of overall survival in the groups receiving 3-field lymphadenectomy compared to those receiving 2-field lymphadenectomy.

Very low quality evidence from 2 RCTs with 212 people with oesophageal cancer suggests a clinically significant beneficial effect of postoperative mortality in the groups receiving 3-field lymphadenectomy compared to those receiving 2-field lymphadenectomy.

Very low quality evidence from 2 RCTs with 212 people with oesophageal cancer indicates that there is no clinically significant difference between groups receiving 3-field lymphadenectomy and those receiving 2-field lymphadenectomy for recurrent nerve palsy.

Very low quality evidence from 2 RCTs with 212 people with oesophageal cancer showed that there is no clinically significant difference between groups receiving 3-field lymphadenectomy and those receiving 2-field lymphadenectomy for anastomotic leak.

Very low quality evidence from 1 RCT with 62 people with oesophageal cancer showed that there is no clinically significant difference between groups receiving 3-field lymphadenectomy and those receiving 2-field lymphadenectomy for pulmonary complication.

Very low quality evidence from 1 RCT with 150 people with oesophageal cancer showed that there is no clinically significant difference between groups receiving 3-field lymphadenectomy and those receiving 2-field lymphadenectomy for chylothorax.

Very low quality evidence from 1 RCT with 62 people with oesophageal cancer showed that there is no clinically significant difference between groups receiving 3-field lymphadenectomy and those receiving 2-field lymphadenectomy for phrenic nerve palsy.

Very low quality evidence from 1 RCT with 62 people with oesophageal cancer showed a clinically significant harmful effect of tracheostomy in the groups receiving 3-field lymphadenectomy compared to those receiving 2-field lymphadenectomy.

Low quality evidence from 1 RCT with 150 people with oesophageal cancer reported that there may be a clinically significant harmful effect in the group receiving 3-field lymphadenectomy in comparison with 2-field lymphadenectomy for any surgical complication, however, there is an uncertainty around the estimate.

8.3.6.4 3-field versus 2-field lymphadenectomy for oesophageal cancer (observational studies)

Very low quality evidence from two observational studies of 562 people with oesophageal cancer suggested a clinically significant improvement in the overall survival of patients who underwent 3-field when compared to those receiving 2-field lymphadenectomy. 5-year overall survival was between13.6% to 38.3% better with 3-field than 2-field lymphadenectomy.

Very low quality evidence from 1 observational study of 510 people with oesophageal cancer showed no clinically significant difference in the risk of anastomotic leak when comparing patients who underwent 3-field and 2-field lymphadenectomy.

Very low quality evidence from 1 observational study of 510 people with oesophageal cancer showed a clinically significant harmful effect of 3-field lymphadenectomy in the risk of vocal cord paralysis in comparison with 2-field lymphadenectomy.

Very low quality evidence from 1 observational study of 510 people with oesophageal cancer showed no clinically significant difference in the risk of wound infection when comparing patients who underwent 3-field and 2-field lymphadenectomy.

Very low quality evidence from 1 observational study of 510 people with oesophageal cancer showed no clinically significant difference in the risk of haemorrhage when comparing patients who underwent 3-field and 2-field lymphadenectomy.

Very low quality evidence from 1 observational study of 510 people with oesophageal cancer showed no clinically significant difference in the risk of chylothorax when comparing patients who underwent 3-field and 2-field lymphadenectomy.

Very low quality evidence from 1 observational study of 510 people with oesophageal cancer showed a clinically significant harmful effect of 3-field lymphadenectomy in the risk of any postoperative complication in people who underwent 3-field lymphadenectomy in comparison with 2-field lymphadenectomy.

Very low quality evidence from 1 observational study of 510 people with oesophageal cancer showed no clinically significant difference in the risk of pneumonia when comparing patients who underwent 3-field and 2-field lymphadenectomy.

8.3.7 Evidence to recommendations

8.3.7.1 Relative value placed on the outcomes considered

As lymph node dissection is part of the radical treatment of osesophago-gastric cancer the critical outcomes for this topic were overall survival and disease-free survival. However, as with any surgical procedure the choice of treatment is made on a balance of the risks and benefits of the procedure, so treatment-related morbidity, R0 resection and postoperative

mortality were also important. Other important outcomes of interest that were not reported in the literature were number of lymph nodes retrieved, health-related quality of life and patient reported outcomes. In order to evaluate the efficacy and safety of surgical lymph node dissection in gastric and oesophageal cancer, mortality, survival and morbidity outcomes were considered critical and important to decision-making.

For gastric cancer disease-specific survival was not specified in the protocol, but considered important when making recommendations and evaluating the evidence. This was considered in addition to the critical survival outcomes since it allowed differentiation between overall survival and post-operative mortality allowing insight into people who died from other causes not related to gastric cancer.

8.3.7.2 Quality of the evidence

The quality of each study was assessed using the Cochrane risk of bias checklists and the quality of the evidence for an outcome (i.e. across studies) was assessed using GRADE. The evidence quality ranged from very low to high.

Gastric cancer

For gastric cancer the low quality of evidence was due to problems with imprecision and indirectness of the evidence. A major limitation was the influence of indirectness. Many studies performed in the Far East reported favourable outcomes for more extensive lymph node dissection, and this may be due ot the fact that at the time the studies were conducted, surgery was of a more uniform standard in the Far East.. These outcomes were, however not reproduced in Western studies.

Many trials were conducted prior to 2000. The Committee thought that diagnostic imaging techniques, surgical experience and technique, and post-operative care have improved substantially since the publication of these trials. Outcomes were therefore considered in reality to be better than those reported in included trials. The Committee cautioned that the East Asian trials should be considered in the context of their limited applicability to the UK patient population due to epigenetic differences, cancer screening with its impact on detection of early stage disease, and greater surgical experience. Heterogeneity was noted in the variable and inconsistent administration of additional treatments such as chemotherapy and radiotherapy. Lastly, the applicability of the majority of trials to current UK practice was further limited by surgical resection of additional visceral organs such as the spleen and distal tail of the pancreas. The more invasive and extensive surgical procedures were noted to carry poorer post-operative morbidity and mortality outcomes compared to preservation of these organs.

Oesophageal cancer

Evidence for lymph node dissection for oesophageal cancer was taken from two randomised trials of very limited quality. These trials reported results of treatment of different anatomical tumour sites and reported variable use of additional therapies (e.g. chemotherapy and radiotherapy). Since both trials were conducted in the Far East, the comparability of the study populations and interventions to the UK setting was thus considered poor. In addition there there was very low quality evidence from two observational studies which compared 2-field and 3-field lymphadenectomy. Both these studies were conducted in the Japan, so again their applicability to the UK setting was considered to be poor.

8.3.7.3 Consideration of clinical benefits and harms

For gastric cancer, the Committee considered that overall survival and disease-specific survival were improved in D2 when compared to D1 lymph node dissection, although the improvements were marginal and not statistically significant. D2 was recommended in preference over D3 lymph node dissection which carried a higher morbidity rate compared to

D2 lymph node dissection. The Committee agreed that offering D2 dissection provided the best balance between benefits and harms: although the benefits of D2 were marginal compared to D1, there was no gain in overall survival between D2 and D3 but D3 was associated with increased morbidity.

For oesophageal cancer, overall survival and disease-specific survival were considered to be better in two-field as compared to no lymph node dissection. Two-field lymph node dissection was associated with a lower rate of morbidity than three-field lymph node dissection.

The Committee thought that the harms associated with current surgical technique and experience of two-field compared to no lymph node dissection were lower than previously reported, and that since the studies used as a basis for the evidence review had been conducted, there had been greater standardisation of surgical techniques, and improvements in surgical techniques and post-operative care. They acknowledge however, the potential for under-treatment when comparing two-field and three-field lymph node dissection, but this is outweighed by the increased morbidity from three-field lymph node dissection.

8.3.7.4 Consideration of economic benefits and harms

No health economic evidence was identified and no health economic model was built for this topic.

Gastric cancer

The recommendations for gastric and oesophageal cancer reflect current practice and are unlikely to result in a large resource impact. For gastric cancer D2 may cost more than D1 lymph node dissection, but this is offset by cost savings which result from better clinical outcomes (lower recurrence rates and the associated costs of managing recurrence).

Oesophageal cancer

For oesophageal cancer the increased cost of two- field compared to no lymph node dissection is potentially offset by cost savings due to better clinical outcomes (lower rates of recurrence and its associated costs).

8.3.7.5 Other considerations

The Committee consider recommendations will not lead to a change in clinical practice since they reinforce current practice.

For oesophageal cancer, surgical approach may dictate extent of lymph node dissection.

8.3.7.6 Key conclusions

Gastric cancer

The Committee recommended D2 lymph node dissection, based on the most benefit that was associated with the lowest relative increase in harms. The Committee thought that the harms associated with current surgical technique and experience of D2 and D1 were lower than previously reported. They acknowledge however, the potential for under-treatment when comparing D2 and D3 lymph node dissection. Although postoperative mortality appeared higher with D2 dissection in older studies the Committee considered that surgical technique, experience and care has improved since publication of these trials and does not routinely involve splenectomy and distal pancreatectomy. Current postoperative mortality is thus likely to be lower and disease-specific survival is higher with current D2 lymph node dissection techniques.

Oesophageal cancer

The Committee recommended two-field lymph node dissection and discounted the apparent overall survival benefit of three-field lymph node dissection based on their clinical judgement. The Committee based recommendations on their clinical judgement due to the limited quality and applicability of the clinical evidence evaluated in addition to the lack of evidence for one-field lymph node dissection, two-field lymph node dissection and contemporary trials.

8.3.8 Recommendations

25. When performing a curative gastrectomy for people with gastric cancer, consider a D2 lymph node dissection.

26. When performing a curative oesophagectomy for people with oesophageal cancer, consider two-field lymph node dissection.

8.4 Localised oesophageal and gastro-oesophageal junctional adenocarcinoma

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

8.4.1 Introduction

For people with localised oesophageal or oesophago-gastric cancer radical surgery is often recommended. As a sole modality of treatment, surgery is associated with a high rate of loco-regional or metastatic recurrence. In order to improve disease-free survival and overall survival, people 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 oesophago-gastric junctional cancer who are suitable for surgical resection. It aims to explore which intervention is optimal in terms of overall survival, disease-free survival and disease-related and treatment-related morbidity and mortality, and to determine the optimal timing of therapy in relation to surgery.

8.4.2 Description of clinical evidence

This review included evidence from 29 trials for 10 comparisons of different timing and choice of chemotherapy or chemoradiotherapy in relation to surgery for cancer of the oesophagus or gastro-oesophageal junctional cancer. If there was mixed population with gastric cancers, only data for subgroup of oesophageal or oesophago-gastric population were analysed. If the subgroup population were not able to be extracted and if more than one-third of the population were not oesophageal or oesophago-gastric junctional cancers, the studies were excluded. Studies with mainly Barret's dysplasia or gastric carcinoma were excluded from the review. Studies with prior chemotherapy or radiotherapy were also excluded. Details of the studies excluded can be found in excluded studies list.

The comparisons of interest and trials reporting on these comparisons are summarised below with references to studies being extracted. Please see clinical evidence table (Appendix F) for further details of the included studies.

1. Preoperative chemotherapy versus postoperative chemotherapy

a. Ando 2012/Hirao 2011 (extracted from Ando 2012 randomised controlled trials/RCT and Hirao 2011 RCT)

2. Preoperative chemotherapy versus surgery alone
   a. Baba 1998/Baba 2000 (extracted from Kidane 2015 systematic review/SR)
   b. Law 1997 (extracted from Kidane 2015 SR and Law 1997 RCT)
   c. MRC Allum 2002 (extracted from Kidane 2015 SR and MRC 2002 RCT)
   d. Nygaard 1992 (extracted from Kidane 2015 SR)
   e. Schlag 1992 (extracted from Kidane 2015 SR and Schlag 1992 RCT)
3. Postoperative chemotherapy versus surgery alone
   a. Ando 2003 (extracted from Ando 2003 RCT)
4. Perioperative chemotherapy versus preoperative chemotherapy
   a. Zhao 2015 (i) (extracted from Zhao 2015i RCT)
5. Perioperative chemotherapy versus postoperative chemotherapy
   a. Ancona 2001 (extracted from Ancona 2001 RCT)
6. Perioperative chemotherapy versus surgery alone
   a. Ychou 2011 (extracted from Ychou 2011 RCT)
   b. Kelsen 1998/Kelsen 2007 (extracted from Kidane 2015 RCT)
7. Preoperative chemoradiotherapy versus preoperative chemotherapy
   a. Klevebro 2016 (extracted from Klevebro 2016 RCT)
   b. Burmeister 2011 (extracted from Burmeister 2011 RCT)
8. Preoperative chemoradiotherapy versus surgery alone
   a. Apinop 1994 (extracted from Kumagai 2014 SR and Apinop 1994 RCT)
   b. Bagheri 2012 (extracted from Kumagai 2014 SR)
   c. Bass 2014 (extracted from Bass 2014 RCT)
   d. Bosset 1997 (extracted from Kumagai 2014 SR and Bosset 1997 RCT)
   e. Burmeister 2005 (extracted from Kumagai 2014 SR and Burmeister 2005 RCT)
   f. Lee 2004 (extracted from Kumagai 2014 SR and Lee 2004 RCT)
   g. Le Prise 1994 (extracted from Kumagai 2014 SR and Le Prise 1994 RCT)
   h. Lv 2010 (extracted from Kumagai 2014 SR and Lv2010 RCT)
   i. Mariette 2014/Robb 2015 (extracted from Mariette 2014 RCT and Robb 2015 RCT)
   j. Mashhadi 2015 (extracted from Mashhadi 2015 RCT)
   k. Natsugoe 2006 (extracted from Kumagai 2014 SR and Natsugoe 2006 RCT)
   l. Tepper 2008 (extracted from Kumagai 2014 SR and Tepper 2008 RCT)
   m. Van Hagen 2012/Shapiro 2015/Oppedijk 2014 (extracted from Kumagai 2014 SR, van Hagen 2012 RCT, Shapiro 2015 RCT and Oppedijk 2014 RCT)
   n. Zhao 2015 (ii)(extracted from Zhao 2015(ii)RCT)
9. Postoperative chemoradiotherapy versus postoperative chemotherapy
   a. Tachibana 2003 (extracted from Tachibana 2003 RCT)
10. Postoperative chemoradiotherapy versus surgery alone
   a. Lv2010 (extracted from Kumagai 2014 SR and Lv 2010 RCT)

Evidence from these are summarised in the clinical GRADE evidence profiles below. See also the study selection flow chart in Appendix K, forest plots in Appendix H, study evidence tables in Appendix F and exclusion list in Appendix J.

8.4.3 Summary of included studies

A summary of the studies that were included in this review are presented in Table 72 to Table 80.

8.4.3.1 Preoperative chemotherapy versus postoperative chemotherapy

Table 72: Summary of included studies: Preoperative chemotherapy versus postoperative chemotherapy

Study	Population	Intervention/Comparison	Outcomes
Ando 2012/ Hirao 2011 RCT; Japan; n=330	SCC thoracic oesophagus Age (median): 61 years Male: 60% N0 tumour: 34%	Pre-CT: Sx done within 5 weeks of CT Post-CT: Sx done 2-10 weeks after CT CT: cisplatin (80 mg/m^2) for 2 hours on day 1 and 5 fluorouracil (800 mg/m^2) on day 1 to 5, repeated twice every 3 weeks. Surgery: total or subtotal thoracic oesophagectomy and regional lymphadenectomy with curative intent through right or left thoracotomy	Disease free interval, Overall survival, R0 tumour resection rate, Treatment related mortality, Anastomotic leakage, Wound infections, Pulmonary complications, Cardiovascular complications

n=total number of patients
CT= chemotherapy; Pre-CT= Preoperative chemotherapy; Post-CT=Postoperative chemotherapy; RCT= randomised controlled trials; SCC=Squamous cell carcinoma; Sx=Surgery

Outcomes for tumour regression grade and health-related quality of life or patients' reported outcomes measures (PROMs) were unable to be extracted.

8.4.3.2 Preoperative chemotherapy versus surgery alone

Table 73: Summary of included studies: Preoperative chemotherapy versus surgery alone

Study	Population	Intervention/Comparison	Outcomes
Ancona 2001 RCT; Italy; n=96	100% SCC of oesophagus Age(mean): 58 years Male: 81%	CT: Cisplatin 100 mg/m^2 x 1 D x 2-3 cycles + 5-FU 1000 mg/m^2 x 1 D x 2-3 cycles Surgery: right thoractomy, abdomen, left neck with gastric tranposition, 2-field lymph nodes Post-CT and radiation were given as additive therapy for people with residual disease.	Overall survival, Anastomotic leakage, Cardiac complications, Pulmonary complications, Infectious complications, Postoperative mortality, R0 tumour resection rate
Baba 1998/Baba 2000 RCT; Japan; n=42	100% SCC	CT: Cisplatin 70 mg/m^2 x 1D x 2 cycles + 5-FU 700 mg/m^2 x 5 Ds x 2 cycles + Leucovorin 20 mg/m^2 x 5 Ds x 2 cycles Surgery: right thoracotomy, laparotomy, neck incision, gastric or colon interposition with 2-field or 3-field node dissections	Anastomotic leaks, Pulmonary complications

Study	Population	Intervention/Comparison	Outcomes
Law 1997 RCT; Hong Kong; n=147	100% SCC of thoracic oesophagus Age (mean) : 63.5 years Male: 85%	CT: Cisplatin 100 mg/m^2 x 1D x 2 cycles + 5-FU 500 mg/m^2 x 5Ds x 2 cycles Surgery: Abdominothoracic or transhiatal with gastric interposition and removal of adjacent nodes	Overall survival, Anastomotic leaks, Cardiac complications, Pulmonary complications, Infectious complications, Postoperative mortality, R0 tumour resection rate
MRC Allum 2002 RCT; UK; n=802	31% SCC, 66% Adenocarcinoma and 3% undifferentiated carcinoma of oesophagus Age(median): 63 years Male %: 75	CT: Cisplatin 80 mg/m^2 x 1D x 2 cycles + 5-FU 1000 mg/m^2 x 4 Ds x 2cycles Surgery: Oesophagectomy External beam radiotherapy was given irrespective of randomisation (25-32.5 Gy in 10 fractions).	Overall survival, Anastomotic leaks, Cardiac complications, Pulmonary complications, Infectious complications, Postoperative mortality, R0 tumour resection rate
Nygaard 1992 RCT; Scandinavia; n=106	100% SCC of oesophagus Age (median): 63 years Male: 71%	CT: Cisplatin 20 mg/m^2 x 5Ds x 2 cycles + Bleomycin 10mg/m^2 x 5Ds x 2 cycles Surgery: laparotomy and right thoracotomy with stomach interposition	Overall survival, Anastomotic leaks, Pulmonary complications, Postoperative mortality, R0 tumour resection rate
Schlag 1992 RCT; Germany; n=46	SCC of oesophagus, Age: 56.8 years Male: 89%	CT: Cisplatin 20 mg/m^2 for 5 days for 3 cycles + 5 FU 1000 mg/m^2 for 5 days for 3 cycles if responder after 1st cycle Surgery: Abdominothoracic or thoracoabdominocervical with gastric or colon interposition + 2-field lymph node resection	Overall survival, R0 tumour resection rate

n=total number of patients
CT= chemotherapy; D/Ds= day/days; 5 FU = 5-fluorouracil; RCT= randomised controlled trials; SCC=Squamous cell carcinoma

Outcomes for disease-free survival, tumour regression grade and health-related quality of life or patients' reported outcomes measures (PROMs) were unable to be extracted.

8.4.3.3 Postoperative chemotherapy versus surgery alone

Table 74: Summary of included studies: Postoperative chemotherapy versus surgery alone

Study	Population	Intervention/Comparison	Outcomes
Ando 2003 RCT; Japan; n=242	SCC thoracic oesophagus Stage IIA Age: 59 years Male: 90%	CT: cisplatin (80 mg/m^2) for 2 hours on day 1 and 5 FU (800 mg/m^2) on day 1 to 5, repeated twice every 3 weeks. Surgery: oesophagectomy via right thoracotomy	Disease free interval

n=total number of patients
CT= chemotherapy; 5 FU = 5-fluorouracil; RCT= randomised controlled trials; SCC=Squamous cell carcinoma

Outcomes for overall survival, treatment-related morbidity, treatment-related mortality, complete resection (R0) at surgery, tumour regression grade and health-related quality of life or patients' reported outcomes measures (PROMs) were unable to be extracted.

8.4.3.4 Perioperative chemotherapy versus preoperative chemotherapy

Table 75: Summary of included studies: Perioperative chemotherapy versus preoperative chemotherapy

Study	Population	Intervention/Comparison	Outcomes
Zhao 2015(i) RCT; China: n=346	SCC of oesophagus Age: 59 years Male: 86%	Both groups had surgery and two preoperative cycles of CT and peri-CT group had two additional postoperative cycles of CT. Surgery was scheduled within 2-4 weeks of second pre-CT cycle. Post-CTwas initiated within 5 weeks after surgery. CT: Each 3 week cycle consisted of paclitaxcel IV infusion (100 mg/m^2 on D1), Cisplatin (60 mg/m^2) IV on day 1 and 5 and 5-FU (700 mg/m^2) from day 1-5. Surgery: Oesophagectomy through left thoracotomy/transhiatal/Lewis-Ivor approach depending on the site of the tumour.	Overall survival; Relapse free survival

n=total number of patients

CT= chemotherapy; 5 FU = 5-fluorouracil; Peri-CT= Perioperative chemotherapy; Pre-CT= Preoperative chemotherapy; Post-CT= Postoperative chemotherapy; RCT= randomised controlled trials; SCC=Squamous cell carcinoma

Outcomes for treatment-related morbidity, treatment-related mortality, complete resection (R0) at surgery, tumour regression grade and health-related quality of life or patients' reported outcomes measures (PROMs) were unable to be extracted.

8.4.3.5 Perioperative chemotherapy versus surgery alone

Table 76: Summary of included studies: Perioperative chemotherapy versus surgery alone

Study	Population	Intervention/Comparison	Outcomes
Kelsen 1998/Kelsen 2007 RCT; USA and Canada; n=467	44% SCC, 51% Adenocarcinoma of oesophagus Age (mean): 61.5 years Male: 84%	CT: Cisplatin 100 mg/m^2 x 1D for 3 cycles + 5FU 1000 mg/m^{2}x 5Ds for 3 cycles (if responder , postop cisplatin 75 mg/m^2+ 5FU 1000 mg/m^2 for 2 cycles) Surgery: Abdominothoracic or thoracoabdominocervical or transhiatal with gastric or colon interposition) + radiation if positive margins. Surgery was done 2 to 4 weeks after third cycle completion of CT. Radiation was given if there was positive margin in either group.	Overall survival, Disease free survival, Postoperative mortality, R0 tumour resection rate
Ychou 2011 RCT; France; n=224	Adenocarcinoma of lower third of	CT: Each cycle involved 5 FU (800mg/m^2/day IV infusion x 5 Ds) and cisplatin (100 mg/m^2 x	Overall survival, Disease free survival, Any complications,

Study	Population	Intervention/Comparison	Outcomes
	oesophagus or GEJ or stomach Age (median): 63 years Male: 84%	1-hour infusion on every 28th day). A total of 6 CT cycles (2 or 3 pre-CT plus 3 or 4 post-CT) were given in peri-CT group. Surgery: complete excision of the tumour with an extended lymphadenectomy and was done 4 to 6 weeeks after last cycle completion of CT.	Postoperative mortality, R0 tumour resection rate

n=total number of patients
CT= chemotherapy; D/Ds= day/days; 5 FU = 5-fluorouracil; GEJ=gastrooesophageal junction; Peri-CT= Perioperative chemotherapy; Pre-CT=Preoperative chemotherapy; Post-CT= Postoperative chemotherapy; RCT= randomised controlled trials; SCC=Squamous cell carcinoma

Outcomes for tumour regression grade and health-related quality of life or patients' reported outcomes measures (PROMs) were unable to be extracted.

8.4.3.6 Preoperative chemoradiotherapy versus preoperative chemotherapy

Table 77: Summary of included studies: Preoperative chemoradiotherapy versus preoperative chemotherapy

Study	Population	Intervention/Comparison	Outcomes
Burmeister 2011 RCT; Australia; n=75	Adenocarcinoma of thoracic oesophagus or GEJ Age (median): 61 years Male: 87%	CT: 2 cycles - cisplatin 80 mg/m^2 on day 1 followed by a 96 hour infusion of 5 FU (1000 mg/m^2/d). The 2nd cycle started on day 21. RT: the second cycle started together with radiation (35 Gy in 15 fractions over 3 weeks) with the dose of 5FU reduced to 800 mg/m^2/d in CRT group. Surgery: resection of the primary tumor with enbloc resection of lymph nodes through Ivor-lewis or 3-stage thoracoscopic approach	Anastomotic leaks, Treatment-related mortality, Wound infection, Cardiac complications, , R0 Tumour resection rate, Tumour resection grade
Klevebro 2016; Norway and Sweden; n=181	28%SCC and 73% adenocarcinoma Age (median): 63 years Male: 83%	CT: 3 cycles of cisplatin, 100 mg/m^2 day 1 and fluorouracil 750 mg/m^2/24 hr, days 1-5; repeated cycle on every 21 days. RT: 40Gy (2 Gy/day in 20 fractions, 5 days a week) was given with chemotherapy cycles 2 and 3 (concurrent) in CRT group. Surgery: Ivor-Lewis procedure or McKeown procedure (if middle and upper thirds of oesophagus)	Overall survival, Progression-free survival, Anastomotic leaks, Treatment-related mortality, Cardiac complications, Any treatment-related complication R0 Tumour resection rate, Tumour resection grade

n=total number of patients
CT= chemotherapy; CRT= Chemoradiothearpy; 5 FU = 5-fluorouracil; GEJ= Gastrooesophageal junction; RCT= randomised controlled trials; RT=Radiotherapy; SCC=Squamous cell carcinoma

Outcomes for health-related quality of life or patients' reported outcomes measures (PROMs) were unable to be extracted.

8.4.3.7 Preoperative chemoradiotherapy versus surgery alone

Table 78: Summary of included studies: Preoperative chemoradiotherpy versus surgery alone

Study	Population	Intervention/Comparison	Outcomes
Apinop 1994 RCT; Thailand; n=69	100% SCC Age: 59.7 years Male: 78%	CRT: Cisplatin 100 mg/m^2 on days 1 and 29; 5 FU 1000 mg/m^2 per day on days 1-4 and 29-32 AND 40Gy, 2Gy per fraction over 4 weeks (concurrent) Surgery: Right thoracotomy and laparotomy and was done 4 weeks after completion of CT.	Overall survival, Anastomotic leak, Treatment-related mortality
Bagheri 2012 RCT; Iran; n=40	Unknown tumour type (AC or SCC)	CRT: "cisplatin and 5 FU based", 40 Gy over 4 weeks (Concurrent) Surgery: Not reported in details	Treatment-related mortality
Bass 2014 RCT; Ireland; n=211	46% SCC and 54% AC Age (median): 66 years Male: 63%	CRT: Cisplatin 60 mg/m^2 days 1 and 29; 5 FU 1000 mg/m^2 per day on days 1-4 and 29-32 AND 50.4 Gy, 1.8 Gy per fraction over 5.6 weeks (concurrent) Surgery: Left oesophgectomy+Laparotomy/Lweis-Tanner/Transhiatal/3-stage oesophagectomy	Overall survival
Bosset 1997 RCT; France; n=282	100% SCC Age: 56.7 years Male: 93%	CRT: Cisplatin 80 mg/m^2 0-2 days before each course of radiotherapy AND 37 Gy, 3.7Gy per fraction in two 1-week courses, separated by 2 weeks (sequential) Surgery: 2-stage or 3-stage oesophagectomy	Overall survival, Disease free survival, Any postoperative complication, R0 tumour resection rate, Treatment-related mortality
Burmeister 2005 RCT; Australia, New Zealand and Singapore; n=256	37% SCC Age: 61.5 years Male: 82%	CRT: Cisplatin 80 mg/m^2 on day 1; 5FU 800 mg/m^2 per day on days 1-4 AND 35 Gy in 15 fractions over 3 weeks (concurrent) Surgery: Not reported in details and radical lymphadenectomy was not mandatory	Overall survival, R0 tumour resection rate,
Lee 2004 RCT; Korea; n=101	100% SCC Age (median): 63 years Male: 92%	CRT: Cisplatin 60 mg/m^2 on days 1 and 22; 5 FU 1000mg/m^2 per day on days 2-5 AND 45.6 Gy, 1.2 Gy per fraction over 28 days (concurrent) Surgery: Two-stage or three-stage approach and en-bloc lymphadenectomy	Overall survival, Disease free survival, Any postoperative complication, R0 tumour resection rate, Treatment-related mortality
Le Prise 1994 RCT; France; n=86	100% SCC Age(median): 56 years	CRT: Cisplatin 100mg/m^2 on days 1 and 21; 5 FU 600 mg/m^2 per day on days 2-5 and 22-25	Anastomotic leak, Any postoperative complication, R0 tumour

	Male: 93%	AND 20Gy in 10 fractions over 12 days (sequential) Surgery: Not reported in details	resection rate, Treatment-related mortality
Lv 2010 RCT; China; n=160	100% SCC Age ≥ 60 years: 56 % Male: 64%	CRT: cisplatin 20 mg/m^2 on days 1-3 and 22-24, paclitaxel 135 mg/m^2 starting on days 1 and 22 of RT (40 Gy in 20 fractions over 4 weeks) (concurrent) Surgery: Right or Left oesophagectomy	Overall survival, Anastomotic leak, R0 tumour resection rate, Treatment-related mortality, Haemorrhage (>300 ml), Stenosis
Mariette 2014/ Robb 2015 RCT; France; n=195	70.3% SCC Age(median): 57.8 years Male: 86%	CRT: 2 cycles of 5 FU (800 mg/m^2 per 24 hours from days 1 to 4 and 29 to 32) and Cisplatin (75 mg/m^2 by infusion on day 1 or 2 and again on day 29 or 30) or (15 mg/m^2 from days 1 to 5 and 29 to 33) AND RT (45 Gy in 25 fractions over 5 weeks) (concurrent) Surgery: Not reported in details and was done 4 to 6 weeks after completion of CT or within 4 weeks of random assignment.	Overall survival, Disease free survival, Any postoperative complication, R0 tumour resection rate, Infection,
Mashhadi 2015 RCT; Iran; n=100	72%SCC Age: 55 years Male: 53%	CRT: Cisplatin (20 mg/m^2) and 5 FU (700 mg/m^2/infusion over 24 hours) AND 50 Gy RT (4000 cGy) (concurrent) Surgery: Transhiatal oesophagectomy	Anastomotic leak, Intraoperative blood loss,
Natsugoe 2006 RCT; Japan; n=45	100% SCC	CRT: Cisplatin 7 mg days 1-5, 8-12, 15-19 and 22-26; 5 FU 350 mg/day on days 1-28 AND 40 Gy, 2 Gy per fraction over 4 weeks (concurrent) Surgery: Not reported in details	Anastomotic leak, Treatment-related mortality
Tepper 2008 RCT; USA; n=56	SCC and AC	CRT: Cisplatin 60 mg/m^2 days 1 and 29; 5 FU 1000 mg/m^2 per day on days 1-4 and 29-32 AND a total of 50.4 Gy RT (1.8 Gy per fraction over 5.6 weeks) (concurrent) Surgery: Not reported in details	Overall survival, Anastomotic leak, Treatment-related mortality
van Hagen 2012/Shapiro 2015/Opped dijk 2014 RCT; Netherlands; n=368	23% SCC Age(median): 60 years Male: 78%	CRT: carboplatin area under curve 2 mg per ml per min and paclitaxel 50 mg/m^2 on day 1 weekly for 5 weeks AND 41.4 Gy, 1.8 Gy per fraction over 4.6 weeks (concurrent) Surgery: Transthoracic or Transhiatal oesophagectomy	Overall survival, Disease free survival, R0 tumour resection rate
Zhao 2015 (ii) RCT; China; n=76	Adenocarcinoma of GEJ Age(median): 59 years Male: 84%	CRT: Two cycles of Capecitabine (1000 mg/m^2 twice daily x days 1-14) and oxaliplatin (130 mg/m^2 IV infusion on day 1) before and 6 cycles after surgery AND a total of 45 Gy in 25 fractions over 5 weeks (concurrent)	R0 tumour resection rate,

		Surgery: proximal subtotal gastrectomy or total gastrectomy and subsequent LN dissection	

n=total number of patients
AC= Adenocarcinoma; CT= chemotherapy; D/Ds= day/days; CRT= Chemoradiothearpy; 5 FU = 5-fluorouracil; GEJ= Gastrooesophageal junction; Peri-CT= Perioperative chemotherapy; Pre-CT=Preoperative chemotherapy; Post-CT= Postoperative chemotherapy; RCT= randomised controlled trials; RT=Radiotherapy; SCC=Squamous cell carcinoma

Outcomes for tumour regression grade and health-related quality of life or patients' reported outcomes measures (PROMs) were unable to be extracted.

8.4.3.8 Postoperative chemoradiotherapy versus postoperative chemotherapy

Table 79: Summary of included studies: Postoperative chemoradiotherpay versus postoperative chemotherapy

Study	Population	Intervention/Comparison	Outcomes
Tachibana 2003 RCT; Japan; n=45	SCC of oesophagus Age < 60 years: 27 % Male: 91%	CT: Cisplatin (50 mg/m^2) on day 1 and 15 and 5 FU (300 mg/m^2) given daily for 5 weeks RT: A total of 45-50 Gy RT, 2 Gy/day 5 times per week for 4 to 5 weeks) Surgery: Right transthoracic subtotal oesophagectomy and cervical incision for oesophagogastrostomy and laparotomy	Overall survival

n=total number of patients
CT= chemotherapy; 5 FU = 5-fluorouracil; Post-CT= Postoperative chemotherapy; RCT= randomised controlled trials; SCC=Squamous cell carcinoma

Outcomes for disease-free survival, treatment-related morbidity, treatment-related mortality, complete resection (R0) at surgery, tumour regression grade and health-related quality of life or patients' reported outcomes measures (PROMs) were unable to be extracted.

8.4.3.9 Postoperative chemoradiotherapy versus surgery alone

Table 80: Summary of included studies: Postoperative chemoradiotherapy versus surgery alone

Study	Population	Intervention/Comparison	Outcomes
Lv 2010 RCT; China; n=160	100% SCC Age ≥ 60 years: 56 % Male: 64%	CRT: cisplatin 20 mg/m^2 on days 1-3 and 22-24, paclitaxel 135 mg/m^2 starting on days 1 and 22 of RT (40 Gy in 20 fractions over 4 weeks) (concurrent) Surgery: Right or Left oesophagectomy	Overall survival; Treatment-related mortality; Radical resection

n=total number of patients
CRT= chemoradiotherapy; RCT= randomised controlled trials; RT=radiotherapy; SCC=Squamous cell carcinoma

Outcomes for treatment-related morbidity, tumour regression grade and health-related quality of life or patients' reported outcomes measures (PROMs) were unable to be extracted.

8.4.4 Clinical evidence profiles

Subgroup analyses were performed according to type of histology of oesophageal cancer: squamous cell carcinoma (SCC), adenocarcinoma (AC) or mixed or unknown, type of chemotherapy (single drug, double drugs or triple drugs) and type of radiotherapy (≤40 Gy or >40Gy) where relevant.

The clinical evidence profiles for this review question to determine the optimal choice and timing of chemotherapy or chemoradiotherapy in relation to surgery for people with localised oesophageal or gastro-oesophageal junctional carcinoma are presented in Table 81 to Table 89.

8.4.4.1 Preoperative chemotherapy versus postoperative chemotherapy

Table 81: Summary clinical evidence profile. Preoperative chemotherapy versus postoperative chemotherapy

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk Postoperative CT	Corresponding risk Preoperative CT (95%CI)			
Overall survival (OS)	5 year OS 43%	5 year OS 54% (43% to 63%)	HR 0.73 (0.54 to 0.99)	330 (1 study)	low[1,2]
R0 tumour resection rate	910 per 1000	955 per 1000 (901 to 1000)	RR 1.05 (0.99 to 1.12)	330 (1 study)	moderate[1]
Progression free survival	5 year PFS 39%	5 year PFS 45% (34% to 55%)	HR 0.84 (0.63 to 1.12)	330 (1 study)	low[1,2]
Treatment related mortality	12 per 1000	7 per 1000 (1 to 71)	RR 0.53 (0.05 to 5.78)	315 (1 study)	very low[1,3]
Anastomotic leakage	148 per 1000	124 per 1000 (71 to 218)	RR 0.84 (0.48 to 1.47)	315 (1 study)	very low[1,3]
Wound infection	123 per 1000	105 per 1000 (57 to 194)	RR 0.85 (0.46 to 1.57)	315 (1 study)	very low[1,3]
Pulmonary complication	130 per 1000	157 per 1000 (91 to 270)	RR 1.21 (0.7 to 2.08)	315 (1 study)	very low[2,3]
Cardiovascular complications	19 per 1000	26 per 1000 (6 to 115)	RR 1.41 (0.32 to 6.21)	315 (1 study)	very low[1,3]

[1] *Unclear randomisation, allocation, concealment and blinding*
[2] *95%CI crossed 1 default minimally important difference (MID).*
[3] *95%CI crossed 2 MIDs.*

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk Postoperative CT	Corresponding ris k Preoperative CT (95%CI)			

95%CI=95% Confidence interval; CT=Chemotherapy; HR=Hazard ration;OS= Overall survival; RR=Relative Risk

8.4.4.2 Preoperative chemotherapy versus surgery alone

Table 82: Summary clinical evidence profile. Preoperative chemotherapy and surgery alone

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk Surgery alone	Corresponding risk Preoperative CT (95%CI)			
Overall survival (OS) (Histology subtype) - SCC	OS* 16%	OS* 10% (7% to 16%)	HR 0.83 (0.7 to 1)	378 (4 studies)	low[1,2]
Overall survival (OS) (Histology subtype) - Mixed	5 year OS 14%	5 year OS 19% (15% to 24%)	HR 0.84 (0.72 to 0.98)	802 (1 study)	low[1,2]
Overall survival (CT subtype) - Cisplatin+5-FU	OS* 16%	OS* 10% (8% to 14%)	HR 0.84 (0.74 to 0.95)	1182 (5 studies)	low[1,2]
Anastomotic leaks - SCC	47 per 1000	65 per 1000 (30 to 140)	RR 1.38 (0.64 to 2.99)	391 (4 studies)	very low[1,3]
Anastomotic leaks - Mixed	65 per 1000	58 per 1000 (34 to 99)	RR 0.89 (0.52 to 1.53)	802 (1 study)	very low[1,3]
Anastomotic leaks - Cisplatin+5-FU	59 per 1000	60 per 1000 (39 to 94)	RR 1.02 (0.66 to 1.59)	1193 (5 studies)	very low[1,3]
Cardiac complications - SCC	165 per 1000	172 per 1000 (101 to 293)	RR 1.04 (0.61 to 1.77)	243 (2 studies)	very low[1,3]
Cardiac complications - Mixed	37 per 1000	35 per 1000 (17 to 72)	RR 0.94 (0.46 to 1.92)	802 (1 study)	very low[1,3]
Cardiac complications - Cisplatin+5FU	67 per 1000	66 per 1000 (43 to 102)	RR 0.99 (0.65 to 1.53)	1045 (3 studies)	very low[1,3]
Pulmonary complications - SCC	260 per 1000	224 per 1000 (161 to 315)	RR 0.86 (0.62 to 1.21)	391 (4 studies)	very low[1,3]
Pulmonary complications - MIxed	144 per 1000	140 per 1000 (100 to 196)	RR 0.97 (0.69 to 1.36)	802 (1 study)	very low[1,3]
Pulmonary complications - Cisplatine+5FU	182 per 1000	167 per 1000 (131 to 213)	RR 0.92 (0.72 to 1.17)	1193 (5 studies)	low[1,2]

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk Surgery alone	Corresponding risk Preoperative CT (95%CI)			
Infectious complications - SCC	83 per 1000	57 per 1000 (22 to 145)	RR 0.69 (0.27 to 1.76)	243 (2 studies)	very low[1,3]
Infectious complications - Mixed	80 per 1000	53 per 1000 (31 to 89)	RR 0.66 (0.39 to 1.12)	802 (1 study)	low[1,2]
Infectious complications - Cisplatin+5FU	80 per 1000	54 per 1000 (34 to 85)	RR 0.67 (0.42 to 1.06)	1045 (3 studies)	low[1,2]
Postoperative mortality - SCC	76 per 1000	66 per 1000 (31 to 141)	RR 0.87 (0.41 to 1.85)	349 (3 studies)	very low[1,3]
Postoperative mortality - Mixed	100 per 1000	90 per 1000 (59 to 138)	RR 0.9 (0.59 to 1.39)	802 (1 study)	very low[1,3]
Postoperative mortality - Cisplatin+5-FU	92 per 1000	83 per 1000 (57 to 120)	RR 0.90 (0.62 to 1.30)	1151 (4 studies)	very low[1,3]
R0 tumour resection rate - SCC	308 per 1000	351 per 1000 (280 to 443)	RR 1.14 (0.91 to 1.44)	395 (4 studies)	low[1,2]
R0 tumour resection rate - Mixed	535 per 1000	583 per 1000 (513 to 658)	RR 1.09 (0.96 to 1.23)	802 (1 study)	moderate[1]
R0 tumour resection rate - Cisplain+5FU	461 per 1000	507 per 1000 (456 to 567)	RR 1.10 (0.99 to 1.23)	1197 (5 studies)	low[1,2]

[1] Unclear randomisation, allocation concealment and blinding
[2] 95%CI crossed 1 default MID.
[3] 95%CI crossed 2 default MIDs

95%CI=95% Confidence interval; CT= Chemotherapy; 5-FU = 5-Fluorouracil; HR=Hazard ration;OS= Overall survival; RR=Relative Risk; SCC=squamous cell carcinoma

**OS was calculated from survival rate at 5 years or, if it was less than 5 years, the survival rate from the last year available.*

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8.4.4.3 Postoperative chemotherapy versus surgery alone

Table 83: Summary clinical evidence profile. Postoperative chemotherapy versus sugery alone

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk Surgery alone	Corresponding risk Postoperative CT			
Disease free survival (DFS)	5 year DFS 45%	5 year DFS 55% (43% to 66%)	HR 0.75 (0.53 to 1.07)	242 (1 study)	low[1,2]

[1] *Unclear randomisation, allocation concealment and blinding*
[2] *95%CI crossed 1 default MID*
95%CI=95% Confidence interval; DFS=Disease free survival; HR=Hazard ratio

8.4.4.4 Perioperative chemotherapy versus preoperative chemotherapy

Table 84: Summary clinical evidence profile. Perioperative chemotherapy versus preoperative chemotherapy

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk Preoperative CT	Corresponding risk Perioperative CT			
Overall survival (OS)	5 year OS 22%	5 year OS 30% (22% to 39%)	HR 0.79 (0.62 to 1)	343 (1 study)	low[1,2]
Relapse free survival (RFS)	5 year RFS 19%	5 year RFS 36% (28% to 43%)	HR 0.62 (0.51 to 0.76)	343 (1 study)	low[1,2]

[1] *Unclear randomisation, allocation concealment and blinding*
[2] *95%CI crossed 1 default MID*
95%CI= 95% Confidence interval; CT=Chemotherapy; HR=Hazard ration; OS=Overall survival; RFS=Relapse free survival

8.4.4.5 Perioperative chemotherapy versus surgery alone

Table 85: Summary clinical evidence profile. Perioperative chemotherapy versus surgery alone

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk Surgery alone	Corresponding risk Perioperative CT			
Overall survival (OS)	5 year OS 22%	5 year OS 25% (21% to 29%)	HR 0.91 (0.81 to 1.03)	691 (2 studies)	moderate[1]
Overall survival - AC	5 year OS 24%	5 year OS 30% (25% to 35%)	HR 0.85 (0.74 to 0.98)	224 (1 study)	low[1,2]

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk Surgery alone	Corresponding risk Perioperative CT			
Overall survival - Mixed	5 year OS 20%	5 year OS 18% (12% to 25%)	HR 1.07 (0.87 to 1.32)	467 (1 study)	low[1,2]
Disease free survival (DFS)	5 year DFS 18%	5 year DFS 23% (18% to 29%)	HR 0.85 (0.72 to 1)	664 (2 studies)	very low[1,2,3]
Disease free survival - AC	5 year DFS 24%	5 year DFS 34% (23% to 45%)	HR 0.65 (0.48 to 0.89)	224 (1 study)	low[1,2]
Disease free survival - Mixed	5 year DFS 20%	5 year DFS 22% (16% to 29%)	HR 0.94 (0.77 to 1.13)	440 (1 study)	low[1,2]
Any complications - AC	189 per 1000	248 per 1000 (149 to 409)	RR 1.31 (0.79 to 2.16)	224 (1 study)	low[1,2]
Postoperative mortality	52 per 1000	43 per 1000 (22 to 85)	RR 0.83 (0.43 to 1.62)	691 (2 studies)	very low[1,4]
Postoperative mortality - AC	45 per 1000	44 per 1000 (13 to 149)	RR 0.98 (0.29 to 3.3)	224 (1 study)	very low[1,4]
Postoperative mortality - Mixed	56 per 1000	43 per 1000 (19 to 96)	RR 0.77 (0.35 to 1.73)	467 (1 study)	very low[1,4]
R0 tumour resection rate	626 per 1000	670 per 1000 (576 to 783)	RR 1.07 (0.92 to 1.25)	691 (2 studies)	very low[1,2,3]
R0 tumour resection rate - AC	730 per 1000	839 per 1000 (730 to 963)	RR 1.15 (1 to 1.32)	224 (1 study)	low[1,2]
R0 tumour resection rate - Mixed	577 per 1000	571 per 1000 (490 to 669)	RR 0.99 (0.85 to 1.16)	467 (1 study)	moderate[1]

[1] *Unclear randomisation, allocation concealment and blinding*
[2] *95%CI crossed 1 default MID*
[3] *I2=69%*
[4] *95%CI crossed 2 default MIDs*

AC= Adenocarcinoma; 95%CI= 95% Confidence interval; CT=Chemotherapy; DFS = Disease free survival; HR=Hazard ration; OS=Overall survival; RR=relative risk

8.4.4.6 Preoperative chemoradiotherapy versus preoperative chemotherapy

Table 86: Summary clinical evidence profile. Preoperative chemoradiotherapy versus preoperative chemotherapy

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk Preoperative Chemotherapy	Corresponding risk Preoperative Chemoradiotherapy			
Overall survival (OS) (Mixed)	3 year OS 49%	3 year OS 45% (30% to 59%)	HR 1.11 (0.74 to 1.67)	181 (1 study)	very low[1,2]
Post-operative complication: Anastomotic leak	71 per 1000	94 per 1000 (41 to 215)	RR 1.32 (0.58 to 3.03)	256 (2 studies)	very low[1,2]
Post-operative complication: Anastomotic leak - AC	56 per 1000	51 per 1000 (8 to 345)	RR 0.92 (0.14 to 6.21)	75 (1 study)	very low[1,2]
Post-operative complication: Anastomotic leak - Mixed	77 per 1000	111 per 1000 (45 to 279)	RR 1.44 (0.58 to 3.63)	181 (1 study)	very low[1,2]
Mortality	16 per 1000	40 per 1000 (8 to 200)	RR 2.53 (0.5 to 12.69)	256 (2 studies)	very low[1,2]
Mortality - AC	-	-	No event in either arm	75 (1 study)	low[1,4]
Mortality - Mixed	22 per 1000	56 per 1000 (11 to 279)	RR 2.53 (0.5 to 12.69)	181 (1 study)	very low[1,2]
Wound infection (AC)	28 per 1000	128 per 1000 (16 to 1000)	RR 4.62 (0.57 to 37.64)	75 (1 study)	very low[1,2]
R0 resection	738 per 1000	826 per 1000 (686 to 996)	RR 1.12 (0.93 to 1.35)	125 (2 studies)	low[1,3]
R0 resection - AC	806 per 1000	846 per 1000 (685 to 1000)	RR 1.05 (0.85 to 1.29)	75 (1 study)	low[1,3]
R0 resection - Mixed	640 per 1000	800 per 1000 (563 to 1000)	RR 1.25 (0.88 to 1.78)	50 (1 study)	low[1,3]
Cardiac complications	79 per 1000	106 per 1000 (50 to 227)	RR 1.35 (0.63 to 2.88)	256 (2 studies)	very low[1,2]
Cardiac complications - AC	167 per 1000	180 per 1000 (67 to 483)	RR 1.08 (0.4 to 2.9)	75 (1 study)	very low[1,2]
Cardiac complications - Mixed	44 per 1000	78 per 1000 (24 to 257)	RR 1.77 (0.54 to 5.84)	181 (1 study)	very low[1,2]
Poor tumour regression grade*	780 per 1000	514 per 1000 (382 to 702)	RR 0.66 (0.49 to 0.90)	256 (2 studies)	Very low[1,3,5]
Poor TRG* – AC	917 per 1000	697 per 1000	917 per 1000	697 per 1000	low[1,3]
Poor TRG* - Mixed	725 per 1000	413 per 1000 (312 to 544)	RR 0.57 (0.43, 0.75)	181 (1 study)	low[1,3]

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk Preoperative Chemotherapy	Corresponding risk Preoperative Chemoradiotherapy			
Treatment-related morbidity: Any complication (Mixed)	385 per 1000	465 per 1000 (331 to 658)	RR 1.21 (0.86 to 1.71)	181 (1 study)	low[1,3]

[1] *Unclear randomisation, allocation concealment and blinding*
[2] *95%CI crossed 2 default MID*
[3] *95%CI crossed 1 default MID*
[4] *no event in either arm*
[5] *I^2>50%*

AC= Adenocarcinoma; 95%CI= 95% Confidence interval; CT=Chemotherapy; HR=Hazard ration; OS=Overall survival; RR=relative risk; TRG=Tumour regression grade

- **Poor tumour regression grade was defined as tumour regression grade of more than 2 or more than 50% of tumour cells.*

8.4.4.7 Preoperative chemoradiotherapy versus surgery alone

Table 87: Summary clinical evidence profile. Preoperative chemoradiotherapy versus surgery alone

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk Surgery alone	Corresponding risk Preoperative chemoradiotherapy			
Post-operative complication: Anastomotic leak	39 per 1000	56 per 1000 (27 to 118)	RR 1.44 (0.69 to 3.01)	492 (6 studies)	very low[1,2]
Post-operative complication: Anastomotic leak - SCC	44 per 1000	55 per 1000 (25 to 120)	RR 1.26 (0.58 to 2.74)	440 (5 studies)	very low[1,2]
Post-operative complication: Anastomotic leak - Mixed	0 per 1000	0 per 1000 (0 to 0)	RR 5 (0.25 to 99.34)	52 (1 study)	very low[1,2]
Post-operative complication: Anastomotic leak - </= 40Gy RT	44 per 1000	55 per 1000 (25 to 120)	RR 1.26 (0.58 to 2.74)	440 (5 studies)	very low[1,2]
Post-operative complication: Anastomotic leak - >40Gy RT	0 per 1000	0 per 1000 (0 to 0)	RR 5 (0.25 to 99.34)	52 (1 study)	very low[1,2]
Any post-operative complication - SCC	310 per 1000	316 per 1000 (248 to 400)	RR 1.02 (0.8 to 1.29)	605 (4 studies)	low[1,3]

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk Surgery alone	Corresponding risk Preoperative chemoradiotherapy			
Any post-operative complication - Single drug CT	263 per 1000	326 per 1000 (226 to 470)	RR 1.24 (0.86 to 1.79)	275 (1 study)	low[1,3]
Any post-operative complication - Double drug CT	346 per 1000	305 per 1000 (225 to 416)	RR 0.88 (0.65 to 1.2)	330 (3 studies)	very low[1,2]
Any post-operative complication - </=40Gy RT	302 per 1000	347 per 1000 (253 to 468)	RR 1.15 (0.84 to 1.55)	352 (2 studies)	low[1,2]
Any post-operative complication - >40Gy RT	321 per 1000	273 per 1000 (186 to 401)	RR 0.85 (0.58 to 1.25)	253 (2 studies)	very low[1,2]
30-day mortality	31 per 1000	72 per 1000 (26 to 199)	RR 2.28 (0.82 to 6.34)	310 (3 studies)	low[1,3]
30-day mortality - SCC	29 per 1000	75 per 1000 (24 to 230)	RR 2.6 (0.85 to 8)	270 (2 studies)	low[1,3]
30-day mortality - Unknown	50 per 1000	50 per 1000 (4 to 745)	RR 1 (0.07 to 14.9)	40 (1 study)	very low[1,2]
30-day mortality - </=40Gy RT	57 per 1000	71 per 1000 (20 to 255)	RR 1.25 (0.35 to 4.46)	140 (2 studies)	very low[1,2]
30-day mortality - >40Gy RT	11 per 1000	74 per 1000 (9 to 602)	RR 6.59 (0.81 to 53.59)	170 (1 study)	very low[1,2]
Blood loss in surgery (ml) (SCC; double; <=40Gy))		The mean blood loss in surgery (ml) (scc; double; <=40gy)) in the intervention groups was 10 higher (1.92 to 18.08 higher)		100 (1 study)	low[1,4]
R0/T0 resection rate	594 per 1000	730 per 1000 (641 to 831)	RR 1.23 (1.08 to 1.4)	1359 (8 studies)	Very low[1,3,5]
R0/T0 resection rate - SCC	528 per 1000	623 per 1000 (496 to 781)	1.18 (0.94 to 1.48)	705 (5 studies)	low[1,3]
R0/T0 resection rate - AC	800 per 1000	992 per 1000 (872 to 1000)	1.24 (1.09 to 1.42)	76 (1 study)	low[1,3]
R0/T0 resection rate - Mixed	647 per 1000	867 per 1000 (802 to 938)	1.34 (1.24 to 1.45)	578 (2 studies)	low[1,3]
R0/T0 resection rate - Single drug CT	0 per 1000	0 per 1000 (0 to 0)	49.6 (4.8 to 512.16)	206 (1 study)	moderate[1]

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk Surgery alone	Corresponding risk Preoperative chemoradiotherapy			
R0/T0 resection rate - Double drug CT	688 per 1000	833 per 1000 (750 to 915)	1.21 (1.09 to 1.33)	1153 (7 studies)	very low[1,3,5]
R0/T0 resection rate - </=40Gy RT	404 per 1000	602 per 1000 (408 to 877)	1.49 (1.01 to 2.17)	708 (4 studies)	very low[1,3,6]
R0/T0 resection rate - >40Gy RT	790 per 1000	924 per 1000 (822 to 1000)	1.17 (1.04 to 1.32)	651 (4 studies)	very low[1,3,6]
Treatment-related mortality	39 per 1000	79 per 1000 (45 to 139)	RR 2.03 (1.16 to 3.55)	827 (8 studies)	low[1,3]
Treatment-related mortality - SCC	38 per 1000	83 per 1000 (46 to 150)	RR 2.17 (1.2 to 3.91)	733 (6 studies)	low[1,3]
Treatment-related mortality - Mixed	38 per 1000	36 per 1000 (2 to 542)	RR 0.93 (0.06 to 14.09)	54 (1 study)	very low[1,2]
Treatment-related mortality - Unknown	50 per 1000	50 per 1000 (4 to 745)	RR 1 (0.07 to 14.9)	40 (1 study)	very low[1,2]
Treatment-related mortality - Single drug CT	36 per 1000	127 per 1000 (49 to 332)	RR 3.47 (1.33 to 9.09)	279 (1 study)	moderate[1]
Treatment-related mortality - Double drug CT	40 per 1000	52 per 1000 (25 to 107)	RR 1.28 (0.61 to 2.66)	548 (7 studies)	low[2]
Treatment-related mortality - </=40Gy RT	42 per 1000	88 per 1000 (49 to 159)	RR 2.11 (1.17 to 3.82)	674 (6 studies)	low[1,3]
Treatment-related mortality - >40Gy RT	27 per 1000	38 per 1000 (6 to 221)	RR 1.4 (0.24 to 8.16)	153 (2 studies)	low[1,3]
Intraoperative treatment-related morbidity: Haemorrhage (>300 mL) (SCC; Double; </=40Gy)	25 per 1000	100 per 1000 (22 to 457)	RR 4 (0.88 to 18.26)	160 (1 study)	low[1,3]
Overall survival (OS)	OS* 27%	OS* 38% (33% to 42%)	HR 0.75 (0.67 to 0.84)	1688 (9 studies)	very low[1,3,5]
OS - SCC	OS* 26%	OS* 35%(29% to 40%)	HR 0.79 (0.68 to 0.92)	988 (7 studies)	low[1,3]
OS - AC	5 year OS 28%	5 year OS 44% (35% to 53%)	HR 0.64 (0.5 to 0.82)	388 (2 studies)	low[1,3]
OS - Mixed	5 year OS (21%)	5 year OS 31% (21% to 40%)	HR 0.76 (0.59 to 0.99)	312 (2 studies)	very low[1,3,6]
OS - Single drug CT	5 year OS 22%	5 year OS 23% (14% to 34%)	HR 0.96 (0.72 to 1.28)	282 (1 study)	very low[1,2]
OS - Double drug CT	OS* 25%	OS* 38% (34% to 43%)	HR 0.69 (0.61 to 0.78)	1413 (8 studies)	low[1,3,5]

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk Surgery alone	Corresponding risk Preoperative chemoradiotherapy			
OS - </=40Gy RT	5 year OS 20%	5 year OS 29% (24% to 34%)	HR 0.77 (0.67 to 0.89)	978 (5 studies)	low[1,3]
OS - >40Gy RT	OS* 36%	OS* 52% (45% to 58%)	HR 0.65 (0.54 to 0.79)	717 (4 studies)	very low[1,3,5]
Disease free survival (DFS)	DFS* 34%	DFS 46%(40% to 52%)	HR 0.77 (0.63 to 0.95)	577 (3 studies)	low[1,3]
Disease free survival - SCC	DFS* 34%	DFS 46%(40% to 52%)	HR 0.77 (0.63 to 0.95)	577 (3 studies)	low[1,3]
Disease free survival - Single drug CT	5 year DFS 24%	5 year DFS 40% (29% to 51%)	HR 0.64 (0.47 to 0.86)	282 (1 study)	low[1,3]
Disease free survival - Double drug CT	DFS* 31%	DFS* 33% (23% to 44%)	HR 0.94 (0.70 to 1.25)	295 (2 studies)	very low[1,2]
Disease free survival - </=40Gy RT	5 year DFS 24%	5 year DFS 40% (29% to 51%)	HR 0.64 (0.47 to 0.86)	282 (1 study)	low[1,3]
Disease free survival - >40Gy RT	DFS* 31%	DFS* 33% (23% to 44%)	HR 0.94 (0.70 to 1.25)	295 (2 studies)	very low[1,2]
Post-operative complication: stenosis (SCC; Double CT; </=40Gy RT)	12 per 1000	25 per 1000 (2 to 270)	RR 2 (0.19 to 21.62)	160 (1 study)	very low[1,2]

[1] Unclear randomisation, allocation concealment and blinding
[2] 95%CI crossed 2 default MIDs
[3] 95%CI crossed 1 default MID
[4] Default MID: +/-7.5ml; 95% CI crossed 1 MID
[5] I^2>50%
[6] I^2>80%

AC= Adenocarcinoma; 95%CI= 95% Confidence interval; CT=Chemotherapy; CRT=Chemoradiotherapy; DFS=Disease free survival; HR=Hazard ration; OS=Overall survival; RR=relative risk; RT=Radiotherapy; SCC=Squamous cell carcinoma

**OS/DFS was calculated from survival rate at 5 years or, if it was less than 5 years, the survival rate from the last year available.*

8.4.4.8 Postoperative chemoradiotherapy versus postoperative chemotherapy

Table 88: Summary clinical evidence profile. Postoperative chemoradiotherapy versus postoperative chemotherapy

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk Postoperative CT	Corresponding risk Postoperative CRT			
Overall survival	5-years OS 38%	5-years OS 37% (9% to 67%)	HR 1.02 (0.42 to 2.44)	45 (1 study)	very low[1,2]

[1] Unclear randomisation, allocation concealment and blinding
[2] 95%CI crossed 2 default MIDs
95%CI=95% Confidence interval; CRT=Chemoradiotherapy; CT=Chemotherapy; HR=Hazard ratio

8.4.4.9 Postoperative chemoradiotherapy versus surgery alone

Table 89: Summary clinical evidence profile. Postoperative chemoradiotherapy versus surgery alone

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk Postoperative CRT	Corresponding risk Surgery alone			
Number going for radical resection	800 per 1000	784 per 1000 (664 to 920)	RR 0.98 (0.83 to 1.15)	158 (1 study)	moderate[1]
Treatment related mortality	0 per 1000	0 per 1000	No event in either arm	158 (1 study)	low[1,3]
Overall survival	10- year OS 6%	16% (7% to 27%)	HR 0.66 (0.47 to 0.94)	158 (1 study)	low[1,2]

[1] Unclear randomisation, allocation concealment and blinding
[2] 95%CI crossed 1 default MID.
[3]no event in either arm

95%CI=95% Confidence interval; CRT=Chemoradiotherapy;HR=Hazard ratio; RR=relative risk; OS=overall survival

8.4.5 Evidence statements

8.4.5.1 Preoperative chemotherapy versus postoperative chemotherapy

8.4.5.1.1 Overall survival

Low quality evidence from 1 RCT with 330 people with oesophageal and gastro-oesophageal junctional cancer suitable for surgical treatment showed that there was a clinically significant beneficial effect of preoperative chemotherapy compared with postoperative chemotherapy for overall survival.

8.4.5.1.2 Progression-free survival

Low quality evidence from 1 RCT with 330 people with oesophageal and gastro-oesophageal junctional cancer suitable for surgical treatment reported that there was no clinically significant difference between preoperative chemotherapy and postoperative chemotherapy for progression free survival.

8.4.5.1.3 Treatment related morbidity: anastomotic leakage, wound infection, pulmonary complication and cardiovascular complication

Very low quality evidence from 1 RCT with 315 people with oesophageal and gastro-oesophageal junctional cancer suitable for surgical treatment provided the evidence that there was no clinically significant difference between preoperative chemotherapy and postoperative chemotherapy for anastomotic leakage, wound infections, pulmonary complications and cardiovascular complications.

8.4.5.1.4 Treatment related mortality

Very low quality evidence from 1 RCT with 315 people with oesophageal and gastro-oesophageal junctional cancer suitable for surgical treatment showed that there was no clinically significant difference between preoperative chemotherapy and postoperative chemotherapy for treatment-related mortality.

8.4.5.1.5 R0 tumour resection rate

Moderate quality evidence from 1 RCT with 330 people with oesophageal and gastro-oesophageal junctional cancer suitable for surgical treatment showed that there was no clinically significant difference between preoperative chemotherapy and postoperative chemotherapy for R0 tumour resection rate.

8.4.5.2 Preoperative chemotherapy versus surgery alone

8.4.5.2.1 Overall survival

Low quality evidence from 5 RCTs with 1182 people with oesophageal and gastro-oesophageal junctional cancer suitable for surgical treatment showed that there was a clinically significant beneficial effect of preoperative chemotherapy (cisplatin plus 5-fluorouracil) compared with surgery alone for overall survival.

Subgroup analysis according to type of histology of oesophageal cancer:

SCC: Low quality evidence from 4 RCTs with 378 people with oesophageal and gastro-oesophageal junctional cancer suitable for surgical treatment provided the evidence that there may be a clinically significant beneficial effect of preoperative chemotherapy (cisplatin plus 5-fluorouracil) compared with surgery alone for overall survival, however, there is an uncertainty around the estimate.

Mixed: Low quality evidence from 1 RCT with 804 people with oesophageal and gastro-oesophageal junctional cancer suitable for surgical treatment reported that there was a clinically significant beneficial effect of preoperative chemotherapy (cisplatin plus 5-fluorouracil) compared with surgery alone for overall survival.

8.4.5.2.2 Treatment-related morbidity: anastomotic leakage, cardiac complications, pulmonary complications and infectious complications

Very low to low quality evidence from 5 RCTs with 1193 people with oesophageal and gastro-oesophageal junctional cancer suitable for surgical treatment showed that there was no clinically significant difference between preoperative chemotherapy (cisplatin plus 5-fluorouracil) and surgery alone for anastomotic leakage and pulmonary complications.

Very low to low quality evidence from 3 RCTs with 1045 people with oesophageal and gastro-oesophageal junctional cancers suitable for surgical treatment showed that there was no clinically significant difference between preoperative chemotherapy (cisplatin plus 5-fluorouracil) and surgery alone for cardiac complications and infectious complications.

Subgroup analysis according to type of histology of oesophageal cancer:

Very low to low quality evidence suggested that there was no subgroup difference between preoperative chemotherapy (cisplatin plus 5-fluorouracil) and surgery alone for anastomotic leakage, pulmonary complications, cardiac complications and infectious complications.

8.4.5.2.3 Postoperative mortality

Very low quality evidence from 4 RCTs with 1151 people with oesophageal and gastro-oesophageal junctional cancer suitable for surgical treatment showed that there was no clinically significant difference between preoperative chemotherapy (cisplatin plus 5-fluorouracil) compared with surgery alone for postoperative mortality.

Subgroup analysis according to type of histology of oesophageal cancer:

Very low quality evidence suggested that there was no subgroup difference between preoperative chemotherapy (cisplatin plus 5-fluorouracil) and surgery alone for postoperative mortality.

8.4.5.2.4 R0 tumour resection rate

Low quality evidence from 5 RCTs with 1197 people with oesophageal and gastro-oesophageal junctional cancers suitable for surgical treatment showed that there may be a clinically significant beneficial effect of preoperative chemotherapy (cisplatin plus 5-fluorouracil) compared with surgery alone for R0 tumour resection rate, however, there is an uncertainty around the estimate.

Subgroup analysis according to type of histology of oesophageal cancer:

Low to moderate quality evidence suggested that there was no subgroup difference between preoperative chemotherapy (cisplatin plus 5-fluorouracil) and surgery alone for R0 tumour resection rate.

8.4.5.3 Postoperative chemotherapy versus surgery alone

8.4.5.3.1 Disease free survival

Low quality evidence from 1 RCT with 242 people with oesophageal and gastro-oesophageal junctional cancer suitable for surgical treatment showed that there was no clinically significant difference between postoperative chemotherapy (cisplatin plus 5-fluorouracil) and surgery alone for disease free survival.

8.4.5.4 Perioperative chemotherapy versus preoperative chemotherapy

8.4.5.4.1 Overall survival

Low quality evidence from 1 RCT with 343 people with oesophageal and gastro-oesophageal junctional cancer suitable for surgical treatment showed that there may be a clinically significant beneficial effect of perioperative chemotherapy (paclitaxel, cisplatin and 5-fluorouracil, PCF) compared with preoperative chemotherapy (PCF) alone for overall survival, however there is uncertainty around the estimate.

8.4.5.4.2 Relapse free survival

Low quality evidence from 1 RCT with 343 people with oesophageal and gastro-oesophageal junctional cancer suitable for surgical treatment showed that there is a clinically significant beneficial effect of perioperative chemotherapy (paclitaxel, cisplatin and 5-fluorouracil, PCF) compared with preoperative chemotherapy (PCF) alone for relapse free survival.

8.4.5.5 Perioperative chemotherapy versus surgery alone

8.4.5.5.1 Overall survival

Moderate quality evidence from 2 RCTs with 691 people with oesophageal and gastro-oesophageal junctional cancer suitable for surgical treatment showed that there may be clinically significant beneficial effect of perioperative chemotherapy (cisplatin plus 5-fluorouracil) compared with surgery alone for overall survival, however there is uncertainty around the estimate.

Subgroup analysis according to type of histology of oesophageal cancer:

AC: Low quality evidence from 1 RCT with 224 people with oesophageal and gastro-oesophageal junctional cancer suitable for surgical treatment showed that there is a clinically significant beneficial effect of perioperative chemotherapy (cisplatin plus 5-fluorouracil) compared with surgery alone for overall survival.

Mixed: Low quality evidence from 1 RCT with 467 people with oesophageal and gastro-oesophageal junctional cancer suitable for surgical treatment showed that there is no clinically significant difference between perioperative chemotherapy (cisplatin plus 5-fluorouracil) and surgery alone for overall survival.

8.4.5.5.2 Disease free survival

Very low quality evidence from 2 RCTs with 664 people with oesophageal and gastro-oesophageal junctional cancer suitable for surgical treatment provided the evidence that there may be a clinically significant beneficial effect of perioperative chemotherapy (cisplatin plus 5-fluorouracil) compared with surgery alone for disease free survival, however there is uncertainty around the estimate.

Subgroup analysis according to type of histology of oesophageal cancer:

AC: Low quality evidence from 1 RCT with 224 people with oesophageal and gastro-oesophageal junctional cancer suitable for surgical treatment provided the evidence that there may be a clinically significant beneficial effect of perioperative chemotherapy (cisplatin plus 5-fluorouracil) compared with surgery alone for disease free survival.

Mixed: Low quality evidence from 1 RCT with 440 people with oesophageal and gastro-oesophageal junctional cancer suitable for surgical treatment provided the evidence that there is no clinically significant beneficial effect of perioperative chemotherapy (cisplatin plus 5-fluorouracil) and surgery alone for disease free survival.

8.4.5.5.3 Any complications

Low quality evidence from 1 RCT with 224 people with oesophageal and gastro-oesophageal junctional cancer suitable for surgical treatment provided the evidence that there is no clinically significant beneficial effect of perioperative chemotherapy (cisplatin plus 5-fluorouracil) and surgery alone for any complications.

8.4.5.5.4 Postoperative mortality

Very low quality evidence from 2 RCTs with 691 people with oesophageal and gastro-oesophageal junctional cancer suitable for surgical treatment reported that there is no clinically significant beneficial effect of perioperative chemotherapy (Cisplatin plus 5-fluorouracil) and surgery alone for postoperative mortality.

Subgroup analysis according to type of histology of oesophageal cancer:

Very low quality evidence suggested that there was no subgroup difference between perioperative chemotherapy (cisplatin plus 5-fluorouracil) and surgery alone for postoperative mortality.

8.4.5.5.5 R0 tumour resection rate

Very low quality evidence from 2 RCTs with 691 people with oesophageal and gastro-oesophageal junctional cancer suitable for surgical treatment reported that there is no clinically significant difference between perioperative chemotherapy (cisplatin plus 5-fluorouracil) and surgery alone for R0 tumour resection rate.

Subgroup analysis according to type of histology of oesophageal cancer:

AC: Low quality evidence from 1 RCT with 224 people with oesophageal and gastro-oesophageal junctional cancer suitable for surgical treatment reported that there may be a clinically significant beneficial effect of perioperative chemotherapy (cisplatin plus 5-fluorouracil) and surgery alone for R0 tumour resection rate.

Mixed: Moderate quality evidence from 1 RCT with 467 people with oesophageal and gastro-oesophageal junctional cancer suitable for surgical treatment reported that there is no clinically significant beneficial effect of perioperative chemotherapy (cisplatin plus 5-fluorouracil) and surgery alone for R0 tumour resection rate.

8.4.5.6 Preoperative chemoradiotherapy versus preoperative chemotherapy

8.4.5.6.1 Overall survival

Very low quality evidence from 1 RCT with 181 people with oesophageal and gastro-oesophageal junctional cancer suitable for surgical treatment showed that there is no clinically significant difference between preoperative chemoradiotherapy and preoperative chemotherapy for overall survival.

8.4.5.6.2 Treatment-related morbidity

Low quality evidence from 1 RCT with 181 people with oesophageal and gastro-oesophageal junctional cancer suitable for surgical treatment showed that there is no clinically significant difference between preoperative chemoradiotherapy and preoperative chemotherapy for any treatment-related morbidity.

Very quality evidence from 2 RCTs with 256 people with oesophageal and gastro-oesophageal junctional cancer suitable for surgical treatment showed that there is no clinically significant difference between preoperative chemoradiotherapy and preoperative chemotherapy for anastomotic leakage and cardiac complications.

Subgroup analysis according to type of histology of oesophageal cancer:

Very low quality evidence suggested that there was no subgroup difference between preoperative chemoradiotherapy and preoperative chemotherapy for anastomotic leakage and cardiac complications.

8.4.5.6.3 Treatment-related mortality

Very low quality evidence from 2 RCTs with 256 people with oesophageal and gastro-oesophageal junctional cancer suitable for surgical treatment showed that there is no clinically significant difference between preoperative chemoradiotherapy and preoperative chemotherapy for treatment-related mortality.

Subgroup analysis according to type of histology of oesophageal cancer:

Low to very low quality evidence suggested that there was no subgroup difference between preoperative chemoradiotherapy and preoperative chemotherapy for treatment-related mortality.

8.4.5.6.4 R0 tumour resection rate

Low quality evidence from 2 RCTs with 125 people with oesophageal and gastro-oesophageal junctional cancer suitable for surgical treatment showed that there is no clinically significant difference between preoperative chemoradiotherapy and preoperative chemotherapy for R0 tumour resection rate.

Subgroup analysis according to type of histology of oesophageal cancer:

Low quality evidence suggested that there was no subgroup difference between preoperative chemoradiotherapy and preoperative chemotherapy for R0 tumour resection rate.

8.4.5.6.5 Tumour regression grade (TRG): Poor TRG (TRG >2 or < 50% cells response to adjuvant therapy)

Very low quality evidence from 2 RCTs with 256 people with oesophageal and gastro-oesophageal junctional cancer suitable for surgical treatment showed that there is a clinically significant beneficial effect of preoperative chemoradiotherapy compared with preoperative chemotherapy for poor tumour regression grade.

Subgroup analysis according to type of histology of oesophageal cancer:

AC: Low quality evidence from 2 RCTs with 75 people with oesophageal and gastro-oesophageal junctional cancer suitable for surgical treatment showed that there is a clinically significant beneficial effect of preoperative chemoradiotherapy compared with preoperative chemotherapy for poor tumour regression grade.

Mixed: Low quality evidence from 1 RCT with 181 people with oesophageal and gastro-oesophageal junctional cancer suitable for surgical treatment showed that there is a clinically significant beneficial effect of preoperative chemoradiotherapy compared with preoperative chemotherapy for TRG 1.

8.4.5.7 Preoperative chemoradiotherapy versus surgery alone

8.4.5.7.1 Overall survival

Very low quality evidence from 9 RCTs with 1688 people with oesophageal and gastro-oesophageal junctional cancer suitable for surgical treatment showed that there is a clinically significant beneficial effect of preoperative chemoradiotherapy compared with surgery alone for overall survival.

Subgroup analysis according to type of histology of oesophageal cancer:

SCC: Low quality evidence from 7 RCTs with 988 people with oesophageal and gastro-oesophageal junctional cancer suitable for surgical treatment showed that there is a clinically significant beneficial effect of preoperative chemoradiotherapy compared with surgery alone for overall survival.

AC: Low quality evidence from 2 RCTs with 388 people with oesophageal and gastro-oesophageal junctional cancer suitable for surgical treatment showed that there is a clinically significant beneficial effect of preoperative chemoradiotherapy compared with surgery alone for overall survival.

Mixed: Very low quality evidence from 2 RCTs with 312 people with oesophageal and gastro-oesophageal junctional cancer suitable for surgical treatment showed that there is a

clinically significant beneficial effect of preoperative chemoradiotherapy compared with surgery alone for overall survival.

Subgroup analysis according to type of chemotherapy:

Single drug: Very low quality evidence from 1 RCT with 282 people with oesophageal and gastro-oesophageal junctional cancer suitable for surgical treatment showed that there is no clinically significant difference between preoperative chemoradiotherapy and surgery alone for overall survival.

Double drug: Low quality evidence from 8 RCTs with 1413 people with oesophageal and gastro-oesophageal junctional cancer suitable for surgical treatment showed that there is a clinically significant beneficial effect of preoperative chemoradiotherapy compared with surgery alone for overall survival.

Subgroup analysis according to type of radiotherapy:

≤ 40Gy radiotherapy: Low quality evidence from 5 RCTs with 978 people with oesophageal and gastro-oesophageal junctional cancer suitable for surgical treatment showed that there is a clinically significant beneficial effect of preoperative chemoradiotherapy compared with surgery alone for overall survival.

>40Gy radiotherapy: Very low quality evidence from 4 RCTs with 717 people with oesophageal and gastro-oesophageal junctional cancer suitable for surgical treatment showed that there is a clinically significant beneficial effect of preoperative chemoradiotherapy compared with surgery alone for overall survival.

8.4.5.7.2 Disease-free survival in SCC

Low quality evidence from 3 RCTs with 577 people with oesophageal and gastro-oesophageal junctional cancer (SCC subtype) suitable for surgical treatment showed that there is a clinically significant beneficial effect of preoperative chemoradiotherapy compared with surgery alone for disease free survival.

Subgroup analysis according to type of chemotherapy:

Single drug: Low quality evidence from 1 RCT with 282 people with oesophageal and gastro-oesophageal junctional cancer suitable for surgical treatment showed that there is a clinically significant beneficial effect of preoperative chemoradiotherapy and surgery alone for disease free survival.

Double drug: Very low quality evidence from 2 RCTs with 295 people with oesophageal and gastro-oesophageal junctional cancer suitable for surgical treatment showed that there is no clinically significant difference between preoperative chemoradiotherapy and surgery alone for disease free survival.

Subgroup analysis according to type of radiotherapy:

≤ 40Gy radiotherapy: Low quality evidence from 1 RCT with 282 people with oesophageal and gastro-oesophageal junctional cancer suitable for surgical treatment showed that there is a clinically significant beneficial effect of preoperative chemoradiotherapy compared with surgery alone for disease free survival.

>40Gy radiotherapy: Very low quality evidence from 2 RCTs with 295 people with oesophageal and gastro-oesophageal junctional cancer suitable for surgical treatment showed that there is no clinically significant difference between preoperative chemoradiotherapy and surgery alone for disease free survival.

8.4.5.7.3 Treatment-related morbidity in SCC

- **Any complication**

Low quality evidence from 4 RCTs with 605 people with oesophageal and gastro-oesophageal junctional cancer suitable for surgical treatment showed that there is no clinically significant difference between preoperative chemoradiotherapy and surgery alone for any complication.

Subgroup analysis according to type of chemotherapy or type of radiotherapy:

Very low to low quality evidence suggested that there was no subgroup difference between preoperative chemoradiotherapy and surgery alone for any complication.

- **Anastomotic leak**

Very low quality evidence from 6 RCTs with 492 people with oesophageal and gastro-oesophageal junctional cancer suitable for surgical treatment showed that there is no clinically significant difference between preoperative chemoradiotherapy and surgery alone for anastomotic leak.

Subgroup analysis according to type of histology or type of radiotherapy of oesophageal cancer:

Very low quality evidence suggested that there was no subgroup difference between preoperative chemoradiotherapy and surgery alone for anastomotic leak.

- **Haemorrhage (>300 mL)**

Low quality evidence from 1 RCT with 160 people with oesophageal and gastro-oesophageal junctional cancer (SCC subtype) suitable for surgical treatment showed that there is no clinically significant difference between preoperative chemoradiotherapy (double drug chemotherapy, ≤ 40Gy radiotherapy) and surgery alone for intraoperative haemorrhage of more than 300 ml.

- **Stenosis**

Very low quality evidence from 1 RCT with 160 people with oesophageal and gastro-oesophageal junctional cancer (SCC subtype) suitable for surgical treatment showed that there is no clinically significant difference between preoperative chemoradiotherapy (double drug chemotherapy, ≤ 40Gy radiotherapy) and surgery alone for stenosis complication.

8.4.5.7.4 Treatment-related mortality

Low quality evidence from 8 RCTs with 827 people with oesophageal and gastro-oesophageal junctional cancer suitable for surgical treatment showed that there is a clinically significant harmful effect of preoperative chemoradiotherapy compared with surgery alone for treatment related mortality.

Subgroup analysis according to type of histology of oesophageal cancer:

SCC: Low quality evidence from 6 RCTs with 733 people with oesophageal and gastro-oesophageal junctional cancer (SCC subtype) suitable for surgical treatment showed that there is a clinically significant harmful effect of preoperative chemoradiotherapy compared with surgery alone for treatment related mortality.

Mixed: Very low quality evidence from 1 RCT with 54 people with oesophageal and gastro-oesophageal junctional cancer (mixed subtype) suitable for surgical treatment showed that there is no clinically significant difference between preoperative chemoradiotherapy and surgery alone for treatment related mortality.

Unknown: Very low quality evidence from 1 RCT with 40 people with oesophageal and gastro-oesophageal junctional cancer (unknown subtype) suitable for surgical treatment showed that there is no clinically significant difference between preoperative chemoradiotherapy and surgery alone for treatment related mortality.

Subgroup analysis according to type of chemotherapy:

Single drug: Moderate quality evidence from 1 RCT with 279 people with oesophageal and gastro-oesophageal junctional cancer suitable for surgical treatment showed that there is a clinically significant harmful effect of preoperative chemoradiotherapy (single drug chemotherapy) compared with surgery alone for treatment related mortality.

Double drug: Low quality evidence from 7 RCTs with 548 people with oesophageal and gastro-oesophageal junctional cancer suitable for surgical treatment showed that there is no clinically significant difference between preoperative chemoradiotherapy (double drug chemotherapy) and surgery alone for treatment related mortality.

Subgroup analysis according to type of radiotherapy:

≤ 40Gy radiotherapy: Low quality evidence from 6 RCTs with 674 people with oesophageal and gastro-oesophageal junctional cancer suitable for surgical treatment showed that there is a clinically significant harmful effect of preoperative chemoradiotherapy (≤ 40Gy radiotherapy) compared with surgery alone for treatment related mortality.

>40Gy radiotherapy: Low quality evidence from 2 RCTs with 153 people with oesophageal and gastro-oesophageal junctional cancer suitable for surgical treatment showed that there is no clinically significant difference between preoperative chemoradiotherapy (>40Gy radiotherapy) and surgery alone for treatment related mortality.

8.4.5.7.5 R0/T0 tumour resection rate

Very low quality evidence from 8 RCTs with 1359 people with oesophageal and gastro-oesophageal junctional cancer suitable for surgical treatment showed that there is a clinically significant beneficial effect of preoperative chemoradiotherapy compared with surgery alone for R0 tumour resection rate.

Subgroup analysis according to type of histology of oesophageal cancer:

SCC: Low quality evidence from 5 RCTs with 705 people with oesophageal and gastro-oesophageal junctional cancer (SCC subtype) suitable for surgical treatment showed that there is no clinically significant difference between preoperative chemoradiotherapy and surgery alone for R0 tumour resection rate.

AC: Low quality evidence from 1 RCT with 76 people with oesophageal and gastro-oesophageal junctional cancer (AC subtype) suitable for surgical treatment showed that there is a clinically significant beneficial effect of preoperative chemoradiotherapy compared with surgery alone for R0 tumour resection rate.

Mixed: Low quality evidence from 2 RCTs with 578 people with oesophageal and gastro-oesophageal junctional cancer (mixed subtype) suitable for surgical treatment showed that there is a clinically significant beneficial effect of preoperative chemoradiotherapy compared with surgery alone for R0 tumour resection rate.

Subgroup analysis according to type of chemotherapy:

Single drug: Moderate quality evidence from 1 RCT with 206 people with oesophageal and gastro-oesophageal junctional cancer suitable for surgical treatment showed that there is a clinically significant beneficial effect of preoperative chemoradiotherapy (single drug chemotherapy) compared with surgery alone for R0 tumour resection rate.

Double drug: Very low quality evidence from 7 RCTs with 1153 people with oesophageal and gastro-oesophageal junctional cancer suitable for surgical treatment showed that there is a clinically significant beneficial effect of preoperative chemoradiotherapy (double drug chemotherapy) compared with surgery alone for R0 tumour resection rate.

Subgroup analysis according to type of radiotherapy:

≤ 40Gy radiotherapy: Very low quality evidence from 4 RCTs with 708 people with oesophageal and gastro-oesophageal junctional cancer suitable for surgical treatment showed that there is a clinically significant beneficial effect of preoperative chemoradiotherapy (≤ 40Gy radiotherapy) compared with surgery alone for R0 tumour resection rate.

>40Gy radiotherapy: Very low quality evidence from 4 RCTs with 651 people with oesophageal and gastro-oesophageal junctional cancer suitable for surgical treatment showed that there is a clinically significant beneficial effect of preoperative chemoradiotherapy (> 40Gy radiotherapy) compared with surgery alone for R0 tumour resection rate.

8.4.5.8 Postoperative chemoradiotherapy versus postoperative chemotherapy

8.4.5.8.1 Overall survival

Very low quality evidence from 1 RCT with 45 people with oesophageal and gastro-oesophageal junctional cancer suitable for surgical treatment showed that there is no clinically significant difference between postoperative chemoradiotherapy and postoperative chemotherapy for overall survival.

8.4.5.9 Postoperative chemoradiotherapy versus surgery alone

8.4.5.9.1 Overall survival

Low quality evidence from 1 RCT with 158 people with oesophageal and gastro-oesophageal junctional cancer suitable for surgical treatment showed that there is a clinically significant beneficial effect of postoperative chemoradiotherapy versus surgery alone for overall survival.

8.4.5.9.2 Treatment-related mortality

Low quality evidence from 1 RCT with 158 people with oesophageal and gastro-oesophageal junctional cancer suitable for surgical treatment showed that there is no event of treatment-related death in either postoperative chemoradiotherapy arm or surgery alone arm.

8.4.5.9.3 Radical resection rate

Moderate quality evidence from 1 RCT with 158 people with oesophageal and gastro-oesophageal junctional cancer suitable for surgical treatment reported that there is no clinically significant difference between postoperative chemoradiotherapy and surgery alone for radical resection rate.

8.4.6 Economic evidence

A systematic review of the economic literature was conducted but no relevant studies were identified which were applicable to this review question. Economic modelling was not undertaken for this question because other topics were agreed as higher priorities for economic evaluation.

8.4.7 Evidence to recommendations

8.4.7.1 Relative value placed on outcomes considered

As the purpose of this evidence review was to determine the treatment required to prevent recurrence of disease after surgery, and so to improve overall survival and disease-free

survival the Committee considered the critical outcomes for this review were overall survival and disease-free survival. In addition, treatment-related morbidity was a critical outcome as it would help define the benefits versus harms of treatments and so help in the selection of treatments. Other outcomes that were considered important were treatment-related mortality, complete resection at surgery and tumour regression grade. The Committee had included patient-reported outcome measures and health-related quality of life as less important outcomes to be considered, but no outcomes of this type were found in the evidence review.

8.4.7.2 Quality of evidence

The evidence for this review was taken from 29 randomised controlled trials and the quality was assessed using GRADE. The evidence ranged from very low to moderate in quality. In addition, the Committee noted that some of the earlier trials included in the analysis were poorly powered, were likely to have poorer surgical techniques, and were likely to have less rigorous quality assurance of radiotherapy. They also used chemotherapy and chemoradiotherapy schedules which were no longer considered current standard of practice. In reviewing the evidence the Committee therefore gave more weight to more recent studies. The Committee also recognised the heterogenous nature of the trials in respect of tumour locations and pathological sub-types which further made interpretation of the evidence difficult.

8.4.7.3 Consideration of clinical benefits and harms

The Committee discussed the evidence available for chemotherapy and chemoradiotherapy used before, after or before and after surgery to assess the relative benefits and harms of using these treatments in addition to surgery to prevent recuurence.

Compared to surgery alone, there was evidence for preoperative chemotherapy, postoperative chemotherapy, perioperative chemotherapy and preoperative chemoradiotherapy:

Preoperative chemotherapy led to improved overall survival compared to surgery alone, with no difference in treatment-related morbidity or postoperative mortality. For postoperative chemotherapy compared to surgery alone, there was no difference in disease-free survival. For the comparison of perioperative chemotherapy compared to surgery alone there was no difference in overall survival rates. However, perioperative chemotherapy was more effective compared to preoperative chemotherapy in terms of relapse-free survival. Based on this evidence the Committee considered that it may be beneficial to use preoperative chemotherapy, or perioperative chemotherapy to improve outcomes in this group of patients.

The comparison of preoperative chemoradiotherapy with surgery alone, showed improved overall survival, disease-free survival, and no difference in complications such as anastamotic leak or stenosis, but worse rates of treatment-related mortality. However, the Committee discussed that the benefit of preoperative chemoradiotherapy, and the increase seen in overall survival and disease-free survival seen in the total population and in the adenocarcinoma and squamouse cell carcinoma sub-groups, may outweigh the possible harms.

The choice of which treatment offered the greatest benefits was also evaluated by comparing different regimens with each other:

Preoperative chemoradiotherapy showed no difference in overall survival, treatment-related morbidity or treatment-related mortality compared to preoperative chemotherapy.

Postoperative chemoradiotherapy showed similar survival rates to postoperative chemotherapy and compared to surgery alone, with similar rates of treatment-related mortality compared to surgery alone.

The Committee discussed theses treatment options available and identified that, compared to surgery alone, preoperative chemotherapy, perioperative chemotherapy and preoperative chemoradiotherapy could be expected to improved outcomes, although there may be some increases in morbidity or mortality and that the choice should therefore be discussed with the patient.

The Committee agreed that the recommendations to use any of these options was likely to lead to improved disease-free outcomes and overall survival and to reduce variation of practice. The use of chemotherapy or chemoradiotherapy was associated with some treatment-related morbidity and mortality. However, the Committee decided that the increase in survival and disease-free survival outweighed the potential increase in side-effects seen with therapy.

8.4.7.4 Consideration of economic benefits and harms

A systematic review of the economic literature was conducted but no relevant studies were identified which were applicable to this review question.

The economic implications of this topic were considered but not thought to be substantial as the recommendations reflect current clinical practice. However, there is known to be some variation in practice and it is possible that the recommendations could increase the use of chemoradiotherapy or chemotherapy in some centres. If this is the case, then the increased costs associated with chemotherapy or chemoradiotherapy would be expected to be cost-effective as the benefits in terms of overall and disease-free survival would be expected to translate into QALY gains.

8.4.7.5 Other considerations

The Committee agreed that their recommendation reflected current clinical practice and so would not lead to a change in practice for many centres. Due to the lack of evidence for the comparison of perioperative chemotherapy versus preoperative chemoradiotherapy, the Committee discussed making a research recommendation, but were aware of an ongoing clinical trial already that was investigating this comparison and therefore decided not to make a research recommendation that would duplicate this ongoing work. The Committee fully supported random allocation to this ongoing trial.

8.4.7.6 Key conclusions

The Committee considered a number of comparisons available in the evidence review. For the comparison of chemotherapy before surgery compared to surgery alone there was a benefit for overall survival with no significant difference in the reported treatment-related morbidity and therefore this treatment option was recommended by the Committee.

For the comparison of peri-operative chemotherapy compared to surgery alone there was evidence for increased overall survival and disease-free survival with no significant difference in the rates of complications and post-operative mortality so this treatment option was also recommended by the Committee.

For the comparison of pre-operative chemoradiotherapy compared to surgery alone there was evidence for increased overall and disease-free survival, although treatment-related mortality was higher in the pre-operative chemotherapy group. There was no significant difference between the groups for other measures of treatment-related morbidity. The Committee therefore included this treatment option in their recommendations.

For comparison of post-operative chemotherapy compared to surgery alone, there was no difference in disease-free survival and so this treatment was not recommended by the Committee. For the comparison of post-operative chemoradiotherapy compared to surgery alone there was an increase overall survival but the population in this comparison was mainly

a squamous cell carcinoma population and therefore not felt to be robust enough evidence on which to base a recommendation for the population in question.

8.4.8 Recommendations

Localised oesophageal and gastro-oesophageal junctional adenocarcinoma

27. For people with localised oesophageal and gastro-oesophageal junctional adenocarcinoma (excluding T1N0 tumours) who are going to have surgical resection, offer a choice of:

- chemotherapy, before or before and after surgery or
- chemoradiotherapy, before surgery.

Make the choice after discussing the benefits, risks and treatment consequences of each option with the person and those important to them (as appropriate).

8.5 Gastric Cancer

Review question: What is the optimal choice of chemotherapy or chemoradiotherapy in relation to surgical treatment for gastric cancer?

8.5.1 Introduction

For people with localised gastric cancer radical surgery is often recommended. As a sole modality of treatment surgery is associated with a high rate of loco-regional or metastatic recurrence. In order to improve disease-free survival and overall survival, people 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 gastric cancer who are suitable for surgical resection. It also aims to explore which intervention is optimal in terms of overall survival, disease-free survival and disease related and treatment related morbidity and mortality, as well as the optimal timing of therapy in relation to surgery.

8.5.2 Description of clinical evidence

The Committee considered the following comparisons were of utmost importance for this review:

- Postoperative chemoradiotherapy vs postoperative chemotherapy
- Postoperative chemotherapy vs surgery alone
- Preoperative chemotherapy vs surgery alone
- Postoperative chemoradiotherapy vs surgery alone
- Perioperative chemotherapy vs preoperative chemotherapy
- Perioperative chemotherapy vs surgery alone
- Preoperative chemotherapy drug A vs preoperative chemotherapy drug B (comparing chemo drug types)
- Perioperative chemotherapy drug A vs drug B
- Perioperative chemotherapy versus Perioperative chemoradiotherapy
- Intraperitoneal chemotherapy vs surgery alone
- Intraperitoneal chemotherapy vs systemic chemotherapy

There was no randomised controlled trials (RCT) evidence for perioperative chemotherapy compared with preoperative chemotherapy, preoperative chemotherapy A compared with preoperative chemotherapy B as well as perioperative chemotherapy A compared with perioperative chemotherapy B.

There were a total of 19 studies included in this review for nine different comparisons (Bamias 2010; Bang 2012; Bouche 2005; Chipponi 2004; Cunningham 2006; Diaz-Nieto 2013; Di Costanzo 2008; Feingold 2017; Imano 2010; Kodera 2017; Leong 2017; Macdonald 2001; Miyashiro 2011; Schuhmacher 2009; Verheij 2016; Wu 2007; Yan 2007; Yu 2012; Zhou 2016). Studies comparing chemotherapeutic drugs which were not included in the protocol were excluded mostly. However, mitomycin was included if it was given intraperitoneally as this was usual route of administration of this drug. It should also be noted that intraperitoneal chemotherapy other than intraoperative onset of administration were not considered. Details of the studies excluded can be found in the excluded studies list.

The comparisons of interest and trials reporting on these comparisons are summarised below with references to studies being extracted:

1. Postoperative chemoradiotherapy versus postoperative chemotherapy
    - Bamias 2010 (Bamias 2010 RCT)
    - Kim 2012 (Zhou 2016 SR)
    - Kwon 2010 (Zhou 2016 SR)
    - Lee 2012 (Zhou 2016 SR)
    - Yu 2012 (Yu 2012 RCT)
    - Zhu 2012 (Zhou 2016 SR)
2. Post-operative chemotherapy versus surgery alone
    - Bang 2012 (Bang 2012 RCT)
    - Bouche 2005 (Diaz-Nieto 2013 SR; Bouche 2005 RCT)
    - Chipponi 2004 (Diaz-Nieto 2013 SR; Chipponi 2004 RCT)
    - DiConstanzo 2008 (Diaz-Nieto 2013 SR)
    - Neri 2001 (Diaz-Nieto 2013 SR)
3. Preoperative chemotherapy versus surgery alone
    - Imano 2010 (Imano 2010 RCT)
    - Kobayashi 2000 (Wu 2007 SR)
    - Schuhmacher 2009 (Schuhmacher 2009 RCT)
    - Wang 2000 (Wu 2007 SR)
4. Post-op chemoradiotherapy vs surgery alone
    - MacDonald 2001 (MacDonald 2001 RCT)
5. Perioperative chemotherapy vs surgery alone
    - Cunningham 2006 (Cunningham 2006 RCT)
6. Perioperative chemotherapy vs Perioperative chemoradiotherapy (Postoperative radiation only)
    - Verheij 2016 RCT (Verheij 2016 RCT)
7. Perioperative chemotherapy vs Perioperative chemoradiotherapy (Preoperative radiation only)
    - Leong 2017 RCT (Leong 2017 RCT)
8. Intraperitoneal chemotherapy vs surgery alone
    - Fujimura 1994 RCT (Feingold 2017 SR)
    - Hamazoe 1994 RCT (Feingold 2017 SR)

- Miyashiro 2011 RCT (Feingold 2017 SR; Miyashiro 2005 RCT)
- Takahashi 1995 RCT (Feingold 2017 SR)
- Yonemura 2001 RCT(Feingold 2017 SR)

9. Intraperitoneal chemotherapy vs systemic chemotherapy
    - Kodera 2017 (Kodera 2017 RCT)
    - Fujimoto 1999 RCT(Feingold 2017 SR)
    - Ikeguchi 1995 RCT (Feingold 2017 SR)
    - Kang 2014 RCT(Feingold 2017 SR)
    - Shimoyama 1999 RCT(Feingold 2017 SR)

Evidence from these are summarised in the clinical GRADE evidence profiles below (Table 98 to Table 106). See also the study selection flow chart in Appendix K, forest plots in Appendix H, study evidence tables in Appendix F and exclusion list in Appendix J.

8.5.3 Summary of included studies

A summary of the studies that were included in this review are presented in Table 90 to Table 97.

Table 90: Summary of included studies: Postoperative chemoradiotherapy versus postoperative chemotherapy

Study	Population	Intervention / Comparison	Outcomes
Bamias 2010 n=143; Greece; RCT	Median age(range) in years = 63 (32-79) Male%=70%	Post-op CT (doxetaxel with cisplatin) vs post-op CRT (doxetaxcel with cisplatin+RT)	Overall survival; Disease-free survival; Treatment-related morbidities
Yu 2012; n=68; China; RCT	Mean age=57 years Male%= 63% All T3/T4 stage	Post-op CT (5-FU+THF for 5 cycles) vs post-op concurrent CRT (5FU+THF+RT)	Overall survival; Disease-free survival; Adverse events
Zhou 2016; K=4 (Kim 2012 RCT, Kwon 2010 RCT, Lee 2012 RCT, Zhu 2012 RCT); n=960; SR	Age in range=46-59 years Male%=69%	Post-op CT vs post-op CRT	Overall survival; Disease-free survival; Adverse events

K=total number of trials; n= total number of participants; CRT=chemoradiotherapy; CT=chemotherapy; 5-FU=5-Fluorouracil; IV=intravenous; Post-op=post-operative; Pre-op=pre-operative; RCT=randomised controlled trials; RT=radiotherapy; SR=systematic review; THF=tetrahydrofolate

Outcomes for treatment-related mortality, tumour regression grade, health-related quality of life or patients' reported outcomes measures (PROMs) and complete resection (R0) at surgery were unable to be extracted.

Table 91: Summary of included studies: Postoperative chemotherapy versus surgery alone

Study	Population	Intervention / Comparison	Outcomes
Bang 2012 n=1035; Korea and China; RCT	Mean age±SD in years= 56±11.4 Male%=71% T stage= II-IIIb	Post-op CT (capeticitabine+oxaliplatin) vs surgery alone	Overall survival; Disease-free survival; Adverse events
Bouche 2005*; n=260; France; RCT	Median age±SE in years=61±0.9 Male%=71.5% T stage 3/4 = 77.3% Histology: Well-differentiated= 47.7%; poorly differentiated= 23.9%; signet-ring cell= 24.2%; Other=4.2%	Post-op CT (5-FU+cisplatin) vs surgery alone	Overall survival; Disease-free survival; Treatment-related mortality
*Chipponi 2004; N=205; France; RCT	Mean age: 61 years Male %: 66 (+) ve LN = 83	Post-op CT (leucovorin+5-FU) vs Surgery alone	Treatment-related mortality
Diaz-Nieto 2013; K=4 (Bouche 2005 RCT*; Chipponi 2004 RCT*; DiConstanzo 2008 RCT; Neri 2001 RCT); n=878; Europe; SR	Mean age= 61 years	Post-op CT vs surgery alone	Overall survival; Disease-free survival; Adverse events

K=total number of trials; n= total number of participants; CT=chemotherapy; 5-FU=5-Fluorouracil; IV=intravenous; Post-op=post-operative; RCT=randomised controlled trials; SR=systematic review;
**Outcomes for Bouche 2005 RCT and Chipponi 2004 RCT were extracted mainly from Diaz-Nieto 2013 SR with additional relevant data from Bouche 2005 RCT and Chipponi 2004 RCT, respectively.*

Outcomes for tumour regression grade, health-related quality of life or patients' reported outcomes measures (PROMs) and complete resection (R0) at surgery were unable to be extracted.

Table 92: Summary of included studies: Preoperative chemotherapy versus surgery alone

Study	Population	Intervention / Comparison	Outcomes
Imano 2010; n=63; Japan; RCT	Mean age range = 58.4-61.5 years	Pre-op CT(5-FU alone or cisplatin alone or 5FU+cisplatin) vs surgery alone	Overall survival; Operative complications
Schuhmacher 2009; n=144; Europe; RCT	Median age (range) in years= 57(26-70) Male%=69.4% T3%:T4%=93.8%:6.3%	Pre-op CT (cisplatin and fluorouracil) vs surgery alone	Overall survival; Disease-free survival; Operative complications; Post-op mortality; R0 resection rate
Wu 2007;K=2 (Kobayashi 2000	Male%=73%	Pre-op CT vs surgery alone	Death at the end of follow-up; R0 resection; Grade II-IV toxicity

Study	Population	Intervention / Comparison	Outcomes
RCT, Wang 2000 RCT); n=121; Asian; SR			

K=total number of trials; n= total number of participants; CT=chemotherapy; 5-FU=5-Fluorouracil; IV=intravenous; Pre-op=pre-operative; RCT=randomised controlled trials; SR=systematic review; SE=standard error

Outcomes for tumour regression grade and health-related quality of life or patients' reported outcomes measures (PROMs) were unable to be extracted.

Table 93: Summary of included studies: Postoperative chemoradiotherapy versus surgery alone

Study	Population	Intervention / Comparison	Outcomes
Macdonald 2001; n=556; USA; RCT	Median age= 60 years Male%=72%	Post-op CRT(fluorouracil+ leucovorin+RT) vs surgery alone	Overall survival; Relapse-free survival; Adverse events

K=total number of trials; n= total number of participants; CRT=chemoradiotherapy; Post-op=post-operative; RCT=randomised controlled trials; RT=radiotherapy;

Outcomes for disease-free survival, treatment-related mortality, tumour regression grade, health-related quality of life or patients' reported outcomes measures (PROMs) and complete resection (R0) at surgery were unable to be extracted.

Table 94: Summary of included studies: Perioperative chemotherapy versus surgery alone

Study	Population	Intervention / Comparison	Outcomes
Cunningham 2006; n=503; UK and others; RCT	Median age= 62 years Male%=79%	Peri-op CT (epirubicin+ cisplatin+ fluorouracil) vs surgery alone	Overall survival; Progression-free survival; Adverse events; Curative resection

K=total number of trials; n= total number of participants; CT=chemotherapy; Peri-op=peri-operative; RCT=randomised controlled trials

Outcomes for disease free survival, treatment-related mortality, tumour regression grade and health-related quality of life or patients' reported outcomes measures (PROMs) were unable to be extracted.

Table 95: Summary of included studies: Perioperative chemotherapy versus perioperative chemoradiotherapy

Study	Population	Intervention / Comparison	Outcomes
Leong 2017; n=120; Australia, New Zealand, Europe and Canada; RCT	Male%=76% Age≥70=27% Tstage 3/4=83%	Perioperative chemoradiotherapy (radiation given preoperatively) (epirubicin, cisplatin and 5FU) vs peri-operative chemotherapy alone	Operative complications, haematological toxicity, gastrointestinal toxicity

Study	Population	Intervention / Comparison	Outcomes
Verheij 2016; n=788; Netherlands, Sweden and Denmark; RCT	Stage Ib to Iva resectable gastric cancer Age (median): 61 years Male%: 70	Peri-op CRT (radiation given postoperatively) vs Peri-op CT(3 cycles of ECC/EOC) 3 courses of ECC/EOC was given in both groups preoperatively. After surgery, CT group received another 3 courses of ECC/EOC whereas CRT group received 45Gy RT in 25 fractions combined with weekly cisplatin and daily capecitabine.	5-year survival, Haematological toxicity (grade 3 or higher), Gastrointestinal toxicity (grade 3 or higher)

K=total number of trials; n= total number of participants; CRT=chemoradiotherapy; CT=chemotherapy; ECC/EOC=epirubicin, cisplatin/oxaliplatin and capecitabine; 5-FU=5-Fluorouracil; Peri-op=peri-operative; RCT=randomised controlled trials; RT=radiotherapy

Outcomes for disease free survival, treatment-related mortality, tumour regression grade, health-related quality of life or patients' reported outcomes measures (PROMs) and complete resection (R0) at surgery were unable to be extracted.

Table 96: Summary of included studies: Intraperitoneal chemotherapy versus surgery alone

Study	Population	Intervention / Comparison	Outcomes
Miyashiro 2011*; n=268; Japan; RCT	Median age (range)= 58(23-75) years Male%=68%	IP CT (cisplatin+5FU) vs surgery alone	Overall survival; Perioperative mortality
Feingold 2017; K=5 (Fujimura 1994 RCT; Hamazoe 1994 RCT; Miyashiro 2011 RCT*; Takahashi 1995 RCT; Yonemura 2001 RCT); n=660; Eastern countries; SR	Gastric cancer without established peritoneal carcinomatosis and without neoadjuvant systemic chemotherapy T4 % = 36	Intraperitoneal CT vs Surgery alone	Overall survival, Disease free survival

K=total number of trials; n= total number of participants; CT=chemotherapy; 5-FU=5-Fluorouracil; IP=intraperitoneal; RCT=randomised controlled trials; SR=systematic review

** Outcomes for Miyashiro 2011 RCT were extracted mainly from Feingold 2017 SR with additional relevant data from Miyashiro 2011 RCT.*

Outcomes for treatment-related morbidities, tumour regression grade, health-related quality of life or patients' reported outcomes measures (PROMs) and complete resection (R0) at surgery were unable to be extracted.

Table 97: Summary of included studies: Intraperitoneal chemotherapy versus systemic chemotherapy

Study	Population	Intervention / Comparison	Outcomes
Kodera 2017; n=86; Japan; RCT	Age median (range)= 67(26-86) years Male%=72% Large cell type3/4 %= 77%	Post-op IP CT vs post-op systemic (IV) CT	Treatment-related mortality, Treatment-related morbidity
Feingold 2017; K=4 (Fujimoto 1999 RCT, Ikeguchi 1999 RCT, Kang 2014 RCT, Shimoyama 1999 RCT); n=899; Eastern countries; SR	Gastric cancer without established peritoneal carcinomatosis and without neoadjuvant systemic chemotherapy T4 % = 36	Intraperitoneal CT vs IV CT + Surgery	Overall survival, Disease free survival

K=total number of trials; n= total number of participants; CT=chemotherapy; 5-FU=5-Fluorouracil; IP=intraperitoneal; IV=intravenous; RCT=randomised controlled trials; SR=systematic review

Outcomes for tumour regression grade, health-related quality of life or patients' reported outcomes measures (PROMs) and complete resection (R0) at surgery were unable to be extracted.

8.5.4 Clinical evidence profile

The clinical evidence profiles for this review question (choice of chemotherapy or chemoradiotherapy in relation to surgical treatment for gastric cancer) are presented in Table 98 to Table 106.

Table 98: Summary clinical evidence profile. Post-operative chemoradiotherapy versus post-operative chemotherapy

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)
	Assumed risk post-op chemotherapy	Corresponding risk post-op chemoradiotherapy			
Overall survival (OS)	5-year OS 52%	5 year OS 55% (49% to 61%)	HR 0.91 (0.76 to 1.09)	1171 (6 studies)	Low[1,2,3,4,5,6]
Disease-free Survival (DFS)	5-year DFS 52%	5 year DFS 61% (56% to 66%)	HR 0.75 (0.63 to 0.88)	1171 (6 studies)	Low[1,2,3,4,5,6]
Neutropenia : Grade 3-4	245 per 1000	306 per 1000 (255 to 370)	RR 1.25 (1.04 to 1.51)	1079 (5 studies)	Low[1,2,3,4,5,6]

[1] *Bamias 2010: unclear random sequence generation*
[2] *Yu 2012: unclear random sequence generation and allocation concealment*

[3] Kwon 2010: unclear random sequence generation and allocation concealment
[4] Zhu 2012: unclear random sequence generation and allocation concealment
[5] Lee 2012: unclear random sequence generation and allocation concealment
[6] Effect estimate crosses 1 default MIDs

95%CI=95% confidence interval; OS=Overall survival; DFS=Disease free survival; RR=relative risk; HR=Hazard ratio; D

Table 99: Summary clinical evidence profile. Post-operative chemotherapy versus surgery alone

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)
	Assumed risk surgery alone	Corresponding risk post-op chemotherapy			
Overall survival (OS)	5-year OS 39%	5-year OS 50% (43% to 56%)	HR 0.74 (0.61 to 0.9)	1913 (5 studies)	Low[1,2,3,4,5]
Disease-free survival (DFS)	5-year DFS 46%	5-year DFS 57% (51% to 62%)	HR 0.73 (0.62 to 0.87)	1571 (3 studies)	Low[1,3,6]
Any toxicity: Grade 3-4	63 per 1000	562 per 1000 (394 to 802)	RR 8.96 (6.28 to 12.78)	974 (1 study)	High
Neutropenia: Grade 3-4	2 per 1000	216 per 1000 (30 to 1000)	RR 103.12 (14.45 to 735.8)	974 (1 study)	High
Treatment-related mortality	3 per 1000	12 per 1000 (3 to 54)	RR 4.22 (0.91 to 19.59)	714 (3 studies)	Low[2,3,4]

[1] Bouche 2005: unclear random sequence generation and allocation concealment
[2] Chipponi 2004: unclear allocation concealment
[3] Di Costanzo 2008: high risk of attrition bias, unclear random sequence generation and allocation concealment,
[4] Neri 2001: unclear random sequence generation and allocation concealment
[5] I-squared statistic > 50%
[67] HR crosses one default MID
95%CI=95% Confidence interval; OS=Overall survival; DFS=Disease free survival; RR=relative risk; HR=Hazard ratio;

Table 100: Summary clinical evidence profile. Pre-operative chemothrapy versus surgery alone

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)
	Assumed risk surgery alone	Corresponding risk pre-operative chemotherapy			
Overall survival (OS)	5-year OS 48%	5-year OS 54% (37% to 68%)	HR 0.84 (0.53 to 1.35)	144 (1 study)	Very low[1,2]
Progression-free survival(PFS)	5-year PFS 38%	5-year PFS 48% (32% to 62%)	HR 0.76 (0.5 to 1.17)	144 (1 study)	Low[1,3]

Death at end of follow-up	486 per 1000	447 per 1000 (360 to 554)	RR 0.92 (0.74 to 1.14)	375 (3 studies)	Low[1,4,5,6]
R0 resection	750 per 1000	818 per 1000 (653 to 1000)	RR 1.09 (0.87 to 1.36)	315 (2 studies)	Very low[1,4,6,7]
Toxicity: Grade 3-4	0 per 1000	0 per 1000 (0 to 0)	RR 0.79 (0.06 to 9.71)	28 (1 study)	Very low[4,8]
Post-op complication (any)	162 per 1000	272 per 1000 (139 to 527)	RR 1.68 (0.86 to 3.26)	138 (1 study)	Low[1,6]
Anastomotic Leak	24 per 1000	35 per 1000 (6 to 201)	RR 1.46 (0.25 to 8.45)	201 (2 studies)	Very low[1,8]
Surgical site infection	12 per 1000	19 per 1000 (3 to 122)	RR 1.57 (0.24 to 10.29)	201 (2 studies)	Very low[1,8,9]
Post-op pneumonia	62 per 1000	8 per 1000 (1 to 172)	RR 0.12 (0.01 to 2.76)	63 (1 study)	Very low[8,9]
Transfusion	59 per 1000	143 per 1000 (47 to 434)	RR 2.43 (0.8 to 7.37)	138 (1 study)	Low[1,6]
Surgical Mortality	15 per 1000	43 per 1000 (5 to 402)	RR 2.91 (0.31 to 27.33)	138 (1 study)	Very low[1,8]

[1] Schuhmacher 2009: unclear random sequence generation and allocation concealment
[2] HR crosses 2 MIDs
[3] HR crosses 1 default MID
[4] Kobayahsi 2000: unlcear random allocation
[5] Wang 2000: inadequate allocation concealment, unclear random allocation
[6] Effect estimate crosses 1 MID
[7] I-squared statistic> 50%
[8] Effect estimate crosses 2 default MIDs
[9] Imano 2010: unclear random sequence generation
95%CI=95% Confidence interval; OS=Overall survivalP DFS=Progressionse free survival; RR=relative risk; HR=Hazard ratio;

Table 101: Summary clinical evidence profile. Post-operative chemoradiotherapy versus surgery alone

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)
	Assumed risk postop chemoradiotherapy	Corresponding risk surgery			
Overall survival (OS)	6-year OS 15%	6-year OS 24%	HR 1.35 (1.09 to 1.67)	556 (1 study)	Low[1,2]
Relapse-free survival (RFS)	6-year RFS 11%	6-year RFS 24%	HR 1.52 (1.23 to 1.89)	556 (1 study)	Moderate[1]

[1] *MacDonald 2001: unclear allocation concealment and random sequence generation*
[2] *HR crosses 1 MID*
95%CI=95% Confidence interval; OS=Overall survival; RFS=Relapse free survival; RR=relative risk; HR=Hazard ratio

Table 102: Summary clinical evidence profile. Perioperative chemotherapy versus surgery alone

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)
	Assumed risk surgery alone	Corresponding risk peri-operative chemotherapy			
Overall survival (OS)	5-year OS 25%	5-year OS 35% (28% to 44%)	HR 0.75 (0.6 to 0.93)	503 (1 study)	Low[1,2]
Progression-free survival (PFS)	5-year PFS 17%	5-year PFS 31%(23% to 39%)	HR 0.66 (0.53 to 0.82)	503 (1 study)	Low[1,2]
Curative resection	664 per 1000	691 per 1000 (611 to 784)	RR 1.04 (0.92 to 1.18)	494 (1 study)	Moderate[1]

[1] *Cunningham 2006: random sequence generation not described*
[2] *HR crosses 1 default MID*
95%CI=95% Confidence interval; OS=Overall survival DFS=Progressionse free survival; RR=relative risk; HR=Hazard ratio

Table 103: Summary clinical evidence profile. Perioperative chemotherapy versus perioperative chemoradiotherapy (post-operative radiation only)

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk Post-op CRT	Corresponding risk Peri-op CT			
5-year survival rate	410 per 1000	414 per 1000 (349 to 488)	RR 1.01 (0.85 to 1.19)	788 (1 study)	low[1]
Haematological toxicity (grade 3 or higher)	339 per 1000	441 per 1000 (370 to 526)	RR 1.3 (1.09 to 1.55)	788 (1 study)	very low[1,2]
GI toxicity (grade 3 or higher)	420 per 1000	370 per 1000 (311 to 437)	RR 0.88 (0.74 to 1.04)	788 (1 study)	very low[1,2]

[1] *Randomisation method was not described in details and all the outcomes considered were not reported.*
[2] *95%CI crossed one boundary of default MID*
95%CI=95% confidence interval; CT=chemotherapy; CRT=chemoradiotherapy; RR=relative risk; GI=gastrointestinal

Table 104: Summary clinical evidence profile. Perioperative chemotherapy versus perioperative chemoradiotherapy (pre-operative radiation only)

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk Peri-op CT	Corresponding risk Peri-op CT plus pre-op radiation			
Surgical complications: anastamotc leak	56 per 1000	79 per 1000 (17 to 334)	RR 1.41 (0.33 to 6.00)	120 (1 study)	low[1]
Surgical complications: chest infection	93 per 1000	99 per 1000 (31 to 319)	RR 1.06 (0.33 to 3.44)	120 (1 study)	low[1]
Surgical complications: overall	220 per 1000	223 per 1000 (102 to 442)	RR 0.97 (0.47 to 2.00)	120 (1 study)	low[1]
Haematological complications: neutropenia	400 per 1000	452 per 1000 (296 to 684)	RR 1.13 (0.74 to 1.71)	120 (1 study)	low[1]
Haemotological complications: overall	500 per 1000	515 per 1000 (365 to 735)	RR 1.03 (0.73 to 1.47)	120 (1 study)	low[1]
Gastrointestinal complications: overall	317 per 1000	301 per 1000 (174 to 513)	RR 0.95 (0.55 to 1.62)	120 (1 study)	low[1]

[1] 95%CI crossed both boundaries of default MIDs

95%CI=95% confidence interval; CT=chemotherapy; RR=relative risk;RR=relative risk.

Table 105: Summary clinical evidence profile. Intraperitoneal chemotherapy versus surgery alone

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)
	Assumed risk surgery alone	Corresponding risk intraperitoneal chemotherapy			
Perioperative mortality	8 per 1000	22 per 1000 (2 to 211)	RR 2.96 (0.31 to 28.05)	268 (1 studies)	Very low[1,2]
Overall survival rate - Normothermic intraperative IPC	256 per 1000	585 per 1000 (330 to 1000)	RR 2.29 (1.29 to 4.07)	208 (3 studies)	moderate[1]
Overall survival rate - Hyperthermic intraoperative IPC	458 per 1000	619 per 1000 (454 to 834)	RR 1.35 (0.99 to 1.82)	184 (3 studies)	low[1,4]
Disease free survival rate - Normothermic	556 per 1000	579 per 1000 (467 to 712)	RR 1.04 (0.84 to 1.28)	268 (1 study)	low[1,4]

intraoperative CT					
Neutropenia	11 per 1000	73 per 1000 (10 to 550)	RR 6.53 (0.87 to 48.94)	223 (2 studies)	low[1,4]

[1] Unclear on attrition rate
[2] 95%CI crossed two boundries of MID
[3] Not intention to treat analysis
[4] 95%CI crossed one boundary of MID
[5] one study was not intention to treat analysis and two studies were unclear on attrition rates
[6] one study unclear on attrition rate and one other study was not intention to treat analyisis
RR=relative risk; 95%CI=95%confidence interval;IPC=intraperitoneal chemotherapy; CT=chemotherapy

Table 106: Summary clinical evidence profile. Intraperitoneal chemotherapy versus intravenous chemotherapy

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)
	Assumed risk intravenous chemotherapy	Corresponding risk intraperitoneal chemotherapy			
Perioperative mortality	23 per 1000	1 per 1000 (0 to 203)	RR 0.38 (0.02 to 8.95)	83 (1 study)	Very low[1,2]
Treatment-related morbidity: Neutropenia	250 per 1000	205 per 1000 (93 to 458)	RR 0.82 (0.37 to 1.83)	83 (1 study)	Very Low[1,2]
Overall survival rate	507 per 1000	608 per 1000 (517 to 715)	RR 1.2 (1.02 to 1.41)	1167 (5 studies)	low[4,3]
Overall survival rate - Normothermic intraoperative IPC	521 per 1000	646 per 1000 (495 to 844)	RR 1.53 (0.83 to 2.79)	584 (2 studies)	very low[4,3,5]
Overall survival rate - Hyperthermic intraoperative IPC	470 per 1000	564 per 1000 (451 to 695)	RR 1.2 (0.96 to 1.48)	315 (2 studies)	low[4,3]

[1] unclear on blinding and selective outcome reporting
[2] 95%CI crossed two boundries of MID
[3] 95%CI crossed one boundary of MID
[4] All five studies were of fair quality of cochrane risk of bias assessment
[5] I2 > 50%
RR=relative risk; 95%CI=95%confidence interval;IPC=intraperitoneal chemotherapy; CT=chemotherapy D

8.5.5 Economic evidence

Two relevant studies were identified in a literature review of published cost-effectiveness analyses on this topic; Hisashige et al. 2016 and Wang et al. 2008 (see table 1 in Appendix L). The base case results of Hisashige et al. 2016 showed that, in comparison to surgery alone, the addition of adjuvant chemotherapy provided one additional QALY at a cost of $3,016. In probabilistic and deterministic sensitivity analysis, the addition of adjuvant chemotherapy was found to be cost-effective in most modelled scenarios.

The base case results of Wang et al. 2008 showed that, in comparison to surgery alone, the addition of adjuvant chemoradiotherapy provided one additional QALY at a cost of $38,400. In probabilistic sensitivity analysis, the addition of adjuvant chemoradiotherapy was found to have a 67% probability of being cost-effective at a threshold of $50,000 per QALY.

Overall, the analyses can be considered to show the potential cost-effectiveness of chemotherapy or chemoradiotherapy in addition to surgical treatment. However, decisive conclusions could not be drawn because the analyses were only partially applicable to the decision problem in the UK setting as they were based on the health care perspective of Japan and the United States. Furthermore, some potentially serious limitations were identified including the use of assumptions to quantify changes in QoL.

8.5.6 Evidence statements

8.5.6.1 Post-operative chemoradiotherapy versus post-operative chemotherapy

8.5.6.1.1 Overall survival

Low quality evidence from 6 RCTs with 1171 people with gastric cancer suitable for surgical treatment showed that there was no clinically significant difference between post-operative chemoradiotherapy and post-operative chemotherapy for overall survival.

8.5.6.1.2 Disease-free survival

Low quality evidence from 6 RCTs with 1171 people with gastric cancer suitable for surgical treatment showed that there was a clinically significant beneficial effect of postoperative chemoradiotherapy compared with postoperative chemotherapy for disease-free survival.

8.5.6.1.3 Treatment-related morbidities: Grade 3-4 neutropenia

Low quality evidence from 5 RCTs with 1079 people with gastric cancer suitable for surgical treatment showed that there was a clinically significant harmful effect of post-operative chemoradiotherapy compared with post-operative chemotherapy for grade 3-4 neutropenia.

8.5.6.2 Post-operative chemotherapy versus surgery alone

8.5.6.2.1 Overall survival

Low quality evidence from 5 RCTs with 1913 people with gastric cancer suitable for surgical treatment showed that there was a clinically significant beneficial effect of post-operative chemotherapy compared with surgery alone for overall survival.

8.5.6.2.2 Disease-free survival

Low quality evidence from 3 RCTs with 1571 people with gastric cancer suitable for surgical treatment showed that there was a clinically significant beneficial effect of post-operative chemotherapy compared with surgery alone for disease-free survival.

8.5.6.2.3 Treatment-related morbidity: Grade 3-4 toxicities

High quality evidence from 1 RCTs with 974 people with gastric cancer suitable for surgical treatment reported that there was a clinically significant harmful effect of post-operative chemotherapy compared with surgery alone for any grade 3-4 toxicities as well as grade 3-4 neutropenia.

8.5.6.2.4 Treatment-related mortality

Low quality evidence from 3 RCTs with 714 people with gastric cancer suitable for surgical treatment showed that there may be a clinically significant harmful effect of post-operative

chemotherapy compared with surgery alone for treatment-related mortality, however there was uncertainty around the estimate.

8.5.6.3 Pre-operative chemotherapy versus surgery alone

8.5.6.3.1 Overall survival

Very low quality evidence from 1 RCT with 144 people with gastric cancer suitable for surgical treatment reported that there was no clinically significant difference between pre-operative chemotherapy and surgery alone for overall survival.

8.5.6.3.2 Progression-free survival

Low quality evidence from 1 RCT with 144 people with gastric cancer suitable for surgical treatment reported that there was no clinically significant difference between pre-operative chemotherapy and surgery alone for progression-free survival.

8.5.6.3.3 Death at the end of follow-up

Low quality evidence from 1 RCT with 375 people with gastric cancer suitable for surgical treatment reported that there was no clinically significant difference between pre-operative chemotherapy and surgery alone for number of death at the end of follow-up period.

8.5.6.3.4 Treatment-related mortality: operative mortality

Very low quality evidence from 1 RCT with 138 people with gastric cancer suitable for surgical treatment reported that there was no clinically significant difference between preoperative chemotherapy and surgery alone for operative mortality.

8.5.6.3.5 Treatment-related morbidity: operative complications

Very low quality evidence from 2 RCTs with 201 people with gastric cancer suitable for surgical treatment reported that there was no clinically significant difference between pre-operative chemotherapy and surgery alone for anastomotic leakage or surgical site infection.

Very low to low quality evidence from 1 RCT with 138 people with gastric cancer suitable for surgical treatment reported that there was no clinically significant difference between pre-operative chemotherapy and surgery alone for any operative complication or transfusion related complication.

Very low quality evidence from 1 RCT with 63 people with gastric cancer suitable for surgical treatment reported that there was no clinically significant difference between pre-operative chemotherapy and surgery alone for post-operative pneumonia.

8.5.6.3.6 Treatment-related morbidity: grade 3-4 toxicities

Very low quality evidence from 1 RCT reported that there was no clinically significant difference between preoperative chemotherapy and surgery alone for any grade 3-4 toxicity.

8.5.6.3.7 Complete resection (R0) at surgery

Very low quality evidence from 2 RCTs with 315 people with gastric cancer suitable for surgical treatment showed that there was no clinically significant difference between pre-operative chemotherapy and surgery alone for complete resection (R0).

8.5.6.4 Post-operative chemoradiotherapy versus surgery alone

8.5.6.4.1 Overall survival

Low quality evidence from 1 RCT with 556 people with gastric cancer suitable for surgical treatment showed that there was a clinically significant beneficial effect of post-operative chemoradiotherapy compared with surgery alone for overall survival.

8.5.6.4.2 Relapse-free survival

Moderate quality evidence from 1 RCT with 556 people with gastric cancer suitable for surgical treatment showed that there was a clinically significant beneficial effect of post-operative chemoradiotherapy compared with surgery alone for relapse-free survival.

8.5.6.5 Perioperative chemotherapy versus surgery alone

8.5.6.5.1 Overall survival

Low quality evidence from 1 RCT with 503 people with gastric cancer suitable for surgical treatment showed that there was a clinically significant beneficial effect of peri-operative chemotherapy compared with surgery alone for overall survival.

8.5.6.5.2 Progression-free survival

Low quality evidence from 1 RCT with 503 people with gastric cancer suitable for surgical treatment showed that there was a clinically significant beneficial effect of peri-operative chemotherapy compared with surgery alone for progression-free survival.

8.5.6.5.3 Curative resection

Moderate quality evidence from 1 RCT with 494 people with gastric cancer suitable for surgical treatment showed that there was no clinically significant difference between peri-operative chemotherapy and surgery alone for curative resection.

8.5.6.6 Perioperative chemotherapy versus perioperative chemoradiotherapy (post-operative radiation only)

8.5.6.6.1 5-year survival

Low quality evidence from 1 RCT with 788 people with gastric cancer suitable for surgical treatment reported that there was no clinically significant difference between perioperative chemotherapy and perioperative chemoradiotherapy for 5-year survival.

8.5.6.6.2 Haematological toxicity (grade 3 or higher)

Very low quality evidence from 1 RCT with 788 people with gastric cancer suitable for surgical treatment reported that there was a clinically significant harmful effect of perioperative chemotherapy compared with perioperative chemoradiotherapy for grade 3 or higher haematological toxicity.

8.5.6.6.3 Gastrointestinal toxicity (grade 3 or higher)

Very low quality evidence from 1 RCT with 788 people with gastric cancer suitable for surgical treatment reported that there was no clinically significant difference between perioperative chemotherapy and perioperative chemoradiotherapy for grade 3 or higher gastrointestinal toxicity.

8.5.6.7 Perioperative chemotherapy versus perioperative chemoradiotherapy (pre-operative radiation only)

8.5.6.7.1 Treatment related morbidity: surgical anastamotic leak

Low quality evidence from 1 RCT with 120 people with gastric cancer suitable for surgical treatment reported that there was no clinically significant difference between perioperative chemotherapy and perioperative chemoradiotherapy for anastamotic leak.

8.5.6.7.2 Treatment related morbidity: post-operative chest infection

Low quality evidence from 1 RCT with 120 people with gastric cancer suitable for surgical treatment reported that there was no clinically significant difference between perioperative chemotherapy and perioperative chemoradiotherapy for post-operative chest infection.

8.5.6.7.3 Treatment related morbidity: surgical complications

Low quality evidence from 1 RCT with 120 people with gastric cancer suitable for surgical treatment reported that there was no clinically significant difference between perioperative chemotherapy and perioperative chemoradiotherapy for overall surgical complications.

8.5.6.7.4 Treatment related morbidity: neutropenia

Low quality evidence from 1 RCT with 120 people with gastric cancer suitable for surgical treatment reported that there was no clinically significant difference between perioperative chemotherapy and perioperative chemoradiotherapy for incidence of neutropenia.

8.5.6.7.5 Treatment related morbidity: haematological complications

Low quality evidence from 1 RCT with 120 people with gastric cancer suitable for surgical treatment reported that there was no clinically significant difference between perioperative chemotherapy and perioperative chemoradiotherapy for overall haematological complications (grade 3 toxicity or higher).

8.5.6.7.6 Treatment related morbidity: gastrointestinal complications

Low quality evidence from 1 RCT with 120 people with gastric cancer suitable for surgical treatment reported that there was no clinically significant difference between perioperative chemotherapy and perioperative chemoradiotherapy for overall gastrointestinal complications (grade 3 toxicity or higher).

8.5.6.8 Intraperitoneal chemotherapy versus surgery alone

8.5.6.8.1 Overall survival rate

Very low quality evidence from 6 RCTs with 392 people with gastric cancer suitable for surgical treatment reported that there was a clinically significant beneficial effect of intraperitoneal chemotherapy compared with surgery alone for overall survival rate.

Subgroup analysis according to type of chemotherapy

Moderate quality evidence from 3 RCTs with 208 people with gastric cancer suitable for surgical treatment reported that there was a clinically significant beneficial effect of normothermic intraoperative intraperitoneal chemotherapy compared with surgery alone for overall survival rate.

Low quality evidence from 3 RCTs with 184 people with gastric cancer suitable for surgical treatment reported that there may be a clinically significant beneficial effect of hyperthermic intraoperative intraperitoneal chemotherapy compared with surgery alone for overall survival rate, however, there is an uncertainty around the estimate.

8.5.6.8.2 Perioperative mortality

Very low quality evidence from 1 RCT with 268 people with gastric cancer suitable for surgical treatment reported that there was no clinically significant difference between intraperitoneal chemotherapy and surgery alone for perioperative mortality.

8.5.6.8.3 Disease free survival rate

Low quality evidence from 1 RCT with 268 people with gastric cancer suitable for surgical treatment reported that there is no clinically significant difference between intraoperative intraperitoneal chemotherapy and systemic chemotherapy for disease free survival rate.

8.5.6.9 Intraperitoneal chemotherapy versus systemic chemotherapy

8.5.6.9.1 Perioperative mortality

Very low quality evidence from 1 RCT with 83 people with gastric cancer suitable for surgical treatment reported that there was no clinically significant difference between postoperative intraperitoneal chemotherapy and postoperative systemic chemotherapy for perioperative mortality.

8.5.6.9.2 Treatment-related morbidity: grade 3-4 neutropenia

Very low quality evidence from 1 RCT with 83 people with gastric cancer suitable for surgical treatment reported that there was no clinically significant difference between postoperative intraperitoneal chemotherapy and postoperative systemic chemotherapy for treatment-related grade 3-4 neutropenia.

8.5.6.9.3 Overall survival rate

Low quality evidence from 4 RCTs with 899 people with gastric cancer suitable for surgical treatment reported that there is a clinically significant beneficial effect of intraoperative intraperitoneal chemotherapy compared with systemic chemotherapy for overall survival rate.

Subgroup analysis according to type of chemotherapy

Very low quality evidence from 2 RCTs with 584 people with gastric cancer suitable for surgical treatment reported that there was no clinically significant difference between normothermic intraoperative intraperitoneal chemotherapy and systemic chemotherapy for overall survival rate.

Low quality evidence from 2 RCTs with 315 people with gastric cancer suitable for surgical treatment reported that there may be a clinically significant beneficial effect of hyperthermic intraoperative intraperitoneal chemotherapy compared with systemic chemotherapy for overall survival rate, however, there is an uncertainty around the estimate.

8.5.7 Evidence to recommendations

8.5.7.1 Relative value placed on the outcomes considered

As the purpose of this evidence review was to determine the treatment required to prevent recurrence of disease after surgery, and so to improve overall survival and disease-free survival theCommittee considered that the most important outcomes to use when identifying the optimal choice of chemotherapy or chemoradiotherapy were overall survival and disease-free survival. Treatment-related morbidity was also considered important as this would allow a decision on treatments to be made that balanced the benefits and harms of those treatments. Additional outcomes that could add extra information for this decision-making

process were treatment-related mortality and complete resection at surgery and these outcomes were therefore reviewed when available.

It had been hoped that quality of life or patient-reported outcomes would also be included but no studies identified had these as reported outcomes. The degree of tumour regression (defined as tumour regression grade on a scale of 0 to 4 or 1 to 5) was not used as an outcome because of the variation in definitions, and due to complications arising from the different directions of the scales used (i.e. some scales use Grade 1 to define complete regression and some use Grade 5 for compete regression).

8.5.7.2 Quality of the evidence

The evidence for this review was taken from randomised controlled trials (some of which were identified from existing systematic reviews) and quality was assessed using GRADE methodology. The evidence was of very low to high quality.

The studies did not control for the quality of surgery and this may have had an impact on the size of the effect. A number of studies were conducted in Asia/Far East and the Committee felt, at the time these studies were conducted (some recruited patients up to 25 years ago), surgery in Asia/Far East was more standardised than that conducted in the UK. This would have meant that the addition of chemotherapy and chemoradiotherapy would have had less of an effect on overall outcomes than UK studies where the outcomes after surgery alone would have been poorer. However, taking this into consideration meant that the effect sizes seen from the Asian/Far East studies may be increased when applied to the UK population. It was also noted by the Committee that since the Improving Outcomes Guidance (IOG) published in 2001, surgery in the UK had become more standardised.

8.5.7.3 Consideration of clinical benefits and harms

For the comparions included in this review the Committee assessed the changes in outcomes and the treatment-related morbidity or mortality when different treatments were compared to surgery alone:

Preoperative chemotherapy did not improve overall survival or progression-free survival compared to surgery alone, and there were similar rates of treatment-related morbidity and mortality, so the Committee felt the benefits of preoperative chemotherapy did not outweigh the harms.

Postoperative chemotherapy improved overall survival and disease-free survival compared to surgery alone, although there was an increased rate of treatment-related morbidity (but not mortality) with postoperative chemotherapy.

Perioperative chemotherapy improved overall survival and progression-free survival compared to surgery alone, although there were no treatment-related morbidity results which cpould be evaluated for inclusion in the evidence-review.

Postoperative chemoradiotherapy improved survival and relapse-free survival compared to surgery alone.

Based on this evidence the Committee agreed that perioperative chemotherapy or post operative chemotherapy or postoperative chemoradiotherapy in addition to surgery were likely to improve outcomes for this group of patients.

The Committee also considered comparisons of different treatments against each other:

Postoperative chemoradiotherapy improved overall survival and disease-free survival compared to postoperative chemotherapy, although the chemoradiotherapy did lead to more neutropenia.

This evidence confirmed to the Committee that postoperative chemotherapy could be used as an alternative to postoperative chemoradiotherapy, as although the survival outcomes may not be so great there was the benefit of reduced toxicity with the chemotherapy alone.

Finally, the Committee reviewed the evidence that showed there was no difference in the 5-year survival between perioperative chemotherapy and perioperative chemoradiotherapy (post-operative radiation), but the haematological toxicity was greater with chemotherapy..

Overall, based on this evidence, the Committee agreed that recommending the use of perioperative chemotherapy would be likely to improve outcomes in patients undergoing curative surgical resection. There was also evidence of improved outcomes with postoperative chemotherapy or chemoradiotherapy compared to surgery alone and so this was recommended for patients who had not received pre-operative chemotherapy. There was no benefit seen with preoperative chemotherapy alone compared to surgery alone so this was not recommended.

The Committee felt these recommendations would standardise treatment and would possibly improve outcomes, while reducing treatment-related morbidity from unnecessary treatment. Both perioperative and postoperative chemotherapy increased treatment-related morbidity (and for postoperative chemotherapy treatment-related mortality), but the Committee felt that likely improved overall survival and disease-free survival outweighed the toxicity of the treatments.

8.5.7.4 Consideration of economic benefits and resource use

Two relevant studies were identified in a literature review of published cost-effectiveness analyses on this topic; Hisashige et al. 2016 and Wang et al. 2008. The analyses were considered to show the potential cost-effectiveness of chemotherapy or chemoradiotherapy in addition to surgical treatment. However, decisive conclusions could not be drawn because the analyses were only partially applicable to the decision problem in the UK setting as they were based on the health care perspective of Japan and the United States.

The economic implications of the recommendations made by the Committee were thought to be negligible as they reflect current clinical practice.

If there are centres where practice is not currently in line with the recommendations then there could be increased costs associated with the use of chemotherapy. However, the use of chemotherapy would be expected to be cost-effective as the benefits in terms of overall and disease-free survival would be expected to translate into significant QALY gains.

8.5.7.5 Other considerations

There was also evidence included in the review for intraperitoneal chemotherapy. Intraoperative, intraperitoneal chemotherapy can be delivered under either normothermic or hyperthermic conditions. The addition of hyperthermia synergistically increases the cytotoxicity of certain chemotherapeutic agents. The data for both intraperitoneal chemotherapy compared to surgery alone and intraperitoneal chemotherapy compared to intravenous chemotherapy were included in the review. For both comparisons the overall survival was greater for intraperitoneal chemotherapy compared with surgery alone and intravenous chemotherapy. However the Committee felt that these results should be interpreted with caution, in view of the recruited populations which were all from Japan or the Far East and so did not reflect the UK population, and the intravenous chemotherapeutic agents used, which do not represent current UK regimens. Given the uncertain benefit of intraperitoneal chemotherapy, a research recommendation was therefore written.

8.5.7.6 Key conclusions

The Committee agreed that the evidence for improved overall survival and disease-free survival with perioperative chemotherapy compared to surgery alone allowed them to recommend this as an option. Although this was based on 1 RCT, this was a large study predominantly carried out in the UK, which study showed both increased overall survival and increased disease-free survival. The addition of radiotherapy (either pre- or post-operative radiotherapy) to perioperative chemotherapy did not increase overall survival compared to perioperative chemotherapy alone but there was some evidence of increased treatment-related morbidity.

There was also evidence for improved overall survival and disease-free survival for postoperative chemotherapy compared to surgery alone and postoperative chemoradiotherapy compared to surgery alone, and so these were recommended as treatment options in people who had not received preoperative chemotherapy. It was noted by the Committee that there were increased rates of treatment-related morbidity and mortality reported with postoperative chemotherapy compared to surgery alone.

The evidence for the use of preoperative chemotherapy compared to surgery alone suggested there was no benefit to overall survival or disease-free survival with this option, so this was not recommended as a treatment option.

8.5.8 Recommendations

28. Offer chemotherapy before and after surgery to people with gastric cancer who are having radical surgical resection.

29. Consider chemotherapy or chemoradiotherapy after surgery for people with gastric cancer who did not have chemotherapy before surgery with curative intent.

8.5.9 Research recommendations

3. What is the role of intraperitoneal chemotherapy following surgical resection for gastric cancer?

Why this is important

People undergoing surgical resection for gastric cancer are often treated with systemic (usually intravenous) chemotherapy. An alternative method of delivering chemotherapy to these people is by intraperitoneal administration, usually as an intraoperative procedure.

Increasing expertise in the management of peritoneal disease and recent innovations in drug delivery (such as the use of hyperthermic and normothermic intraperitoneal administration) have increased the range of options for treatment of gastric cancer, but there is a paucity of evidence for these interventions, and that which is available has provided some conflicting results.

Further investigation into the role of intraperitoneal chemotherapy in gastric cancer is needed to guide best clinical practice, with studies comparing intraperitoneal chemotherapy against current treatment standards, such as appropriate surgery and perioperative systemic chemotherapy.

Table 107: Research recommendation rationale

Research question	What is the role of intraperitoneal chemotherapy following surgical resection for gastric cancer?
Importance to 'patients' or the population	Use of intraperitoneal chemotherapy would increases the range of treatment options for people with gastric cancer.
Relevance to NICE guidance	A lack of good quality, relevant evidence, has mean that current guidelines have been unable to make definitive recommendations on the role of intraperitoneal chemotherapy for gastric cancer.
Relevance to the NHS	Disease relapse in gastric cancer leads to significant morbidity. Additional treatment options, such as intraperitoneal chemotherapy, which may lead to decreased relapse rates after surgery would be associated with improved outcomes.
National priorities	NHS Outcomes Framework for 2016-17: Improving 1-year and 5-year survival for all cancers.
Current evidence base	Unclear – most studies in this setting have been performed in the Far East and reflect surgical and chemotherapy practices over 30 years old. Studies have shown some conflicting results.
Equality	No special considerations required.

Table 108: Research recommendation statements

Criterion	Explanation
Population	People with gastric cancer being treated with radical surgery
Intervention	Intraperitoneal chemotherapy at the cessation of D2 gastrectomy
Comparator (without the risk factor)	No intraperitoneal chemotherapy at the cessation of D2 gastrectomy
Outcome	Disease-free and overall survival
Study design	Phase Ib toxicity, Phase II feasibility and Phase III randomised controlled trial
Timeframe	5 years

8.6 Squamous cell carcinoma of the oesophagus

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

8.6.1 Introduction

Squamous cell carcinoma (SCC) of the oesophagus remains an important health issue in the UK. While the incidence of SCC is declining it still accounts for a proportion of all cases of oesophageal cancer. 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 (multimodal).

The aim of this review is to explore the most effective treatment options available for SCC of the oesophagus, including evaluating whether non-surgical treatment is as effective as surgery, and whether multimodal therapy is superior to single modality treatment.

8.6.2 Description of clinical evidence

This review included evidence from 36 randomised controlled trials (RCTs) (of which three had more than two arms) (n=1741) for eight comparisons between different curative treatments of SCC of the oesophagus. Studies were included if more than two-thirds of the

population were SCC, or separate data for the SCC subgroup were extractable. The comparisons of interest and trials reporting on these comparisons are summarised below, with details of the studies extracted:

1. Chemoradiotherapy (CRT) followed by surgery versus surgery alone:
    a. Apinop 1994 (Extracted from Kumagai 2014 systematic review (SR) and Apinop 1994 RCT)
    b. Bosset 1997 (Extracted from Kumagai 2014 SR and Bosset 1997 RCT)
    c. Burmeister 2005 (Extracted from Kumagai 2014 SR and Burmeister 2005 RCT)
    d. Cao 2009 (Extracted from Kumagai 2014 SR and Cao 2009 RCT)
    e. Lee 2004 (Extracted from Kumagai 2014 SR and Lee 2004 RCT)
    f. Le Prise 1994 (Extracted from Kumagai 2014 SR and Le Prise 1994 RCT)
    g. Lv 2010 (Extracted from Lv2010 RCT)
    h. Mariette 2014 (Extracted from Mariette 2014 RCT)
    i. Mashhadi 2015 (Extracted from Mashhadi 2015 RCT)
    j. Natsugoe 2006 (Extracted from Kumagai 2014 SR)
    k. Nygaard 1992 (Extracted from Kumagai 2014 SR and Nygaard 1992 RCT)
    l. Van Hagen 2012 (Extracted from Kumagai 2014 SR and van Hagen 2012 RCT)
2. Chemoradiotherapy followed by surgery versus chemoradiotherapy alone:
    a. Bedenne 2007/Bonnetain 2006 (Extracted from Pottgen 2012 SR, Bedenne 2007 and Bonnetain 2006 RCT)
    b. Stahl 2005 (Extracted from Pottgen 2012 SR)
3. Chemoradiotherapy followed by surgery versus chemotherapy (CT) followed by surgery:
    a. Cao 2009 (Extracted from Kuamagai 2014 SR and Cao 2009 RCT)
    b. Klevebro 2015 (Extracted from Klevebro 2015 RCT)
    c. Nygaard 1992 (Extracted from Kumagai 2014 and Nygaard 1992 RCT)
4. Surgery followed by chemoradiotherapy versus surgery alone
    a. Lv 2010 (Extracted from Lv2010 RCT)
5. Chemoradiotherapy alone versus surgery alone
    a. Chiu 2005/Teoh 2012 (Extracted from Pottgen 2012 SR, Chiu 2005 and Teoh 2012 RCT)
6. Surgery alone versus Radiotherapy (RT) alone
    a. Badwe 1998 (Extracted in Badwe 1998 RCT)
    b. Fok 1994 (Extracted in Fok 1994 RCT)
7. Chemotherapy followed by surgery versus surgery alone
    a. Ancona 2001 (Extracted from Kumagai 2014 and Ancona 2001 RCT)
    b. Baba 2000 (Extracted from Kumagai 2000 SR)
    c. Boonstra 2011 (Extracted from Kumagai 2000 SR, Boonstra 2011 RCT)
    d. Cao 2009 (Extracted from Kuamagai 2014 SR and Cao 2009 RCT)
    e. Law 1997 (Extracted from Kumagai 2014 SR and Law 1997 RCT)
    f. Maipang 1994 (Extracted from Maipang 1994 RCT)
    g. MRC 2002 (Extracted from Kumagai 2014 SR and MRC 2002 RCT)
    h. Nygaard 1992 (Extracted from Kumagai 2014 SR and Nygaard 1992 RCT)
    i. Schlag 1992 (Extracted from Schlag 1992 RCT)
8. Chemoradiotherapy versus Radiotherapy alone
    a. Araujo 1991 (Extracted from Wong 2006 SR and Araujo 1991 RCT)
    b. Cooper 1999 (Extracted from Wong 2006 SR)

c. Gao 2002 (Extracted from Wong 2006 SR)
d. Han 2012 (Extracted from Zhu 2015 SR)
e. Hatlevoll 1992 (Extracted from Wong 2006 SR and Hatlevoll 1992 RCT)
f. Herskovic 1992/Al-Sarraf 1997 (Extracted from Zhu 2015 SR)
g. Kumar 2007 (Extracted from Zhu 2015 SR and Kumar 2007 RCT)
h. Slabber 1998 (Extracted from Wong 2006 SR)
i. Smith 1998 (Extracted from Smith 1998 RCT)
j. Zhao 2005 (Extracted from Zhu 2015 SR and Zhao 2005 RCT)
k. Zhu 2000 (Extracted from Wong 2006 SR)

Evidence from these studies are summarised in the clinical GRADE evidence profiles below (Table 117 to Table 124). See also the study selection flow chart in Appendix K, forest plots in Appendix H, exclusion list in Appendix J and clinical evidence profiles of included studies in Appendix F.

8.6.3 Summary of included studies

A summary of the studies that were included in this review are presented in Table 109 to Table 116.

8.6.3.1 Chemoradiotherapy followed by surgery versus surgery alone

Table 109. Summary of included studies: Chemoradiotherapy followed by surgery versus surgery alone

Study ID	Population	CRT	Surgery	Outcomes
Apinop 1994 RCT; Thailand; n=69	100% SCC Age (mean): 59.7 years Male %: 78.3	Cisplatin 100 mg/m^2 on days 1 and 29; 5 FU 1000 mg/m^2 per day on days 1-4 and 29-32 AND 40Gy, 2Gy per fraction RT over 4 weeks (concurrent)	Right thoracotomy and laparotomy and anastomosis in the chest	Anastomotic leak, Treatment-related mortality, Overall survival
Bosset 1997 RCT; France; n=282	100% SCC Age (mean): 56.7 years Male %: 93.3 Node (+)ve tumour: 23%	Cisplatin 80 mg/m^2 0-2 days before each course of radiotherapy AND 37 Gy, 3.7Gy per fraction RT in two 1-week courses, separated by 2 weeks (sequential)	Two or three stage surgical approach depending on the site of tumour and two-field lymph node resection	Any postoperative complication, Disease free survival, Treatment-related mortality, Postoperative mortality, Overall
Burmeister 2005 RCT; Australia, New Zealand, Singapore; n=256	SCC %: 37 Age (mean): 61.5 years Male %: 82 (+)ve regional node %: 15.5	Cisplatin 80 mg/m^2 on day 1; 5 FU 800 mg/m2 per day on days 1-4 AND 35 Gy in 15 fractions RT over 3 weeks (concurrent)	No particular approach was stipulated and radical lymphadenectomy was not mandatory	Disease free survival, Overall survival, Progression free survival
Cao 2009 RCT; China; n=236	100% SCC Male %: 54 Stage III or IV %: 94	Cisplatin (20 mg/m^2) and 5-FU (500 mg/m^2) per day on days 1–5	Oesophagectomy through left thoracotomy with 2-	Anastomotic leak, 30-day mortality,

		and mitomycin 10mg/m^2 per day on day 1 AND 40Gy RT in 20 fractions over 4 weeks (concurrent)	field lymphadenectomy	Treatment-related mortality, Postoperative mortality
Lee 2004 RCT; Korea; n=101	100% SCC Age (median): 63 years Male: 92%	Cisplatin 60 mg/m^2 on days 1 and 22; 5 FU 1000mg/m^2 per day on days 2-5 AND 45.6 Gy, 1.2 Gy per fraction over 28 days (concurrent)	Two-stage or three-stage approach and en-bloc lymphadenectomy	Any postoperative complication, Disease free survival, Treatment-related mortality, Postoperative mortality, Overall survival
Le Prise 1994 RCT; France; n=86	100% SCC Age (median) : 56 years Male %: 93	Cisplatin 100mg/m2 on days 1 and 21; 5FU 600 mg/m2 per day on days 2-5 and 22-25 AND 20Gy in 10 fractions over 12 days (sequential)	Not reported in details	Anastomotic leak, Any postoperative complication, Treatment-related mortality, Postoperative mortality, Overall survival
Lv 2010 RCT; China; n=160	100% SCC Age (≥60 years) %: 56 Male %: 64	Cisplatin 20 mg/m^2 on days 1–3 and 22–24 and paclitaxel 135 mg/m^2 starting on days 1 and 22 of RT AND 40 Gy RT, in 20 fractions over 4weeks (concurrent)	Oesophagectomy through left or right thoracotomy with 2-field lymphadenectomy	Anastomotic leak, Disease free survival, stenosis, Treatment-related mortality, Intraoperative haemorrhage, Overall survival
Mariette 2014 RCT; France; n=195	SCC %: 70.3 Age (median): 57.8 years Male %: 85.6 N0 %: 72.3	Two cycles of 5 FU and cisplatin from days 1 to 4 and 29 to 32 AND a total dose of 45 Gy in 25 fractions RT over 5 weeks. Surgery was done 4 to 6 weeks after completion of CRT. (concurrent)	Transthoracic oesophagectomy with extended two-field lymphadenectomy	Any postoperative complication, 30-day mortality, Disease free survival,Infection, Postoperative mortality, Overall survival
Mashhadi 2015 RCT; Iran; n=100	SCC %: 72 Age (mean): 55 years Male %: 53	Cisplatin followed by 50 Gy RT and on the first and final days of RT, cisplatin (20 mg/m^2) and 5 FU (700 mg/m^2/infusion over 24 hours) (concurrent)	Transhiatal oesophagectomy with cervical anastomosis	Anastomotic leak, Intraoperative blood loss, Postoperative mortality

Natsugoe 2006 RCT; Japan; n=45	100% SCC	Cisplatin 7 mg on days 1-5, 8-12, 15-19 and 22-26; 5 FU 350 mg/day on days 1-28 AND 40 Gy RT, 2 Gy per fraction over 4 weeks (concurrent)	Not reported in details	Anastomotic leak, Treatment-related mortality, Postoperative mortality
Nygaard 1992 RCT; Norway; n=217*	100% SCC Age (median): 62.6 years Male %: 71	Cisplatin 20 mg/m^2 on days 1-5 and 15-19 and bleomycin 5 mg/m^2 on days 1-5 and 15-19 AND 35 Gy RT, 1.75 Gy per fraction over 4 weeks (sequential)	Laparotomy with right thoracotomy	Anastomotic leak, Any postoperative complication, 30-day mortality, Infection, Postoperative mortality
van Hagen 2012 RCT; Netherlands; n=368 (SCC subgroup n=84)	SCC %: 23 Age (median): 60 years Male %: 78	Carboplatin and paclitaxel on day 1 weekly AND 41.4 Gy RT, 1.8 Gy per fraction over 4.6 weeks (concurrent)	Transthoracic approach with 2-field lymphadenectomy and transhiatal resection for those extending to oesophago-gastric extension and gastric tube reconstruction and cervical anastomosis	Overall survival, Progression free survival

n=total number of patients; (+)ve= positive
**only 186 participants was included in analysis.*
CRT=Chemoradiotherapy; CT= chemotherapy; 5 FU = 5-fluorouracil; RCT= randomised controlled trials; RT=Radiotherapy; SCC=Squamous cell carcinoma; Sx=Surgery
Note – The same type of surgery was applied in either arm, unless specified.

Outcomes for number going on to salvage resection, health related quality of life or patient-reported outcome measures were not able to be extracted.

8.6.3.2 Chemoradiotherapy followed by surgery versus chemoradiotherapy alone

Table 110. Summary of included studies: Chemoradiotherapy followed by surgery versus chemoradiotherapy alone

Study ID	Population	CRT followed by Surgery	Surgery	Outcomes
Bedenne 2007/Bonnetain 2006 RCT; France; n=259	SCC%: 89 Age (mean): 57 years Male %: 94 T3-4/ N0-1/ M0 thoracic oesophageal cancers	Induction CRT: two cycles of cisplatin and 5 FU AND 15 Gy/3Gy or 46 Gy/2Gy RT (concurrent) Sx: No recommended type of surgery	Three cycles of cisplatin and 5 FU AND 15Gy/3Gy (OR) two cycles of cisplatin and 5FU AND 66Gy/2 Gy	Overall survival, Quality of life, Overall survival

Stahl 2005 RCT; Germany; n=174	100% SCC T3-4/ N0-1/ M0 thoracic oesophageal cancers	Induction CRT: 5 three cycles of FU, leucovorin, etoposide and cisplatin AND 40Gy/2Gy (concurrent) Sx: Two-stage approach with two-field lymphadenectomy	Cisplatin and etoposide AND 60Gy/2Gy then brachytherapy (OR) cisplatin and etoposide AND 50Gy/2Gy plus 15Gy/1.5 Gy twice daily	Overall mortality, Treatment-related mortality, Overall survival

n=total number of patients;
CRT=Chemoradiotherapy; 5 FU = 5-fluorouracil; RCT= randomised controlled trials; RT=Radiotherapy; SCC=Squamous cell carcinoma; Sx=Surgery

Outcomes for disease free survival, treatment-related morbidity or number going on to salvage resection were not able to be extracted.

8.6.3.3 Chemoradiotherapy followed by surgery versus chemotherapy followed by surgery

Table 111. Summary of included studies: Chemoradiotherapy followed by surgery versus chemotherapy followed by surgery

Study ID	Population	CRT/CT	Surgery	Outcomes
Cao 2009 RCT; China; n=237	100%SCC Male%: 53 Stage III or IV %: 93	CT: cisplatin (20 mg/m^2/day) and 5FU (500 mg/m^2/day) 24hr infusion on days 1-5 with mitomycin infusion (10 mg/m^2/day) on day 1 CRT: same CT used AND a total of 40Gy RT in daily fractions of 2 Gy (days 1–5, 8–12, 15–19, and 22–26) (concurrent)	Oesophagectomy through left thoracotomy with 2-field lymphadenectomy	Anastomotic leak, Any postoperative mortality, Any mortality, Overall survival, Stenosis
Klevebro 2015 RCT; Norway/Sweden; n=181 (SCC subgroup n=50)	Age (median); 63 years Male%: 83 N0 tumour %: SCC%: 28	CT: three cycles of cisplatin (100 mg/m^2, day 1) and 5 FU (750 mg/m^2/24 hr, days 1-5). Each cycle lasted 21 days. CRT: same CT used AND a total of 40Gy RT (2 Gy/day in 20 fractions, 5 days a week) with CT cycles 2 and 3 (concurrent)	Ivor-Lewis or McKeown or Transhiatal approach depending on the site of tumour	Any mortality, Overall survival, Progression-free survival
Nygaard 1992 RCT; Norway; n=217	100% SCC Age (median): 63 years Male %: 71	CT: cisplatin (20 mg/m^2 on days 1-5 and 15-19) and bleomycin (5 mg/m^2 on days 1-5 and 15-19) CRT: same CT used and a total of 35 Gy RT (1.75 Gy/fraction over 4 weeks) (sequential)	Laparotomy with right thoracotomy	Any treatment-related complication, Anastomotic leak, Any mortality, Any postoperative mortality,

n=total number of patients;
CRT=Chemoradiotherapy; CT= Chemotherapy 5 FU = 5-fluorouracil; RCT= randomised controlled trials; RT=Radiotherapy; SCC=Squamous cell carcinoma; Sx=Surgery
Note – The same type of surgery was applied in either arm, unless specified.

Outcomes for disease free survival, health related quality of life or number going on to salvage resection were not able to be extracted.

8.6.3.4 Surgery followed by chemoradiotherapy versus surgery alone

Table 112. Summary of included studies: Surgery followed by chemoradiotherpy versus surgery alone

Study ID	Population	CRT	Surgery	Outcomes
Lv 2010 RCT; China; n=160	100% SCC Age (≥60 years) %: 56 Male %: 64	Cisplatin 20 mg/m^2 on days 1–3 and 22–24 and paclitaxel 135 mg/m^2 starting on days 1 and 22 of RT AND 40 Gy RT, in 20 fractions over 4weeks (concurrent)	Oesophagectomy through left or right thoracotomy with 2-field lymphadenectomy	10-years overall survival rate, 10-years progression free survival rate

n=total number of patients;
CRT=Chemoradiotherapy; RCT= randomised controlled trials; RT=Radiotherapy; SCC=Squamous cell carcinoma
Note – The same type of surgery was applied in either arm, unless specified.

Outcomes for disease free survival, treatment-related mortality, treatment related morbidity, health related quality of life or number going on to salvage resection were not able to be extracted.

8.6.3.5 Chemoradiotherapy alone versus surgery alone

Table 113. Summary of included studies: Chemoradiotherapy alone versus surgery alone

Study ID	Population	CRT	Surgery	Outcomes
Chiu 2005/Teoh 2012 RCT; China; n=80	100% SCC Age (mean): 62 years	Two cycles of cisplatin and 5FU (3-weeky cycle) AND 50-60 Gy RT in 20-30 fractions over 5-6 weeks	Two or three stage approach with two-field lymphadenectomy	Overall survival, Disease free survival, 30-days mortality

n=total number of patients;
CRT=Chemoradiotherapy; 5FU= 5-fluorouracil; RCT= randomised controlled trials; RT=Radiotherapy; SCC=Squamous cell carcinoma

Outcomes for treatment-related mortality, treatment related morbidity, health related quality of life or number going on to salvage resection were not able to be extracted.

8.6.3.6 Surgery alone versus radiotherapy alone

Table 114. Summary of included studies: Surgery alone versus radiotherapy alone

Study ID	Population	Surgery	RT	Outcomes
Badwe 1998 RCT; n=99; India	100% SCC Age (mean): 52 years Male %: 71	Standard Ivor-Lewis approach or total oesophagectomy	50 Gy in 28 fractions followed by an external boost of 15 Gy in 8 fractions or intraluminal radiotherapy of 15 Gy with 200 cGy/hour dose rate at 1 cm off axis	Overall survival, Treatment-related mortality

Fok 1994 RCT; n=74; Hong Kong	100% SCC Age(mean): 56 years	3-stage oesophagectomy	45 to 53 Gy over four to five weeks	Overall survival, Treatment-related mortality

n=total number of patients;
RCT= randomised controlled trials; RT=Radiotherapy; SCC=Squamous cell carcinoma

Outcomes for disease free survival, treatment related morbidity, health related quality of life or number going on to salvage resection were not able to be extracted.

8.6.3.7 Chemotherapy followed by surgery versus surgery alone

Table 115. Summary of included studies: Chemotherapy followed by surgery versus surgery alone

Study ID	Population	Chemotherapy	Surgery	Outcomes
Ancona 2001 RCT; Italy; n=96	100% SCC Age(mean): 58 years Male: 81%	Cisplatin 100 mg/m^2 x 1 D x 2-3 cycles + 5-FU 1000 mg/m^2 x 1 D x 2-3 cycles Post-CT and radiation were given as additive therapy for people with residual disease.	Laparotomy, right thoracotomy and left cervical incision with en bloc lymphadenectomy	Any postoperative complication, Anastomotic leak, Postoperative mortality, Treatment-related mortality, Overall survival
Baba 1998/Baba 2000 RCT; Japan; n=42	100% SCC	Cisplatin 70 mg/m^2 x 1D x 2 cycles + 5-FU 700 mg/m^2 x 5 Ds x 2 cycles + Leucovorin 20 mg/m^2 x 5 Ds x 2 cycles	Right thoracotomy, laparotomy and cervicotomy with two-field or three-field resection	Anastomotic leak, Postoperative mortality, Treatment-related mortality
Boonstra 2011 RCT; Netherlands; n=169	100% SCC Age (median): 60 years Male %: 75	Cisplatin (80 mg/m^2 on days 1 and 22), IV etoposide (100mg/m^2 on days 1,2,22,23) and etoposide (oral) 200mg/m^2 on days 3,5,24,26	Right or transhiatal thoracotomy depending on tumour site with en bloc lymphadenectomy	Any postoperative complication, Anastomotic leak, 30-days mortality, Postoperative mortality, Treatment-related mortality, Disease free survival, Overall survival
Cao 2009 RCT; China; n=237	100%SCC Male%: 53 Stage III or IV %: 93	Cisplatin (20 mg/m^2/day) and 5-FU (500 mg/m^2/day) 24hr infusion on days 1-5 with mitomycin infusion (10 mg/m^2/day) on day 1	Oesophagectomy through left thoracotomy with 2-field lymphadenectomy	Anastomotic leak, 30-days mortality, Postoperative mortality, Treatment-related mortality
Law 1997 RCT; Hong Kong; n=147	100% SCC Age (mean) : 63.5 years Male: 85%	Cisplatin 100 mg/m^2 x 1D x 2 cycles + 5-FU 500 mg/m^2 x 5Ds x 2 cycles	Laparotomy and right thoracotomy with mediastinal lymphadenectomy (or transhiatal with cervical anastomosis only	Anastomotic leak, 30-days mortality, Postoperative mortality, Treatment-related mortality,

			for those with cardiopulmonary reserves)	Intraoperative blood loss, Wound infection,
Maipang 1994; Thailand; n=46	100% SCC Age(mean): 64.5 years	Cisplatin day 1, vinblastine on days 1, 8, 15, 22 and bleomycin on day 3 over 4 days. The cycle repeated on day 29. Surgery performed 2 weeks after completion of 2nd cycle	Standard Ivor-lewis oesophagectomy and cervical anastomosis	Treatment-related mortality, Overall survival
MRC Allum 2002 RCT; UK; n=802 (SCC subgroup = 247)	31% SCC Age(median): 63 years Male %: 75	Cisplatin 80 mg/m^2 x 1D x 2 cycles + 5-FU 1000 mg/m^2 x 4 Ds x 2 cycles External beam radiotherapy was given irrespective of randomisation (25-32.5 Gy in 10 fractions).	Surgical approach depending on the tumour site and local practice	Overall survival
Nygaard 1992 RCT; Scandinavia; n=106	100% SCC of oesophagus; Age(median): 63 years Male: 71%	Cisplatin 20 mg/m^2 x 5Ds x 2 cycles + bleomycin 10mg/m^2 x 5Ds x 2 cycles	Laparotomy with right thoracotomy	Any postoperative complication, Anastomotic leak, 30-days mortality, Postoperative mortality
Schlag 1992 RCT; Germany; n=46	SCC of oesophagus, Age: 56.8 years Male: 89%	Cisplatin 20 mg/m^2 for 5 days for 3 cycles + 5-FU 1000 mg/m^2 for 5 days for 3 cycles if responder after 1st cycle	Abdominothoracic oesophagectomy or thoracoabdomino-cervical approach depending on the site of tumour with 2-field lymph node resection	

n=total number of patients;

CT= Chemotherapy; 5 FU= 5-fluorouracil; IV=intravenous; Post-CT= postoperative chemotherapy; RCT= randomised controlled trials; SCC=Squamous cell carcinoma

Note – The same type of surgery was applied in either arm, unless specified.

Outcomes for health related quality of life or number going on to salvage resection were not able to be extracted.

8.6.3.8 Chemoradiotherapy versus radiotherapy alone

Table 116. Summary of included studies: Chemoradiotherapy versus radiotherapy alone

Study ID	Population	Chemoradiotherapy/ Radiotherapy	Outcomes
Araujo 1991 RCT; Brazil; n=59	100% SCC < 70 years Stage II	CT: 5-FU IV infusion day 1-3, mitomycin day 1, bleomycin IM day 1,7,14,21,28 RT: 50 Gy in 25 fr (BED= 38) CRT: concurrent	Stenosis, Overall survival

Cooper 1999 RCT; USA; n=129*	SCC%: 83 Also include mediastinal and supraclavicular lymph nodes	CT: 5-FU infusion day 1-4, for weeks 1,5,8,11 RT: 50 Gy in 25 fr (BED = 38) (RT only arm) RT: 64 Gy in 32 fr (BED= 44.8) (CRT arm) CRT: concurrent	Overall survival, Disease free survival
Gao 2002 RCT; China; n=81	100% SCC Age ≤ 70 years No supraclavicular lymph nodes No distant metastatsis	CT: Cisplatin 20 mg/d day 1-5, for weeks 1,4 RT: 30 Gy in 15 fr, OD, week 1-3, then 30 Gy in 20 fr, BID, week 4-5 (BED= 51) CRT: concurrent	Overall survival, Disease free survival
Han 2012 RCT; China; n=130	100% SCC	CT: nedaplatin + 5-FU RT: Conventional fraction 64-66 Gy CRT: concurrent	Overall survival
Hatlevoll 1992 RCT; Norway; n=100	100% SCC Age < 75 years Inoperable tumour	CT: ciplatin day 1-5, day 15-19, bleomycin day 1-5, day 15-19 RT: 35 Gy in 20 fr, 3 week gap, 28 Gy in 16 fr (BED= 25) CRT: sequential	Overall survival
Herskovic 1992/Al-Sarraf 1997 RCT; England; n=121	SCC %: 92	CT: cisplatin + 5-FU RT: conventional fraction 50 Gy CRT: concurrent	Overall survival
Kumar 2007 RCT; India; n=125	100% SCC	CT: cisplatin RT: conventional fraction plus LCAF RT 50-64 Gy CRT: concurrent	Stenosis, Overall survival
Slabber 1998 RCT; South Africa; n=36	100% SCC T3NxM0	CT: cisplatin 15 mg/m^2/day bolus, 5-FU 600 mg/m^2/day infusion day 1-5,29,33 RT: 20 Gy in 5 fr day 1-5, then 20 Gy in 5 fr day 29-33 (BED= 34) CRT: concurrent	Overall survival
Smith 1998 RCT; USA; n=119	100% SCC Male %: 80 Stage I or II	CT: 5FU (1000 mg/m^2/day day 2-4, repeated on day 28) and mitomycin (10mg/m^2 day 2) RT: a total of 6000 cGy over 6.5 to 7 weeks CRT: concurrent	Treatment-related mortality, Overall survival
Zhao 2005 RCT; China; n=111	100% SCC	CT: cisplatin+5-FU RT: conventional fraction+LCAF 68.4 Gy CRT: concurrent	Treatment-related mortality, Stenosis, Overall survival

Zhu 2000 RCT; China; n=66	100% SCC Age < 70 years Excluded supraclavicular lymph nodes	CT: carboplatin 100mg/d x 5 days Day 1-5, 27-31 RT: external beam RT 60 Gy in 30 fr OR 38 Gy in 19 fr, then 12 Gy in 6 fr, then intracavitary 15-16 Gy in 3 fr (BED= 45) CRT: concurrent	Overall survival

n=total number of patients;
**only 121 participants were included for analyses.*
BED= biological equivalent dose; CRT= chemoradiotherapy; CT=chemotherapy; fr= fraction; 5-FU = 5-fluorouracil; IM=intramuscular; IV=intravascular; LCAF= late course accelerated fractionation raditotherapy; RCT= randomised controlled trials; RT=Radiotherapy; SCC=Squamous cell carcinoma
Note: The same form of radiotherapy was given in either arm, unless specified.

Outcomes for health related quality of life or number going on to salvage resection were not able to be extracted.

8.6.4 Clinical evidence profiles

Subgroup analyses were performed according to type of chemoradiotherapy or type of surgical approach, where relevant. The clinical evidence profiles for curative treatment of squamous cell carcinoma of the oesophagus can be found in Table 117 to Table 124.

8.6.4.1 Chemoradiotherapy followed by surgery versus surgery alone

Table 117. Summary clinical evidence profile. Chemoradiotherapy followed by surgery versus surgery alone

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)
	Assumed risk surgery alone	Corresponding risk chemoradiotherapy followed by surgery			
Postoperative mortality - Any chemoradiotherapy and/or Surgery	42 per 1000	80 per 1000 (50 to 130)	RR 1.9 (1.18 to 3.07)	1069 (8 studies)	low [1,2,3,4,5,6,7,8,9]
Postoperative mortality – Concomitant CRT	32 per 1000	73 per 1000 (41 to 130)	RR 2.25 (1.26 to 4.02)	907 (6 studies)	moderate [1,2,3,4,6,7,8]
Postoperative mortality – Sequential CRT	100 per 1000	126 per 1000 (54 to 297)	RR 1.26 (0.54 to 2.97)	162 (2 studies)	very low [5,10]
Postoperative mortality – Transhiatal approach	120 per 1000	100 per 1000 (32 to 306)	RR 0.83 (0.27 to 2.55)	100 (1 study)	very low [3,10]
Postoperative mortality - 2-stage approach	132 per 1000	170 per 1000 (61 to 478)	RR 1.29 (0.46 to 3.63)	85 (1 study)	very low [5,10]
Postoperative mortality - 2 or 3 stage approach	33 per 1000	104 per 1000 (50 to 217)	RR 3.16 (1.51 to 6.6)	528 (3 studies)	moderate [6,7,8]

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)
	Assumed risk surgery alone	Corresponding risk chemoradiotherapy followed by surgery			
Postoperative mortality - Left thoracotomy approach			No event in either arm	236 (1 study)	low[1,18]
Postoperative mortality - Unspecified surgical approach	46 per 1000	71 per 1000 (18 to 272)	RR 1.53 (0.39 to 5.9)	120 (2 studies)	very low [2,4,10]
30-day mortality – Any chemoradiotherapy and/or surgical approach	24 per 1000	51 per 1000 (21 to 123)	RR 2.07 (0.85 to 5.03)	491 (3 studies)	low [1,5,8,9]
30-day mortality – Concomitant CRT	5 per 1000	32 per 1000 (4 to 259)	RR 6.59 (0.81 to 53.59)	406 (2 studies)	low [1,8,9]
30-day mortality – Sequential CRT	132 per 1000	170 per 1000 (61 to 478)	RR 1.29 (0.46 to 3.63)	85 (1 study)	very low [5,10]
30-day mortality - 2-stage approach	132 per 1000	170 per 1000 (61 to 478)	RR 1.29 (0.46 to 3.63)	85 (1 study)	very low [5,10]
30-day mortality - 2 or 3 stage approach	11 per 1000	74 per 1000 (9 to 602)	RR 6.59 (0.81 to 53.59)	170 (1 study)	low [8,9]
30-day mortality - Left thoracic approach			No event in either arm	236 (1 study)	low[1,18]
Treatment-related mortality - Any chemoradiotherapy and/or surgical approach	29 per 1000	63 per 1000 (35 to 114)	RR 2.17 (1.2 to 3.91)	969 (7 studies)	low [1,2,4,6,7,9,11,12]
Treatment-related mortality – Concomitant CRT	25 per 1000	61 per 1000 (32 to 116)	RR 2.43 (1.27 to 4.63)	888 (6 studies)	moderate [1,4,6,7,11,12]
Treatment-related mortality – Sequential CRT	71 per 1000	77 per 1000 (16 to 359)	RR 1.08 (0.23 to 5.02)	81 (1 study)	very low [2,10]
Treatment-related mortality - 2-stage approach	147 per 1000	143 per 1000 (46 to 450)	RR 0.97 (0.31 to 3.06)	69 (1 study)	very low [10,11]
Treatment-related mortality - 2 or 3-stage approach	32 per 1000	104 per 1000 (43 to 253)	RR 3.21 (1.32 to 7.79)	378 (2 studies)	moderate [6,7]
Treatment-related mortality - Left thoracotomy approach			No event in either arm	236 (1 study)	low[1,18]

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)
	Assumed risk surgery alone	Corresponding risk chemoradiotherapy followed by surgery			
Treatment-related mortality - Left or right thoracotomy approach	0 per 1000	0 per 1000 (0 to 0)	RR 7 (0.37 to 133.36)	160 (1 study)	very low [10,12]
Treatment-related mortality - Unspecified surgical approach	46 per 1000	63 per 1000 (16 to 246)	RR 1.37 (0.35 to 5.32)	126 (2 studies)	very low [2,4,10]
Overall survival rate – Any type of CRT and/or surgical approach	170 per 1000	241 per 1000 (185 to 313)	RR 1.42 (1.09 to 1.84)	789 (7 studies)	low [2,7,8,9,11,12,13,14]
Overall survival rate – Concomitant CRT	173 per 1000	245 per 1000 (187 to 323)	RR 1.42 (1.08 to 1.87)	703 (6 studies)	low [7,8,9,11,12,13,14]
Overall survival rate – Sequential CRT	149 per 1000	206 per 1000 (82 to 515)	RR 1.38 (0.55 to 3.46)	86 (1 study)	very low [2,10]
Overall survival rate - 2-stage approach	88 per 1000	229 per 1000 (66 to 790)	RR 2.59 (0.75 to 8.95)	69 (1 study)	very low [10,11]
Overall survival rate - 2-stage or transhiatal approach	93 per 1000	195 per 1000 (63 to 599)	RR 2.1 (0.68 to 6.44)	84 (1 study)	very low [10,14]
Overall survival - 2 or 3 stage approach	274 per 1000	288 per 1000 (208 to 400)	RR 1.05 (0.76 to 1.46)	295 (2 studies)	very low [7,8,10]
Overall survival - Left or right thoracotomy	125 per 1000	250 per 1000 (125 to 500)	RR 2 (1 to 4)	160 (1 study)	low [9,12]
Overall survival - Not reported surgical approach	113 per 1000	192 per 1000 (94 to 391)	RR 1.69 (0.83 to 3.45)	181 (2 studies)	low [2,9,13]
Overall survival (OS) - Concomitant CRT and any type of surgical approach	OS* 31%	35% (30% to 41%)	HR 0.89 (0.76 to 1.03)	986 (6 studies)	moderate [6,11,7,8,14,13]
Overall survival - 2 stage approach	5-years OS 10%	16% (5% to 33%)	HR 0.8(0.48 to 1.34)	69 (1 study)	very low [11,10]
Overall survival - 2 or 3 stage approach	OS* 39%	41% (33% to 48%)	HR 0.96(0.79 to 1.18)	577 (3 studies)	low [6,7,8,9]
Overall survival - 2 stage or transhiatal approach	5-years OS 34%	62% (40% to 77%)	HR 0.45 (0.24 to 0.84)	84 (1 study)	low [14,9]

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)
	Assumed risk surgery alone	Corresponding risk chemoradiotherapy followed by surgery			
Overall survival – unspecified surgical approach	5-years OS 25%	29% (19% to 40%)	HR 0.89 (0.67 to 1.19)	256 (1 study)	low [9,12]
Disease free survival rate – Concomitant CRT and any type of surgical approach	278 per 1000	470 per 1000 (328 to 668)	RR 1.69 (1.18 to 2.4)	756 (5 studies)	very low [6,7,8,9,12,13,15]
Disease free survival rate - 2 or 3 stage approach	342 per 1000	495 per 1000 (297 to 823)	RR 1.45 (0.87 to 2.41)	501 (3 studies)	low [6,7,8,9]
Disease free survival rate - Left or right thoracotomy approach	62 per 1000	188 per 1000 (71 to 491)	RR 3 (1.14 to 7.86)	160 (1 study)	low [9,12]
Disease free survival rate - Unspecified surgical approach	320 per 1000	666 per 1000 (422 to 1000)	RR 2.08 (1.32 to 3.28)	95 (1 study)	high[13]
Disease free survival - Cocomitant CRT and 2 or 3 stage open oesophagectomy	-	-	HR 0.77 (0.63 to 0.95)	577 (3 studies)	low[6,7,8,9]
Any post-operative complication – Any type of CRT and/or surgical approach	314 per 1000	317 per 1000 (254 to 398)	RR 1.01 (0.81 to 1.27)	690 (5 studies)	low [2,5,6,7,8,9]
Any post-operative complication – Concomitant CRT	292 per 1000	304 per 1000 (234 to 394)	RR 1.04 (0.8 to 1.35)	528 (3 studies)	very low [2,6,7,8,10]
Any post-operative complication – Sequential CRT	388 per 1000	372 per 1000 (252 to 554)	RR 0.96 (0.65 to 1.43)	162 (2 studies)	very low [5,10]
Any post-operative complication - 2-stage approach	342 per 1000	342 per 1000 (188 to 616)	RR 1 (0.55 to 1.8)	85 (1 study)	very low [5,10]
Any post-operative complication - 2 or 3-stage approach	292 per 1000	304 per 1000 (234 to 394)	RR 1.04 (0.8 to 1.35)	528 (3 studies)	very low [6,7,8,10]
Any post-operative complication – Unspecified surgical approach	429 per 1000	399 per 1000 (236 to 681)	RR 0.93 (0.55 to 1.59)	77 (1 study)	very low [2,10]
Post-operative complication: Anastomotic leak	34 per 1000	45 per 1000 (23 to 87)	RR 1.32 (0.67 to 2.59)	761 (7 studies)	very low [1,2,3,4,5,10,11,12]

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)
	Assumed risk surgery alone	Corresponding risk chemoradiotherapy followed by surgery			
Post-operative complication: Anastomotic leak – Concomitant CRT	26 per 1000	32 per 1000 (14 to 77)	RR 1.23 (0.52 to 2.93)	599 (5 studies)	very low [1,3,4,10,11,12]
Post-operative complication: Anastomotic leak – Sequential CRT	62 per 1000	92 per 1000 (31 to 271)	RR 1.47 (0.5 to 4.33)	162 (2 studies)	very low [5,2,10]
Post-operative complication: Anastomotic leak - Transhiatal approach	20 per 1000	7 per 1000 (0 to 160)	RR 0.33 (0.01 to 7.99)	100 (1 study)	very low [3,10]
Post-operative complication: Anastomotic leak - 2-stage approach	56 per 1000	41 per 1000 (9 to 181)	RR 0.74 (0.17 to 3.26)	145 (2 studies)	very low [5,10,11]
Post-operative complication: Anastomotic leak - Left thoracotomy approach	8 per 1000	25 per 1000 (3 to 241)	RR 3 (0.32 to 28.43)	236 (1 study)	very low [1,10]
Post-operative complication: Anastomotic leak - Left or right thoracotomy approach	0 per 1000	0 per 1000 (0 to 0)	RR 3 (0.12 to 72.56)	160 (1 study)	very low [10,12]
Post-operative complication: Anastomotic leak - Unspecified surgical approach	108 per 1000	163 per 1000 (66 to 405)	RR 1.51 (0.61 to 3.76)	120 (2 studies)	very low [2,4,10]
Post-operative complication: Infection – Any type of CRT and surgical approach	154 per 1000	242 per 1000 (154 to 377)	RR 1.57 (1 to 2.45)	258 (2 studies)	low [5,8,9]
Post-operative complication: Infection – Concomitant CRT	56 per 1000	99 per 1000 (34 to 290)	RR 1.76 (0.6 to 5.16)	170 (1 study)	very low [8,10]
Post-operative complication: Infection – Sequential CRT	366 per 1000	552 per 1000 (344 to 893)	RR 1.51 (0.94 to 2.44)	88 (1 study)	low [5,9]
Post-operative complication: Infection - 2-stage approach	366 per 1000	552 per 1000 (344 to 893)	RR 1.51 (0.94 to 2.44)	88 (1 study)	low [5,9]

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)
	Assumed risk surgery alone	Corresponding risk chemoradiotherapy followed by surgery			
Post-operative complication: Infection - 2 or 3 stage approach	56 per 1000	99 per 1000 (34 to 290)	RR 1.76 (0.6 to 5.16)	170 (1 study)	very low [8,10]
Post-operative complication: stenosis (Concomitant CRT and Left or right thoracotomy approach)	12 per 1000	25 per 1000 (2 to 270)	RR 2 (0.19 to 21.62)	160 (1 study)	very low [10,12]
Blood loss in surgery (ml) (Concomitant CRT and Transhiatal approach)		The mean blood loss in surgery (ml) (concomitant; transhiatal) in the intervention groups was 10 higher (1.92 to 18.08 higher)		100 (1 study)	low [3,16]
Intraoperative treatment-related morbidity: Haemorrhage (>300 mL) (Concomitant CRT and Left or right thoracotomy approach)	25 per 1000	100 per 1000 (22 to 457)	RR 4 (0.88 to 18.26)	160 (1 study)	low [9,12]

[1] Cao 2009 - Unclear randomisation, allocation concealment and blinding
[2] Le Prise 1994 - Unclear randomisation, allocation concealment and blinding
[3] Mashhadi 2015 - Unclear allocation concealment and blinding
[4] Natsugo 2006 - Unclear randomisation, allocation concealment and blinding
[5] Nygaard 1992 - Unclear randomisation, allocation concealment and blinding
[6] Bosset 1997 - Unclear randomisation, allocation concealment and blinding
[7] Lee 2004 - Unclear randomisation, allocation concealment and blinding
[8] Mariette 2014 - Unclear allocation concealment and blinding
[9] 95% CI crossed 1 default MID
[10] 95%CI crossed 2 default MIDs
[11] Apinop 1994 - Unclear randomisation, allocation concealment and blinding
[12] Lv 2010 - Unclear allocation concealment and blinding
[13] Burmeister 2015 - appropriate randomisation and adequate allocation concealment and blinding of research staff and investigators
[14] van Hagen 2012 - unclear randomisation, allocation concealment and blinding
[15] I2>50%
[16] Default MID: +/-7.5 ml; 95% CI crossed 1 MID
[17] I2>80%
[18] No event in either arm

**OS/DFS was calculated from survival rate at 5 years or, if it was less than 5 years, the survival rate from the last year available.*

95% CI = 95% Confidence interval; CRT= chemoradiotherapy; DFS = Disease free survival; OS = overall survival;RR=relative risk; HR=Hazard ratio

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)
	Assumed risk surgery alone	Corresponding risk chemoradiotherapy followed by surgery			

8.6.4.2 Chemoradiotherapy followed by surgery versus chemoradiotherapy alone

Table 118: Summary clinical evidence profile. Chemoradiotherapy (concomitant) followed by surgery versus chemoradiotherapy (concomitant) alone

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)
	Assumed risk CRT alone	Corresponding risk CRT followed by surgery			
Overall mortality estimates - 2-stage approach	872 per 1000	802 per 1000 (706 to 916)	RR 0.92 (0.81 to 1.05)	172 (1 study)	moderate[1]
Treatment related mortality - 2-stage approach	35 per 1000	128 per 1000 (37 to 442)	RR 3.67 (1.06 to 12.68)	172 (1 study)	low [1,2]
3-years overall survival rate - unspecified surgical approach	192 per 1000	179 per 1000 (108 to 298)	RR 0.93 (0.56 to 1.55)	259 (1 study)	very low [3,4]
Overall survival (Concomitant CRT and any type of surgical approach)	OS* 18%	18% (12% to 26%)	HR 0.99 (0.79 – 1.24)	431 (2 studies)	low [1,2,3]
Overall survival – 2 stage oesophagectomy approach	5-years OS 13%	10% (4% to 19%)	HR 1.15 (0.82 – 1.61)	172 (1 study)	low [1,2]
Overall survival – unspecified surgical approach	4-years OS 22%	26% (16% to 37%)	HR 0.89 (0.66 – 1.20)	259 (1 study)	low [2,3]
Quality of life index (Spitzer) at		The mean quality of life index (spitzer) at 5-years follow-up (5-		62 (1 study)	low [3,5]

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)
	Assumed risk CRT alone	Corresponding risk CRT followed by surgery			
5-years follow-up (5-25 months) (surgical approach unspecified)		25 months) in the intervention groups was 0.95 higher (0.2 lower to 2.1 higher)			

[1] *Stahl 2005/2008 - Unclear randomisation and allocation concealment; unblinded*
[2] *95%CI crossed 1 default MID*
[3] *Bonnetain 2006/Bedenne 2007 - Unclear randomisation and blinding*
[4] *95%CI crossed 2 MIDs*
[5] *Default MID: +/- 1.29; 95%CI crossed 1 MID*

**OS was calculated from survival rate at 5 years or, if it was less than 5 years, the survival rate from the last year available.*

95% CI = 95% Confidence interval; CRT= chemoradiotherapy; DFS = Disease free survival; OS = overall surviva; RR=relative risk; HR=Hazard ratio

8.6.4.3 Chemoradiotherapy followed by surgery versus chemotherapy followed by surgery

Table 119: Summary clinical evidence profile. Chemoradiotherapy followed by surgery versus chemotherapy followed by surgery

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)
	Assumed risk CT followed by surgery	Corresponding risk CRT followed by surgery			
Mortality - Any type of CRT and any type of surgical approach	32 per 1000	47 per 1000 (21 to 108)	RR 1.49 (0.65 to 3.39)	506 (3 studies)	very low [1,2,3,4]
Mortality - Concomitant CRT	10 per 1000	24 per 1000 (5 to 121)	RR 2.53 (0.5 to 12.69)	418 (2 studies)	very low [2,3,4]
Mortality – Sequential CRT	146 per 1000	170 per 1000 (64 to 449)	RR 1.16 (0.44 to 3.07)	88 (1 study)	very low [1,4]
Mortality - 2-stage approach	38 per 1000	43 per 1000 (16 to 115)	RR 1.16 (0.44 to 3.07)	325 (2 studies)	very low [1,2,4]
Mortality - 2 or 3-stage approach	22 per 1000	56 per 1000 (11 to 279)	RR 2.53 (0.5 to 12.69)	181 (1 study)	very low [3,4]
Any postoperative mortality - any type of CRT and any type of surgical approach	38 per 1000	43 per 1000 (16 to 115)	RR 1.16 (0.44 to 3.07)	325 (2 studies)	very low [1,2,4]
Any postoperative mortality -			No event in either arm	237 (1 study)	low[2,7]

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)
	Assumed risk CT followed by surgery	Corresponding risk CRT followed by surgery			
Concomitant CRT					
Any postoperative mortality – Sequential CRT	146 per 1000	170 per 1000 (64 to 449)	RR 1.16 (0.44 to 3.07)	88 (1 study)	very low [1,4]
Any postoperative mortality - 2-stage approach	38 per 1000	43 per 1000 (16 to 115)	RR 1.16 (0.44 to 3.07)	325 (2 studies)	very low [1,2,4]
3-years overall survival rate – Concomitant CRT	562 per 1000	709 per 1000 (591 to 844)	RR 1.26 (1.05 to 1.5)	287 (2 studies)	low [2,3,5]
3-years overall survival rate - 2-stage approach	571 per 1000	737 per 1000 (611 to 891)	RR 1.29 (1.07 to 1.56)	237 (1 study)	low [2,5]
3-years overall survival rate - 2 or 3-stage approach	520 per 1000	562 per 1000 (338 to 936)	RR 1.08 (0.65 to 1.8)	50 (1 study)	very low [3,4]
Overall survival (OS) – Concomitant CRT and 2 or 3 stage oeosphagectomy	5-years OS 49%	69% (38% to 87%)	HR 0.52 (0.2 – 1.36)	50 (1 study)	very low [2,5]
Progression-free survival rate – Concomitant CRT and 2 or 3 stage approach	520 per 1000	562 per 1000 (338 to 936)	RR 1.08 (0.65 to 1.8)	50 (1 study)	very low [3,4]
Treatment-related morbidity: Any complication – Sequential CRT and 2-stage approach	341 per 1000	341 per 1000 (191 to 608)	RR 1 (0.56 to 1.78)	88 (1 study)	very low [1,4]
Post-operative complication: Anastomotic leak - any type of CRT and any type of surgical approach	19 per 1000	29 per 1000 (2 to 335)	RR 1.53 (0.13 to 17.89)	325 (2 studies)	very low [1,2,4,6]
Post-operative complication: Anastomotic leak –	0 per 1000	0 per 1000 (0 to 0)	RR 7.06 (0.37 to 135.18)	237 (1 study)	very low [2,4]

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)
	Assumed risk CT followed by surgery	Corresponding risk CRT followed by surgery			
Concomitant CRT					
Post-operative complication: Anastomotic leak - Sequential CRT	73 per 1000	42 per 1000 (7 to 242)	RR 0.58 (0.1 to 3.31)	88 (1 study)	very low [1,4]
Post-operative complication: Anastomotic leak - 2-stage approach	19 per 1000	29 per 1000 (2 to 335)	RR 1.53 (0.13 to 17.89)	325 (2 studies)	very low [1,2,4,6]
Post-operative complication: stenosis – Concomitant CRT and 2-stage approach	0 per 1000	0 per 1000 (0 to 0)	RR 5.04 (0.24 to 103.91)	237 (1 study)	very low [2,4]

[1] Nygaard 1992 - Unclear randomisation, allocation concealment and blinding
[2] Cao 2009 - Unclear randomisation, allocation concealment and blinding
[3] Klevebro 2015 - Unclear randomisation and allocation concealment and blinding
[4] 95% CI crossed 2 default MID
[5] 95% CI crossed 1 default MID
[6] I2>50%
[7] no event in either arm
95% CI = 95% Confidence interval; CRT= chemoradiotherapy; OS = overall survival;RR=relative risk;HR=Hazard ratio

8.6.4.4 Surgery followed by chemoradiotherapy versus surgery alone

Table 120: Summary clinical evidence profile. Surgery (left or right open oesophagectomy) followed by chemoradiotherapy (concomitant) versus surgery (left or right open oesophagectomy) alone

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)
	Assumed risk surgery alone	Corresponding risk surgery followed by CRT			
10-year overall survival rate	125 per 1000	244 per 1000 (121 to 490)	RR 1.95 (0.97 to 3.92)	158 (1 study)	low [1,2]
10-year progression free survival rate	62 per 1000	179 per 1000 (68 to 474)	RR 2.87 (1.09 to 7.59)	158 (1 study)	low [1,2]

[1] Lv 2010 - Unclear allocation concealment and blinding
[2] 95% CI crossed 1 default MID
[3] 95% CI crossed 2 defalt MIDs

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)
	Assumed risk surgery alone	Corresponding risk surgery followed by CRT			

95%CI = 95% confidence interval; CRT = chemoradiotheray;RR=relative risk;

8.6.4.5 Chemoradiotherapy (concomitant) alone versus surgery (2-stage or 3-stage open oesophagectomy) alone

Table 121: Summary clinical evidence profile. Chemoradiotherapy (concomitant) alone versus surgery (2-stage or 3-stage open oesophagectomy) alone

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)
	Assumed risk surgery alone	Corresponding risk CRT alone			
Overall mortality rate (unspecified year)	455 per 1000	418 per 1000 (250 to 691)	RR 0.92 (0.55 to 1.52)	80 (1 study)	very low [1,2]
Overall survival rate at 2 years	545 per 1000	584 per 1000 (398 to 856)	RR 1.07 (0.73 to 1.57)	80 (1 study)	very low [1,2]
Overall survival rate at 5 years	227 per 1000	473 per 1000 (248 to 900)	RR 2.08 (1.09 to 3.96)	80 (1 study)	low [1,3]
Overall survival (OS) at 5 years	5-years OS 47%	50% (26% to 70%)	HR 0.92 (0.47 – 1.79)	80 (1 study)	very low [1,2]
Disease-free survival rate at 2 years	545 per 1000	556 per 1000 (371 to 829)	RR 1.02 (0.68 to 1.52)	80 (1 study)	very low [1,2]
Disease-free survival rate at 5 years	273 per 1000	472 per 1000 (262 to 854)	RR 1.73 (0.96 to 3.13)	80 (1 study)	low [1,3]
30-day mortality	68 per 1000	12 per 1000 (1 to 222)	RR 0.17 (0.01 to 3.26)	80 (1 study)	very low [1,2]

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)
	Assumed risk surgery alone	Corresponding risk CRT alone			

[1] *Chiu 2005/Teoh 2012 - Unclear randomisation, allocation concealment and blinding*
[2] *95% CI crossed 2 default MIDs*
[3] *95% CI crossed 1 default MID*
95%CI = 95% confidence interval; CRT = chemoradiotherapy; OS = Overall survival;RR=relative risk; HR=Hazard ratio

8.6.4.6 Surgery alone versus radiotherapy alone

Table 122: Summary clinical evidence profile. Surgery alone versus radiotherapy alone

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)
	Assumed risk radiotherapy alone	Corresponding risk surgery alone			
Treatment-related mortality - any type of surgical approach	88 per 1000	108 per 1000 (7 to 1000)	RR 1.23 (0.08 to 20.09)	163 (2 studies)	very low [1,2,3,4]
Treatment-related mortality - 2-stage approach	0 per 1000	0 per 1000 (0 to 0)	RR 6.84 (0.36 to 128.68)	87 (1 study)	very low [1,3]
Treatment-related mortality - 3-stage approach	189 per 1000	78 per 1000 (21 to 276)	RR 0.41 (0.11 to 1.46)	76 (1 study)	very low [2,4]
Overall survival rate - any type of surgical approach	218 per 1000	371 per 1000 (229 to 597)	RR 1.7 (1.05 to 2.74)	161 (2 studies)	low [1,2,5]
Overall survival rate - 2-stage approach	326 per 1000	547 per 1000 (329 to 905)	RR 1.68 (1.01 to 2.78)	87 (1 study)	low [1,5]
Overall survival rate - 3-stage approach	86 per 1000	153 per 1000 (41 to 569)	RR 1.79 (0.48 to 6.64)	74 (1 study)	very low [2,4]
Overall survival (OS)– 3 stage approach	5-years OS 7%	31% (15% to 49%)	HR 0.44 (0.27 – 0.72)	74 (1 study)	moderate[3]

[1] *Badwe 1998 - Unclear randomisation and blinding*
[2] *Fok 1994 - Unclear randomisation, allocation concealment and blinding*
[3] *I2>50%*
[4] *95% CI crossed 2 default MIDs*
[5] *95% CI crossed 1 default MID*

95%CI = 95% confidence interval; CRT = chemoradiotherapy; OS = Overall survival;RR=relative risk; HR=Hazard ratio

8.6.4.7 Chemotherapy followed by surgery versus surgery alone

Table 123: Summary clinical evidence profile. Chemotherapy followed by surgery versus surgery alone

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)
	Assumed risk surgery alone	Corresponding risk CT followed by surgery			
30-day mortality - Any type of surgical approach)	39 per 1000	32 per 1000 (15 to 72)	RR 0.84 (0.38 to 1.86)	614 (4 studies)	very low [1,2,3,4,5]
30-day mortality - 2-stage approach	132 per 1000	146 per 1000 (49 to 441)	RR 1.11 (0.37 to 3.35)	79 (1 study)	very low [1,5]
30-day mortality - 2 stage or transhiatal approach	45 per 1000	26 per 1000 (2 to 297)	RR 0.57 (0.05 to 6.57)	298 (2 studies)	very low [2,4,5]
30-day mortality - Left thoracotomy approach			No event in either arm	237 (1 study)	low[3,12]
Treatment-related mortality - Any type of surgical approach	30 per 1000	45 per 1000 (22 to 92)	RR 1.48 (0.73 to 3.03)	728 (6 studies)	very low [2,3,4,5,6,7,8]
Treatment-related mortality - 3 stage approach	29 per 1000	41 per 1000 (9 to 202)	RR 1.4 (0.29 to 6.87)	136 (2 studies)	very low [5,6,7]
Treatment-related mortality - 2 or 3 stage approach	0 per 1000	0 per 1000 (0 to 0)	RR 8.28 (0.47 to 145.5)	46 (1 study)	very low [5,8]
Treatment-related mortality - 2-stage or transhiatal approach	58 per 1000	64 per 1000 (27 to 154)	RR 1.11 (0.47 to 2.66)	309 (2 studies)	very low [2,4,5]
Treatment-related mortality - Left thoracotomy approach			No event in either arm	237 (1 study)	low[3,12]
Postoperative mortality - any type of surgical approach	42 per 1000	46 per 1000 (24 to 88)	RR 1.1 (0.57 to 2.09)	743 (6 studies)	very low [1,2,3,4,5,6,7]
Postoperative mortality - 2-stage approach	132 per 1000	146 per 1000 (49 to 441)	RR 1.11 (0.37 to 3.35)	79 (1 study)	very low [1,5]
Postoperative mortality - 3-stage approach	29 per 1000	32 per 1000 (6 to 187)	RR 1.1 (0.19 to 6.36)	129 (2 studies)	very low [5,6,7]
Postoperative mortality - 2 stage or transhiatal approach	58 per 1000	63 per 1000 (26 to 154)	RR 1.09 (0.44 to 2.65)	298 (2 studies)	very low [2,4,5]
Postoperative mortality - Left thoracotomy approach			No event in either arm	237 (1 study)	low[3,12]

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)
	Assumed risk surgery alone	Corresponding risk CT followed by surgery			
Overall survival rate - any type of surgical approach	83 per 1000	115 per 1000 (65 to 206)	RR 1.39 (0.78 to 2.49)	387 (3 studies)	very low [5,6,8,9]
Overall survival rate - 3 stage approach	64 per 1000	149 per 1000 (41 to 541)	RR 2.33 (0.64 to 8.48)	94 (1 study)	very low [5,6]
Overall survival rate - 2 or 3 stage approach	364 per 1000	291 per 1000 (127 to 673)	RR 0.8 (0.35 to 1.85)	46 (1 study)	very low [5,8]
Overall survival rate– unspecified surgical approach	40 per 1000	73 per 1000 (25 to 212)	RR 1.81 (0.63 to 5.26)	247 (1 study)	very low [5,9]
Overall survival (OS) – Any type of surgical approach	5-years OS 13%	22% (15% to 29%)	HR 0.75 (0.60 – 0.93)	416 (2 studies)	low [3,10,4]
Overall survival – 2 stage or transhiatal oesophagectomy	5-years OS 15%	26% (16% to 38%)	HR 0.71 (0.51 – 0.98)	169 (1 study)	low [3,4]
Overall survival – unspecified surgical approach	5-years OS 12%	19% (11% to 29%)	HR 0.78 (0.58 – 1.04)	247 (1 study)	low [10,4]
Disease free survival rate - 2 stage or transhiatal approach	107 per 1000	224 per 1000 (107 to 465)	RR 2.09 (1 to 4.34)	169 (1 study)	low [2,10]
Disease free survival (DFS) – 2 stage or transhiatal approach	5-years DFS 13%	23% (13% to 35%)	HR 0.72 (0.52 – 1.00)	169 (1 study)	low [3,4]
Anastomotic leakage - any type of surgical approach	50 per 1000	58 per 1000 (33 to 101)	RR 1.15 (0.65 to 2.02)	743 (6 studies)	very low [1,2,3,4,5,6,7]
Anastomotic leakage - 2-stage approach	53 per 1000	73 per 1000 (13 to 414)	RR 1.39 (0.25 to 7.87)	79 (1 study)	very low [1,5]
Anastomotic leakage - 3-stage approach	103 per 1000	106 per 1000 (42 to 269)	RR 1.03 (0.41 to 2.61)	129 (2 studies)	very low [5,6,7]
Anastomotic leakage - 2-stage or transhiatal approach	58 per 1000	76 per 1000 (34 to 172)	RR 1.31 (0.58 to 2.97)	298 (2 studies)	very low [2,4,5]
Anastomotic leakage - Left thoracic approach	8 per 1000	3 per 1000 (0 to 68)	RR 0.33 (0.01 to 8.03)	237 (1 study)	very low [3,5]
Treatment-related morbidity: blood loss - 2-stage or transhiatal approach		The mean treatment-related morbidity: blood loss (2-stage or transhiatal approach) in the intervention groups was		129 (1 study)	moderate [4]

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)
	Assumed risk surgery alone	Corresponding risk CT followed by surgery			
		62 higher (45.71 to 78.29 higher)			
Treatment-related morbidity: wound infection - 2-stage or transhiatal approach	101 per 1000	67 per 1000 (20 to 217)	RR 0.66 (0.2 to 2.14)	129 (1 study)	very low [4,5]

[1] *Nygaard 1992 - Unclear randomisation, allocation concealment and blinding*
[2] *Boonstra 2011 - Unclear allocation concealment and blinding*
[3] *Cao 2009 - Unclear randomisation, allocation concealment and blinding*
[4] *Law 1997 - Unclear randomisation, allocation concealment and blinding*
[5] *95%CI crossed 2 default MIDs*
[6] *Ancona 2001 - Unclear allocation concealment and blinding*
[7] *Baba 2000 - Unclear randomisation, allocation concealment and blinding*
[8] *Maipang 1994 - Unclear randomisation, allocation concealment and blinding*
[9] *MRC 2002 - Unclear randomisation and blinding*
[10] *95% CI crossed 1 default MID*
[11] *Schlag 1992 - Unclear randomisation, allocation concealment and blinding*
[12] *no event in either arm*
95%CI = 95% confidence interval; CRT = chemoradiotherapy; DFS = Disease free survival; OS = Overall survival;RR=relative risk; HR=Hazard ratio

8.6.4.8 Chemoradiotherapy versus radiotherapy alone

Table 124: Summary clinical evidence profile. Chemoradiotherapy versus radiotherapy alone

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)
	Assumed risk radiotherapy alone	Corresponding risk CRT alone			
Treatment related mortality - concomitant CRT	21 per 1000	25 per 1000 (10 to 62)	RR 1.17 (0.47 to 2.9)	652 (8 studies)	very low [1,2,3,4,5,6,7,8,9]
Overall survival rate – sequential CRT	342 per 1000	137 per 1000 (7 to 1000)	RR 0.4 (0.02 to 8.14)	146 (2 studies)	very low [9,10,11,12]
Overall survival rate at 1 year – Concomitant CRT	493 per 1000	597 per 1000 (488 to 730)	RR 1.21 (0.99 to 1.48)	869 (8 studies)	very low [1,2,3,7,8,10,13,14,15,16]
Overall survival rate at 3 years - Concomitant CRT	149 per 1000	271 per 1000 (209 to 353)	RR 1.82 (1.40 to 2.37)	869 (8 studies)	moderate [1,2,3,7,8,13,14,15]

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)
	Assumed risk radiotherapy alone	Corresponding risk CRT alone			
Overall survival rate at 5 years – Concomitant CRT	76 per 1000	177 per 1000 (114 to 271)	RR 2.33 (1.51 to 3.58)	662 (6 studies)	moderate [1,2,3,7,8,14]
Overall survival – Any type of CRT	OS* 5%	12% (8% to 22%)	HR 0.70 (0.5 to 0.84)	426 (5 studies)	low [1,2,3,6,11,16]
Overall survival (OS) - concomitant CRT	OS* 4%	13% (0% to 19%)	HR 0.63(0.51 – 0.77)	329 (4 studies)	moderate [1,2,3,6,16]
Overall survival – sequential CRT	5-years OS 6%	3% (1% to 11%)	HR 1.21(0.77 – 1.90)	97 (1 study)	low [7,16]
Disease free survival rate – concomitant CRT	657 per 1000	578 per 1000 (315 to 1000)	RR 0.88 (0.48 to 1.63)	199 (2 studies)	very low [2,3,9,17]
Disease free survival (DFS) - Concomitant CRT	1-year DFS 55%	72% (63% to 79%)	HR 0.56 (0.40 – 0.78)	199 (2 studies)	very low [2,3,13,16]
Treatment related morbidity – Concomitant CRT	288 per 1000	313 per 1000 (253 to 391)	RR 1.09 (0.88 to 1.36)	612 (6 studies)	low [1,2,6,7,13,14,16]

[1] *Araujo 1991 - Unclear randomisation, allocation concealment, blinding and unclear outcome report*
[2] *Cooper 1999- Unclear randomisation, allocation concealment and blinding*
[3] *Gao 2002 - Unclear randomisation, allocation concealment and blinding*
[4] *Kaneta 1997 - Unclear randomisation, allocation concealment and blinding*
[5] *Slabber 1998 - Unclear randomisation, allocation concealment and blinding*
[6] *Zhu 2000 - Unclear randomisation, allocation concealment and blinding*
[7] *Zhao 2005 - Unclear allocation concealment and blinding*
[8] *Smith 1998 - Unclear blinding*
[9] *95%CI crossed 2 default MIDs*
[10] *I2>50%*
[11] *Hatlevoll 1992 - Unclear randomisation, allocation concealment and blinding*
[12] *Hishikawa 1991 - Unclear randomisation, allocation concealment and blinding*
[13] *Han 2012 - Unclear randomisation, allocation concealment and blinding*
[14] *Kumar 2007 - Unclear randomisation, allocation concealment and blinding*
[15] *Herskovic 1992/Al-Sarraf 1997 - Unclear randomisation, allocation concealment and blinding*
[16] *95%CI crossed 1 default MID*
[17] *I2=75%*

**OS was calculated from survival rate at 5 years or, if it was less than 5 years, the survival rate from the last year available.*

95%CI = 95% confidence interval; CRT = chemoradiotherapy; DFS = Disease free survival; OS = Overall survival;RR=relative risk; HR=Hazard ratio

8.6.5 Economic evidence

The curative treatment of people with squamous cell carcinoma of the oesophagus was identified as a priority for economic analysis. The aim of the analysis was to estimate the cost-effectiveness of operative approaches for the surgical treatment of oesophageal cancer.

8.6.5.1 Methods

A systematic literature review was conducted to identify economic evaluations that may be applicable to the current decision problem. No relevant economic studies were identified that were directly applicable.

Since the current economic literature didn't adequately address the decision problem, a de novo economic evaluation was undertaken to assess cost-effectiveness. The analysis was developed in Microsoft Excel® and was conducted from the perspective of the NHS and Personal Social Services (PSS) as outlined in the NICE Reference Case (The guidelines manual, NICE November 2012).

8.6.5.1.1 Comparisons considered in the analysis

As a result of inconsistency and incoherence in the effectiveness data as well as concerns about differences in the patient populations indicated for each treatment, it was not possible to model all treatments against each other. Therefore, the analysis has been run as a series of pairwise comparisons. The economic analysis was restricted to the primary comparisons of interest as identified by the Committee. However, due to limitations in the available data, it was not possible to model a comparison of chemoradiotherapy plus surgery and chemoradiotherapy alone, which was the comparison of most interest to Guideline Committee.

The following comparisons were considered in the analysis:

- Chemoradiotherapy followed by surgery in comparison to surgery
- Chemoradiotherapy followed by surgery in comparison to chemotherapy followed by surgery
- Chemoradiotherapy in comparison to surgery
- Chemotherapy followed by surgery in comparison to surgery

8.6.5.1.2 Clinical data and model approach

The economic analysis was based on overall survival and progression free survival estimates for each of the treatments included in the analysis. Overall and disease free survival values were derived based on the treatment effects estimated in the clinical evidence review conducted for this topic (measured using relative risk (RR) estimates). The treatment effects were applied in conjunction with baseline estimates of overall and disease free survival in patients with squamous cell carcinoma from the CROSS trial (Shapiro et al. 2015). Data from the CROSS trial was used to inform the baseline estimates as it was adjudged by the Guideline Committee to be the most representative of current clinical practice.

In the majority of the comparisons considered in the analysis, interventions have been compared against surgery alone. In these cases, five-year overall and disease free survival estimates of 30.2% and 27.9%, respectively have been used as the baseline estimates for the surgery arm (Shapiro et al. 2015). RR estimates for the respective comparators are then applied to this baseline data. For overall survival, RR estimates of 1.42, 2.08 and 1.39 were applied for chemoradiotherapy plus surgery, chemoradiotherapy and chemotherapy plus surgery, respectively. For progression free survival, RR estimates of 1.69, 1.73 and 2.09 were applied for chemoradiotherapy plus surgery, chemoradiotherapy and chemotherapy plus surgery, respectively.

For the comparison of chemoradiotherapy plus surgery in comparison to chemotherapy plus surgery, three-year overall and disease free survival estimates of 68.3% and 61.0%, respectively have been used as the baseline estimates for the chemoradiotherapy plus surgery arm (Shapiro et al. 2015). Note that three year data has been used for this comparison to match the time point for the observed treatment effect. Survival outcomes for chemotherapy plus surgery were estimated using RR estimates of 0.79 and 0.93 for overall and disease free survival, respectively.

Mortality from other causes was captured using 2013-2015 life tables for England and Wales from the office of national statistics (ONS). These life tables give an estimate of the annual probability of death given a person's age and gender. A starting age of 60 and a male proportion of 78.1% were applied in the model based on averages reported in Shapiro et al. 2015 for the chemoradiotherapy plus surgery and surgery alone arms. The other cause mortality estimates were used in conjunction with the overall survival estimates above to estimate the proportion of patients that died of disease-specific and other causes.

8.6.5.1.3 Costs

The costs considered in the model reflect the perspective of the analysis, thus only costs that are relevant to the UK NHS & PSS were included. Where possible, all costs were estimated in 2015/16 prices.

The majority of costs were sourced from NHS reference costs 2015/16 by applying tariffs associated with the appropriate HRG code. Drug costs were calculated using unit cost data from the electronic market information tool (eMit) combined with dose information from the British National Formulary (BNF). Other resource use and cost information were sourced from the Personal Social Services Research Unit (PSSRU) and the advice of the Guideline Committee.

Surgery costs were estimated to be £11,057.41 based on the cost of a 'very complex, oesophageal, stomach or duodenum procedure' (FZ80) from NHS reference costs 2015/16.

The cost of radiotherapy preparation and delivery (per fraction) were sourced from NHS Reference costs 2015/16. It was assumed that 23 fractions of radiotherapy would be delivered in the average radiotherapy regimen. The estimated cost of radiotherapy treatment was £3,563.59.

The average cost of chemotherapy per cycle was based upon the cost of the five chemotherapy regimens which were most likely to be used (as identified by the Guideline Committee). The chemotherapy delivery costs were sourced from NHS Reference Costs 2015/16 and drug costs were sourced from eMit. The chemotherapy costs per cycle were found to be similar for each of the regimens and the average cost per cycle was estimated to be £824.68.

When used in conjunction with surgery, it was assumed that two cycles of chemotherapy would be administered at a cost of £1,649.36. When used in conjunction with radiotherapy, it was assumed that four cycles of chemotherapy would be administered at a cost of £3,298.73. When used as monotherapy (following a recurrence) it was assumed that six cycles of chemotherapy would be administered at a cost of £4,948.09.

Chemotherapy and chemoradiotherapy morbidity costs were estimated based on morbidity data from the CROSS trial, which showed that 22.8% of patients experience events of grade ≥3 during chemoradiotherapy. It was assumed that the cost of an adverse event would be £121.88, which is equal to the cost of a 'consultant led face to face follow-up attendance' (WF01A) in 'Upper Gastrointestinal Surgery' from NHS Reference Costs 2015/16.

The cost of palliative care was estimated using estimates from a costing report by the Nuffield Trust (Georghiou et al. 2014, 'Exploring the cost of care at the end of life'). A cost of

£7,287 was applied based on the average resource use of patients with cancer in the last three months of life.

8.6.5.1.4 Health related quality of life (QoL) values

As recommended in the NICE reference case, the model estimates effectiveness in terms of quality adjusted life years (QALYs). These are estimated by combining the life year estimates with utility values (or QoL weights) associated with being in a particular health state.

QoL values were estimated using data from Graham et al. 2007, a cost-effectiveness analysis of treatments for locally advanced oesophageal cancer (including adenocarcinoma and squamous cell carcinoma). As part of the analysis, QoL values were estimated for surgical and multi-modal treatments at various time points. For the present analysis it was assumed that the pre-treamtent values would best represent the QoL value with disease while the post-treatment value would best represent the QoL value for patients that are disease-free. A QoL value of 0.595 was applied for patients with disease, based on the average of the QoL values at 0 to 6 months in patients treated with surgery (0.630) and multimodal treatment (0.560). A QoL value of 0.650 was applied for patients that are disease-free, based on the average of the QoL values at 6 to 12 months in patients treated with surgery (0.670) and multimodal treatment (0.630).

8.6.5.2 Results

8.6.5.2.1 Base case results

The base case results of the analysis are presented in

Table 125: Base case results for chemoradiotherapy and surgery in comparison to surgery alone to Table 128. It can be seen that chemoradiotherapy and surgery was found to be more costly (£6,511) and more effective (0.48 QALYs) than surgery alone and resulted in an ICER of £13,704 per QALY. Therefore chemoradiotherapy and surgery was deemed to be cost-effective in comparison to surgery alone as this value is below the NICE threshold of £20,000 per QALY. Chemoradiotherapy and surgery was found to be more costly (£5,021) and more effective (0.34 QALYs) than chemotherapy and surgery and resulted in an ICER of £14,940 per QALY. Therefore chemoradiothearpy and surgery was deemed to be cost-effective in comparison to chemotherapy and surgery as this value is lower than the NICE threshold of £20,000 per QALY. Chemoradiotherapy was found to be less costly (£4,916) and more effective (1.48 QALYs) than surgery alone. Therefore chemoradiotherapy was considered to be dominant in comparison to surgery alone. Chemotherapy and surgery was found to be more costly (£1,326) and more effective (0.44 QALYs) than surgery alone and resulted in an ICER of £3,025 per QALY. Therefore chemotherapy and surgery was deemed to be cost-effective in comparison to surgery alone as this value is below the NICE threshold of £20,000 per QALY.

Table 125: Base case results for chemoradiotherapy and surgery in comparison to surgery alone

Strategy	Cost		QALYs		ICER (cost per QALY
	Total	Incremental	Total	Incremental	
Surgery	£17,655	-	4.33	-	**-**
ChemoRT + surgery	£24,166	*£6,511*	4.81	*0.48*	**£13,704**

Table 126: Base case results for chemoradiotherapy and surgery in comparison to chemotherapy and surgery

Strategy	Cost		QALYs		ICER (cost per QALY
	Total	Incremental	Total	Incremental	
Chemo + surgery	£19,145	-	4.47	-	-
ChemoRT + surgery	£24,166	*£5,021*	4.81	*0.34*	**£14,940**

Table 127: Base case results for chemoradiotherapy in comparison to surgery

Strategy	Cost		QALYs		ICER (cost per QALY
	Total	Incremental	Total	Incremental	
Surgery	£17,655	-	4.33	-	-
ChemoRT	£12,739	*-£4,916*	5.81	*1.48*	**Dominant**

Table 128: Base case results for chemotherapy and surgery in comparison to surgery alone

Strategy	Cost		QALYs		ICER (cost per QALY
	Total	Incremental	Total	Incremental	
Surgery	£17,655	-	4.33	-	-
Chemo+surgery	£18,981	*£1,326*	4.77	*0.44*	**£3,025**

8.6.5.2.2 Sensitivity analysis results

A series of deterministic sensitivity analyses were conducted, whereby an input parameter is changed, the model is re-run and the new cost-effectiveness result is recorded. This analysis is a useful way of estimating uncertainty and determining the key drivers of the model result. It was found that the conclusion of the analysis remained unchanged in the majority of modelled scenarios. Notable exceptions were scenarios in which the lower RR estimates were applied for disease-free survival or overall survival outcomes.

Probabilistic sensitivity analysis (PSA) was conducted (using 10,000 PSA runs) to assess the combined parameter uncertainty in the model. In this analysis, the mean values that were utilised in the base case are replaced with values drawn from distributions around the mean values. The probability of each treatment being cost-effective was assessed using a NICE threshold of £20,000 per QALY.

For the comparison between chemoradiotherapy plus surgery and surgery alone, it was found that chemoradiotherapy plus surgery had a 66% probability of being cost-effective while surgery alone had a 34% probability of being cost-effective. For the comparison between chemoradiotherapy plus surgery and chemotherapy plus surgery, it was found that chemoradiotherapy plus surgery had a 51% probability of being cost-effective while chemotherapy plus surgery had a 49% probability of being cost-effective. For the comparison between chemoradiotherapy and surgery, it was found that chemoradiotherapy had a 98% probability of being cost-effective while surgery had a 2% probability of being cost-effective. For the comparison between chemotherapy plus surgery and surgery alone, it was found that chemotherapy plus surgery had a 73% probability of being cost-effective while surgery alone had a 27% probability of being cost-effective.

8.6.5.3 Conclusion

Due to a lack of evidence it was not possible to directly compare all the interventions against each other. The analysis therefore took the form of pairwise comparisons. The analysis suggest that chemoradiotherapy and surgery was cost-effective in comparison to both surgery alone and chemotherapy plus surgery. The analysis also showed that chemoradiotherapy alone was cost-effective in comparison to surgery alone. Thus,

essentially, the analysis confirms that the two approaches most likely to be used in current clinical practice are preferred against other treatment options.

Ideally, the analysis would have considered the comparison between chemoradiotherapy and surgery versus chemoradiotherapy alone. Indeed, the Committee identified this as the key comparison of interest in the analysis. However, there was insufficient clinical evidence to model this comparison in any meaningful way. Therefore, further research is required to address the aspect of the decision problem that is of most interest to clinical practice.

8.6.6 Evidence statements

8.6.6.1 Chemoradiotherapy followed by surgery versus surgery alone

8.6.6.1.1 Postoperative mortality

Low quality evidence from 8 RCTs with 1069 people with squamous cell carcinoma of oesophagus showed that there is a clinically significant harmful effect of chemoradiotherapy followed by surgery compared with surgery alone for postoperative morality rate.

Subgroup analysis according to type of chemoradiotherapy

Concomitant: Moderate quality evidence from 6 RCTs with 907 people with squamous cell carcinoma of oesophagus showed that there is a clinically significant harmful effect of concomitant chemoradiotherapy followed by surgery compared with surgery alone for postoperative morality rate.

Sequential: Very low quality evidence from 2 RCTs with 162 people with squamous cell carcinoma of oesophagus showed that there is no clinically significant difference between sequential chemoradiotherapy followed by surgery and surgery alone for postoperative morality rate.

Subgroup analysis according to type of surgical approach

Transhiatal: Low quality evidence from 1 RCT with 100 people with squamous cell carcinoma of oesophagus showed that there is no clinically significant difference between chemoradiotherapy followed by transhiatal oesophagectomy and transhiatal oesophagectomy alone for postoperative morality rate.

2-stage oesophagectomy: Low quality evidence from 1 RCT with 85 people with squamous cell carcinoma of oesophagus showed that there is no clinically significant difference between chemoradiotherapy followed by 2-stage oesophagectomy and 2-stage oesophagectomy alone for postoperative morality rate.

2- or 3-stage oesophagectomy: Moderate quality evidence from 3 RCTs with 528 people with squamous cell carcinoma of oesophagus showed that there is a clinically significant harmful effect of chemoradiotherapy followed by 2- or 3-stage oesophagectomy compared with 2- or 3-stage oesophagectomy alone for postoperative morality rate.

Left thoracotomic oesophagectomy: Moderate quality evidence from 1 RCT with 236 people with squamous cell carcinoma of oesophagus showed that there were no events for postoperative mortality in either chemoradiotherapy followed by left thoracotomic oesophagectomy or left thoracotomic oesophagectomy alone, for postoperative morality rate.

Unspecified oesophagectomy: Very low quality evidence from 2 RCTs with 120 people with squamous cell carcinoma of oesophagus showed that there is no clinically significant difference between chemoradiotherapy followed by unspecified oesophagectomy compared with unspecified oesophagectomy alone for postoperative morality rate.

8.6.6.1.2 30-day mortality

Low quality evidence from 3 RCTs with 491 people with squamous cell carcinoma of oesophagus indicated that there is no clinically significant difference between chemoradiotherapy (concomitant or sequential) followed by surgery and surgery alone for 30-day mortality rate (RR 2.07, 95% CI 0.85 – 5.03).

Subgroup analysis according to type of chemoradiotherapy

Concomitant: Very low quality evidence from 2 RCTs with 406 people with squamous cell carcinoma of oesophagus indicated that there is no clinically significant difference between concomitant chemoradiotherapy followed by surgery and surgery alone for 30-day mortality rate.

Sequential: Very low quality evidence from 1 RCT with 85 people with squamous cell carcinoma of oesophagus indicated that there is no clinically significant difference between sequential chemoradiotherapy followed by surgery and surgery alone for 30-day mortality rate.

Subgroup analysis according to type of surgical approach

2-stage oesophagectomy: Very low quality evidence from 1 RCT with 85 people with squamous cell carcinoma of oesophagus indicated that there is no clinically significant difference between chemoradiotherapy followed by 2-stage oesophagectomy and 2-stage oesophagectomy alone for 30-day mortality rate.

2- or 3-stage oesophagectomy: Very low quality evidence from 1 RCT with 170 people with squamous cell carcinoma of oesophagus indicated that there is no clinically significant difference between chemoradiotherapy followed by 2- or 3-stage oesophagectomy and 2- or 3-stage oesophagectomy alone for 30-day mortality rate.

Left thoracotomic oesophagectomy: Very low quality evidence from 1 RCT with 236 people with squamous cell carcinoma of oesophagus indicated that there were no events of 30-day mortality in either chemoradiotherapy followed by left thoractomic oesophagectomy and left thoracotomic oesophagectomy alone for 30-day mortality rate.

8.6.6.1.3 Treatment-related mortality

Low quality evidence from 7 RCTs with 969 people with squamous cell carcinoma of oesophagus showed that there is a clinically significant harmful effect of concomitant chemoradiotherapy followed by surgery compared with surgery alone for treatment-related morality rate.

Subgroup analysis according to type of chemoradiotherapy

Concomitant: Moderate quality evidence from 6 RCTs with 888 people with squamous cell carcinoma of oesophagus showed that there is a clinically significant harmful effect of concomitant chemoradiotherapy followed by surgery compared with surgery alone for treatment-related morality rate.

Sequential: Very low quality evidence from 1 RCT with 81 people with squamous cell carcinoma of oesophagus showed that there is no clinically significant difference between sequential chemoradiotherapy followed by surgery and surgery alone for treatment-related morality rate.

Subgroup analysis according to type of surgical approach

2-stage oesophagectomy: Very low quality evidence from 1 RCT with 69 people with squamous cell carcinoma of oesophagus showed that there is no clinically significant

difference between chemoradiotherapy followed by 2-stage oesophagectomy compared with 2-stage oesophagectomy alone for treatment-related morality rate.

2- or 3-stage oesophagectomy: Moderate quality evidence from 1 RCT with 69 people with squamous cell carcinoma of oesophagus showed that there is a clinically significant harmful effect of chemoradiotherapy followed by 2- or 3-stage oesophagectomy compared with 2- or 3-stage oesophagectomy alone for treatment-related morality rate.

Left or right thoractomic oesophagectomy: Very low quality evidence from 1 RCT with 160 people with squamous cell carcinoma of oesophagus showed that there is no clinically significant difference between chemoradiotherapy followed by left or right thoractomic oesophagectomy compared with left or right thoractomic oesophagectomy alone for treatment-related morality rate.

Left thoractomic oesophagectomy Moderate quality evidence from 1 RCT with 236 people with squamous cell carcinoma of oesophagus showed that there were no events of treatment-related mortality in either chemoradiotherapy followed by left thoractomic oesophagectomy or left thoractomic oesophagectomy alone for treatment-related morality rate.

Unspecified oesophagectomy: Very low quality evidence from 2 RCTs with 126 people with squamous cell carcinoma of oesophagus showed that there is no clinically significant difference between chemoradiotherapy followed by unspecified oesophagectomy compared with unspecified oesophagectomy alone for treatment-related morality rate.

8.6.6.1.4 Overall survival rate

Low quality evidence from 7 RCTs with 789 people with squamous cell carcinoma of oesophagus indicated that there is a clinically significant beneficial effect of concomitant chemoradiotherapy followed by surgery compared with surgery alone for overall survival rate.

Subgroup analysis according to type of chemoradiotherapy:

Concomitant: Low quality evidence from 6 RCTs with 703 people with squamous cell carcinoma of oesophagus indicated that there is a clinically significant beneficial effect of concomitant chemoradiotherapy followed by surgery compared with surgery alone for overall survival rate.

Sequential: Very low quality evidence from 1 RCT with 86 people with squamous cell carcinoma of oesophagus indicated that there is no clinically significant difference between sequential chemoradiotherapy followed by surgery compared with surgery alone for overall survival rate.

Subgroup analysis according to surgical approach:

2-stage oesophagectomy: Very low quality evidence from 1 RCT with 69 people with squamous cell carcinoma of oesophagus indicated that there is no clinically significant difference between concomitant chemoradiotherapy followed by 2-stage oesophagectomy and 2-stage oesophagectomy alone for overall survival rate.

2-stage thoracotomic or transhiatal oesophagectomy: Very low quality evidence from 1 RCT with 84 people with squamous cell carcinoma of oesophagus indicated that there is no clinically significant difference between concomitant chemoradiotherapy followed by 2-stage thoracotomic or transhiatal oesophagectomy and 2-stage thoractomic or transhiatal oesophagectomy alone for overall survival rate.

2- or 3-stage oesophagectomy: Low quality evidence from 2 RCTs with 295 people with squamous cell carcinoma of oesophagus indicated that there is no clinically significant difference between concomitant chemoradiotherapy followed by 2- or 3- stage oesophagectomy and 2- or 3- stage oesophagectomy alone for overall survival rate.

Left or right thoractomic oesophagectomy: Low quality evidence from 1 RCT with 160 people with squamous cell carcinoma of oesophagus indicated that there may be a clinically significant beneficial effect of concomitant chemoradiotherapy followed by left or right thoractomic oesophagectomy compared with left or right thoractomic oesophagectomy alone for overall survival rate, but there is uncertainty around the estimate.

Unspecified oesophagectomy: Low quality evidence from 2 RCTs with 181 people with squamous cell carcinoma of oesophagus indicated that there is no clinically significant difference between concomitant chemoradiotherapy followed by unspecified oesophagectomy and unspecified oesophagectomy alone for overall survival rate.

8.6.6.1.5 Overall survival

Moderate quality evidence from 6 RCTs with 986 people with squamous cell carcinoma of oesophagus indicated that there was no clinically significant difference between concomitant chemoradiotherapy followed by surgery compared with surgery alone for overall survival.

Subgroup analysis according to surgical approach

2-stage open oesophagectomy: Very low quality evidence from 1 RCT with 69 people with squamous cell carcinoma of oesophagus indicated that there was no clinically significant difference between concomitant chemoradiotherapy followed by 2-stage open oesophagectomy and 2-stage open oesophagectomy alone for overall survival.

2-or 3-stage open oesophagectomy: Moderate quality evidence from 2 RCTs with 577 people with squamous cell carcinoma of oesophagus indicated that there was no clinically significant difference between concomitant chemoradiotherapy followed by 2- or 3-stage open oesophagectomy and 2- or 3- stage open oesophagectomy alone for overall survival.

2-stage open or transhiatal oesophagectomy: Low quality evidence from 1 RCT with 84 people with squamous cell carcinoma of oesophagus indicated that there was a clinically significant beneficial effect of concomitant chemoradiotherapy followed by 2-stage open or transhiatal oesophagectomy compared with 2-stage open or transhiatal oesophagectomy alone for overall survival.

Unreported oesophagectomy: Low quality evidence from 1 RCT with 256 people with squamous cell carcinoma of oesophagus indicated that there was no clinically significant difference between concomitant chemoradiotherapy followed by unreported oesophagectomy and unreported oesophagectomy alone for overall survival.

8.6.6.1.6 Disease free survival rate

Very low quality evidence from 5 RCTs with 756 people with squamous cell carcinoma of oesophagus indicated that there is a clinically significant beneficial effect of concomitant chemoradiotherapy followed by surgery compared with surgery alone for disease free survival rate.

Subgroup analysis according to surgical approach:

2- or 3-stage oesophagectomy: Low quality evidence from 3 RCTs with 501 people with squamous cell carcinoma of oesophagus indicated that there is no clinically significant difference between concomitant chemoradiotherapy followed by 2- or 3-stage oesophagectomy and 2- or 3- stage oesophagectomy alone for disease free survival rate.

Left or right open oesophagectomy: Low quality evidence from 1 RCT with 160 people with squamous cell carcinoma of oesophagus indicated that there is a clinically significant beneficial effect of concomitant chemoradiotherapy followed by left or right open oesophagectomy compared with left or right open oesophagectomy alone for disease free survival rate.

Unspecified oesophagectomy: High quality evidence from 1 RCT with 95 people with squamous cell carcinoma of oesophagus indicated that there is a clinically significant beneficial effect of concomitant chemoradiotherapy followed by unspecified oesophagectomy compared with unspecified oesophagectomy alone for disease free survival rate.

8.6.6.1.7 Disease free survival

Low quality evidence from 3 RCTs with 577 people with squamous cell carcinoma of oesophagus indicated that there was a clinically significant beneficial effect of concomitant chemoradiotherapy followed by 2- or 3-stage open oesophagectomy compared with 2- or 3-stage open oesophagectomy alone for disease free survival.

8.6.6.1.8 Any postoperative complication

Low quality evidence from 5 RCTs with 690 people with squamous cell carcinoma of oesophagus suggested that there is no clinically significant difference between chemoradiotherapy followed by surgery and surgery alone for any postoperative complication.

Subgroup analysis according to type of chemoradiotherapy

Concomitant: Low quality evidence from 4 RCTs with 605 people with squamous cell carcinoma of oesophagus suggested that there is no clinically significant difference between concomitant chemoradiotherapy followed by surgery and surgery alone for any postoperative complication.

Sequential: Very low quality evidence from 1 RCT with 85 people with squamous cell carcinoma of oesophagus suggested that there is no clinically significant difference between sequential chemoradiotherapy followed by surgery and surgery alone for any postoperative complication.

Subgroup analysis according to surgical approach

2-stage oesophagectomy: Very low quality evidence from 1 RCT with 85 people with squamous cell carcinoma of oesophagus suggested that there is no clinically significant difference between chemoradiotherapy followed by 2-stage oesophagectomy and 2-stage oesophagectomy alone for any postoperative complication.

2- or 3-stage oesophagectomy Low quality evidence from 3 RCTs with 528 people with squamous cell carcinoma of oesophagus suggested that there is no clinically significant difference between chemoradiotherapy followed by 2- or 3-stage oesophagectomy and 2- or 3-stage oesophagectomy alone for any postoperative complication.

Unspecified oesophagectomy: Very low quality evidence from 1 RCT with 77 people with squamous cell carcinoma of oesophagus suggested that there is no clinically significant difference between chemoradiotherapy followed by unspecified oesophagectomy and unspecified oesophagectomy alone for any postoperative complication.

8.6.6.1.9 Treatment-related post-operative complication: Anastomotic leak

Very low quality evidence from 7 RCTs with 761 people with squamous cell carcinoma of oesophagus indicated that there is no clinically significant difference between chemoradiotherapy followed by surgery and surgery alone for postoperative anastomotic leak.

Subgroup analysis according to type of chemoradiotherapy:

Concomitant: Very low quality evidence from 5 RCTs with 599 people with squamous cell carcinoma of oesophagus indicated that there is no clinically significant difference between

concomitant chemoradiotherapy followed by surgery and surgery alone for postoperative anastomotic leak.

Sequential: Very low quality evidence from 2 RCTs with 162 people with squamous cell carcinoma of oesophagus indicated that there is no clinically significant difference between sequential chemoradiotherapy followed by surgery and surgery alone for postoperative anastomotic leak.

Subgroup analysis according to surgical approach:

Transhiatal oesophagectomy: Very low quality evidence from 1 RCT with 100 people with squamous cell carcinoma of oesophagus indicated that there is no clinically significant difference between chemoradiotherapy followed by transhiatal oesophagectomy and transhiatal oesophagectomy alone for postoperative anastomotic leak.

2-stage open oesophagectomy Very low quality evidence from 2 RCTs with 145 people with squamous cell carcinoma of oesophagus indicated that there is no clinically significant difference between chemoradiotherapy followed by 2-stage open oesophagectomy and 2-stage oesophagectomy alone for postoperative anastomotic leak.

Left thoractomic oesophagectomy: Very low quality evidence from 1 RCT with 236 people with squamous cell carcinoma of oesophagus indicated that there is no clinically significant difference between chemoradiotherapy followed by left thoractomic oesophagectomy and left thoractomic oesophagectomy alone for postoperative anastomotic leak.

Left or right open oesophagectomy: Very low quality evidence from 1 RCT with 160 people with squamous cell carcinoma of oesophagus indicated that there is no clinically significant difference between chemoradiotherapy followed by left or right open oesophagectomy and left or right oesophagectomy alone for postoperative anastomotic leak.

Unspecified oesophagectomy: Very low quality evidence from 2 RCTs with 120 people with squamous cell carcinoma of oesophagus indicated that there is no clinically significant difference between chemoradiotherapy followed by unspecified oesophagectomy and unspecified oesophagectomy alone for postoperative anastomotic leak.

8.6.6.1.10 Treatment-related postoperative morbidity: Infection

Low quality evidence from 2 RCTs with 258 people with squamous cell carcinoma of oesophagus showed that there may be a clinically significant harmful effect of chemoradiotherapy followed by surgery compared with surgery alone for postoperative infection, but there is uncertainty around the estimate.

Subgroup analysis according to type of chemoradiotherapy:

Concomitant: Very low quality evidence from 1 RCT with 170 people with squamous cell carcinoma of oesophagus showed that there is no clinically significant difference between concomitant chemoradiotherapy followed by surgery and surgery alone for postoperative infection.

Sequential: Low quality evidence from 1 RCT with 88 people with squamous cell carcinoma of oesophagus showed that there may be a clinically significant harmful effect of sequential chemoradiotherapy followed by surgery and surgery alone for postoperative infection, however there is uncertainty around the estimate.

Subgroup analysis according to surgical approach:

2-stage open oesophagectomy: Low quality evidence from 1 RCT with 88 people with squamous cell carcinoma of oesophagus showed that there may be a clinically significant harmful effect of chemoradiotherapy followed by 2-stage open oesophagectomy and 2-stage

oesophagectomy alone for postoperative infection, however there is uncertainty around the estimate.

2- or 3-stage oesophagectomy Very low quality evidence from 1 RCT with 170 people with squamous cell carcinoma of oesophagus showed that there is no clinically significant difference between chemoradiotherapy followed by 2- or 3-stage oesophagectomy compared with 2- or 3-stage oesophagectomy alone for postoperative infection.

8.6.6.1.11 Treatment-related postoperative morbidity: Stenosis

Very low quality evidence from 1 RCT with 160 people with squamous cell carcinoma of oesophagus indicated that there is no clinically significant difference between concomitant chemoradiotherapy followed by 2- or 3-stage open oesophagectomy and 2-or 3-stage open oesophagectomy alone for postoperative stenosis.

8.6.6.1.12 Treatment-related intraoperative morbidity: Bleeding

Low quality evidence from 1 RCT with 100 people with squamous cell carcinoma of oesophagus showed that there is a clinically increased harmful effect of concomitant chemoradiotherapy followed by transhiatal oesophagectomy compared with transhiatal oesophagectomy alone for the amount of blood loss in surgery (mean difference of 10.00 mL more blood loss with concomitant chemoradiotherapy followed by transhiatal oesophagectomy, 95% CI from 1.92 to – 18.08 ml more).

Low quality evidence from 1 RCT with 160 people with squamous cell carcinoma of oesophagus showed that there is no clinically significant difference between concomitant chemoradiotherapy followed by left or right open oesophagectomy and left or right open oesophagectomy alone for the risk of operative haemorrhage of more than 300 mL.

8.6.6.2 Chemoradiotherapy followed by surgery versus chemoradiotherapy alone

8.6.6.2.1 Overall mortality estimates

Moderate quality evidence from 1 RCT with 172 people with squamous cell carcinoma of oesophagus showed that there was no clinically significant difference between concomitant chemoradiotherapy followed by 2-stage oesophagectomy and concomitant chemoradiotherapy alone for overall mortality estimate.

8.6.6.2.2 Treatment-related mortality

Low quality evidence from 1 RCT with 172 people with squamous cell carcinoma of oesophagus suggested that there is a clinically significant harmful effect of concomitant chemoradiotherapy followed by 2-stage oesophagectomy compared with concomitant chemoradiotherapy alone for treatment-related mortality rate.

8.6.6.2.3 3-year overall survival rate

Very low quality evidence from 1 RCT with 259 people with squamous cell carcinoma of oesophagus indicated that there is no clinically significant difference between concomitant chemoradiotherapy followed by unspecified oesophagectomy and concomitant chemoradiotherapy alone for 3-year overall survival rate.

8.6.6.2.4 Overall survival

Low quality evidence from 2 RCTs with 431 people with squamous cell carcinoma of oesophagus suggested that there was no clinically significant difference between concomitant chemoradiotherapy followed by surgery and concomitant chemoradiotherapy alone for overall survival.

Subgroup analysis according to surgical approach

2-stage open oesophagectomy: Low quality evidence from 1 RCT with 172 people with squamous cell carcinoma of oesophagus suggested that there was no clinically significant difference between concomitant chemoradiotherapy followed by 2-stage open oesophagectomy and concomitant chemoradiotherapy alone for overall survival.

Unreported oesophagectomy: Low quality evidence from 1 RCT with 259 people with squamous cell carcinoma of oesophagus suggested that there was no clinically significant difference between concomitant chemoradiotherapy followed by unreported oesophagectomy and concomitant chemoradiotherapy alone for overall survival.

8.6.6.2.5 Quality of life (Spitzer) at 5-year follow-up (range 5 to 25 months)

Low quality evidence from 1 RCT with 62 people with squamous cell carcinoma of oesophagus showed that there is no clinically significant difference between concomitant chemoradiotherapy followed by unspecified oesophagectomy and concomitant chemoradiotherapy alone for quality of life measured by Spitzer checklists at 5-year follow-up (mean difference of 0.95 higher with chemoradiotherapy followed by surgery, 95% CI from 0.2 lower to 2.1 scores higher).

8.6.6.3 Chemoradiotherapy followed by surgery versus chemotherapy followed by surgery alone

8.6.6.3.1 Mortality

Very low quality evidence from 3 RCTs with 506 people with squamous cell carcinoma of oesophagus showed that there is no clinically significant difference between chemoradiotherapy followed by surgery and chemotherapy followed by surgery for mortality.

Subgroup analysis according to type of chemoradiotherapy

Concomitant: Very low quality evidence from 2 RCTs with 418 people with squamous cell carcinoma of oesophagus showed that there is no clinically significant difference between concomitant chemoradiotherapy followed by surgery and chemotherapy followed by surgery for mortality.

Sequential: Very low quality evidence from 1 RCT with 88 people with squamous cell carcinoma of oesophagus showed that there is no clinically significant difference between sequential chemoradiotherapy followed by surgery and chemotherapy followed by surgery for mortality.

Subgroup analysis according to surgical approach

2-stage open oesophagectomy: Very low quality evidence from 2 RCTs with 325 people with squamous cell carcinoma of oesophagus showed that there is no clinically significant difference between chemoradiotherapy followed by 2-stage open oesophagectomy and chemotherapy followed by 2-stage open oesophagectomy for mortality.

2- or 3-stage open stage oesophagectomy Very low quality evidence from 1 RCT with 181 people with squamous cell carcinoma of oesophagus showed that there is no clinically significant difference between chemoradiotherapy followed by 2- or 3-stage open oesophagectomy and chemotherapy followed by 2- or 3-stage open or transhiatal oesophagectomy for mortality.

8.6.6.3.2 Any postoperative mortality

Very low quality evidence from 2 RCTs with 325 people with squamous cell carcinoma of oesophagus indicated that there is no clinically significant difference between chemoradiotherapy followed by 2-stage oesophagectomy and chemotherapy followed by 2-stage oesophagectomy for any postoperative mortality.

Subgroup analysis according to type of chemoradiotherapy

Concomitant: Moderate quality evidence from 2 RCTs with 325 people with squamous cell carcinoma of oesophagus showed that there is no event of any postoperative mortality in either concomitant chemoradiotherapy followed by 2-stage open oesophagectomy or chemotherapy followed by 2-stage open oesophagectomy.

Sequential: Very low quality evidence from 1 RCT with 88 people with squamous cell carcinoma of oesophagus showed that there is no clinically significant difference between sequential chemoradiotherapy followed by 2-stage oesophagectomy and chemotherapy followed by 2-stage oesophagectomy for any postoperative mortality.

8.6.6.3.3 3-year overall survival rate

Low quality evidence from 2 RCTs with 287 people with squamous cell carcinoma of oesophagus showed that there is a clinically significant beneficial effect of concomitant chemoradiotherapy followed by surgery compared with chemotherapy followed by surgery for 3-year overall survival rate.

Subgroup analysis according to surgical approach

2-stage open esophagectomy: Low quality evidence from 1 RCT with 237 people with squamous cell carcinoma of oesophagus showed that there is a clinically significant beneficial effect of chemoradiotherapy followed by 2-stage open oesophagectomy compared with chemotherapy followed by 2-stage open oesophagectomy for 3-year overall survival rate.

2- or 3-stage oesophagectomy Very low quality evidence from 1 RCT with 50 people with squamous cell carcinoma of oesophagus showed that there is no clinically significant difference between chemoradiotherapy followed by 2-stage or 3-stage open oesophagectomy compared with chemotherapy followed by 2-stage or 3-stage open oesophagectomy for 3-years overall survival rate.

8.6.6.3.4 Overall survival

Very low quality evidence from 1 RCT with 50 people with squamous cell carcinoma of oesophagus showed that there was no clinically significant difference between concomitant chemoradiotherapy followed by 2- or 3- stage open oesophagectomy and chemotherapy followed by 2- or 3-stage open oesophagectomy for overall survival.

8.6.6.3.5 Progression-free survival rate

Very low quality evidence from 1 RCT with 50 people with squamous cell carcinoma of oesophagus indicated that there is no clinically significant difference between concomitant chemoradiotherapy followed by 2-stage or 3-stage open oesophagectomy and chemotherapy followed by 2-stage or 3-stage open oesophagectomy for any progression-free survival rate.

8.6.6.3.6 Treatment-related postoperative morbidity: Anastomotic leak

Very low quality evidence from 2 RCTs with 325 people with squamous cell carcinoma of oesophagus indicated that there is no clinically significant difference between chemoradiotherapy followed by 2-stage open oesophagectomy and chemotherapy followed by 2-stage open oesophagectomy for the risk of postoperative anastomotic leak.

Subgroup analysis according to type of chemoradiotherapy

Concomitant: Very low quality evidence from 1 RCT with 237 people with squamous cell carcinoma of oesophagus indicated that there is no clinically significant difference between concomitant chemoradiotherapy followed by 2-stage open oesophagectomy and

chemotherapy followed by 2-stage open oesophagectomy for the risk of postoperative anastomotic leak.

Sequential: Very low quality evidence from 1 RCT with 88 people with squamous cell carcinoma of oesophagus indicated that there is no clinically significant difference between sequential chemoradiotherapy followed by 2-stage open oesophagectomy and chemotherapy followed by 2-stage open oesophagectomy for the risk of postoperative anastomotic leak.

8.6.6.3.7 Treatment-related postoperative morbidity: Stenosis

Very low quality evidence from 1 RCT with 237 people with squamous cell carcinoma of oesophagus showed that there is no clinically significant difference between concomitant chemoradiotherapy followed by 2-stage open oesophagectomy and chemotherapy followed by 2-stage open oesophagectomy for any postoperative stenosis.

8.6.6.4 Surgery (left or right open oesophagectomy) followed by chemoradiotherapy (concomitant) versus surgery (left or right open oesophagectomy) alone

8.6.6.4.1 10-year overall survival rate

Low quality evidence from 1 RCT with 158 people with squamous cell carcinoma of oesophagus indicated that there is no clinically significant difference between left or right open oesophagectomy followed by concomitant chemoradiotherapy and left or right open oesophagectomy alone for 10-year overall survival rate.

8.6.6.4.2 10-year progression-free survival rate

Low quality evidence from 1 RCT with 158 people with squamous cell carcinoma of oesophagus indicated that there is a clinically significant beneficial effect of left or right open oesophagectomy followed by concomitant chemoradiotherapy compared with left or right open oesophagectomy alone for 10-year progression free survival rate.

8.6.6.5 Chemoradiotherapy (concomitant) alone versus surgery (2-stage or 3-stage open oesophagectomy) alone

8.6.6.5.1 Overall mortality rate (unspecified year)

Very low quality evidence from 1 RCT with 80 people with squamous cell carcinoma of oesophagus indicated that there is no clinically significant difference between concomitant chemoradiotherapy alone and 2-stage or 3-stage oesophagectomy alone for overall mortality estimates.

8.6.6.5.2 Overall survival rate at 2 years

Very low quality evidence from 1 RCT with 80 people with squamous cell carcinoma of oesophagus suggested that there is no clinically significant difference between concomitant chemoradiotherapy alone and 2-stage or 3-stage oesophagectomy alone for overall survival rate at 2 years.

8.6.6.5.3 Overall survival rate at 5 years

Low quality evidence from 1 RCT with 80 people with squamous cell carcinoma of oesophagus showed that there is a clinically significant beneficial effect of concomitant chemoradiotherapy alone compared with 2-stage or 3-stage oesophagectomy alone for overall survival rates at 5 years.

8.6.6.5.4 Overall survival

Very low quality evidence from 1 RCT with 80 people with squamous cell carcinoma of oesophagus suggested that there was no clinically significant difference between concomitant chemoradiotherapy alone and 2-stage or 3-stage open oesophagectomy alone for overall survival.

8.6.6.5.5 Disease-free survival rate at 2 years

Very low quality evidence from 1 RCT with 80 people with squamous cell carcinoma of oesophagus indicated that there is no clinically significant difference between concomitant chemoradiotherapy alone and 2-stage or 3-stage oesophagectomy alone for disease-free survival rate at 2 years.

8.6.6.5.6 Disease-free survival rate at 5 years

Low quality evidence from 1 RCT with 80 people with squamous cell carcinoma of oesophagus showed that there may be a clinically significant beneficial effect of concomitant chemoradiotherapy alone compared with 2-stage or 3-stage oesophagectomy alone for disease-free survival rate at 5 years, however there is uncertainty around the estimate.

8.6.6.5.7 30-day mortality rate

Very low quality evidence from 1 RCT with 80 people with squamous cell carcinoma of oesophagus showed that there is no clinically significant difference between concomitant chemoradiotherapy alone and 2-stage or 3-stage oesophagectomy alone for 30-day mortality rate.

8.6.6.6 Surgery alone versus radiotherapy alone

8.6.6.6.1 Treatment-related mortality

Very low quality evidence from 2 RCTs with 163 people with squamous cell carcinoma of oesophagus indicated that that there is no clinically significant difference between surgery alone and radiotherapy alone for treatment-related mortality.

Subgroup analysis according to surgical approach

2-stage open oesophagectomy Very low quality evidence from 1 RCT with 87 people with squamous cell carcinoma of oesophagus indicated that there is no clinically significant difference between 2-stage open oesophagectomy alone and radiotherapy alone for treatment-related mortality.

3-stage oesophagectomy Very low quality evidence from 1 RCT with 76 people with squamous cell carcinoma of oesophagus indicated that there is no clinically significant difference between 3-stage open oesophagectomy alone and radiotherapy alone for treatment-related mortality.

8.6.6.6.2 Overall survival rate

Low quality evidence from 2 RCTs with 161 people with squamous cell carcinoma of oesophagus indicated that there is a clinically significant beneficial effect of surgery alone compared with radiotherapy alone for overall survival rate.

Subgroup analysis according to surgical approach

2-stage open oesophagectomy Low quality evidence from 1 RCT with 87 people with squamous cell carcinoma of oesophagus indicated that there is a clinically significant beneficial effect of 2-stage open oesophagectomy compared with radiotherapy alone for overall survival rate.

3-stage oesophagectomy Very low quality evidence from 1 RCT with 74 people with squamous cell carcinoma of oesophagus indicated that there is no clinically significant difference between 3-stage open oesophagectomy compared with radiotherapy alone for overall survival rate.

8.6.6.6.3 Overall survival

Moderate quality evidence from 1 RCT with 74 people with squamous cell carcinoma of oesophagus indicated that there was clinically significant beneficial effect of 3-stage open oesophagectomy alone compared with radiotherapy alone for overall survival.

8.6.6.7 Chemotherapy followed by surgery versus surgery alone

8.6.6.7.1 30-day mortality rate

Very low quality evidence from 4 RCTs with 614 people with squamous cell carcinoma of oesophagus indicated that there is no clinically significant difference between chemotherapy followed by surgery and surgery alone for 30-day mortality rate.

Subgroup analysis according to surgical approach

2-stage open oesophagectomy: Very low quality evidence from 1 RCT with 79 people with squamous cell carcinoma of oesophagus indicated that there is no clinically significant difference between chemotherapy followed by 2-stage open oesophagectomy and 2-stage open oesophagectomy alone for 30-day mortality rate.

2-stage open or transhiatal oesophagectomy: Very low quality evidence from 2 RCTs with 298 people with squamous cell carcinoma of oesophagus indicated that there is no clinically significant difference between chemotherapy followed by 2-stage open or transhiatal oesophagectomy and 2-stage oesophagectomy alone for 30-day mortality rate.

Left open oesophagectomy: Moderate quality evidence from 1 RCT with 79 people with squamous cell carcinoma of oesophagus indicated that there is no event of 30-day mortality in either chemotherapy followed by left open oesophagectomy or left open oesophagectomy alone.

8.6.6.7.2 Treatment-related mortality

Very low quality evidence from 6 RCTs with 728 people with squamous cell carcinoma of oesophagus showed that there is no clinically significant difference between chemotherapy followed by surgery and surgery alone for treatment-related mortality rate.

Subgroup analysis according to surgical approach

3-stage open oesophagectomy Very low quality evidence from 2 RCTs with 136 people with squamous cell carcinoma of oesophagus showed that there is no clinically significant difference between chemotherapy followed by 3-stage open oesophagectomy and 3-stage open oesophagectomy alone for treatment-related mortality rate.

2- or 3-stage open oesophagectomy: Very low quality evidence from 1 RCT with 46 people with squamous cell carcinoma of oesophagus showed that there is no clinically significant difference between chemotherapy followed by 2- or 3-stage open oesophagectomy and 2- or 3-stage open oesophagectomy alone for treatment-related mortality rate.

2-stage open or transhiatal oesophagectomy: Very low quality evidence from 2 RCTs with 309 people with squamous cell carcinoma of oesophagus showed that there is no clinically significant difference between chemotherapy followed by 2-stage open or transhiatal oesophagectomy and 2-stage open or transhiatal oesophagectomy alone for treatment-related mortality rate.

Left open oesophagectomy: Moderate quality evidence from 2 RCTs with 237 people with squamous cell carcinoma of oesophagus showed that there were no events of treatment related mortality in either chemotherapy followed by left open oesophagectomy or left open oesophagectomy alone.

8.6.6.7.3 Postoperative mortality

Very low quality evidence from 6 RCTs with 743 people with squamous cell carcinoma of oesophagus indicated that that there is no clinically significant difference between chemotherapy followed by surgery and surgery alone for postoperative mortality rate.

Subgroup analysis according to surgical approach

2-stage open oesophagectomy: Very low quality evidence from 1 RCT with 79 people with squamous cell carcinoma of oesophagus indicated that that there is no clinically significant difference between chemotherapy followed by 2-stage open oesophagectomy and 2-stage open oesophagectomy alone for postoperative mortality rate.

3-stage oesophagectomy: Very low quality evidence from 2 RCTs with 129 people with squamous cell carcinoma of oesophagus indicated that that there is no clinically significant difference between chemotherapy followed by 3-stage open oesophagectomy and 3-stage open oesophagectomy alone for postoperative mortality rate.

2-stage open or transhiatal oesophagectomy: Very low quality evidence from 2 RCTs with 298 people with squamous cell carcinoma of oesophagus indicated that that there is no clinically significant difference between chemotherapy followed by 2-stage open or transhiatal oesophagectomy and 2-stage open or transhiatal oesophagectomy alone for postoperative mortality rate.

Left open oesophagectomy Very low quality evidence from 1 RCT with 237 people with squamous cell carcinoma of oesophagus indicated that that there is no event of postoperative mortality rate in either chemotherapy followed by left open oesophagectomy or left open oesophagectomy alone.

8.6.6.7.4 Overall survival rate

Very low quality evidence from 3 RCTs with 387 people with squamous cell carcinoma of oesophagus indicated that there is no clinically significant difference between chemotherapy followed by surgery and surgery alone for overall survival rate.

Subgroup analysis according to surgical approach

3-stage open oesophagectomy: Very low quality evidence from 1 RCT with 94 people with squamous cell carcinoma of oesophagus indicated that there is no clinically significant difference between chemotherapy followed by 3-stage open oesophagectomy and 3-stage open oesophagectomy alone for overall survival rate.

2- or 3-stage open oesophagectomy: Very low quality evidence from 1 RCT with 46 people with squamous cell carcinoma of oesophagus indicated that there is no clinically significant difference between chemotherapy followed by 2- or 3-stage open oesophagectomy and 2- or 3-stage open oesophagectomy alone for overall survival rate.

Unspecified oesophagectomy: Very low quality evidence from 1 RCT with 247 people with squamous cell carcinoma of oesophagus indicated that there is no clinically significant difference between chemotherapy followed by unspecified oesophagectomy and unspecified oesophagectomy alone for overall survival rate.

8.6.6.7.5 Overall survival

Low quality evidence from 2 RCTs with 416 people with squamous cell carcinoma of oesophagus indicated that there is clinically significant beneficial effect of chemotherapy followed by surgery compared with surgery alone for overall survival (HR 0.75, 95% CI 0.60-0.93).

Subgroup analysis according to surgical approach

2-stage open or transhiatal oesophagectomy: Low quality evidence from 1 RCT with 169 people with squamous cell carcinoma of oesophagus indicated that there was clinically significant beneficial effect of chemotherapy followed by 2-stage open or transhiatal oesophagectomy compared with 2-stage open or transhiatal oesophagectomy alone for overall survival.

Unreported oesophagectomy: Low quality evidence from 1 RCT with 247 people with squamous cell carcinoma of oesophagus indicated that there may be clinically significant beneficial effect of chemotherapy followed by unreported oesophagectomy compared with unreported oesophagectomy alone for overall survival, however there was uncertainty around the effect estimate.

8.6.6.7.6 Disease-free survival rate

Low quality evidence from 1 RCT with 169 people with squamous cell carcinoma of oesophagus showed that there may be a clinically significant beneficial effect of chemotherapy followed by 2-stage open or transhiatal oesophagectomy compared with 2-stage open or transhiatal oesophagectomy alone for disease free survival rate, however there is uncertainty around the effect estimate.

8.6.6.7.7 Disease-free survival

Low quality evidence from 1 RCT with 169 people with squamous cell carcinoma of oesophagus showed that there may be a clinically significant beneficial effect of chemotherapy followed by 2-stage open or transhiatal oesophagectomy compared with 2-stage open or transhiatal oesophagectomy alone for disease free survival, however there was uncertainty around the effect estimate.

8.6.6.7.8 Treatment-related postoperative morbidity: Anastomotic leak

Very low quality evidence from 6 RCTs with 743 people with squamous cell carcinoma of oesophagus showed that there is no clinically significant difference between chemotherapy followed by surgery compared with surgery alone for postoperative anastomotic leak.

Subgroup analysis according to surgical approach

2-stage open oesophagectomy: Very low quality evidence from 1 RCT with 79 people with squamous cell carcinoma of oesophagus showed that there is no clinically significant difference between chemotherapy followed by 2-stage open oesophagectomy compared with 2-stage open oesophagectomy alone for postoperative anastomotic leak.

3-stage open oesophagectomy: Very low quality evidence from 2 RCTs with 129 people with squamous cell carcinoma of oesophagus showed that there is no clinically significant difference between chemotherapy followed by 3-stage open oesophagectomy compared with 3-stage open oesophagectomy alone for postoperative anastomotic leak.

2-stage open or transhiatal oesophagectomy: Very low quality evidence from 2 RCTs with 298 people with squamous cell carcinoma of oesophagus showed that there is no clinically significant difference between chemotherapy followed by 2-stage open or transhiatal oesophagectomy compared with 2-stage open or transhiatal oesophagectomy alone for postoperative anastomotic leak.

Left open oesophagectomy: Very low quality evidence from 1 RCT with 237 people with squamous cell carcinoma of oesophagus showed that there is no clinically significant difference between chemotherapy followed by left open oesophagectomy compared with left open oesophagectomy alone for postoperative anastomotic leak.

8.6.6.7.9 Treatment-related intraoperative morbidity: bleeding

Moderate quality evidence from 1 study with 129 people with squamous cell carcinoma of oesophagus suggested that there is a clinically significant harmful effect of chemotherapy followed by 2-stage open or transhiatal oesophagectomy compared with 2-stage open or transhiatal oesophagectomy alone for operative blood loss (mean difference of 62 mL higher with chemotherapy followed by surgery, 95% CI from 45.71 to 78.29 mL higher).

8.6.6.7.10 Treatment-related postoperative morbidity: wound infection

Very low quality evidence from 1 RCT with 129 people with squamous cell carcinoma of oesophagus showed that there is no clinically significant difference between chemotherapy followed by 2-stage open or transhiatal oesophagectomy compared with 2-stage open or transhiatal oesophagectomy alone for postoperative wound infection.

8.6.6.8 Chemoradiotherapy versus radiotherapy alone

8.6.6.8.1 Treatment-related mortality

Very low quality evidence from 8 RCTs with 652 people with squamous cell carcinoma of oesophagus showed that there is no clinically significant difference between concomitant chemoradiotherapy and radiotherapy alone for treatment-related mortality rate.

8.6.6.8.2 Overall survival rate

Very low quality evidence from 2 RCTs with 146 people with squamous cell carcinoma of oesophagus showed that there is no clinically significant difference between sequential chemoradiotherapy and radiotherapy alone for treatment-related mortality rate.

8.6.6.8.3 Overall survival rate at 1 year, 3 years and 5 years

Very low quality evidence from 8 RCTs with 869 people with squamous cell carcinoma of oesophagus indicated that there may be a clinically significant beneficial effect of concomitant chemotherapy compared with radiotherapy alone for overall survival rate at 1 year, but there is uncertainty around the estimate.

Moderate quality evidence from 8 RCTs with 869 people with squamous cell carcinoma of the oesophagus showed that there is a clinically significant beneficial effect of concomitant chemoradiotherapy compared with radiotherapy alone for overall survival rate at 3 years.

Moderate quality evidence from 6 RCTs with 662 people with squamous cell carcinoma of the oesophagus showed that there is a clinically significant beneficial effect of concomitant chemoradiotherapy compared with radiotherapy alone for overall survival rate at 5 years.

8.6.6.8.4 Overall survival

Low quality evidence from 5 RCTs with 426 people with squamous cell carcinoma of oesophagus showed that there was a clinically significant beneficial effect of chemoradiotherapy compared with radiotherapy alone for overall survival.

Subgroup analysis according to type of chemoradiotherapy

Concomitant: Moderate quality evidence from 4 RCTs with 329 people with squamous cell carcinoma of oesophagus showed that there was clinically significant beneficial effect of concomitant chemoradiotherapy compared with radiotherapy alone for overall survival.

Sequential: Low quality evidence from 1 RCT with 97 people with squamous cell carcinoma of oesophagus reported that there was no clinically significant difference between sequential chemoradiotherapy and radiotherapy alone for overall survival.

8.6.6.8.5 Disease-free survival rate

Very low quality evidence from 2 RCTs with 199 people with squamous cell carcinoma of oesophagus showed that there is no clinically significant difference between concomitant chemoradiotherapy and radiotherapy alone for disease-free survival rate.

8.6.6.8.6 Disease-free survival

Very low quality evidence from 2 RCTs with 199 people with squamous cell carcinoma of oesophagus showed that there was clinically significant beneficial effect of concomitant chemoradiotherapy compared with radiotherapy alone for disesase-free survival rate.

8.6.6.8.7 Any treatment-related morbidity

Low quality evidence from 6 RCTs with 612 people with squamous cell carcinoma of oesophagus showed that there is no clinically significant difference between concomitant chemoradiotherapy and radiotherapy alone for any treatment-related morbidity.

8.6.7 Evidence to recommendations

8.6.7.1 Relative value placed on the outcomes considered

As the aim of this review was to determine the most effective radical treatment for squamous cell carcinoma, the critical outcomes for this evidence review were overall survival, disease-free survival. Treatment-related morbidity and mortality were also considered important as they would allow a decision to be made about the relative benefits and harms of different treatment options. Another outcome measure that was felt to be important for non-surgical treatment was the number of patients going on to salvage resection. Health-related quality of life and patient-reported outcome measures were also considered important, although none of these were reported in the evidence identified for this review.

8.6.7.2 Quality of the evidence

The evidence for this review was taken from 36 randomised controlled trials and the quality of the evidence for individual outcomes was assessed using GRADE. Over all the comparisons and outcomes the quality of the evidence ranged from very low to high. Across the 8 comparisons the quality of the evidence can be summarised as:

Chemoradiotherapy then surgery versus surgery alone: very low to moderate

Chemoradiotherapy then surgery versus chemoradiotherapy alone: very low to moderate

Chemoradiotherapy then surgery versus chemotherapy then surgery alone: very low to low

Surgery then chemoradiotherapy versus surgery alone: low

Chemoradiotherapy versus surgery: very low to low

Surgery versus radiotherapy: very low to moderate

Chemotherapy then surgery versus surgery alone: very low to modearate

Chemoradiotherapy versus radiotherapy: very low to moderate

For 1 comparison (pre-operative chemoradiotherapy and surgery compared to chemoradiotherapy alone) data was available from two clinical trials that had formed part of a

previous systematic review. However, the Committee noted that the radiotherapy protocol used in this study was not up to date, there was no surgical quality assurance and that the study population was mixed. The Committee therefore agreed that they could not use this evidence as the basis for making any recommendations and instead they made a research recommendation for this comparison.

8.6.7.3 Consideration of benefits and harms

Due to the large number of pair-wise comparisons included in this review the Committee had to balance the relative effectiveness of these treatments with the morbidity or treatment-related mortality associated with each treatment. There were also a number of sub-groups for type of chemotherapy and surgical approach to take into consideration.

Chemoradiotherapy followed by surgery increased overall survival and disease-free survival compared to surgery alone, but with an increased rate of post-operative mortality.

There was no difference in mortality rates or overall survival between chemoradiotherapy followed by surgery compared to chemoradiotherapy alone, and treatment-related mortality was greater with the combination.

Chemoradiotherapy followed by surgery increased 3-year survival but had no effect on overall survival compared to chemotherapy then surgery, and both treatments led to similar rates of post-operative mortality.

There was no difference in the overall survival rates for surgery followed by chemoradiotherapy compared to surgery alone, but progression-free survival was increased.

Chemoradiotherapy alone had increased rates of 5-year survival and 5-year progression-free survival compared to surgery alone, with similar rates of 30-day mortality.

Surgery led to improved overall survival compared to radiotherapy alone, but treatment-related mortality was similar or increased, depending on the exact procedure.

Chemotherapy then surgery led to similar rates of overall survival and post-operative mortality compared to surgery alone, but disease-free survival was greater with chemotherapy than surgery.

Chemoradiotherapy led to similar rates of overall survival and treatment-related morbidity and mortality compared to radiotherapy, but did lead to increased 5-year survival.

Balancing these benefits and harms the Committee identified that chemoradiotherapy followed by surgery or chemoradiotherapy alone both led to survival benefits compared to surgery alone or surgery and chemotherapy, and that there was no difference in the survival rates between the two options so both were recommended as alternatives.

The Committee agreed that their recommendations would improve rational selection of treatments and were likely to lead to improved disease-free and overall survival, and that although chemoradiotherapy and surgery may lead to some increases in treatment-related morbidity compared to chemoradiotherapy alone, the choice of treatment could be made after discussion with the patient.

8.6.7.4 Consideration of economic benefits and harms

A health economic model was developed which considered the cost-effectiveness of the key interventions of interest (as identified by the Committee).

Due to a lack of evidence it was not possible to directly compare all the interventions against each other. The analysis therefore took the form of pairwise comparisons, which limits the conclusion that can be drawn.

The results of the base case analysis suggest that chemoradiotherapy and surgery was cost-effective in comparison to surgery alone with an ICER of £13,704 per QALY below the NICE threshold of £20,000 per QALY. Chemotherapy and surgery was also found to be cost-effective in comparison to surgery alone with an ICER of £3,025 per QALY. When comparing chemoradiotherapy and surgery against chemotherapy and surgery, chemoradiotherapy and surgery was found to be cost-effective with an ICER of £14,940 per QALY. Chemoradiotherapy was found to be less costly and more effective than surgery alone and was therefore dominant.

In deterministic sensitivity analysis, it was found that the conclusion of the analyses remained unchanged in the majority of modelled scenarios. The most notable excpetion was where the lower RR estimate was applied for overall survival outcomes. In probabilistic sensitivity analysis it was found that, in comparison to surgery alone, chemoradiotherapy and surgery had a 66% probability of being cost-effective at the NICE threshold of £20,000 per QALY. Chemotherpay and surgery was found to have a 73% probability of being cost-effective in comparison to surgery. When comparing chemoradiotherapy and surgery against chemotherapy and surgery, chemoradiotherapy and surgery was found to have a 51% probability of being cost-effective while chemotherapy and surgery had a 49% probability of being cost-effective. In the comparison between chemoradiotherapy and surgery and surgery alone, chemoradiotherapy was found to have a very high probability of being cost-effective (98%).

While the committee found the results to be of some interest, they were not thought to have practice changing implications. Indeed, the results essentially confirm that the two strategies that are most likely to be used in current practice; chemoradiotherapy or chemoradiotherapy plus surgery, are cost-effective in comparison to alternative treatments. Ideally, the analysis would have considered the comparison between chemoradiotherapy and surgery versus chemoradiotherapy alone. Indeed, the Committee identified this as the key comparison of interest in the analysis. However, there was insufficient clinical evidence to model this comparison in any meaningful way.

No substantial resource impact is expected as a result of the recommendations because they reflect current practice.

8.6.7.5 Other considerations

The Committee agreed that their recommendations reflected current clinical practice and so would lead to very little change in practice for most centres.

A lack of good quality evidence comparing definitive chemoradiotherapy or pre-operative chemoradiotherapy followed by surgical resection did not allow the Committee to make a recommendation of one of these treatment options over another, and they agreed that the choice would therefore be made in consultation with the patient. They also made a research recommendation to try and help define which of these options was more effective.

8.6.7.6 Key conclusions

From the comparisons included in the evidence review the Committee concluded that there was evidence for improved overall survival and disease-free survival, as well as a reduced number of salvage resections, when pre-operative chemoradiotherapy was used in addition to surgery, compared to surgery alone, although rates of treatment-related mortality were higher with the combination than with surgery alone.

Chemoradiotherapy alone showed increased 5-year survival compared to surgery alone, so the Committee also recommended this as a treatment option.

Other comparisons backed up the recommendations that pre-operative chemoradiotherapy and surgery or chemoradiotherapy alone were the most effective treatments:

chemoradiotherapy and surgery led to improved overall survival compared to chemotherapy and surgery, and there was no difference in overall survival between post-operative chemoradiotherapy and surgery compared to surgery alone.

Radiotherapy alone or chemotherapy and surgery did not show survival benefits compared to surgery alone, and a comparison of chemoradiotherapy alone versus radiotherapy alone showed survival benefit for chemoradiotherapy.

8.6.8 Recommendations

Squamous cell carcinoma of the oesophagus

30. Offer people with resectable non-metastatic squamous cell carcinoma of the oesophagus the choice of:

- radical chemoradiotherapy **or**
- chemoradiotherapy before surgical resection.

Discuss the benefits, risks and treatment consequences of each option with the person and those who are important to them (as appropriate).

8.6.9 Research recommendation

4. Does the addition of surgery to chemoradiotherapy improve disease-free and overall survival in people with squamous cell carcinoma of the oesophagus?

Why this is important?

The aetiology of squamous cell carcinoma (SCC) of the oesophagus is changing. Patients with SCC are now fitter, with fewer co-morbidities than in previous years. Standard radical treatment for SCC of the oesophagus is usually chemo-radiotherapy, which is associated with a median survival of between 12 and 18 months. Given a fitter patient population, surgery may be a therapeutic option but its effectiveness in addition to chemo-radiotherapy is unknown and a randomised controlled study to investigate whether the combination improves disease-free and overall survival would provide useful information to guide future clinical practice.

Table 129: Research recommendation rationale

Research question	Does the addition of surgery to chemoradiotherapy improve disease-free and overall survival in people with squamous cell carcinoma of the oesophagus?
Importance to 'patients' or the population	It is important to understand if the addition of surgery to standard treatment (chemoradiotherapy) will offer significant improvements in survival (both overall and disease free) when compared with standard treatment. The study would also determine whether there was increased morbidity due to surgery, and whether this was balanced by improvements in disease-free and overall survival.
Relevance to NICE guidance	In the current guidelines it has not been possible to recommend a definitive treatment option in patients with SCC as there is little or no data to support a policy of surgery following chemoradiotherapy. This study would allow a clearer recommendation to be made for this group of people.
Relevance to the NHS	A clearer recommendation would allow better targeting of resources.

Research question	Does the addition of surgery to chemoradiotherapy improve disease-free and overall survival in people with squamous cell carcinoma of the oesophagus?
National priorities	NHS Outcomes Framework for 2016-17: Improving 1-year and 5-year survival for all cancers
Current evidence base	A sub-group analysis from a retrospective review suggests a survival advantage to chemoradiotherapy followed by surgery, but data from randomised controlled trials is not available
Equality	No special considerations required.

1 **Table 130: Research recommendation statements**

Criterion	Explanation
Population	Patients with SCC of the oesophagus suitable for surgery
Intervention	Chemoradiotherapy with oesophagectomy
Comparator (without the risk factor)	Patients undergoing chemoradiotherapy only
Outcome	Overall survival, disease-free survival, morbidity and mortality, quality of life, patient-reported outcome measures
Study design	Randomised controlled trial
Timeframe	5 years

9 Palliative management

9.1 Non-metastatic oesophageal cancer not suitable for surgery

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

9.1.1 Introduction

In people with non-metastatic oesophageal cancer there will be a sub-group in whom the risk of radical surgery outweighs the potential benefit. This may be due to patient-related issues (such as co-morbidities or reduced fitness/performance status) or tumour-related issues (such as locally advanced T4 cancer). Personal preference to avoid surgery is also not uncommon.

For people with well differentiated, localised tumours that have not progressed beyond the submucosa endoscopic treatment is offered. However, for the majority of people with more advanced non-metastatic oesophageal cancer, non-surgical treatment options may include systemic chemotherapy, radiotherapy or chemoradiotherapy.

This review aimed to identify the most effective non-surgical treatments for people with non-metastatic oesophageal cancer, and to identify people most likely to benefit from these treatments.

9.1.2 Description of the clinical evidence

Five studies (n= 597) were included in the review, detailed by 6 articles (Ajani 2008, Gao 2009, Kumar 2007, Liu 2012/Zhao 2005, Wobbes 2001). Evidence from these are summarised in the clinical GRADE evidence profiles below. Two studies were published in China with the other 3 published in the India, USA and Europe. Squamous cell carcinoma was the only histology included in 3 studies (Kumar 2007, Liu 2012, Wobbes 2001) and comprised the majority of patients in 1 study (Gao 2009). Adenocarcinoma was the primary histology included in 1 study (Ajani 2008).

The review provided evidence for the critical outcomes of overall survival, disease-free survival and the important outcomes of disease-related morbidity, treatment-related morbidity and treatment-related mortality. No evidence was found for the critical outcome of health-related quality of life or the less important outcome of secondary resectability.

A total of 2 comparisons are included in this review: comparison one is chemoradiotherapy versus radiotherapy and includes 4 studies with 525 people (Gao 2009, Kumar 2007, Liu 2012, Wobbes 2001); comparison two is 5-fluorouracil (5-FU)-based chemoradiotherapy versus non-5-FU chemoradiotherapy and includes 1 study with 72 people (Ajani 2008). No evidence was found for other possible comparison groups.

See also the study selection flow chart in Appendix K, forest plots in Appendix H, study evidence tables in Appendix F and exclusion list in Appendix J.

9.1.3 Summary of included studies

A summary of the included studies is shown in Table 131 and Table 132

1 **Table 131: Summary of included studies: CHemoradiotherapy versus radiotherapy**

Study	Participants	RT	CRT
Gao, F., Jia, L., Du., A clinical study of combination of radiotherapy and IP regimen in the treatment of patients with local advanced esophageal cancer, Chinese-German Journal of Clinical Oncology, 8, 506-509, 2009 China RCT	N=68 Sex: 45 M/ 23 F Age: Mean= 57.55 (Range 33-78) T Stage: 47 II/ 21 III Histology: 66 SCC/1 AC/1 small cell carcinoma Exclusion Distant metastases Reasons inoperable: NR	The total dose administered was 60Gy (fractions not described).	Concurrent versus sequential not reported RT: same as RT group CT: Intravenous irinotecan was administered (65mg/m²) on the first day. Intravenous cisplatin (30mg/m²) was administered on the first and eighth day. Cycles were repeated every 21 days for a total of four cycles.
Kumar, S., Dimri, K., Khurana, R., A randomised trial of radiotherapy compared with cisplatin chemo-radiotherapy in patients with unresectable squamous cell cancer of the esophagus, Radiotherapy & OncologyRadiother Oncol, 83, 139-47, 2007 India RCT	N=125 Sex: 92 M/ 33 F Age: Mean = 54.72 (Range 24-76) T Stage: 2 I/73 II/ 50 III N Stage: 59 N0/ 66 N1 Histology: SCC only Inclusion Deemed inoperable or declined surgery Exclusion Metastatic disease	External beam radiotherapy (EBRT) to a dose of 50 Gy in 25 fractions over 5 weeks followed 1–2 weeks later with 2 applications of 6 Gy high-dose-rate (HDR) intraluminal radiotherapy (ILRT) spaced a week apart if the esophageal lumen could be negotiated without resorting to endoscopic dilatation. In 2003 with subsequent patients, in both arms, planned for 66 Gy in 33 fractions over 6.5 weeks and the exclusion of HDR-ILRT.	Concurrent CRT RT: same as RT group CT: once weekly cisplatin 35mg/m² for a total of 6-7 cycles. On the day of chemotherapy, radiation was delivered within 30-60 minutes following the infusion.
Liu, M., Shi, X., Guo, X., Long-term outcome of irradiation with or without chemotherapy for esophageal squamous cell carcinoma: a final report on a prospective trial, Radiation	N= 111 Sex: 78 M/ 33 F Age: Mean= 57.37 (Range 39-74) Stage: T1-2N0 22/ T3-4N0 74/ T1-4N1 15 Histology: SCC only Exclusion Distant metastases Reason Inoperable: NR	This consisted of 2 phases. In the first phase, 41.4Gy in 23 fractions was delivered by conventional fractionation (1.8Gy per fraction, one fraction per day, five fractions per week). In the second phase, 27 Gy was given in	Concurrent CRT RT: same as RT group CT: once daily cis-platinum 25mg/m² and 5-Fluorouracil of 600mg/m² for three consecutive days. This was administered once per month for four

Study	Participants	RT	CRT
OncologyRadiat, 7, 142, 2012 China RCT Data from an earlier publication from the same study (Zhao et al 2005) are also included here.		18 fractions by two 1.5Gy fractions per day, with an interval of > 6 hours. This gave a total of 68.4Gy in 41 fractions for 6.4 weeks.	months, during and after irradiation.
Wobbes, T., Baron, B., Paillot, B., Prospective randomised study of split-course radiotherapy versus cisplatin plus split-course radiotherapy in inoperable squamous cell carcinoma of the oesophagus, European journal of cancer (Oxford, England : 1990), 37, 470-7, 2001 France, Belgium, Netherlands RCT	N= 221 Sex: 195 M/ 7 F Age: Mean= 59.99 (Range 40-75) T Stage: 33 I/136 II/ 33 III/ 1 unknown N Stage: 137 N0/ 7 N1/ 1 N2/ 1 N3/ NX 56 M Stage: M0 197/ 6 M1 Histology: SCC only Inclusion Patients who are inoperable due to local physical condition or refused surgery Exclusion Evidence of distant metastasis	Radiotherapy two courses of 20 Gy in 5 fr of 4 Gy in 5 days. Total dose 55-60 Gy in classical fractionated protocol. Rest interval 2 weeks between courses.	Concurrent CRT CT given 3-4 days before RT and then every 3-4 weeks. RT: same as RT group CT: cisplatin 100 mg/m² IV over 30 minutes

Table 132: Summary of included studies: 5-FU-based chemoradiotherapy versus non-5-FU-based chemoradiotherapy

Study	Participants	Non-5FU based CRT	5-FU based CRT
Ajani, J. A., Winter, K., Komaki, R., Phase II randomized trial of two nonoperative regimens of induction chemotherapy followed by chemoradiation in patients with localized carcinoma of the esophagus: RTOG 0113, Journal of Clinical OncologyJ Clin Oncol, 26, 4551-6, 2008 USA RCT	N= 84 Mean age= 59.90 (Range 28-80) Sex: 56 M/ 16 F Histology: 25 SCC/ 47 AC Tumour stage: 1 T1/ 18 T2/ 48 T3/ 3 T4/ 2 Tx Inclusion: Deemed to have technically unresectable disease, or declined surgery, or medically unfit for surgery Exclusion: Evidence of metastatic cancer	Paclitaxel 175mg/m² was administered over 3 hours, followed by cisplatin 75mg/m² on day 1. This regimen was repeated on day 21. During radiation, patients received cisplatin 30mg/m² on days 1,8,15,22,29 and 36, and paclitaxel 60mg/m² as a continuous infusion over 96 hours on the same days. Radiation therapy: Same for both arms. Daily fractions size was 1.8Gy, and the total dose was 50.4Gy	Fluorouracil 700mg/m²/24 hours via an outpatient portable pump on days 1 through 5, cisplatin 15mg/m² on days 1 through 5, and paclitaxel 200mg/m² as a 24 hour infusion on day 1. Granulocyte colony stimulating factor or pegfilgrastim was started or administered on day 6. This regimen was repeated on day 29. During radiation, patients received fluorouracil 300mg/m² as continuous infusion for 96 hours (Monday to Friday) during each

Study	Participants	Non-5FU based CRT	5-FU based CRT
		delivered in 28 fractions.	of the 5 radiation therapy weeks, and paclitaxel 50mg/m² over three hours once per week during each of the radiation weeks.

9.1.4 Clinical evidence profiles

The clinical evidence profiles for this review question are presented in Table 133 and Table 134

Table 133. Summary clinical evidence profile. Chemoradiotherapy versus radiotherapy

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk with chemoradiotherapy	Corresponding risk with radiotherapy			
Overall Survival	14% at 3 years[2]	21% at 3 years (from 15% to 28%)	HR 0.8 (0.65 to 0.97)	457 (3 studies)	moderate [3]
Treatment-Related Mortality (related to treatment toxicity) Follow-up: 10 years	93 per 1000	35 per 1000 (7 to 173)	RR 0.38 (0.08 to 1.87)	111 (1 study)	very low[3,4]
One-Year Progression Free Survival Follow-up: 1 years	336 per 1000	312 per 1000 (101 to 970)	RR 0.93 (0.3 to 2.89)	289 (2 studies)	very low [5,6]
Three-Year Progression Free Survival Follow-up: 3 years	82 per 1000	72 per 1000 (28 to 173)	OR 0.87 (0.32 to 2.35)	221 (1 study)	very low[3,4]
Treatment-Related Toxicity - Nausea and Vomiting WHO Toxicity Grade 3/4	97 per 1000	11 per 1000 (2 to 53)	RR 0.11 (0.02 to 0.55)	289 (2 studies)	low[1,7]
Treatment-Related Toxicity - Esophagitis Grade 2-4	490 per 1000	397 per 1000 (294 to 534)	RR 0.81 (0.6 to 1.09)	193 (2 studies)	low[1,6]

CI, confidence interval; HR, hazard ratio; OR, odds ratio; RR, relative risk
1 Due to inadequate reporting of randomisation process and blinding. Gao 2009: very limited details on methodology.
2 3 year overall survival taken from RT arm of Kumar 2007
3 Unclear reporting of allocation concealment and randomisation process.
4 Very serious imprecision as 95% CI cross two default MIDs.

6 Very serious heterogeneity. I-squared> 80%. Also presented by subgroup (chemotherapy class) due to heterogeneity.
7 Serious imprecision. 95% CI crosses one default MID.
8 Downgraded for serious inconsistency. I-squared statistic 50-74.99.

Table 134. Summary clinical evidence profile. 5-FU versus non-5-FU chemoradiotherapy

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk with non-5-FU based CRT	Corresponding risk with 5-FU-based chemoradiotherapy (CRT)			
1-Year Overall Mortality Rate	314 per 1000	242 per 1000 (116 to 515)	RR 0.77 (0.37 to 1.64)	72 (1 study)	low[1]
2-Year Overall Mortality Rate	657 per 1000	782 per 1000 (585 to 1000)	RR 1.19 (0.89 to 1.6)	72 (1 study)	moderate[2]
Treatment-Related Mortality (due to treatment-related toxicity)	57 per 1000	27 per 1000 (2 to 285)	RR 0.47 (0.04 to 4.99)	72 (1 study)	low[3]
Treatment-Related Morbidity: Grade 4/5 Toxicity WHO Toxicity Grading	429 per 1000	296 per 1000 (159 to 557)	RR 0.69 (0.37 to 1.3)	72 (1 study)	low[3]

CI, confidence interval; MID, minimal important difference; RR, relative risk;

[1] 95% CI for effect estimate crosses two MIDs
[2] 95% CI for effect estimate crosses one MID
[3] Very serious imprecision. 95% CI crosses two default MIDs.

9.1.5 Economic evidence

A systematic review of the economic literature was conducted but no relevant studies were identified which were applicable to this review question. Economic modelling was not undertaken for this question because other topics were agreed as higher priorities for economic evaluation.

9.1.6 Evidence statements

9.1.6.1 Chemoradiotherapy versus radiotherapy

9.1.6.1.1 Overall survival

Moderate quality evidence from 3 RCTs with 457 people with oesophageal cancer indicated there is a clinically significant overall survival benefit in groups receiving radiotherapy plus chemotherapy compared to those groups receiving radiotherapy alone.

9.1.6.1.2 Treatment-related mortality

Very low quality evidence from 1 RCT with 111 people with oesophageal cancer indicated there is no clinically significant difference in risk of treatment-related mortality between groups receiving radiotherapy plus chemotherapy compared to group receiving radiotherapy alone.

9.1.6.1.3 One year progression-free survival

Very low quality evidence from 2 RCTs with 289 people with oesophageal cancer indicated there is no clinically significant difference in progression-free survival at 1 year in groups receiving radiotherapy plus chemotherapy compared to those groups receiving radiotherapy alone.

9.1.6.1.4 Three year progression-free survival

Very low quality evidence from 1 RCT with 221 people with oesophageal cancer indicated there is no clinically significant difference in progression-free survival at 3 years in the group receiving radiotherapy plus chemotherapy compared to the group receiving radiotherapy alone.

9.1.6.1.5 Treatment-related toxicity: nausea and vomiting

Low quality evidence from 2 RCTs with 289 people with oesophageal cancer indicated there is a clinically significant harmful effect of grade 3 or 4 nausea and vomiting in groups receiving radiotherapy plus chemotherapy compared to those groups receiving radiotherapy alone.

9.1.6.1.6 Treatment-related toxicity: oesophagitis

Low quality evidence from 2 RCTs with 193 people with oesophageal cancer indicated there is no clinically significant difference in risk of oesophagitis in groups receiving radiotherapy plus chemotherapy compared to those groups receiving radiotherapy alone.

9.1.6.2 5-FU-based chemoradiotherapy versus non-5-FU-based chemoradiotherapy

9.1.6.2.1 One year overall survival

Low quality evidence from 1 RCT with 72 people with oesophageal cancer indicated there is no clinically significant difference in risk of all-cause mortality at 1 year in groups receiving 5-FU-based chemoradiotherapy compared to those groups receiving non-5-FU based chemoradiotherapy.

9.1.6.2.2 Two year overall survival

Moderate quality evidence from 1 RCT with 72 people with oesophageal cancer indicated there is no clinically significant difference in risk of all-cause mortality at 2 years in groups receiving 5-FU-based chemoradiotherapy compared to those groups receiving non-5-FU based chemoradiotherapy.

9.1.6.2.3 Treatment-related mortality

Low quality evidence from 1 RCT with 72 people with oesophageal cancer indicated there is no clinically significant difference in risk of treatment-related mortality in groups receiving 5-FU-based chemoradiotherapy compared to those groups receiving non-5-FU-based chemoradiotherapy.

9.1.6.2.4 Treatment-related morbidity: Grade 4/5 toxicity

Low quality evidence from 1 RCT with 72 people with oesophageal cancer indicated there is no clinically significant difference in risk of treatment-related morbidity in groups receiving 5-FU-based chemoradiotherapy compared to those groups receiving non-5-FU based chemoradiotherapy.

9.1.7 Evidence to recommendations

9.1.7.1 Relative value placed on the outcomes considered

Although this question related to palliative management of patients who would not receive radical surgery, these patients are still being actively managed (as opposed to receiving 'palliative care') and therefore overall survival and disease-free survival were still considered to be critical outcomes. However, health-related quality of life, treatment-related morbidity, treatment-related mortality, and secondary resectability were all considered to be important when drafting the recommendations to allow a balanced view to be taken bewtween the benefits and harms of the treatments

There was no evidence available for health-related quality of life, secondary resectability and dysphagia outcomes. There was evidence available for two comparisons; one comparing definitive radiotherapy and chemoradiotherapy and one comparing two different chemotherapy regimens. For comparisons on other interventions including best supportive care, stenting, chemotherapy or sequence of interventions there was no evidence.

9.1.7.2 Quality of the evidence

The quality of each study was assessed using the Cochrane risk of bias checklists and the quality of the evidence for a particular outcome (i.e. across studies) was assessed using GRADE. The quality of the available evidence ranged from very low to moderate.

For the comparison between radiotherapy versus chemoradiotherapy, the quality was rated as moderate for overall survival and very low for one-year survival. Subgroup analysis by chemotherapy regimen was rated as very low quality for non-FU based regimens and low quality for FU-based regimens. Evidence for 2-year, 5-year and 10-year mortality was rated as low quality while evidence for 3-year survival was rated as moderate quality. Evidence for treatment-related mortality as well as 1 and 3-year progression-free survival was rated as very low quality. Evidence for treatment-related toxicity (nausea and vomiting and oesophagitis) was rated as low quality. The main reason for downgrading evidence was due to risk of bias, imprecision and heterogeneity. Most studies identified had unclear randomisation and allocation concealment.

For the comparison between FU-based and non-FU-based chemoradiotherapy, quality was rated as low for 1-year survival, treatment-related mortality and treatment-related morbidity. Evidence for 2-year overall survival was of moderate quality. The reason for downgrading evidence in this area was due to imprecision. The effect estimates crossed one or two default minimally important differences for the outcomes.

Considering the evidence base overall, there was found to be a general lack of randomised controlled trials available. This was found to be particular true comparison groups such as chemotherapy alone, stenting or best supportive care.

The search protocol was date limited to 2000 as the Committee advised that the key clinical evidence on which current standard of practice was based had been published since this date, but key articles providing the supporting evidence for the current standard practice of chemoradiotherapy are not included in evidence review. One included study, Wobbes 2001, raised concerns as the recruitment for this study had taken place between 1983 and 1989, many years prior to the cut off publication date.The overall lack of high quality evidence

resulted in weak recommendation being made by the Committee. In addition, some recommendations were based solely on the clinical experience of the Committee, such as treatment with chemotherapy alone and the reconsideration of surgery after initial treatment.

The Committee thought that the evidence base was sufficient to make general recommendations but were unable to comment on the optimal sequence and combination of treatments options due to a lack of evidence. The Committee therefore made a research recommendation on the optimal sequencing and combination of treatment options for those not suitable for surgery.

9.1.7.3 Consideration of benefits and harms

Evidence was only available for two comparisons for this review: chemoradiotherapy was shown to lead to improved overall survival compared to radiotherapy, although there was no difference in 1-year or 3-year progression-free survival. There were some differences in treatment-related toxicity, noteably increased rates of nausea and vomiting with chemoradiotherapy compared to radiotherapy, but no diffrences in treatment-related mortality or oesophagitis. For the comparison of 5-FU-containing regimens and non-5-FU containg regimens there was no difference seen in 1-year or 2-year overall survival or in treatment-related mortality.

The benefit of using chemoradiotherapy rather than radiotherapy alone is that it should lead to an increase in overall survival. This potential for improved overall survival was deemed to outweigh the potential for increased morbidity due to toxicity-related side effects. Furthermore, the recommendations suggest an individualised approach to treatment selection, which should ensure that the harms and benefits are appropriately balanced on an individual level.

The Committee considered that the recommendations are unlikely to significantly change practice and so no major changes are expected in terms of clinical benefits and harms. The main benefit of the recommendations was thought to be that they will encourages consistency in the treatment approach for this heterogeneous group of patients and ensures that all treatment options are given due consideration.

The Committee did not anticipate an increase in chemotherapy and chemoradiotherapy-related toxicity based on the recommendations as they are not likely to change practice.

9.1.7.4 Consideration of economic benefits and harms

A systematic review of the economic literature was conducted but no relevant studies were identified which were applicable to this review question.

The economic implications of this topic were considered but not thought to be substantial as the recommendations generally reflect current practice.

There is the potential for increased costs associated with reassessing suitability for surgery in some centres where this is not already part of current practice. However, in such cases, these assessment costs would be balanced against the potential savings that be accrued if people receive more appropriate and effective treatment. Therefore no significant resource impact is anticipated.

9.1.7.5 Other considerations

The assessment and reconsideration for surgery is a potential change in practice for some centres. No other changes in practice are anticipated to implement the recommendations as the Committee thought that most people are receiving chemoradiotherapy where appropriate.

9.1.7.6 Key conclusions

The Committee agreed that the evidence as well as their own clinical experience, provided a clear basis to recommend the use of chemoradiotherapy over radiotherapy alone. The Committee also agreed that it was important to list the treatment options for those patients whose cancer cannot be encompassed within a radiotherapy field. It was also thought important to encourage assessment of the response to chemotherapy or chemoradiotherapy to determine suitability for surgery.

9.1.8 Recommendations

Non-metastatic oesophageal cancer that is not suitable for surgery

31. Consider chemoradiotherapy for people with non-metastatic oesophageal cancer that can be encompassed within a radiotherapy field.

32. When the cancer cannot be encompassed within a high-dose radiotherapy field, consider one or more of:

- chemotherapy
- local tumour treatment, including stenting or palliative radiotherapy
- best supportive care.

Discuss the benefits, risks and treatment consequences of each option with the person and those who are important to them (as appropriate).

33. After treatment, assess the tumour's response to chemotherapy or chemoradiotherapy and reconsider if surgery is an option.

9.1.9 Research recommendations

5. What is the optimal combination and sequence of chemotherapy and radiotherapy, and selection criteria, for patients with non-metastatic oesophageal cancer who are not suitable for surgery?

Why this is important?

Patients with non-metastatic oesophageal cancer not suitable for radical treatment account for approximately 30% of all presentations of oesophageal cancer, and the optimal treatment to provide these patients with durable symptomatic responses and improved overall survival remain unclear.

Possible treatment options range from stent insertion to radical chemoradiotherapy, and identifying the correct approach for each individual patient could prevent unnecessary toxicity and would improve patient outcomes. The poorly-defined management pathway for these patients remains a significant unmet need, and research is needed to clarify the optimal treatments, and their sequencing.

Table 135: Research recommendation rationale

Research question	What is the optimal combination and sequence of chemotherapy and radiotherapy, and selection criteria, for patients with non-metastatic oesophageal cancer who are not suitable for surgery?
Importance to 'patients' or the population	In this group of patients the treatment pathway is unclear, and thus survival and health-related quality of life outcomes may not be optimal.

Research question	What is the optimal combination and sequence of chemotherapy and radiotherapy, and selection criteria, for patients with non-metastatic oesophageal cancer who are not suitable for surgery?
Relevance to NICE guidance	Due to a lack of clinical evidence current NICE guidelines have been unable to make clear recommendations for this group of patients.
Relevance to the NHS	Effective, evidence-based treatment pathways for this group of patients would lead to improved disease-free and overall survival with reduced toxicities
National priorities	NHS Outcomes Framework for 2016-17: Improving 1-year and 5-year survival for all cancers.
Current evidence base	Lack of randomised controlled trials, particularly comparing chemotherapy, stenting or best supportive care.
Equality	No special considerations required.

Table 136: Research recommendation statements

Criterion	Explanation
Population	Patients with non-metastatic oesophageal cancer not suitable for surgery
Intervention	Chemotherapy, radiotherapy, chemoradiotherapy, stenting, best supportive care
Comparator (without the risk factor)	• Each other
Outcome	• Overall survival, disease-free survival, morbidity, mortality, patient-reported outcomes, quality of life
Study design	Prospective randomised controlled study
Timeframe	5 years

9.2 First-line palliative chemotherapy

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

9.2.1 Introduction

For people with oesophago-gastric cancer who are not suitable for radical treatment, then alternative, palliative options should be considered in conjunction with ongoing supportive care. Chemotherapy still has an important role to play in this scenario, but the benefits of chemotherapy – improved overall and disease free survival with accompanying symptom relief – must be carefully balanced against the putative side effects and potential lack of efficacy.

Optimal chemotherapeutic practice ranges from single agents to multiple drug combinations, and the best choice of therapy is dependent upon multiple factors including patient's wishes, co-morbidities and the possibility of trial entry.

This review was based on the premise that the decision to give first-line palliative chemortherapy had already been made, and the aim was to assess the choice of therapies available for this situation and to identify the most effective combinations for people suitable only for palliative treatment.

9.2.2 Description of clinical evidence

Clinical evidence for 10 comparisons was available for this review:

1. 5-fluorouracil (5-FU) alone versus combination therapy
    a. Bouche 2004 (Data extracted from Bouche RCT and Wagner 2010 systematic review)
    b. Colucci 1995 (Data extracted from Wagner 2010 systematic review)
    c. Loehrer 1994 (Data extracted from Loehrer RCT)
    d. Lutz 2007 (Data extracted from Wagner 2010 systematic review)
    e. Ohtsu 2003 (Data extracted from Ohstu RCT)
    f. Kim 1993 (Data extracted from Kim RCT)
2. 5-FU/cisplatin/anthracycline versus 5-FU/cisplatin alone
    a. KRGCC 1992 (Data extracted from Wagner 2010 systematic review)
    b. Kim 2001 (Data extracted from Wagner 2010 systematic review)
    c. Yun 2010 (Data extracted from Mohammad 2015 systematic review)
3. 5-FU/cisplatin/anthracycline versus 5-FU/anthracycline alone
    a. Kikuchi 1990 (Data extracted from Wagner 2010 systematic review)
    b. Roth 1999 (Data extracted from Wagner 2010 systematic review)
4. Irinotecan versus non-irinotecan containing combinations
    a. Bouche 2004 (Data extracted from Bouche RCT and Wagner 2010 systematic review)
    b. Dank 2008 (Data extracted from Wagner 2010 systematic and Curran 2009 RCT)
    c. Moehler 2009 ((Data extracted from Wagner 2010 systematic review)
    d. Park 2008 (Data extracted from Mohammad 2015 systematic review)
5. Docetaxel versus non-docetaxel containing combinations
    a. Thuss-Patience 2005 (Data extracted from Wagner 2010 systematic review)
    b. Van Cutsem 2006 (Data extracted from Wagner 2010 systematic review)
    c. Ridwelski 2008 (Data extracted from Wagner 2010 systematic review)
    d. Sadighi 2006 (Data extracted from Wagner 2010 systematic review and Sadighi 2006 RCT)
    e. Roth 2007 (Data extracted from Roth RCT and Wagner 2010 systematic review)
    f. Al-Batran 2013 (Data extracted from Al-Batran RCT)
    g. Wang 2015 (Data extracted from Wang RCT)
6. Capecitabine versus IV 5-FU combinations
    a. Kang 2009 (Data extracted from Wagner 2010 systematic review)
    b. Cunningham 2008 (Data extracted from Cunningham RCT)
7. Cisplatin versus oxaliplatin combinations
    a. Al-Batran 2008 (Data extracted from Wagner 2010 systematic review)
    b. Popov 2008 (Data extracted from Wagner 2010 systematic review)
    c. Kim 2014 (Data extracted from Kim RCT)
    d. Cunningham 2008 (Data extracted from Cunningham RCT)
8. 5-FU combination versus non-5-FU combination
    a. Roy 2012 (Data extracted from Roy RCT)
    b. Van Cutsem 2015 (Data extracted from Mohammad systematic review)
    c. Pozzo 2004 (Data extracted from Pozzo RCT)
9. Platinum combination versus taxane combination
    a. Lee 2015 (Data extracted from Lee RCT)
10. Other combinations

a. Guimbauld 2014 (Data extracted form Guimbauld RCT and Mohammad systematic review)

Evidence from these studies are summarised in the summary of included studies (Table 10) and the summary clinical evidence profiles (Table 132 to Table 147). See also the study selection flow chart in Appendix K, forest plots in Appendix H, study evidence tables in Appendix F and exclusion list in Appendix J.

9.2.3 Summary of included studies

A summary of the studies included in this review is presented in Table 137.

Table 137: Summary of included studies

Study details	Participants	Interventions
Al-Batran 2013 Country/ies where the study was carried out: Germany Study type: RCT Study dates: August 2007 and October 2008	Sample size n=143 patients Characteristics FLOT: n=72 (21F/51M) Median age 69y Tumour site: OG junction 37.5 %/ Gastric 45% 69.4 % metastatic FLO: n=71 (26F/45M) Median age 70y Tumour site: OG junction 33.8%/ Gastric 66.2% Inclusion criteria ≥65 years locally advanced or metastatic adenocarcinoma of the stomach or oesophagogastric junction	Interventions Docetaxel versus non-docetaxel FLOT: oxaliplatin 85 mg/m^2 + leucovorin 200 mg/m^2 + docetaxel 50 mg/m^2, each as an intravenous infusion followed by 5-FU 2600 mg/m^2 as a 24-h continuous infusion x8 cycles FLO: oxaliplatin 85 mg/m^2 + leucovorin 200 mg/m^2 each as an intravenous infusion followed by 5-FU 2600 mg/m^2 as a 24-h continuous infusion x8 cycles
Curran 2009 Country/ies where the study was carried out Ireland; Multi-centre Study type RCT Study dates January 2000 - March 2002	Sample size n=337 Characteristics IF: n=170 Sex: 125 M/45 F Median age: 58 (range 29-76) CF: Sex: 108 M/ 55 F Median age: 59 (28-77) Inclusion criteria Locally recurrent/metastatic adenocarcinoma of stomach or oesophagastric junction	Interventions Irinotecan versus cisplatin-based combination IF arm: irinotecan 80 mg/m^2 as a 30-min i.v. infusion, followed by FA 500 mg/m^2 as a 2-h i.v. infusion, immediately followed by 5-FU 2000 mg/m^2 as a 22-h i.v. infusion, day 1 every week for 6 weeks followed by a 1-week rest. CF arm: cisplatin 100 mg/m^2 as a 1- to 3-h i.v. infusion, day 1, followed by 5-FU 1000 mg/m^2/day as a 24-h i.v. infusion, days 1–5, every 4 weeks

Study details	Participants	Interventions
	18-75y	Treatment was administered until disease progression, unacceptable toxicity or consent withdrawal.
Kim, 1993 Country/ies where the study was carried out: Korea Study type: RCT Study dates: From August, 1986 to June, 1990	Sample size n= 214 FP= 112, FU= 102, (FAM arm not relevant) Characteristics Median age= 54 (19-77) 205 M/ 90 F Inclusion criteria histological confirmation of adenocarcinoma in gastric mucosa	Interventions 5-FU alone versus combination In all 3 regimens, 5-FU was diluted in 1000 ml of 5% dextrose and infused intravenously over 12 hours. Drug administration was postponed by 1 week if there was no hematologic recovery (leukocyte count > 3000/mm^3 or platelet count > 75,000/mm^3). 5FU: 1000 mg/m^2 IV Days 1-5 every 3 wks 5FU + cisplatin: as above + cisplatin 60 mg/m^2 IV Day 1 every 3 wks
Kim, 2014 Country/ies where the study was carried out: Korea Study type: RCT Study dates March 2007 and July 2009	Sample size n= 77 Characteristics D + cisplatin: Median= 56 (range 35-74) 74% male Previous adjuvant chemo: 42% D+ oxaliplatin: Median= 58 (range 39-75) 67% male previous adjuvant chemo: 26% Inclusion criteria histologically confirmed gastric adenocarcinoma age <= 75 years	Interventions Cisplatin versus oxaliplatin Chemotherapy consisted of docetaxel (35 mg/m^2 on days 1 and 8) plus cisplatin (60 mg/m^2 on day 1 every 3 weeks) or oxaliplatin (120 mg/m^2 on day 1 every 3 weeks). Docetaxel was infused intravenously in 200 ml of 5 % glucose over 60 min, cisplatin was administered in 150 ml of normal saline over 60 min with intravenous pre- and post-hydration, and oxaliplatin was diluted in 500 ml of 5 % glucose solution and administered over 90 min. all patients were premedicated with 12 mg dexamethasone i.v. before each docetaxel infusion to prevent fluid retention and hypersensitivity reactions.
Lee 2015 Country/ies where the study was carried out: Korea Study type: RCT . Study dates October 2008 and October 2012	Sample size n= 94 (CC arm= 46, CP arm= 48) Characteristics Median age= 63 years (range 34-82) 98% male 59 primary advanced disease/ 35 recurrent disease (after surgery or dCRT) Previous chemotherapy: 19	Interventions Taxane combination versus cisplatin combination CC = capecitabine 1000 mg/m^2 orally twice a day on days 1–14 plus 75 mg/m^2 of cisplatin intravenously on day 1 CP= capecitabine as for CC plus 80 mg/m^2 of paclitaxel intravenously on days 1 and 8 An identical dose regimen of capecitabine was used for both treatment arms. Study treatment was repeated every 3 weeks until documented disease progression, unacceptable toxicity, or patient refusal.

Study details	Participants	Interventions
	Inclusion criteria squamous cell carcinoma of the esophagus	
Mohammad 2015 Country/ies where the study was carried out: The Netherlands Study type: Systematic review of RCTs Study dates Search limits between 1980 and March 2015	Sample size Twenty-two studies with in total 3475 participants investigating a triplet versus a doublet were included. 6 relevant articles are detailed below. Guimbaud 2014 n= 416 Median age= 61 (range 28-84) 84% metastatic 74.5% male Li 2011 n= 94 Median age= 58.5 (Range 20-75) 58.5% metastatic 69% male Park 2008 n= 91 Median age= 53.5 (range 26-73) 100% metastatic 67% male Van Cutsem 2015 n= 254 Median age= 59 100% metastatic 69% male Wang 2015 n= 234 Median age= 57.5 (Range 19-80) 76% metastatic 72.5% male Yun 2010 n= 91 Median age= 56.5 (Range 33-75) NR% metastatic 68% male	Interventions Guimbaud 2014 epirubicin + cisplatin + capecitabine 5-FU + irinotecan Li 2011 placitaxel + cisplatin + 5-FU cisplatin + 5-FU Park 2008 cisplatin + irinotecan +5-FU cisplatin + 5-FU Van Cutsem 2015 docetaxel + oxaliplatin + 5-FU docetaxel + oxaliplatin + capecitabine docetaxel + oxaliplatin Wang 2015 docetaxel + cisplatin + 5-FU cisplatin + 5-FU Yun 2010 epirubicin + cisplatin + capecitabine cisplatin + capecitabine
Roth 2007 Country/ies where the study was carried out Switzerland; Multiple	Sample size n=119 Characteristics ECF group:	Interventions Anthracycline containing regimen versus non-anthracycline containing Patients received 3-weekly cycles of:

Study details	Participants	Interventions
Study type: RCT Study dates: September 1999 and July 2003	median age (range)= 59 (32-71) 75% male 83% metastatic disease previous gastrectomy: 18% TC group: median age (range)= 58 (40-70) 76% male 82% metastatic disease previous gastrectomy: 24% TCF group: median age (range)= 61 (35-78) 73% male 95% metastatic disease previous gastrectomy: 32% Inclusion criteria gastric adenocarcinoma	ECF= epirubicin 50 mg/m^2 IV bolus on day 1, cisplatin 60 mg/m^2 4-hour IV infusion on day1, and 5-FU 200mg/m^2/d continuous IV infusion on days 1 to 21 TC =docetaxel 85 mg/m^2 1-hour IV infusion on day 1 and cisplatin 75 mg/m^2 4-hour IV infusion on day 1 TCF= TC plus FU 300 mg/m^2/d continuous IV infusion on days 1 to 14, for up to eight cycles or until disease progression,un acceptable toxicity, or consent withdrawal.
Sadighi 2006 Country/ies where the study was carried out: Iran Study type: RCT Study dates January 2002 and January 2005,	Sample size N= 86 Characteristics ECF group N= 41 Mean age (SD)= 57.32 (9.83) 81 % male 71% primary disease/ 29% recurrent TCF group N= 44 Mean age (SD)= 55.4 (14.04) 70% male 75% primary disease/ 25% recurrent Inclusion criteria histologically confirmed gastric adenocarcinoma	Interventions Docetaxel versus non-docetaxel regimen three to six cycles every 3 weeks ECF: epirubicin 60 mg/m^2, cisplatin 60 mg/m^2 and 5-FU 750 mg/m^2/day as 5 days continuous infusion TCF: docetaxel 60 mg/m^2, cisplatin 60 mg/m^2 and 5-FU 750 mg/m^2 in the same dose and schedule of ECF
Wagner 2010 Country/ies where the study was carried out: Switzerland & Germany Study type: Systematic review of RCTS	Sample size No. studies=35 trials included in meta-analysis n=5726 Median age unknown Characteristics	KRGGC 1992 Cisplatin+5-FU Cisplatin+5-FU+epirubicin Kim 2001 Cisplatin+5-FU Cisplatin+5-FU+epirubicin Bouche 2004

Study details	Participants	Interventions
Databases searched up until March 2009; selected conference abstracts up until 2008	All relevant studies described below KRGGC 1992 n=60 Median age= NR Kim 2001 n=121 Median age= NR Bouche 2004 n=134 Median age=65 Colucci 1995 n=71 Median age=60 Loehrer 1994 (2 arms only relevant to this review question) n=165 Median age=60 Lutz 2007 n=90 Median age=62 Ohtsu 2003 (2 arms only relevant to this review question) n=280 Median age=62 Popov 2002 n=60 Median age=56 Kikuchi 1990 n=77 Median age=blank Roth 1999 n= 122 Median age= 55 Bouche 2004 n= 134 Median age= 65 Dank 2008 n= 337 Median age= 59 Moehler 2009 n= 118 Median age= 62.5 Thuss-Patience 2005 n= 90 Median age: 62.5	Lv+5-FU bolus+5-FU infusion Cisplatin+Lv+5-FU bolus + 5-FU infusion Irinotecan+Lv+5-FU bolus + 5-FU infusion Colucci 1995 5-FU+Lv Epirubicin+5-FU+Lv Loehrer 1994 (see individual study for arm specific results) 5-FU Epirubicin (this arm not in protocol) 5-FU+epirubicin Lutz 2007 5-FU 5-FU+FA 5-FU+cisplatin+FA Ohtsu 2003 (see individual study for arm specific results) 5-FU 5-FU+cisplatin Uracil+m -itomycin (this arm not included in protocol) Popov 2002 5FU Cisplatin+etoposide+Adriamycin Comparison 4. 5-FU/cisplatin/anthracycline versus 5-FU/anthracycline Kikuchi 1990 5-FU+Adriamycin 5-FU+Adriamycin+cisplatin Roth 1999 5-FU + epirubicin 5-FU + epirubicin + cisplatin Bouche 2004 1. leucovorin + 5-FU 2. leucovorin + 5-FU + cisplatin 3. leucovorin + 5-FU + irinotecan Dank 2008 1. irinotecan + 5-FU + 2. cisplatin + 5-FU + FA Moehler 2009 1. capecitabine + irinotecan 2. capecitabine + cisplatin Thuss-Patience 2005 1. docetaxel + 5-FU 2. epirubicin + cisplatin + 5-FU

Study details	Participants	Interventions
	Van Cutsem 2006 n= 445 Median age: 55 Ridwelski 2008 n= 273 Median age= 62 Sadighi 2006 n= 86 Median age= 56 Roth 2007 n= 121 median age= 59 Kang 2009 n= 316 Median age= 56 Al-Batran 2008 n=220 Median age= 64 Popov 2008 n= 72 Median age= 56	Van Cutsem 2006 1. docetaxel + cisplain + 5-FU 2. cisplatin + 5-FU Ridwelski 2008 1. docetaxel + cisplatin 2. 5-FU + leucovorin + cisplatin Sadighi 2006 epirubicin + 5-FU + cisplatin docetaxel + 5-FU + cisplatin Roth 2007 epirubicin + cisplatin + 5-FU docetaxel + cisplatin docetaxel + cisplatin +5- FU Kang 2009 oral capecitabine + cisplatin 5-FU + cisplatin Al-Batran 2008 oxaplatin + leucovorin + 5-FU cisplatin + leucovorin + 5-FU Popov 2008 oxaliplatin + 5-FU + folinic acid + leucovorin cisplatin + 5-FU+ folinic acid +leucovorin
Van Cutsem 2006 Country/ies where the study was carried out: Multiple; Europe Study type: RCT Study dates: November 1999 and January 2003	Sample size N= 445 (DCF= 221, CF= 224) Characteristics 71% male Median age= 55 (Range: 25-79) Tumour site: 22% GE Junction/ 78% Gastric 97% metastatic disease Previous chemotherapy: 3% Previous radiotherapy: 2% Previous surgery: 31% Inclusion criteria 18 years and older histologically proven gastric or esophagogastric junction adenocarcinoma	Interventions Docetaxel versus non-docetaxel combination DCF: Docetaxel 75 mg/m^2 (1-hour intravenous infusion) plus cisplatin 75 mg/m^2 (1- to 3-hour intravenous infusion) on day 1, followed by fluorouracil 750 mg/m^2/d (continuous intravenous sinfusion) for 5 days (DCF) every 3 weeks CF: Cisplatin 100 mg/m^2 on day 1 followed by fluorouracil 1,000mg/^{m2}/d for 5 days (CF) every 4 weeks. Dose modification criteria were predefined. All patients received appropriate hydration and premedications as previously reported Treatment continued until disease progression, unacceptable toxicity, death, or consent withdrawal.
Bouche 2004 Country/ies where the study was carried out:	Sample size N= 134 Characteristics	Interventions Patients assigned to the LV5-FU2 arm (arm A) received LV 200 mg/m^2

Study details	Participants	Interventions
France Study type: RCT Study dates January 1999 and October 2001	Median age= 65 (range 37-76) 100% metastatic disease 50% received prior surgery 31 % cardiac, 69% gastric cancer Inclusion criteria metastatic gastric or cardial adenocarcinoma between 18-75 years	intravenous (IV) over 2 hours followed by 5-FU 400 mg/m^2 IV bolus then 5-FU 600 mg/m^2 continuous infusion over 22 hours on days 1 and 2, repeated every 14 days (one cycle 15 days). No systematic prophylactic premedication was administered. Patients assigned to the LV5-FU2-cisplatin arm (arm B) received cisplatin 50 mg/m^2 IV over 1 hour on day 1 or 2 with LV5FU2 (one cycle 15 days). Prophylactic medication consisted of IV antiemetics (setrons) and methylprednisolone 120 mg 10 minutes before cisplatin administration, hydration (1 L over 3 hours before and after cisplatin), oral antiemetics, and corticosteroids from days 2 to 5. Patients assigned to the LV5-FU2 irinotecan arm (arm C) received irinotecan 180mg/m^2 IV over 90 minutes on day 1 with LV5FU2 and no systematic prophylactic premedication (one cycle 15 days).
Loehrer 1994 Country/ies where the study was carried out: USA Study type: RCT Study dates January, 1985, through January, 1987	Sample size N= 153 5FU arm= 69 5FU = epirubicin arm= 70 epirubicin alone= 26 (not relevant to this review) Characteristics 5FU arm: median age (range)= 59 (19-79) previous radiotherapy: 3% 5FU + epirubicin arm: median age (range)= 62 (21-83) previous radiotherapy: 3% Inclusion criteria unresectable or metastatic disease histologically confirmed adenocarcinoma of the stomach 18 years and older	Interventions 5-Fluorouracil (5-FU) alone (500 mg/m^2 days 1-5) OR Combination of epirubicin (90 mg/m^2 day 1) and 5-FU (400 mg/m^2 days 1-5). Courses were repeated every four weeks.
Ohtsu, 2003 Country/ies where the study was carried out: Japan	Sample size N= 280 5-FU alone= 105 FP= 105	Interventions The 5-FU-alone regimen consisted of 120-hour continuous-infusion 5-FU 800 mg/m^2/d, which was repeated every 4 weeks.

Study details	Participants	Interventions
Study type RCT Study dates September 1992 and March 1997	UFTM arm= 70 (not relevant to this review question) Characteristics 5-FU group: Median age (range)= 63 (27-75) 75 male/ 29 female 90 metastatic/ 15 locally advanced Prior gastrectomy: 27 FP group: Median age (range)= 63 (19-75) 77 male/ 28 female 90 metastatic/ 15 locally advanced Prior gastrectomy: 29 Inclusion Criteria 75 years or younger	The FP regimen comprised continuous-infusion 5-FU 800 mg/m^2/d along with a 30-minute infusion of CDDP 20 mg/m^2/d with adequate hydration for 5 consecutive days. Cycles were repeated every 4 weeks for up to six courses; the subsequent courses were administered without CDDP in the same schedule as the 5-FU-alone regimen.
Pozzo, 2004 Country/ies where the study was carried out Multiple; 13 European and Israel, Lebanon, Turkey, South Africa Study type: RCT Study dates January 1999 and April 2000	Sample size N= 146 (I/Fu= 74, I/C= 72) Characteristics I + 5-FU group: Median age (range)= 57 (39-75) 77% male 82.4% gastric/ 16.4% gastroesophageal junction + fundus 91.9% metastatic I + cisplatin group Median age (range)= 59 (33-74) 63.9% male 68.1% gastric/ 31.9% gastroesophageal junction + fundus 95.8% metastatic Inclusion criteria 18 to 75 years old histologically confirmed metastatic gastric or oesophageal-gastric junction adenocarcinoma	Interventions Treatment in the irinotecan/ 5-FU/FA arm consisted of a 30-min infusion of irinotecan [80mg/m^2 intravenously (i.v.)] and a 2-h infusion of FA (500mg/m^2 i.v.), followed immediately by a 22-h infusion of 5-FU (2000mg/m^2 i.v.), once weekly for 6 weeks (on days 1, 8, 15, 22, 29 and 36) followed by a 1-week rest. Cycles were repeated every 7 weeks. Treatment in the irinotecan/cisplatin arm consisted of irinotecan (200mg/m^2 i.v.) administered first as a 30-min infusion on day 1, followed on the same day by hyperhydration (1l normal saline during the first hour), then a 4-h infusion of cisplatin (60mg/m^2 i.v.) followed by 1.5 l normal saline over 3h. Cycles were repeated every 3 weeks. Treatment was continued until disease progression, unacceptable toxicity or withdrawal of consent
Roy 2012 Country/ies where the study was carried out 6 European countries Study type: RCT	Sample size N= 85 (DI n=42, DF n= 43) Characteristics 70% male	Interventions DI group: docetaxel 60mg/m^2 (1-h IV infusion, Day 1) followed by irinotecan 250mg/m^2 (30- to 90-min IV infusion, Day 1) every 3 weeks DF group:

Study details	Participants	Interventions
August 1999 and August 2000	Median age= 61 (Range: 38-76) 94.1% metastatic disease Previous adjuvant/neoadjuvant chemo: 3.5% Previous surgery: 36.5% Inclusion criteria age 18-75 years histologically proven gastric adenocarcinoma (including gastro-esophageal junction)	docetaxel 85mg/m^2 (1-h IV infusion, day 1) followed by 5-FU 750mg/m^2 per day (continuous infusion, days 1 to 5) every 3 weeks . Chemotherapy given until disease progression, unacceptable toxicity or withdrawal of consent.
Cunningham 2008 Country/ies where the study was carried out UK and Australia Study type RCT Study dates June 2000 and May 2005	Sample size N=1002 ECF= 263 ECX= 250 EOF= 245 EOX= 244 Characteristics ECF group Median age (range)= 65 (22-83) 81.1% male Site: 34.9% esophagus/ 29.9% GEJ/ 36.1% stomach 79.5% metastatic Histology: 90% adenocarcinoma/ 7.6% Squamous cell carcinoma/ 2.4% undifferentiated ECX group Median age (range)= 64 (22-82) 80.5% male Site: 29.5% esophagus/ 28.2% GEJ/ 42.3% stomach 76.8% metastatic Histology: 89.6% adenocarcinoma/ 9.5% Squamous cell carcinoma/ 0.8% undifferentiated EOF group	Interventions ECF: epirubicin + cisplatin + 5-FU ECX= epirubicin + cisplatin + capecitabine EOF= epirubicin + oxaliplatin +5-FU EOX= epirubicin + oxaliplatin + capecitabine On day 1 of every 3-week cycle, patients in all study groups received an intravenous bolus of epirubicin (50 mg/m2); cisplatin (60 mg/m^2) was given intravenously with hydration in the ECF and ECX groups, and oxaliplatin (at a dose of 130 mg/m^2) was administered intravenously during a 2-hour period in the EOF and EOX groups. Fluorouracil (200 mg/m^2) and capecitabine (at a twice daily dose of 625 mg/m^2) were given throughout treatment in the appropriate groups. Fluorouracil was administered through a CVAD with an empirical dose of 1 mg of warfarin daily for thromboprophylaxis. Antiemetic prophylaxis was routinely administered as described previously. Treatment cycles were repeated every 3 weeks for a maximum of eight cycles unless there was evidence of disease progression or unacceptable toxicity, or the patient withdrew consent or died.

Study details	Participants	Interventions
	Median age (range)= 61 (33-78) 81.3% male Site: 39.6% oesophagus/ 23.4% GEJ/ 37% stomach 77% metastatic Histology: 86% adenocarcinoma/ 12.8% Squamous cell carcinoma/ 1.3% undifferentiated EOX group Median age (range)= 62 (25-80) 82.8% male Site: 34.3% oesophagus/ 22.2% GEJ/ 43.5% stomach 75.7% metastatic Histology: 87.4% adenocarcinoma/ 12.2% Squamous cell carcinoma/ 0.4% undifferentiated Inclusion criteria 18 and over histologically proven adenocarcinoma, squamous cell carcinoma, undifferentiated carcinoma	
Guimbaud 2014 Country/ies where the study was carried out France Study type RCT Study dates: June 2005 and May 2008	Sample size n= 416 (ECX= 209, FOLFIRI= 207) Characteristics Median age (range)= 61.4 (27.9- 83.8) 74.3 % male	Interventions The ECX regimen consisted of epirubicin 50 mg/m^2 (15-minute IV infusion) plus cisplatin 60 mg/m^2 (1-hour IV infusion) on day 1 followed by oral capecitabine 1 g/m^2 twice per day from day 2 to day 15 every 3 weeks; the maximum cumulative dose of epirubicin authorized was 900 mg/m^2 The FOLFIRI regimen consisted of irinotecan 180mg/m^2 (90-minuteIV

Study details	Participants	Interventions
	Tumour location: 32.7 % GEJ/ 65.1 gastric/ 2.2% missing Previous resection: 24.5% Previous CRT: 58.1% Previous chemo alone: 20.9% Inclusion criteria histologically confirmed, unresectable, locally advanced or metastatic gastric or EGJ adenocarcinoma 18 and over	infusion) and leucovorin 400 mg/m^2 (2-hour IV infusion) followed by a fluorouracil 400 mg/m^2 IV bolus and then fluorouracil 2,400 mg/m^2 as a 46-hour continuous infusion every 2 weeks. Dose modifications, appropriate hydration, and premedication were predefined in the study protocol.
Wang 2016 Country/ies where the study was carried out China Study type RCT Study dates NR	Sample size N= 243 (mDCF arm= 121, CF arm= 122) Characteristics 72.2% male Median age (range)= 56.1 (19-80) Tumour site: GOJ 20.9%/ Stomach 69.7% / Other or unknown 9.4% 76.1% metastatic disease Previous radiotherapy: 0.4% Previous surgery: 36.3% Previous adjuvant or neoadjuvant chemotherapy: 19.2% Inclusion criteria 18 years and over histologically proven gastric or GOJ adenocarcinoma	Interventions mDCF: docetaxel 60 mg/^{m2} (1-h intravenous infusion) plus cisplatin at 60 mg/m^2 (1- to 3-h intravenous infusion) on day 1, followed by 5-FU at 600 mg/m^2/day (continuous intravenous infusion) for 5 days CF: cisplatin at 75 mg/m^2 on day 1 followed by 5-FU at 600 mg/m^2/day for 5 days. Treatment was given in 3-week cycles.

Abbreviations: 5-FU - 5-Fluorouracil; GOJ – gastro-oesophageal junction; ECF - epirubicin + cisplatin + 5-FU; ECX - epirubicin + cisplatin + capecitabine; EOF- epirubicin + oxaliplatin +5-FU; EOX - epirubicin + oxaliplatin + capecitabine; OG – oesophagogastric; RCT – randomised controlled trial;

9.2.4 Clinical evidence profile

The clinical evidence profiles for this review question are presented in Table 138 to Table 147

Table 138: Summary clinical evidence profile. Comparison 1: 5-FU single agent chemotherapy versus combination therapy

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)
	Assumed risk with single agent	Corresponding risk with combination chemotherapy			
Overall survival Kaplan Meier Mortality estimates	-	-	HR 0.77 (0.65 to 0.91)	560 (4 studies)	Moderate [12]
Treatment-related death	13 per 1000	18 per 1000 (5 to 58)	RR 1.31 (0.39 to 4.34)	560 (4 studies)	very low [1,2,3]
Treatment-related toxicity: Nausea and vomiting WHO Grade 3/4	63 per 1000	91 per 1000 (44 to 191)	RR 1.44 (0.69 to 3.02)	349 (2 studies)	low[3]
Treatment-related toxicity: Diarrhoea WHO Grade 3/4	29 per 1000	37 per 1000 (2 to 625)	RR 1.28 (0.07 to 21.75)	349 (2 studies)	low [3,4]

[1] *Colucci- unclear allocation concealment, no intention to treat analysis*
[2] *Lutz- single-therapy arm was closed earlier (Simon 2-stage minimax design)*
[3] *95% CI crosses 2 default MIDs*
[4] *I2 > 50%*

Table 139: Summary clinical evidence profile. Comparison 2: 5-FU/cisplatin /anthracycline versus 5-FU/cisplatin alone

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)
	Assumed risk with 5-FU/cisplatin combinations (without anthracyclines)	Corresponding risk with 5-FU/ cisplatin/anthracycline combinations			
Overall survival	-	-	HR 0.70 (0.43, 1.15)	167 (3 studies)	moderate [1]
Progression-free survival	-	-	HR 0.95 (0.58 to 1.57)	0 (1 study)	very low [1,2]

[1] *Yun- unclear blinding of assessors, allocation concealment and randomization sequence*
[2] *95% CI crosses 2 default MID boundaries*

Table 140: Summary clinical evidence profile. Comparison 3: 5-FU/cisplatin/ anthracycline versus 5-FU/anthracycline alone

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)
	Assumed risk with FU /anthracycline combinations (without cisplatin)	Corresponding risk with 5-FU/ cisplatin/anthracycline combinations			
Overall survival	-		HR 0.7 (0.54 to 0.89)	175 (2 studies)	moderate[1]

1 risk of bias

Table 141: Summary clinical evidence profile. Comparison 4: Irinotecan versus non-irinotecan combinations

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)
	Assumed risk with non-irinotecan-containing regimes	Corresponding risk with irinotecan-containing regimes			
Overall survival	-	-	HR 0.87 (0.73 to 1.05)	615 (4 studies)	low [1,2]
Progression-free survival	-	-	HR 0.83 (0.68 to 1.01)	526 (3 studies)	low [1,2]
Treatment-related death	31 per 1000	7 per 1000 (2 to 30)	RR 0.21 (0.05 to 0.98)	526 (3 studies)	moderate [2,3]
Treatment discontinuation due to toxicity	202 per 1000	131 per 1000 (69 to 250)	RR 0.65 (0.34 to 1.24)	535 (3 studies)	moderate[2]

1- risk of bias
2- 95% CI crosses one default MID boundary
3- 0 events in two arms

Table 142: Summary clinical evidence profile. Comparison 5: Docetaxel versus non-docetaxel combinations

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)
	Assumed risk with non-docetaxel containing regimes	Corresponding risk with docetaxel			
Overall survival	-	-	HR 0.87 (0.76 to 1.01)	1048 (4 studies)	moderate[5]

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)
	Assumed risk with non-docetaxel containing regimes	Corresponding risk with docetaxel			
Treatment-related death	23 per 1000	18 per 1000 (8 to 38)	RR 0.75 (0.34 to 1.65)	1067 (5 studies)	very low [1,2,3]
Time to progression	-	-	HR 0.85 (0.56 to 1.29)	603 (3 studies)	very low [1,2,3, 8]
Treatment discontinuation due to toxicity	213 per 1000	181 per 1000 (138 to 234)	RR 0.85 (0.65 to 1.1)	924 (5 studies)	low [2,4,5]
Treatment-related toxicity: Diarrhoea	0 per 1000	0 per 1000 (0 to 0)	RR 31.25 (1.89 to 516.54)	243 (1 study)	low [4,5,6]
Treatment-related toxicity: Nausea and vomiting	115 per 1000	75 per 1000 (33 to 165)	RR 0.65 (0.29 to 1.44)	243 (1 study)	very low [3,4]
Quality of Life: Physical Functioning	-	The mean quality of life: physical functioning in the intervention groups was 1.8 lower (7.84 lower to 4.24 higher)	-	85 (1 study)	low [5,7]
Quality of Life: Role Functioning	-	The mean quality of life: role functioning in the intervention groups was 2.13 higher (4.97 lower to 9.23 higher)	-	85 (1 study)	low [5,7]
Quality of Life: Emotional Functioning	-	The mean quality of life: emotional functioning in the intervention groups was 8.06 higher (2.85 to 13.27 higher)	-	85 (1 study)	low [5,7]
Quality of LIfe: Cognitive Functioning	-	The mean quality of life: cognitive functioning in the intervention groups was 3.6 lower (10.08 lower to 2.88 higher)	-	85 (1 study)	low [5,7]
Quality of Life: Social Functioning	-	The mean quality of life: social functioning in the intervention groups was	-	85 (1 study)	low [5,7]

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)
	Assumed risk with non-docetaxel containing regimes	Corresponding risk with docetaxel			
		7.5 higher (1.39 to 13.61 higher)			
Quality of Life: Global Quality of Life	-	The mean quality of life: global quality of life in the intervention groups was 7.3 higher (0.64 to 13.96 higher)	-	85 (1 study)	low [5,7]

1 Al-Batran: allocation concealment unclear
2 Roth- Docetaxel dose reduced due to toxicity
3 95% CI cross two default MIDs
4 Wang- unclear blinding of outcome assessors
5 95% CI cross one deafult MID
6 0 events in one arm
7 Sadighi- only 71 participants included in QOL analysis (15 did not complete baseline questionnaire)
8 I-squared statistic > 75%

Table 143: Summary clinical evidence profile. Comparison 6: Capecitabine versus IV 5-FU combinations

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)
	Assumed risk with IV 5-FU combinations	Corresponding risk with capecitabine			
Overall survival	-	-	HR 0.87 (0.77, 0.99)	1318 (2 studies)	moderate[2]
Progression-free survival	-	-	HR 0.89 (0.79 to 1.01)	810 (2 studies)	moderate[2]
Treatment-related death	13 per 1000	6 per 1000 (1 to 70)	RR 0.5 (0.05 to 5.42)	311 (1 study)	low[1]
Treatment discontinuation due to toxicity	181 per 1000	179 per 1000 (112 to 289)	RR 0.99 (0.62 to 1.6)	311 (1 study)	low[1]
Treatment-related toxicity: Nausea and vomiting	118 per 1000	96 per 1000 (66 to 137)	RR 0.81 (0.56 to 1.16)	1002 (1 study)	moderate[2]
Treatment-related toxicity: Diarrhoea	65 per 1000	85 per 1000 (55 to 132)	RR 1.31 (0.84 to 2.03)	1002 (1 study)	moderate[2]

[1] 95% CI crosses two default MIDs
[2] 95% CI crosses one default MID

Table 144: Summary clinical evidence profile. Comparison 7: Cisplatin versus oxalipatin combinations

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)
	Assumed risk oxaliplatin containing regimes	Corresponding risk cisplatin containing regimes			
Overall survival	-	-	HR 0.91 (0.80 to 1.04)	1222 (2 studies)	moderate[4]
Progression-free survival	-	-	HR 0.90 (0.79 to 1.02)	1222 (2 studies)	low [4,5]
Treatment-related death	17 per 1000	7 per 1000 (1 to 48)	RR 0.42 (0.06 to 2.81)	363 (3 studies)	very low [1,2,3]
Treatment discontinuation due to toxicity	108 per 1000	107 per 1000 (48 to 222)	RR 0.99 (0.46 to 2.15)	214 (1 study)	very low [3,4]
Treatment-related toxicity: Any grade 3/4 event	658 per 1000	664 per 1000 (487 to 914)	RR 1.01 (0.74 to 1.39)	77 (1 study)	very low [2,3]
Treatment-related toxicity: Diarrhoea	37 per 1000	113 per 1000 (68 to 187)	RR 3.04 (1.83 to 5.04)	1002 (1 study)	high
Treatment-related toxicity: Nausea and vomiting	90 per 1000	126 per 1000 (89 to 182)	RR 1.41 (0.99 to 2.03)	1002 (1 study)	moderate[5]

[1] *Popov 2008: risk of bias in outcome reporting, not ITT*
[2] *Kim 2014: unclear randomization process, allocation concealment*
[3] *95% CI crosses two default MIDs*
[4] *Al-Batran 2008: baseline differences between groups in sex and metastatic disease*
[5] *95% CI crosses one default MID*

Table 145: Summary clinical evidence profile. Comparison 8: 5-FU combinations versus non-5-FU combinations

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)
	Assumed risk with non-5FU-containing combinations	Corresponding risk with 5FU-containing combinations			
Overall survival	-	-	HR 0.59 (0.39, 0.81)	400 (2 studies)	moderate[1]
Overall survival - docetaxel/platinum based +/- 5-FU	-	-	HR 0.61 (0.45 to 0.84)	254 (1 study)	moderate
Overall survival - 5-FU versus cisplatin regimen	-	-	HR 0.56 (0.39 to 0.81)	146 (1 study)	low [1,2]

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)
	Assumed risk with non-5FU-containing combinations	Corresponding risk with 5FU-containing combinations			
Two year survival – 5-FU versus irinotecan regimen	47 per 1000	143 per 1000 (31 to 668)	RR 3.07 (0.66 to 14.37)	85 (1)	very low [3,4]
Progression-free survival	-	-	HR 0.37 (0.28 to 0.48)	400 (2 studies)	moderate[2]
Progression-free survival - Docetaxel/platinum based +/-5-FU	-	-	HR 0.34 (0.25 to 0.48)	254 (1 study)	high
Progression-free survival – 5-FU versus platinum regimen	-	-	HR 0.41 (0.26 to 0.64)	146 (1 study)	moderate[2]
Treatment-related death – 5-FU versus cisplatin regimen	14 per 1000	5 per 1000 (0 to 112)	RR 0.34 (0.01 to 8.27)	146 (1)	very low [2,4,5]
Treatment discontinuation due to toxicity	137 per 1000	88 per 1000 (42 to 183)	RR 0.64 (0.31 to 1.34)	231 (2 studies)	very low [2,3,4]
Treatment discontinuation due to toxicity - 5-FU versus irinotecan regimen	233 per 1000	142 per 1000 (58 to 358)	RR 0.61 (0.25 to 1.54)	85 (1 study)	very low [3,4]
Treatment discontinuation due to toxicity - 5-FU versus cisplatin regimen	81 per 1000	56 per 1000 (16 to 189)	RR 0.69 (0.2 to 2.33)	146 (1 study)	very low [2,4]
Treatment-related toxicity: Diarrhoea – 5-FU versus irinotecan	163 per 1000	428 per 1000 (200 to 918)	RR 2.63 (1.23 to 5.64)	85 (1)	moderate[3]
Treatment-related toxicity: Nausea and vomiting - 5-FU versus irinotecan	-	-	RR 7.17 (0.92 to 55.76)	85 (1)	low [1,3]

1 95% CI crosses one default MID
2 Pozzo 2004: unclear randomization and allocation concealement
3 Roy 2012: unclear randomization and allocation concealment
4 95% CI crosses two default MIDs
5 0 events in one arm

Table 146: Summary clinical evidence profile. Comparison 9: Platinum versus taxane combinations

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)
	Assumed risk with taxane combination	Corresponding risk with platinum combination			
Overall survival	-	-	HR 0.75 (0.47 to 1.2)	94 (1 study)	low [1,2]
Treatment-related death	22 per 1000	42 per 1000 (4 to 444)	RR 1.92 (0.18 to 20.42)	94 (1 study)	very low [1,3]
Treatment discontinuation due to toxicity	87 per 1000	125 per 1000 (37 to 415)	RR 1.44 (0.43 to 4.77)	94 (1 study)	very low [1,3]
Treatment-related toxicity: Any grade 3/4 event	587 per 1000	687 per 1000 (505 to 933)	RR 1.17 (0.86 to 1.59)	94 (1 study)	low [1,2]

1 Lee 2015: unclear randomization, allocation concealment and blinding
2 95% CI cross one default MID
3 95% CI crosses two default MIDs

Table 147: Summary clinical evidence profile. Comparison 10: Other combinations

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)
	Assumed risk with 5-FU/irinotecan	Corresponding risk with other epirubicin/ cisplatin/ capetibacine combinations			
Overall survival	-	-	HR 1.01 (0.82 to 1.24)	416 (1 study)	high
Progression-free survival	-	-	HR 0.99 (0.81 to 1.21)	416 (1 study)	high
Treatment-related death	24 per 1000	34 per 1000 (11 to 104)	RR 1.39 (0.45 to 4.3)	416 (1 study)	low[1]
Treatment-related toxicity: Any grade 3/4 event	382 per 1000	645 per 1000 (530 to 790)	RR 1.69 (1.39 to 2.07)	416 (1 study)	high

1 Downgraded for serious imprecision: 95% CI crosses two default MIDs

9.2.5 Economic evidence

A systematic review of the economic literature was conducted but no relevant studies were identified which were applicable to this review question. Economic modelling was not undertaken for this question because other topics were agreed as higher priorities for economic evaluation.

9.2.6 Evidence statements

9.2.6.1 Comparison 1: Combination versus single-agent chemotherapy

9.2.6.1.1 Overall survival

Moderate quality evidence from 4 RCTs with 560 people with oesophago-gastric cancer indicate there is a clinically significant benefit to overall survival in groups treated with combination chemotherapy versus single-agent 5-FU chemotherapy (HR 0.77, 95% CI: 0.65-0.91).

9.2.6.1.2 Treatment-related death

Very low quality evidence from 4 RCTs with 560 people with oesophago-gastric cancer indicate there is no clinically significant difference in treatment-related death in groups treated with combination chemotherapy versus single-agent 5-FU chemotherapy (OR 1.31, 95% CI: 0.38-4.55).

9.2.6.1.3 Treatment-related toxicity: Nausea and vomiting

Low quality evidence from 2 RCTs with 349 people with oesophago-gastric cancer indicate there is no clinically significant difference in nausea and vomiting in groups treated with combination chemotherapy versus single-agent 5-FU chemotherapy (RR 1.44, 95% CI: 0.69-3.02).

9.2.6.1.4 Treatment-related toxicity: Diarrhoea

Low quality evidence from 2 RCTs with 349 people with oesophago-gastric cancer indicate there is no clinically significant difference in diarrhoea in groups treated with combination chemotherapy versus single-agent 5-FU chemotherapy (RR 1.28, 95% CI: 0.07-21.75).

9.2.6.2 Comparison 2: 5-FU/cisplatin combinations with or without anthracycline

9.2.6.2.1 Overall survival

Moderate quality evidence from 2 RCTs with 167 people with oesophago-gastric cancer indicate there is no clinically significant difference in overall survival in groups treated with 5-FU/cisplatin/anthracycline versus 5-FU/cisplatin alone (HR 0.70, 95% CI: 0.43-1.15).

9.2.6.2.2 Progression-free survival

Moderate quality evidence from 1 RCT with 91 people with oesophago-gastric cancer indicate there is no clinically significant difference in progression-free survival in groups treated with 5-FU/cisplatin/anthracycline versus 5-FU/cisplatin alone (HR 0.95, 95% CI: 0.58-1.57).

9.2.6.3 Comparison 3: 5-FU/anthracycline combinations with or without cisplatin

9.2.6.3.1 Overall survival

Moderate quality evidence from 2 RCTs with 175 people with oesophago-gastric cancer indicate there is a clinically significant benefit to overall survival in groups treated with 5-FU/anthracycline/cisplatin versus 5-FU/anthracycline alone (HR 0.70, 95% CI: 0.54-0.89).

9.2.6.4 Comparison 4: Irinotecan versus non-irinotecan containing combinations

9.2.6.4.1 Overall survival

Low quality evidence from 4 RCTs with 615 people with oesophago-gastric cancer indicated no clinically significant difference in survival in groups treated with irinotecan versus non-irinotecan containing combinations (HR 0.87, 95% CI: 0.73-1.05).

9.2.6.4.2 Progression-free survival

Low quality evidence from 3 RCTs with 526 people with oesophago-gastric cancer indicated there may be a clinically significant difference in progression-free survival in groups treated with irinotecan versus non-irinotecan containing combinations – but there is uncertainty around the estimate (HR 0.83, 95% CI: 0.68-1.01).

9.2.6.4.3 Treatment-related death

Moderate quality evidence from 3 RCTs with 526 people with oesophago-gastric cancer indicated a clinically significant harmful effect in terms of treatment-related death in groups treated with non-irinotecan combinations versus irinotecan combinations (HR 0.21, 95% CI: 0.05-0.98).

9.2.6.4.4 Treatment discontinuation due to toxicity

Moderate quality evidence from 3 RCTs with 535 people with oesophago-gastric cancer indicated no clinically significant difference in treatment discontinuation due to toxicity in groups treated with non-irinotecan combinations versus irinotecan combinations (HR 0.65, 95% CI: 0.34- 1.24).

9.2.6.5 Comparison 5: Docetaxel versus non-docetaxel containing combinations

9.2.6.5.1 Overall survival

Moderate quality evidence from 4 RCTs with 1048 people with oesophago-gastric cancer indicated there may be a clinically significant difference in overall survival in groups treated with docetaxel combinations versus non-docetaxel containing combinations – but there is uncertainty around the estimate (HR 0.87, 95% CI: 0.76-1.01).

9.2.6.5.2 Treatment-related death

Very low quality evidence from 5 RCTs with 1067 people with oesophago-gastric cancer indicated no clinically significant difference in treatment-related death in groups treated with docetaxel combinations versus non-docetaxel containing combinations (OR 0.75, 95% CI: 0.33-1.67).

9.2.6.5.3 Time to progression

Very low quality evidence from 3 RCTs with 603 people with oesophago-gastric cancer indicated no clinically significant difference in time to progression in groups treated with docetaxel combinations versus non-docetaxel containing combinations (HR 0.85, 95% CI: 0.56, 1.29).

9.2.6.5.4 Treatment discontinuation due to toxicity

Low quality evidence from 5 RCTs with 924 people with oesophago-gastric cancer indicated no clinically significant difference in time to progression in groups treated with docetaxel combinations versus non-docetaxel containing combinations (RR 0.85, 95% CI: 0.65, 1.10).

9.2.6.5.5 Treatment-related toxicity: Diarrhoea

Low quality evidence from 1 RCT with 243 people with oesophago-gastric cancer indicated a clinically significant harmful effect in diarrhoea in groups treated with docetaxel combinations versus non-docetaxel containing combinations (RR 31.25, 95% CI: 1.89, 516.54).

9.2.6.5.6 Treatment-related toxicity: nausea and vomiting

Very low quality evidence from 1 RCT with 243 people with oesophago-gastric cancer indicated no clinically significant difference in nausea and vomiting in groups treated with docetaxel combinations versus non-docetaxel containing combinations (RR 0.65, 95% CI: 0.29, 1.44).

9.2.6.5.7 Quality of life

Low quality evidence from 1 RCT with 85 people with oesophago-gastric cancer indicated no clinically significant difference in quality of life for all domains in groups treated with docetaxel combinations versus non-docetaxel containing combinations.

9.2.6.6 Comparison 6: Oral versus IV 5-FU combinations

9.2.6.6.1 Overall survival

Moderate quality evidence from 2 RCTs with 1318 people with oesophago-gastric cancer indicated there is a clinically significant beneficial effect in overall survival in groups treated with oral capecitabine combinations versus IV 5-FU combinations (HR 0.87, 95% CI: 0.77-0.99).

9.2.6.6.2 Progression-free survival

Moderate quality evidence from 2 RCTs with 1318 people with oesophago-gastric cancer indicated there may be a clinically significant difference in progression free survival in groups treated with oral capecitabine combinations versus IV 5-FU combinations – but there is uncertainty around the estimate (HR 0.89, 95% CI: 0.79-1.01).

9.2.6.6.3 Treatment-related death

Low quality evidence from 1 RCT with 311 people with oesophago-gastric cancer indicated no clinically significant difference in treatment-related death in groups treated with oral capecitabine combinations versus IV 5-FU combinations (RR 0.5, 95% CI: 0.05-5.42).

9.2.6.6.4 Treatment discontinuation due to toxicity

Low quality evidence from 1 RCT with 311 people with oesophago-gastric cancer indicated no clinically significant difference in treatment discontinuation due to toxicity in groups treated with oral capecitabine combinations versus IV 5-FU combinations (RR 0.99, 95% CI: 0.62-1.6).

9.2.6.6.5 Treatment-related toxicity: nausea and vomiting

Moderate quality evidence from 1 RCT with 1002 people with oesophago-gastric cancer indicated no clinically significant difference in nausea and vomiting in groups treated with oral capecitabine combinations versus IV 5-FU combinations (RR 0.81, 95% CI: 0.56-1.16).

9.2.6.6.6 Treatment-related toxicity: diarrhoea

Moderate quality evidence from 1 RCT with 1002 people with oesophago-gastric cancer indicated no clinically significant difference in diarrhoea in groups treated with oral capecitabine combinations versus IV 5-FU combinations (RR 1.31, 95% CI: 0.84-2.03).

9.2.6.7 Comparison 7: Cisplatin versus oxaliplatin combinations

9.2.6.7.1 Overall survival

Moderate quality evidence from 2 RCTs with 1222 people with oesophago-gastric cancer indicated no clinically significant difference in overall survival in groups treated with oxaliplatin combinations compared with cisplatin combinations (HR 0.91, 95% CI: 0.80-1.04).

9.2.6.7.2 Progression-free survival

Low quality evidence from 2 RCTs with 1222 people with oesophago-gastric cancer indicated there is no clinically significant difference in progression-free survival in groups treated with oxaliplatin combinations compared with cisplatin combinations (HR 0.90, 95% CI: 0.79-1.02).

9.2.6.7.3 Treatment-related death

Very low quality evidence from 3 RCTs with 363 people with oesophago-gastric cancer indicated no clinically significant difference in treatment-related death in groups treated with oxaliplatin combinations compared with cisplatin combinations (RR 0.42, 95% CI: 0.06-2.81).

9.2.6.7.4 Treatment discontinuation due to toxicity

Very low quality evidence from 1 RCT with 214 people with oesophago-gastric cancer indicated no clinically significant difference in treatment discontinuation due to toxicity in groups treated with oxaliplatin combinations compared with cisplatin combinations (RR 0.99, 95% CI: 0.42-2.36).

9.2.6.7.5 Treatment-related toxicity: any severe

Very low quality evidence from 1 RCT with 77 people with oesophago-gastric cancer indicated no clinically significant difference in any severe toxicity (grade 3 or 4) in groups treated with oxaliplatin combinations compared with cisplatin combinations (RR 1.01, 95% CI: 0.74-1.39).

9.2.6.7.6 Treatment-related toxicity: diarrhoea

High quality evidence from 1 RCT with 1002 people with oesophago-gastric cancer indicated a clinically significant harmful effect in diarrhoea in groups treated with oxaliplatin combinations compared with cisplatin combinations (RR 3.04, 95% CI: 1.83-5.04).

9.2.6.7.7 Treatment-related toxicity: nausea and vomiting

High quality evidence from 1 RCT with 1002 people with oesophago-gastric cancer indicated there may be a clinically significant harmful effect in nausea and vomiting in groups treated with oxaliplatin combinations compared with cisplatin combinations, but there is uncertainty around the estimate (RR 1.41, 95% CI: 0.99-2.03).

9.2.6.8 Comparison 8: 5-FU combinations versus non-5-FU combinations

9.2.6.8.1 Overall survival

Moderate quality evidence from 2 RCTs with 400 people with oesophago-gastric cancer indicated a clinically significant beneficial effect in overall survival in groups treated with 5-FU combinations compared to non-5-FU based combinations (HR 0.59, 95% CI 0.46-0.75).

Subgroups based on chemotherapy regimen:

Moderate quality evidence from 1 RCT with 254 people with oesophago-gastric cancer indicated a clinically significant beneficial effect in overall survival in groups treated with 5-FU

docetaxel/platinum combinations compared to non-5-FU docetaxel/platinum based combinations (HR 0.61, 95% CI 0.45-0.84).

Low quality evidence from 1 RCT with 146 people with oesophago-gastric cancer indicated a clinically significant beneficial effect in overall survival in groups treated with 5-FU combinations compared to non-5-FU cisplatin based combinations (HR 0.56, 95% CI 0.39-0.81).

9.2.6.8.2 Two-year survival

Very low quality evidence from 1 RCT with 85 people with oesophago-gastric cancer indicated no clinically significant difference in two year survival in groups treated with 5-FU combinations compared to non-5-FU irinotecan based combinations (HR 3.07, 95% CI 0.66-14.37).

9.2.6.8.3 Progression-free survival

Moderate quality evidence from 2 RCTs with 400 people with oesophago-gastric cancer indicated a clinically significant beneficial effect in progression free survival in groups treated with 5-FU combinations compared to non-5-FU based combinations (HR 0.37, 95% CI 0.28-0.48).

Subgroups based on chemotherapy regimen:

High quality evidence from 1 RCT with 254 people with oesophago-gastric cancer indicated a clinically significant beneficial effect in progression-free survival in groups treated with 5-FU docetaxel/platinum combinations compared to non-5-FU docetaxel/platinum based combinations (HR 0.34, 95% CI 0.25-0.48).

Moderate quality evidence from 1 RCT with 146 people with oesophago-gastric cancer indicated a clinically significant beneficial effect in progression-free survival in groups treated with 5-FU combinations compared to non-5-FU cisplatin based combinations (HR 0.41, 95% CI 0.26-0.64).

9.2.6.8.4 Treatment-related death

Very low quality evidence from 1 RCT with 146 people with oesophago-gastric cancer indicated there is no clinically significant difference in treatment-related death in groups treated with 5-FU combinations compared to non-5-FU based combinations (RR 0.34, 95% CI: 0.01-8.27).

9.2.6.8.5 Treatment discontinuation due to toxicity

Very low quality evidence from 2 RCTs with 231 people with oesophago-gastric cancer indicated there is no clinically significant difference in discontinuation due to toxicity in groups treated with 5-FU combinations compared to non-5-FU based combinations (RR 0.64, 95% CI: 0.31-1.34).

Subgroups based on chemotherapy regimen:

Very low quality evidence from 1 RCT with 85 people with oesophago-gastric cancer indicated there is no clinically significant difference in discontinuation due to toxicity in groups treated with 5-FU combinations compared to non-5-FU, irinotecan based combinations (RR 0.61, 95% CI: 0.25-1.54).

Very low quality evidence from 1 RCT with 146 people with oesophago-gastric cancer indicated there is no clinically significant difference in discontinuation due to toxicity in groups treated with 5-FU combinations compared to non-5-FU, cisplatin based combinations (RR 0.69, 95% CI: 0.20-2.33).

9.2.6.8.6 Treatment-related toxicity: diarrhoea

Moderate quality evidence from 1 RCT with 85 people with oesophago-gastric cancer indicated there is a clinically significant harmful effect in groups treated with non-5-FU combinations compared to 5-FU based combinations (RR 2.63, 95% CI: 1.23-5.64).

9.2.6.8.7 Treatment-related toxicity: nausea and vomiting

Low quality evidence from 1 RCT with 85 people with oesophago-gastric cancer indicated there is no clinically significant difference in groups treated with non-5-FU combinations compared to 5-FU based combinations (RR 7.17, 95% CI: 0.92- 55.76).

9.2.6.9 Comparison 9: Platinum combinations versus taxane combinations

9.2.6.9.1 Overall survival

Low quality evidence from 1 RCT with 94 people indicated there is no clinically significant difference in overall survival in groups treated with platinum combinations versus taxane combinations (HR 0.75, 95% CI: 0.47-1.20).

9.2.6.9.2 Treatment-related death

Very low quality evidence from 1 RCT with 94 people indicated no clinically significant difference in treatment-related death in groups treated with platinum combinations versus taxane combinations (RR 1.92, 95% CI: 0.18-20.42).

9.2.6.9.3 Treatment discontinuation due to toxicity

Very low quality evidence from 1 RCT with 94 people indicated no clinically significant difference in treatment discontinuation due to toxicity in groups treated with platinum combinations versus taxane combinations (RR 1.44, 95% CI: 0.43-4.77).

9.2.6.9.4 Treatment-related toxicity: any severe

Low quality evidence from 1 RCT with 94 people indicated no clinically significant difference in treatment-related toxicity in groups treated with platinum combinations versus taxane combinations (RR 1.17, 95% CI: 0.86-1.59).

9.2.6.10 Comparison 10: FOLFIRI versus epirubicin/cisplatin/capecitabine

9.2.6.10.1 Overall survival

High quality evidence from 1 RCT with 416 people indicated no clinically significant difference in overall survival in groups treated with FOLFIRI combinations versus epirubicin/cisplatin/capecitabine combinations (HR 1.01, 95% CI: 0.82-1.24).

9.2.6.10.2 Progression-free survival

High quality evidence from 1 RCT with 416 people indicated there is no clinically significant difference in progression-free survival in groups treated with FOLFIRI combinations versus epirubicin/cisplatin/capecitabine combinations (HR 0.99, 95% CI: 0.81-1.21).

9.2.6.10.3 Treatment-related death

Low quality evidence from 1 RCT with 416 people indicated no clinically significant difference in treatment-related death in groups treated with FOLFIRI combinations versus epirubicin/cisplatin/capecitabine combinations (HR 1.39, 95% CI: 0.45-4.30).

9.2.6.10.4 Treatment-related toxicity: any severe

High quality evidence from 1 RCT with 416 people indicated a clinically significant harmful effect in treatment-related toxicity in groups treated with epirubicin/cisplatin/capecitabine combinations versus FOLFIRI combinations (RR 1.69, 95% CI: 1.39-2.07).

9.2.7 Evidence to recommendations

9.2.7.1 Relative value placed on the outcomes considered.

Although this question related to palliative management of patients who would not receive radical treatment, these patients are still being actively managed (as opposed to receiving 'palliative care') and therefore overall survival and progression-free survival were still considered to be critical outcomes. The Committee also considered that treatment-related toxicity was a critical outcome to allow them to balance the benefits and harms of treatment.As this recommendation concerned palliative treatment the Committee agreed that health-related quality of life was important, but this outcome was only reported in 1 study included in the evidence review, and this study was of docetaxel-containing regimen which was later excluded by the Committee based on their clinical experience (see 'Other considerations' section below).

9.2.7.2 Quality of the evidence

The studies included in the review were assessed for risk of bias using the Cochrane risk of bias tool, and the quality of each outcome was assessed using GRADE. Overall the quality of the evidence ranged from very low to high.

The Committee noted that one comparison included patients with squamous cell carcinoma, some studies had mixed populations with oesophageal or gastric cancer, and some were specific to people with oesophageal cancer. They also noted that several studies included a non-Western population. The Committee noted however, that results appeared to be consistent between the Western and Eastern populations in studies.

9.2.7.3 Considerations of benefits and harms

Of the ten comparisons included in the evidence review the Committee assessed which led to improved survival or or progression-free survival, while balancing this against the relative rates of treatment-related death or toxicity. The treatments which led to improved survival included combination chemotherapy compared to 5-FU alone (with no difference in toxicity); 5-FU /anthracycline/cisplatin regimens compared to 5-FU/anthracycline alone (with no data on relative harms available), oral 5-FU vs IV 5-FU (with no difference in treatment-related death, discontinuations, nausea and vomiting or diarrhoea) and 5-FU combination therapy compared to non-5-FU combination therapy (with no difference in treatment-related death, discontinuation or nausea and vomiting, but a reduced rate of diarrhoea in the 5-FU combinations). For all the other combinations there was no difference in overall survival or uncertaintly about the difference, although irinotecan did not lead to greater overall survival compared to non-irinotecan regimens, but did lead to increased progression-free survival.

The Committee agreed that their recommendations were likely to lead to improved survival and progression-free survival in this cohort of people, as well as increasing the standardisation of care. The Committee also agreed that the parameters for selecting patients for chemotherapy would lead to improved case selection.

The use of chemotherapy may increase the potential for treatment-related toxicity, but the Committee tried to minimise this by including performance status parameters and consideration of the presence of other comorbidities in their recommendation. By providing the option, within the recommendation, of double or triple therapy, the Committee also tried

to allow for the tailoring of therapy towards individual patients and their acceptance of the risks and benefits of treatments of different intensities.

9.2.7.4 Consideration of the economic benefits and harms

A systematic review of the economic literature was conducted but no relevant studies were identified which were applicable to this review question.

The economic implications of this topic were considered but not thought to be substantial as the recommendations largely reflect current practice. The number of people receiving treatment is unlikely to increase as a result of the recommendation. However, it is possible that there may be some changes in the treatment received, with more people receiving the appropriate level of treatment.

The economic implications of using triplet rather than doublet treatment are minimal as the difference in the drug costs is very small. There could be some increases associated with managing the increased treatment related toxicity but again this would not be expected to amount to a substantial resource impact.

9.2.7.5 Other considerations

The Committee knew from their clinical experience that chemotherapy has a role to play in the management of patients with locally advanced or metastatic oesophago-gastric cancer, and can improve survival in patients who can tolerate the treatment. The Committee therefore used the evidence available to to recommend the most effective treatment options. Included within the evidence review were some comparisons of chemotherapy regimens containing irinotecan and docetaxel. However, based on their clinical experience the Committee agreed that these agents were not routinely used in current clinical practice, and that there was no rationale or evidence for including them in the recommended chemotherapy combinations.

The Committee also considered the choice of 5-fluorouracil (5-FU) preparations: 5-FU is available for intravenous administration or as an orally administered pro-drug, capecitabine. The Committee agreed that there was some evidence of overall improved survival with the oral formulation but that patient factors (such as dysphagia) should also be taken into account when deciding on the formulation to use.

9.2.7.6 Key conclusions

The Committee's first recommendation was based on their clinical experience and the fact that trastuzuamb has already been approved by NICE as a cost-effective option for the treatment of HER2-positive metastatic gastric adenocarcinoma.

Moderate quality evidence showed that combination therapy with 5-FU and cisplatin or epirubicin led to improved overall survival compared to 5-FU monotherapy, with no difference in any reported treatment-related toxicity, therefore the Committee did not recommend 5-FU monotherapy.

Triple therapy comprising 5-FU, a platinum-based therapy and epirubicin showed similar rates of overall survival and progression-free survival compared to doublet therapy with 5-FU and cisplatin.

However, triple therapy with 5-FU, cisplatin and epirubicin or doxorubicin (both anthracyclines) did improve overall survival compared to double therapy with 5-FU and the anthracycline.

For doublet regimen the Committee therefore chose to recommend 5-FU and a platinum-based regimen, with the option of triple therapy by adding an anthracycline (epirubicin).

Several studies compared regimens containing oral capecitabine with intravenous 5-FU, showing increased overall survival, no difference in progression-free survival and no difference in any treatment-related toxicity with the oral formulation.

A comparison of cisplatin versus oxaliplatin-containing regimens showed no difference between the two platinum-based drugs in terms of overall or progression-free survival, but higher rates of diarrhoea and nausea and vomiting with cisplatin. Nausea and vomiting are recognised adverse effects associated with cisplatin therapy and can often be managed by appropriate use of combination anti-emetics, and cisplatin is less expensive than oxaliplatin. The Committee therefore agreed to leave cisplatin as a treatment option within the recommended regimens, with a clinical decision as to which agent should be used to be decided on an individual patient or unit basis.

The Committee defined the populations who should receive chemotherapy based on their clinical experience, in that those who do best are those people with fewer comorbidities and whose pre-chemotherapy performance status is better (0 to 2).

9.2.8 Recommendations

First-line palliative chemotherapy for locally advanced or metastatic oesophago-gastric cancer

34. Offer trastuzumab (in combination with cisplatin[1] and capecitabine or 5-fluorouracil) as a treatment option to people with HER2-positive metastatic adenocarcinoma of the stomach or gastro-oesophageal junction (also see the NICE technology appraisal guidance on trastuzumab for the treatment of HER2-positive metastatic gastric cancer).

35. Offer first-line palliative combination chemotherapy to people with advanced oesophago-gastric cancer who have a performance status 0 to 2 and no significant comorbidities. Possible drug combinations include:

- doublet treatment: 5-fluorouracil or capecitabine[2] in combination with cisplatin[1] or oxaliplatin[3]
- triplet treatment: 5-fluorouracil or capecitabine in combination with cisplatin or oxaliplatin plus epirubicin[4].

Discuss the benefits, risks and treatment consequences of each option with the person and those important to them (as appropriate).

[1]Although this use is common in UK clinical practice, at the time of publication ([month year]), cisplatin did not have a UK marketing authorisation for oesophageal or gastric cancer. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.

[2]Although this use is common in UK clinical practice, at the time of publication ([month year]), capecitabine did not have a UK marketing authorisation for oesophageal cancer. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.

[3]Although this use is common in UK clinical practice, at the time of publication ([month year]), oxaliplatin did not have a UK marketing authorisation for oesophageal or gastric cancer. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.

[4]Although this use is common in UK clinical practice, at the time of publication ([month year]), epirubicin did not have a UK marketing authorisation for oesophageal cancer. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and

documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information

9.2.9 Research recommendation

6. Can palliative treatment for oesophago-gastric cancer be defined along a molecular strategy such as HER2?

Why this is important?

Standard palliative chemotherapy for oesophago-gastric cancer offers minimal benefit, with median survival advantage being reported as a few months in clinical studies. In a number of other cancers, a molecular targeted strategy has been developed which allows individualisation of therapy and leads to a survival advantage in those subgroups who are found to be suitable for treatment. In addition, in those people for whom molecular subtyping identifies that treatment would have no benefit, there can be avoidance of unnecessary and ineffective treatments, and the related adverse events and treatment-related morbidities.

A molecular strategy, apart from HER2 targeted therapies in gastric adenocarcinoma, has not been widely explored in oesophago-gastric cancer but could lead to improved outcomes for patients.

Table 148: Research recommendation rationale

Research question	Can palliative treatment for oesophago-gastric cancer be defined along a molecular strategy such as HER2?
Importance to 'patients' or the population	A molecular strategy for oesophago-gastric cancer has the potential to deliver improvements similar to those that have been seen in some other cancer sites. A molecular strategy leads to an improved chance of benefit from a targeted treatment, and thus improved survival and fewer adverse events. It also avoids subjecting patients to treatments that will not benefit them.
Relevance to NICE guidance	No studies were identified that directly examined the safety or effectiveness of molecular strategies for treating oesophago-gastric cancer other than those targeting over-expression of the HER2 receptor in gastric adenocarcinoma, where the benefits are limited to a few months over the comparator. Future NICE guidance would greatly benefit from the identification of appropriate strategies.
Relevance to the NHS	Individually tailored treatments based on molecular biology may be more cost effective to the NHS, while reducing unnecessary and ineffective treatment.
National priorities	NHS Outcomes Framework for 2016-17: Improving 1-year and 5-year survival for all cancers.
Current evidence base	Strategies targeting over-expression of the HER 2 receptor are the only molecular strategies to have proven any benefit in oesophago-gastric cancer. These show a survival advantage of a few months over comparator treatments for patients who have metastatic adenocarcinoma of the stomach or gastro-oesophageal junction and who: have not received prior treatment for their metastatic disease and have tumours expressing high levels of HER2 as defined by a positive immunohistochemistry score of 3 (IHC3 positive).
Equality	Patients with oesophago-gastric cancer should have the same access to an individualised molecular treatment strategy as those with other cancers

Table 149: Research recommendation statements

Criterion	Explanation
Population	Patients with oesophago-gastric cancer suitable for palliative treatments only
Intervention	A molecularly determined treatment strategy
Comparator (without the risk factor)	• Standard chemotherapy
Outcome	• Overall survival • Disease-free survival • Treatment-related morbidity and mortality • Quality of life
Study design	Randomised controlled trial
Timeframe	Five years

9.3 Second-line palliative chemotherapy

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

9.3.1 Introduction

The majority of people with locally advanced and metastatic oesophago-gastric cancer whose disease has progressed following initial chemotherapy, will then face future treatment options which are based on ongoing supportive care. However, there are a small group in whom further chemotherapy may be considered. In general these are people who have previously responded to first-line palliative chemotherapy and retain a good performance status. Chemotherapy treatment options within this group tend to be variable and no single treatment has been proven to be significantly better than another.

This review examined the evidence for second-line palliative chemotherapy in order to identify appropriate agents and schedules for use in this group of people. Since it was known that there were few studies available that directly compared the interventions of interest, it was decided that a network meta-analysis would be required for this topic.

9.3.2 Description of clinical evidence

Sixteen randomised trials (N=2353) were included in the review (Bang 2015, Bang 2016, Ford 2014, Higuchi 2014, Hironaka 2013, Kang 2012, Kim B 2015, Kim JY 2015, Maruta 2007, Moehler 2013, Nishikawa 2015, Nishina 2016, Roy 2013, Sym 2013, Tanabe 2015, Thuss-Patience 2011).

Median follow-up ranged from 6-59 months (where reported). Sample sizes ranged from 40-525 participants. Three studies were carried out in Europe (Ford 2014, Moehler 2013 and Thuss-Patience 2011) the remaining thirteen were from East Asia.

Evidence from these are summarised in the clinical evidence profile below. See also the study selection flow chart in Appendix K, forest plots in Appendix H, study evidence tables in Appendix F, GRADE profiles (for direct comparisons) in Appendix G, details of NMA methods in Appendix M and exclusion list in Appendix J.

9.3.3 Summary of included studies

A summary of the studies included in this review is presented in Table 150.

Table 150: Summary of included studies

Study	Intervention/ Comparison	Population[1]	Outcomes
Bang 2015	4-week treatment cycles: Olaparib (100 mg orally twice daily) or placebo, in combination with paclitaxel (80mg/m2 per day intravenously on days 1, 8 and 15).	Recurrent or metastatic gastric adenocarcinoma	• Overall survival • Neutropaenic sepsis • Neutropaenia • Diarrhoea
Bang 2016	4-week treatment cycles: Olaparib (100 mg orally twice daily) or placebo, in combination with paclitaxel (80mg/m2 per day intravenously on days 1, 8 and 15).	Advanced gastric cancer	• Overall survival • Neutropaenia
Ford 2014	Docetaxel 75mg/m2 by IV infusion every 3 weeks for up to six cycles Active symptom control alone.	Advanced adenocarcinoma of the oesophagus, oesophago-gastric junction or stomach	• Overall survival • Progression free survival • Neutropaenic sepsis • Neutropaenia • Treatment related mortality
Hironaka 2013	Paclitaxel (80 mg/m2) was administered intravenously on days 1, 8, and 15, every 4 weeks. Irinotecan (150 mg/m2) was administered intravenously on days 1 and 15, every 4 weeks.	Metastatic or recurrent gastric adenocarcinoma.	• Overall survival • Progression free survival • Nausea • Neutropaenic sepsis • Neutropaenia • Diarrhoea • Treatment related mortality
Higuchi 2014	BIRIP: Irinotecan 60mg/m2 as 60min IV infusion plus cisplatin 30mg/m2 as 90min IV infusion with adequate hydration on day 1 every 2 weeks versus Irinotecan: 150mg/m2 as 90min IV infusion on day 1 every 2 weeks.	Unresectable advanced or recurrent gastric adenocarcinoma	• Overall survival • Progression free survival • Nausea • Neutropaenic sepsis • Neutropaenia • Diarrhoea
Kang 2012	Second line chemotherapy (either docetaxel 60 mg/m2 every 3 weeks or irinotecan 150 mg/m2 every 2 weeks at the discretion of investigators) versus best supportive care.	Advanced gastric cancer	• Overall survival • Progression free survival • Nausea • Neutropaenic sepsis • Neutropaenia • Diarrhoea
Kim B 2015	3-week cycles of docetaxel 75mg/m2 IV day 1 or Docetaxel 60mg/m2 IV plus cisplatin 60mg/≥m2 day 1 or Docetaxel 60mg/m2 plus oral S-1 30mg/m2 BD day 1-14	Metastatic gastric cancer	• Neutropaenic sepsis • Neutropaenia

Study	Intervention/ Comparison	Population[1]	Outcomes
Kim JY 2015	Weekly monotherapy of 36mg/m2 docetaxel (given IV on days 1 and 8) Docetaxel combined with 80mg/m2 oxaliplatin (on day 1 every 3 weeks up a maximum of 9 cycles).	Metastatic or recurrent gastric adenocarcinoma	• Overall survival • Progression free survival • Nausea • Neutropaenic sepsis • Neutropaenia • Diarrhoea
Maruta 2007	Docetaxel (60 mg/m2 1h IV infusion every 3 wks) alone. Docetaxel (60 mg/m2 1-h IV infusion every 3 wk) and 5′DFUR (600 mg/body orally every day).	Metastatic or recurrent, or unresectable locally advanced, gastric cancer	• Overall survival • Nausea • Neutropaenia
Moehler 2013	6-week cycles including FOLFIRI two weekly followed by sunitinib 25mg (2 capsules) or placebo (2 capsules) per oral once daily for 4 weeks followed by 2 weeks rest period to complete a 6 week cycle.	Gastric adenocarcinoma or adenocarcinoma of the oesophagogastric junction or lower oesophagus	• Overall survival • Progression free survival • Nausea • Neutropaenia • Diarrhoea
Nishikawa 2015	Irinotecan /cisplatin: IV Irinotecan (60 mg/m2) and cisplatin (30 mg/m2) on day 1 and every 2 weeks thereafter. Irinotecan monotherapy: intravenous Irinotecan (150 mg/m2) on day 1 and every 2 weeks thereafter.	Advanced gastric cancer	• Overall survival • Progression free survival • Nausea • Neutropaenia • Diarrhoea
Nishina 2016	5-FUci regimen given as 800 mg/m2/day, on days 1–5, every 4 weeks, and the MTX and 5-FU regimen consisted of weekly MTX bolus infusion (100 mg/m2/day, day 1), followed by 5-FU bolus infusion (600 mg/m2/day, day 1) with a 3-h interval, and leucovorin given orally or by intravenous injection (10 mg/m2, repeated every 6 h, days 2–3). Paclitaxel given as a 1-h infusion (80 mg/m2/day, days 1, 8, and 15), every 4 weeks.	Gastric adenocarcinoma; unresectable or recurrent disease with peritoneal metastasis	• Overall survival • Progression free survival • Nausea • Neutropaenic sepsis • Neutropaenia • Diarrhoea • Treatment related mortality
Roy 2013	irinotecan: 300 mg/m2 (90-min infusion on day 1 of each cycle) docetaxel (Taxotere): 75 mg/m2 (60-min infusion on day 1 of each cycle) intravenously as monotherapy administered every 3 weeks	Locally advanced or metastatic gastric or GEJ adenocarcinoma.	• Overall survival • Progression free survival • Nausea • Neutropaenic sepsis • Neutropaenia • Diarrhoea
Sym 2013	Irinotecan: 150 mg/m2 over 90 min mFOLFIRI: irinotecan 150 mg/m2 over 90 min (followed by a 30-min break) followed by leucovorin (folic acid) 20 mg/m2 over 5 min and then 5-FU 1,000	Gastric or gastro-oesophageal junction adenocarcinoma with metastatic disease	• Overall survival • Progression free survival • Neutropaenia • Diarrhoea

Study	Intervention/ Comparison	Population[1]	Outcomes
	mg/m2 per day by continuous intravenous infusion over 2 days.		• Treatment related mortality
Tanabe 2015	S-1 plus irinotecan: oral S-1 twice daily on days 1–14 and IV irinotecan (150 mg/m2) on day 1 of a 21-day cycle. Irinotecan monotherapy: IV dose as above on day 1 of a 14-day cycle.	Gastric or oesophagogastric junction adenocarcinoma.	• Overall survival • Progression free survival • Nausea • Neutropaenic sepsis • Neutropaenia • Diarrhoea • Treatment related mortality
Thuss-Patience 2011	Best supportive care + irinotecan: irinotecan 250 mg/m2 in the first cycle, increased to 350 mg/m2 in subsequent cycles, administered every 3 weeks with antiemetic cover and subcutaneous atropine (0.25 mg) as cholinergic syndrome prophylaxis. Best supportive care	Adenocarcinoma of the stomach or gastrooesophageal junction, metastatic or locally advanced with surgical incurability	• Overall survival •

1. *All had previously been treated with chemotherapy or chemoradiotherapy and had refractory, progressive or recurrent disease*

9.3.4 Clinical evidence profiles

Table 151 summarises the GRADE quality of evidence of outcomes available from direct comparisons. Table 152 gives a judgement on the overall confidence in the relative effectiveness of the treatments for each outcome.

Table 153 to Table 159 present the results of the conventional pair-wise meta-analyses (direct comparisons; upper-right section of tables), together with results from network meta-analyses for every available treatment comparison (lower-left section of tables). These results were obtained using fixed effects models (see Appendix M). Results are presented as hazard ratios (95% CrI) for overall and progression free survival and as risk ratios (95% CI) for nausea, neutropenic sepsis, neutropenia, diarrhoea and treatment related mortality.

Table 160 to Table 166 rank the treatments in order of their likelihood of being the most effective for each outcome, according to the surface under the cumulative ranking curve (SUCRA) for each treatment.

Table 151: GRADE evidence quality for direct comparisons

Comparison	Overall survival	Progression free survival	Nausea (grade 3 or more)	Neutro-paenic sepsis (grade ≥3)	Neutro-paenia (grade ≥3)	Diarrhoea (grade ≥3)	Treatment related mortality
5-FU versus paclitaxel	LOW	MODERATE	VERY LOW	VERY LOW	LOW	LOW	VERY LOW
docetaxel or irinotecan versus BSC	LOW	-	VERY LOW	VERY LOW	LOW	VERY LOW	-

Comparison	Overall survival	Progression free survival	Nausea (grade 3 or more)	Neutro-paenic sepsis (grade ≥3)	Neutro-paenia (grade ≥3)	Diarrhoea (grade ≥3)	Treatment related mortality
docetaxel + cisplatin versus docetaxel + S-1	-	-	-	VERY LOW	VERY LOW	-	-
docetaxel versus BSC	MODERATE	MODERATE	-	VERY LOW	VERY LOW	-	-
docetaxel versus docetaxel + 5'DFUR	MODERATE	-	VERY LOW	-	VERY LOW	-	-
docetaxel versus docetaxel + oxaliplatin	LOW	MODERATE	LOW	VERY LOW	VERY LOW	VERY LOW	-
docetaxel versus docetaxel + S-1	-	-	-	VERY LOW	VERY LOW	-	-
docetaxel versus irinotecan	LOW	LOW	VERY LOW	VERY LOW	VERY LOW	VERY LOW	-
FOLFIRI + sunitinib versus placebo	LOW	LOW	VERY LOW	-	LOW	VERY LOW	-
irinotecan versus irinotecan + 5'FU/leucovorin	LOW	LOW	-	-	VERY LOW	VERY LOW	VERY LOW
irinotecan + cisplatin versus irinotecan	MODERATE	MODERATE	VERY LOW	VERY LOW	LOW	LOW	-
irinotecan versus BSC	MODERATE	-	-	-	-	-	-
olaparib+paclitaxel versus paclitaxel	HIGH	MODERATE	-	LOW	MODERATE	LOW	-
S-1+ Irinotecan versus irinotecan	MODERATE	MODERATE	LOW	LOW	LOW	LOW	LOW
paclitaxel versus irinotecan	MODERATE	MODERATE	VERY LOW	MODERATE	LOW	VERY LOW	VERY LOW

Abbreviations: BSC, best supportive care;
See Appendix G for full GRADE profiles

Table 152: Confidence in relative effectiveness estimates from network meta-analyses

NMA	Study limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Quality
Overall survival	Serious[1]	No serious inconsistency [2,3]	No serious indirectness	No serious imprecision [9]	None	Moderate

NMA	Study limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Quality
Progression free survival	Serious[1]	No serious inconsistency [2,4]	No serious indirectness	No serious imprecision [9]	None	Moderate
Nausea	Serious[1]	No serious inconsistency [2,5]	Serious indirectness [8]	No serious imprecision [9]	None	Low
Neutropaenic sepsis	Serious[1]	No serious inconsistency [2,6]	Serious indirectness [8]	No serious imprecision [9]	None	Low
Neutropenia	Serious[1]	No serious inconsistency [2,7]	Serious indirectness [8]	No serious imprecision [9]	None	Low
Diarrhoea	Serious[1]	No serious inconsistency [2,7]	Serious indirectness [8]	No serious imprecision [9]	None	Low
Treatment related mortality	Serious[1]	No serious inconsistency [2,6]	Serious indirectness [8]	No serious imprecision [9]	None	Low

Abbreviations: NMA, network meta-analysis.

1. Study limitations taken from GRADE analysis of direct comparisons – see Appendix G

2. No closed loops in the network – so it was not possible to check for incoherence

3. Heterogeneity was very low (SD ≈ 0, P = 0.460), though there were only 2 comparisons with multiple studies so there was very little information to assess the statistical similarity between studies

4. Heterogeneity was very low (SD ≈ 0, P = 0.356), though there was only one comparison with multiple studies so there was very little information to assess the statistical similarity between studies

5. Heterogeneity was very low (SD ≈ 0, P not calculable)

6. No multiple studies of the same comparisons – heterogeneity not applicable

7. Heterogeneity was very low (SD ≈ 0, P > 0.50)

8. Definitions of treatment related morbidity and mortality were poorly reported.

9. As judged by visual inspection of the distribution of SUCRA amongst treatments

Table 153: Hazard ratios (95% CI) for overall survival from direct comparisons (light orange area) and indirect comparisons from NMA (grey area) (median follow up range X to Y)

	Placebo / BSC	S-1 + Irinotecan	Irinotecan	Docetaxel + Fluoro	Irinotecan +mFOLFIRI	Docetaxel/ Irinotecan	Olaparib + Paclitaxel	Docetaxel	Paclitaxel	Irinotecan +Cisplatin	Docetaxel +Oxaliplat	FOLFIRI + Sunitinib	Fluoropyrimidine
Placebo / BSC			**0.57 (0.38, 0.85)**			**0.71 (0.54, 0.94)**		**0.65 (0.48, 0.86)**				0.82 (0.5, 1.33)	
S-1 + Irinotecan	**0.56 (0.35, 0.9)**		1.01 (0.8, 1.28)										
Irinotecan	**0.57 (0.38,0.85)**	1.01 (0.8, 1.28)			0.96 (0.57, 1.61)			1.14 (0.79, 1.64)	1.13 (0.86, 1.48)	0.91 (0.71, 1.16)			
Docetaxel + Fluoro	**0.21 (0.08, 0.55)**	0.37 (0.13, 1.04)	0.37 (0.13, 1.00)					**3.11 (1.22, 7.93)**					
Irinotecan +mFOLFIRI	0.54 (0.28, 1.05)	0.97 (0.55, 1.72)	0.96 (0.57, 1.61)	2.62 (0.85, 8.12)									
Docetaxel/ Irinotecan	**0.71 (0.54, 0.94)**	1.27 (0.73, 2.2)	1.26 (0.76, 2.06)	**3.43 (1.24, 9.5)**	1.31 (0.64, 2.68)								
Olaparib + Paclitaxel	**0.47 (0.28, 0.81)**	0.85 (0.56, 1.28)	0.84 (0.6, 1.18)	2.28 (0.79, 6.59)	0.87 (0.47, 1.62)	0.67 (0.36, 1.22)			**1.35 (1.1, 1.66)**				
Docetaxel	**0.65 (0.48, 0.86)**	1.15 (0.75, 1.78)	1.14 (0.79, 1.64)	3.11 (1.22, 7.93)	1.18 (0.63, 2.23)	0.91 (0.61, 1.36)	1.36 (0.83, 2.24)				0.85 (0.49, 1.49)		
Paclitaxel	0.64 (0.39, 1.05)	1.14 (0.79, 1.64)	1.13 (0.86, 1.48)	3.08 (1.09, 8.73)	1.18 (0.65, 2.11)	0.9 (0.51, 1.59)	**1.35 (1.1, 1.66)**	0.99 (0.63, 1.56)					0.89 (0.57, 1.38)

	Placebo / BSC	S-1 + Irinotecan	Irinotecan	Docetaxel + Fluoro	Irinotecan +mFOLFIRI	Docetaxel/ Irinotecan	Olaparib + Paclitaxel	Docetaxel	Paclitaxel	Irinotecan +Cisplatin	Docetaxel +Oxaliplat	FOLFIRI + Sunitinib	Fluoropyrimidine
Irinotecan +Cisplatin	**0.51 (0.32, 0.83)**	0.91 (0.65, 1.29)	0.91 (0.71, 1.16)	2.47 (0.88, 6.95)	0.94 (0.53, 1.67)	0.72 (0.41, 1.26)	1.08 (0.71, 1.65)	0.79 (0.51, 1.23)	0.8 (0.55, 1.16)				
Docetaxel +Oxaliplat	0.55 (0.29, 1.03)	0.98 (0.49, 1.99)	0.97 (0.5, 1.89)	2.66 (0.89, 7.9)	1.01 (0.44, 2.35)	0.78 (0.39, 1.54)	1.16 (0.55, 2.46)	0.85 (0.49, 1.49)	0.86 (0.42, 1.77)	1.08 (0.53, 2.19)			
FOLFIRI + Sunitinib	0.82 (0.5, 1.33)	1.46 (0.74, 2.88)	1.44 (0.76, 2.73)	**3.93 (1.32, 11.8)**	1.5 (0.66, 3.41)	1.15 (0.65, 2.02)	1.72 (0.84, 3.55)	1.27 (0.72, 2.24)	1.28 (0.64, 2.55)	1.59 (0.8, 3.16)	1.48 (0.67, 3.28)		
Fluoropyrimidine	0.57 (0.29, 1.1)	1.01 (0.57, 1.79)	1 (0.6, 1.68)	2.74 (0.88, 8.47)	1.04 (0.5, 2.17)	0.8 (0.39, 1.64)	1.2 (0.74, 1.95)	0.88 (0.47, 1.66)	0.89 (0.57, 1.38)	1.11 (0.62, 1.97)	1.03 (0.44, 2.39)	0.7 (0.31, 1.58)	

Lower half (grey cells) displays indirect NMA results. Upper half (light orange cells) displays direct results from included studies.
Results, read horizontally, show the Hazard ratio for experimental vs control for indirect results and control vs experimental for direct results.
Numbers in bold indicate results where the 95% confidence intervals do not pass 1.

Table 154: Hazard ratios (95% CI) for progression free survival from direct comparisons (light orange area) and indirect comparisons from NMA (grey area) (median follow up range X to Y)

	Placebo / BSC	S-1 + Irinotecan	Irinotecan	Irinotecan +mFOLFIRI	Olaparib + Paclitaxel	Docetaxel	Paclitaxel	Irinotecan +Cisplatin	Docetaxel +Oxaliplat	FOLFIRI + Sunitinib	Fluoropyrimidine
Placebo / BSC						**0.67 (0.48, 0.94)**				1.11 (0.7, 1.76)	
S-1 + Irinotecan	0.68 (0.37, 1.23)		1.18 (0.93, 1.49)								
Irinotecan	0.8 (0.46, 1.38)	1.18 (0.93, 1.49)		0.88 (0.53, 1.47)		0.84 (0.55, 1.29)	1.14 (0.88, 1.48)	**0.77 (0.6, 0.99)**			

	Placebo / BSC	S-1 + Irinotecan	Irinotecan	Irinotecan +mFOLFIRI	Olaparib + Paclitaxel	Docetaxel	Paclitaxel	Irinotecan +Cisplatin	Docetaxel +Oxaliplat	FOLFIRI + Sunitinib	Fluoropyrimidine
Irinotecan +mFOLFIRI	0.71 (0.33, 1.49)	1.04 (0.59, 1.82)	0.88 (0.53, 1.47)								
Olaparib + Paclitaxel	0.76 (0.4, 1.45)	1.13 (0.74, 1.71)	0.96 (0.68, 1.35)	1.08 (0.59, 2)			1.19 (0.95, 1.49)				
Docetaxel	**0.67 (0.48, 0.94)**	0.99 (0.6, 1.62)	0.84 (0.55, 1.29)	0.95 (0.49, 1.85)	0.88 (0.51, 1.52)				**2 (1.08, 3.7)**		
Paclitaxel	0.91 (0.5, 1.66)	1.34 (0.94, 1.91)	1.14 (0.88, 1.48)	1.29 (0.73, 2.28)	1.19 (0.95, 1.49)	1.36 (0.82, 2.24)					**0.58 (0.38, 0.88)**
Irinotecan +Cisplatin	0.62 (0.34, 1.12)	0.91 (0.65, 1.28)	**0.77 (0.6, 0.99)**	0.87 (0.5, 1.54)	0.81 (0.53, 1.23)	0.92 (0.56, 1.51)	**0.68 (0.47, 0.97)**				
Docetaxel +Oxaliplat	1.34 (0.67, 2.7)	1.98 (0.9, 4.35)	1.68 (0.79, 3.57)	1.9 (0.77, 4.71)	1.76 (0.77, 4.01)	**2 (1.08, 3.7)**	1.47 (0.67, 3.27)	2.17 (0.98, 4.8)			
FOLFIRI + Sunitinib	1.11 (0.7, 1.76)	1.64 (0.77, 3.48)	1.39 (0.68, 2.84)	1.57 (0.66, 3.78)	1.45 (0.66, 3.21)	1.66 (0.94, 2.93)	1.22 (0.57, 2.61)	1.8 (0.85, 3.83)	0.83 (0.36, 1.92)		
Fluoropyrimidine	0.53 (0.25, 1.1)	0.78 (0.45, 1.34)	0.66 (0.41, 1.08)	0.75 (0.37, 1.51)	0.69 (0.43, 1.11)	0.79 (0.41, 1.51)	**0.58 (0.38, 0.88)**	0.85 (0.49, 1.48)	**0.39 (0.16, 0.96)**	0.47 (0.2, 1.13)	

Lower half (grey cells) displays indirect NMA results. Upper half (light orange cells) displays direct results from included studies.
Results, read horizontally, show the Hazard ratio for experimental vs control for indirect results and control vs experimental for direct results.
Numbers in bold indicate results where the 95% confidence intervals do not pass 1.

Table 155: Risk ratios (95% CI) for nausea (grade 3 or greater) from direct comparisons (light orange area) and indirect comparisons from NMA (grey area) (follow up)

	Docetaxel	Irinotecan + mFOLFIRI	Docetaxel + Fluoro	Irinotecan	S-1+ Irinotecan	Fluoropyrimidine	Docetaxel + Oxaliplat	Irinotecan + Cisplatin	Paclitaxel	Olaparib + Paclitaxel
Docetaxel			0.33 (0.01,7.45)	5.00 (0.25,101)			3.23 (0.14,75.83)			
Irinotecan + mFOLFIRI	4.83 (0.04,659)			1.03 (0.02,50.42)						
Docetaxel + Fluoro	0.33 (0.01,7.45)	0.07 (<0.01,23.1)								
Irinotecan	5.00 (0.25,101)	1.03 (0.02,50.4)	14.99 (0.20,>999)		0.58 (0.23,1.42)			0.89 (0.33,2.38)	0.40 (0.08,2.04)	
S-1+ Irinotecan	2.88 (0.12,66.5)	0.59 (0.01,32.2)	8.63 (0.10,715)	0.58 (0.23,1.42)						
Fluoropyrimidine	14.67 (0.16,>999)	3.04 (0.02,515)	44.02 (0.19, >999)	2.94 (0.10,84.06)	5.10 (0.16,165)				0.14 (0.01,2.59)	
Docetaxel + Oxaliplat	3.23 (0.14,75.8)	0.67 (<0.01,230)	9.69 (0.12,812)	0.65 (0.01,50.57)	1.12 (0.01,96.39)	0.22 (<0.01,53.9)				
Irinotecan + Cisplatin	4.42 (0.19,105)	0.92 (0.02,50.6)	13.27 (0.16, >999)	0.89 (0.33,2.38)	1.54 (0.40,5.88)	0.30 (0.01,9.96)	1.37 (0.02,120)			
Paclitaxel	2.02 (0.07,61.3)	0.42 (0.01,28.1)	6.05 (0.06,612)	0.40 (0.08,2.04)	0.70 (0.11,4.48)	0.14 (0.01,2.59)	0.62 (0.01,65.25)	0.46 (0.07,3.04)		1.02 (0.02,50.41)
Olaparib + Paclitaxel	2.05 (0.01,367)	0.42 (<0.01,132)	6.15 (0.01, >999)	0.41 (0.01,28.08)	0.71 (0.01,53.67)	0.14 (<0.01,18.5)	0.63 (<0.01,275)	0.46 (0.01,35.54)	1.02 (0.02,50.41)	

Lower half (grey cells) displays indirect NMA results. Upper half (light orange cells) displays direct results from included studies.
Results, read horizontally, show the Hazard ratio for experimental vs control for indirect results and control vs experimental for direct results.
Numbers in bold indicate results where the 95% confidence intervals do not pass 1.

Table 156: Risk ratios (95% CI) for neutropenic sepsis (grade 3 or greater) for nausea from direct comparisons (light orange area) and indirect comparisons from NMA (grey area) (follow up)

	Docetaxel	Docetaxel /Irinotecan	Irinotecan +mFOLFIRI	Docetaxel +Fluoro	Irinotecan	S-1+ Irinotecan	Fluoropyrimidine	Docetaxel + Cisplatin	Docetaxel +Oxaliplat	Irinotecan + Cisplatin	Paclitaxel	Olaparib + Paclitaxel	Placebo / BSC
Docetaxel				0.50 (0.05,5.14)	2.50 (0.51,12.20)			1.44 (0.26,7.83)	11.85 (0.69,204)				0.08 (<0.01, 1.34)
Docetaxel /Irinotecan	0.50 (0.01,28.3)												0.16 (0.01,2.71)
Irinotecan +mFOLFIRI	2.42 (0.04,161)	4.88 (0.01,>999)			1.03 (0.02,50.42)								
Docetaxel +Fluoro	0.50 (0.05,5.14)	1.01 (0.01,107)	0.21 (<0.01, 25.2)					2.88 (0.32,25.68)					
Irinotecan	2.50 (0.51,12.2)	5.04 (0.07,388)	1.03 (0.02,50.4)	5.00 (0.30,83.7)		**11.84 (1.56,89.94)**				0.15 (0.01,2.80)	0.30 (0.09,1.07)		
S-1+ Irinotecan	**29.60 (2.26,388)**	59.7 (0.49,>999)	12.24 (0.15,981)	**59.20 (1.84,>999)**	**11.84 (1.56,89.9)**								
Fluoropyrimidine	3.93 (0.10,148)	7.93 (0.03,>999)	1.63 (0.01,261)	7.87 (0.11,588)	1.57 (0.06,41.23)	0.13 (<0.01, 6.21)					0.19 (0.01,3.91)		
Docetaxel + Cisplatin	1.44 (0.26,7.83)	2.90 (0.04,232)	0.59 (0.01,55.0)	2.88 (0.32,25.68)	0.58 (0.06,5.86)	0.05 (<0.01, 1.06)	0.37 (0.01,20.08)						
Docetaxel +Oxaliplat	11.85 (0.69,204)	23.88 (0.17,>999)	4.90 (0.03,781)	23.69 (0.60,937)	4.74 (0.18,123)	0.40 (0.01,18.56)	3.01 (0.03,303)	8.24 (0.30,226)					
Irinotecan + Cisplatin	0.37 (0.01,10.4)	0.74 (<0.01, 141)	0.15 (<0.01, 20.0)	0.74 (0.01,43.33)	0.15 (0.01,2.80)	**0.01 (<0.01, 0.44)**	0.09 (<0.01,7.59)	0.26 (0.01,10.87)	0.03 (<0.01, 2.51)				

	Docetaxel	Docetaxel /Irinotecan	Irinotecan +mFOLFIRI	Docetaxel +Fluoro	Irinotecan	S-1+ Irinotecan	Fluoropyrimidine	Docetaxel + Cisplatin	Docetaxel +Oxaliplat	Irinotecan + Cisplatin	Paclitaxel	Olaparib + Paclitaxel	Placebo / BSC
Paclitaxel	0.76 (0.10,5.75)	1.53 (0.02,140)	0.31 (0.01,18.64)	1.51 (0.07,33.20)	0.30 (0.09,1.07)	**0.03 (<0.01, 0.28)**	0.19 (0.01,3.91)	0.53 (0.04,7.40)	0.06 (<0.01, 2.10)	2.06 (0.08,50.59)		3.05 (0.13,73.40)	
Olaparib + Paclitaxel	2.31 (0.05,100)	4.65 (0.02,>999)	0.95 (0.01,169)	4.61 (0.05,389)	0.92 (0.03,28.29)	0.08 (<0.01, 4.16)	0.59 (0.01,46.83)	1.60 (0.03,100)	0.19 (<0.01, 22.0)	6.27 (0.07,572)	3.05 (0.13,73.40)		
Placebo / BSC	0.08 (<0.01, 1.34)	0.16 (0.01,2.71)	0.03 (<0.01, 5.12)	0.15 (<0.01, 6.16)	**0.03 (<0.01, 0.81)**	**<0.01 (<0.01, 0.12)**	0.02 (<0.01,1.99)	0.05 (<0.01, 1.49)	0.01 (<0.01, 0.37)	0.21 (<0.01, 17.0)	0.10 (<0.01, 3.39)	0.03 (<0.01, 3.79)	

Lower half (grey cells) displays indirect NMA results. Upper half (light orange cells) displays direct results from included studies.
Results, read horizontally, show the Hazard ratio for experimental vs control for indirect results and control vs experimental for direct results.
Numbers in bold indicate results where the 95% confidence intervals do not pass 1.

Table 157: Risk ratios (95% CI) for neutropenia (grade 3 or greater) from direct comparisons (light orange area) and indirect comparisons from NMA (grey area) (follow up)

	Docetaxel	Docetaxel /Irinotec	Irinotecan +mFOLFIRI	Docetaxel + Fluoro	Irinotecan	S-1+ Irinotecan	Fluoropyrimidine	FOLFIRI + Sunitinib	Docetaxel + Cisplatin	Docetaxel + Oxaliplatin	Irinotecan + Cisplatin	Paclitaxel	Olaparib + Paclitaxel	Placebo / BSC
Docetaxel				0.60 (0.16,2.22)	0.29 (0.06,1.30)				1.15 (0.41,3.25)	**18.31 (1.11,302)**				**0.03 (<0.01, 0.44)**
Docetaxel /Irinotec	0.13 (0.01,2.24)													**0.21 (0.11,0.41)**
Irinotecan +mFOLFIRI	0.38 (0.07,2.07)	2.99 (0.11,83.4)			0.75 (0.35,1.60)									

	Docetaxel	Docetaxel /Irinotec	Irinotecan +mFOLFIRI	Docetaxel + Fluoro	Irinotecan	S-1+ Irinotecan	Fluoropyrimidine	FOLFIRI + Sunitinib	Docetaxel + Cisplatin	Docetaxel + Oxaliplatin	Irinotecan + Cisplatin	Paclitaxel	Olaparib + Paclitaxel	Placebo / BSC
Docetaxel + Fluoro	0.60 (0.16,2.22)	4.71 (0.20,110)	1.57 (0.19,13.4)						1.92 (0.54,6.77)					
Irinotecan	0.29 (0.06,1.30)	2.25 (0.09,57.5)	0.75 (0.35,1.60)	0.48 (0.06,3.53)		**1.44 (1.03,2.03)**					1.17 (0.87,1.57)	0.73 (0.50,1.06)		
S-1+ Irinotecan	0.41 (0.09,1.95)	3.25 (0.12,84.5)	1.09 (0.47,2.48)	0.69 (0.09,5.24)	**1.44 (1.03,2.03)**									
Fluoropyrimidine	0.51 (0.08,3.02)	3.98 (0.14,116)	1.33 (0.39,4.48)	0.84 (0.09,7.74)	1.77 (0.68,4.58)	1.22 (0.45,3.36)						**0.41 (0.17,0.99)**		
FOLFIRI + Sunitinib	0.08 (<0.01, 1.35)	0.61 (0.24,1.53)	0.20 (0.01,5.64)	0.13 (0.01,3.00)	0.27 (0.01,6.87)	0.19 (0.01,4.85)	0.15 (0.01,4.46)							**0.35 (0.19,0.67)**
Docetaxel + Cisplatin	1.15 (0.41,3.25)	9.03 (0.43,191)	3.02 (0.41,22.0)	1.92 (0.54,6.77)	4.01 (0.64,25.2)	2.78 (0.43,18.0)	2.27 (0.29,18.0)	14.87 (0.71,312)						
Docetaxel + Oxaliplatin	**18.31 (1.11,302)**	144 (2.61,> 999)	48.06 (1.82,> 999)	**30.51 (1.38,672)**	**63.88 (2.65,> 999)**	**44.29 (1.80,> 999)**	**36.15 (1.30,> 999)**	**236 (4.32,> 999)**	15.92 (0.80,316)					
Irinotecan + Cisplatin	0.33 (0.07,1.56)	2.63 (0.10,68.2)	0.88 (0.39,1.98)	0.56 (0.07,4.22)	1.17 (0.87,1.57)	0.81 (0.52,1.27)	0.66 (0.24,1.79)	4.33 (0.17,112)	0.29 (0.05,1.87)	**0.02 (<0.01, 0.45)**				
Paclitaxel	**0.21 (0.04,0.99)**	1.64 (0.06,42.8)	0.55 (0.24,1.27)	0.35 (0.05,2.66)	**0.73 (0.50,1.06)**	**0.50 (0.30,0.84)**	0.41 (0.17,0.99)	2.70 (0.10,70.2)	0.18 (0.03,1.18)	**0.01 (<0.01, 0.28)**	0.62 (0.38,1.01)		1.37 (1.09,1.73)	

	Docetaxel	Docetaxel /Irinotec	Irinotecan +mFOLFIRI	Docetaxel + Fluoro	Irinotecan	S-1+ Irinotecan	Fluoropyrimidine	FOLFIRI + Sunitinib	Docetaxel + Cisplatin	Docetaxel + Oxaliplatin	Irinotecan + Cisplatin	Paclitaxel	Olaparib + Paclitaxel	Placebo / BSC
Olaparib + Paclitaxel	0.29 (0.06,1.38)	2.25 (0.09,59.2)	0.75 (0.31,1.80)	0.48 (0.06,3.70)	1.00 (0.64,1.56)	0.69 (0.40,1.21)	0.56 (0.23,1.39)	3.70 (0.14,97.0)	0.25 (0.04,1.64)	**0.02 (<0.01, 0.39)**	0.85 (0.50,1.45)	**1.37 (1.09,1.73)**		
Placebo / BSC	**0.03 (<0.01, 0.44)**	0.21 (0.11,0.41)	0.07 (<0.01, 1.86)	0.05 (<0.01, 0.99)	0.10 (<0.01, 2.27)	**0.07 (<0.01, 1.60)**	0.05 (<0.01, 1.48)	0.35 (0.19,0.67)	**0.02 (<0.01, 0.46)**	**<0.01 (<0.01, 0.08)**	0.08 (<0.01, 1.97)	0.13 (0.01,3.19)	0.10 (<0.01, 2.34)	

Lower half (grey cells) displays indirect NMA results. Upper half (light orange cells) displays direct results from included studies.
Results, read horizontally, show the Hazard ratio for experimental vs control for indirect results and control vs experimental for direct results.
Numbers in bold indicate results where the 95% confidence intervals do not pass 1.

Table 158: Risk ratios (95% CI) for diarrhoea (grade 3 or greater) from direct comparisons (light orange area) and indirect comparisons from NMA (grey area) (follow up)

	Docetaxel	Irinotecan +mFOLFIRI	Irinotecan	S-1+ Irinotecan	Fluoropyrimidine	Docetaxel +Oxaliplat	Irinotecan + Cisplatin	Paclitaxel	Olaparib + Paclitaxel
Docetaxel			**7.99 (1.04,61.24)**			0.31 (0.01,7.26)			
Irinotecan +mFOLFIRI	15.45 (0.69,345)		0.52 (0.05,5.40)						
Irinotecan	**7.99 (1.04,61.24)**	0.52 (0.05,5.40)		0.69 (0.27,1.77)			0.21 (0.04,1.20)	1.01 (0.06,15.91)	
S-1+ Irinotecan	5.52 (0.59,51.99)	0.36 (0.03,4.47)	0.69 (0.27,1.77)						
Fluoropyrimidine	**92.16 (1.05,>999)**	5.96 (0.06,605)	11.53 (0.22,617)	16.69 (0.28,996)				0.09 (<0.01,1.54)	
Docetaxel +Oxaliplat	3.23 (0.14,75.83)	0.21 (<0.01,17.5)	0.40 (0.01,17.28)	0.59 (0.01,28.08)	0.04 (<0.01,8.34)				
Irinotecan + Cisplatin	1.68 (0.11,24.47)	0.11 (0.01,2.02)	0.21 (0.04,1.20)	0.30 (0.04,2.20)	0.02 (<0.01,1.40)	0.52 (0.01,32.61)			

	Docetaxel	Irinotecan +mFOLFIRI	Irinotecan	S-1+ Irinotecan	Fluoropyrimidine	Docetaxel +Oxaliplat	Irinotecan + Cisplatin	Paclitaxel	Olaparib + Paclitaxel
Paclitaxel	8.06 (0.26,249)	0.52 (0.01,19.50)	1.01 (0.06,15.91)	1.46 (0.08,26.91)	0.09 (<0.01,1.54)	2.49 (0.02,264)	4.81 (0.18,126)		0.34 (0.07,1.61)
Olaparib + Paclitaxel	2.73 (0.06,118)	0.18 (<0.01,9.12)	0.34 (0.01,8.13)	0.49 (0.02,13.49)	**0.03 (<0.01,0.78)**	0.85 (0.01,115)	1.63 (0.04,60.72)	0.34 (0.07,1.61)	

Lower half (grey cells) displays indirect NMA results. Upper half (light orange cells) displays direct results from included studies.
Results, read horizontally, show the Hazard ratio for experimental vs control for indirect results and control vs experimental for direct results.
Numbers in bold indicate results where the 95% confidence intervals do not pass 1.

Table 159: Risk ratios (95% CI) for treatment related mortality from direct comparisons (light orange area) and indirect comparisons from NMA (grey area) (follow up)

	Paclitaxel	Irinotecan +mFOLFIRI	Irinotecan	S-1+ Irinotecan	Fluoropyrimidine	Irinotecan + Cisplatin	Olaparib + Paclitaxel
Paclitaxel			4.96 (0.24,102)		3.12 (0.13,74.80)		1.02 (0.02,50.41)
Irinotecan +mFOLFIRI	1.60 (0.02,127)		3.10 (0.13,73.14)	0.61 (0.01,48.73)			
Irinotecan	4.96 (0.24,102)	3.10 (0.13,73.14)				1.03 (0.02,51.18)	
S-1+ Irinotecan	0.98 (0.01,70.67)	0.61 (0.01,48.73)	0.20 (0.01,4.08)				
Fluoropyrimidine	3.12 (0.13,74.80)	1.95 (0.01,435)	0.63 (0.01,50.61)	3.19 (0.02,659)			
Irinotecan + Cisplatin	5.11 (0.04,714)	3.20 (0.02,486)	1.03 (0.02,51.18)	5.22 (0.04,731)	1.64 (<0.01,582)		
Olaparib + Paclitaxel	1.02 (0.02,50.41)	0.64 (<0.01,224)	0.21 (<0.01,28.6)	1.04 (<0.01,341)	0.33 (<0.01,50.0)	0.20 (<0.01,108)	

Lower half (grey cells) displays indirect NMA results. Upper half (light orange cells) displays direct results from included studies.
Results, read horizontally, show the Hazard ratio for experimental vs control for indirect results and control vs experimental for direct results.
Numbers in bold indicate results where the 95% confidence intervals do not pass 1.

Table 160: Treatments ranked by probability of being the most effective in terms of overall survival

Treatment	N	k	SUCRA
Docetaxel + Fluoropyrimidine	12	1	0.97
Olaparib + Paclitaxel	324	2	0.76
Irinotecan + Cisplatin	148	2	0.68
Irinotecan + mFOLFIRI	30	1	0.58
Docetaxel + Oxaliplatin	25	1	0.57
S-1 + Irinotecan	153	1	0.56
Irinotecan	441	7	0.54
Fluoropyrimidine	49	1	0.53
Docetaxel	167	4	0.39
Paclitaxel	486	4	0.36
Docetaxel / Irinotecan	126	1	0.31
FOLFIRI + Sunitinib	45	1	0.21
Placebo / BSC	436	4	0.03

Abbreviations: BSC, best supportive care; k, number of studies; N, number of patients; SUCRA, surface under the cumulative ranking curve.

Table 161: Treatments ranked by probability of being the most effective in terms of progression free survival

Treatment	N	k	SUCRA
Fluoropyrimidine	49	1	0.89
Irinotecan + Cisplatin	148	2	0.80
Docetaxel	167	3	0.70
S-1 + Irinotecan	153	1	0.68
Irinotecan + mFOLFIRI	30	1	0.61
Olaparib + Paclitaxel	263	1	0.53
Irinotecan	441	6	0.45
Paclitaxel	424	3	0.28
Placebo / BSC	374	2	0.26
FOLFIRI + Sunitinib	45	1	0.21
Docetaxel + Oxaliplatin	25	1	0.11

Abbreviations: BSC, best supportive care; k, number of studies; N, number of patients; SUCRA, surface under the cumulative ranking curve.

Table 162: Treatments ranked by probability of being the most effective in terms of nausea

Treatment	N	k	SUCRA
Docetaxel + Fluoropyrimidine	12	1	0.80
Docetaxel	83	3	0.70
Olaparib + Paclitaxel	61	1	0.60
Paclitaxel	224	3	0.60
Docetaxel + Oxaliplatin	25	1	0.50
S-1+ Irinotecan	153	1	0.50
Irinotecan + Cisplatin	148	2	0.40
Irinotecan + mFOLFIRI	30	1	0.40
Irinotecan	486	6	0.30

Treatment	N	k	SUCRA
Fluoropyrimidine	49	1	0.20

Abbreviations: k, number of studies; N, number of patients; SUCRA, surface under the cumulative ranking curve.

Table 163: Treatments ranked by probability of being the most effective in terms of neutropaenic sepsis

Treatment	N	k	SUCRA
Placebo / BSC	146	2	0.90
Irinotecan + Cisplatin	64	1	0.70
Docetaxel + Fluoropyrimidine	23	2	0.70
Docetaxel	178	5	0.60
Paclitaxel	224	3	0.60
Docetaxel / Irinotecan	30	1	0.60
Docetaxel + Cisplatin	24	2	0.50
Olaparib + Paclitaxel	61	1	0.40
Irinotecan + 5'FU/leucovorin (mFOLFIRI)	126	1	0.40
Irinotecan	402	5	0.40
Fluoropyrimidine	49	1	0.30
Docetaxel + Oxaliplatin	25	1	0.20
S-1+ Irinotecan	153	1	0.10

Abbreviations: BSC, best supportive care; k, number of studies; N, number of patients; SUCRA, surface under the cumulative ranking curve.

Table 164: Treatments ranked by probability of being the most effective in terms of neutropaenia

Treatment	N	k	SUCRA
Placebo / BSC	192	3	1.00
Paclitaxel	486	4	0.80
FOLFIRI + Sunitinib	45	1	0.80
Docetaxel / Irinotecan	126	1	0.70
Olaparib + Paclitaxel	324	2	0.60
Irinotecan	486	6	0.60
Irinotecan + Cisplatin	148	2	0.50
Irinotecan + mFOLFIRI	30	1	0.50
S-1+ Irinotecan	153	1	0.40
Fluoropyrimidine	49	1	0.40
Docetaxel + Fluoropyrimidine	23	2	0.40
Docetaxel	178	5	0.20
Docetaxel + Cisplatin	24	2	0.20
Docetaxel + Oxaliplatin	25	1	0.00

Abbreviations: BSC, best supportive care; k, number of studies; N, number of patients; SUCRA, surface under the cumulative ranking curve.

Table 165: Treatments ranked by probability of being the most effective in terms of diarrhoea

Treatment	N	k	SUCRA
Docetaxel	71	2	0.90
Irinotecan + Cisplatin	148	2	0.80
Olaparib + Paclitaxel	61	1	0.70

Treatment	N	k	SUCRA
Docetaxel + Oxaliplatin	25	1	0.60
S-1+ Irinotecan	153	1	0.50
Paclitaxel	224	3	0.40
Irinotecan	486	6	0.40
Irinotecan + mFOLFIRI	30	1	0.30
Fluoropyrimidine	49	1	0.10

Abbreviations: BSC, best supportive care; k, number of studies; N, number of patients; SUCRA, surface under the cumulative ranking curve.

Table 166: Treatments ranked by probability of being the most effective in terms of treatment related mortality

Treatment	N	k	SUCRA
Paclitaxel	224	3	0.70
Olaparib + Paclitaxel	61	1	0.60
S-1+ Irinotecan	153	1	0.60
Irinotecan + mFOLFIRI	30	1	0.50
Fluoropyrimidine	49	1	0.40
Irinotecan + Cisplatin	64	1	0.30
Irinotecan	358	2	0.30

Abbreviations: BSC, best supportive care; k, number of studies; N, number of patients; SUCRA, surface under the cumulative ranking curve.

9.3.5 Economic evidence

Two relevant studies were identified in a literature review of published cost-effectiveness analyses on this topic; Lam et al. 2016 and Meads et al. 2015 (see table 3 in Appendix L). The base case results of Lam et al. 2016 showed that, in cost-effectiveness terms, all chemotherapy regimens were preferred to palliative care with irinotecan found to be the most cost-effective of the chemotherapy regimens.

The base case results of Meads et al. 2015 showed that, in comparison to active symptom control alone, the addition of docetaxel provided one additional QALY at a cost of £27,180. In probabilistic sensitivity analysis (PSA), the addition of docetaxel was found to have a 26% probability of being cost-effective at a threshold of £20,000 per QALY. At an increased threshold of £50,000 per QALY (applicable for treatments that meet the end of life criteria), docetaxel was found to have a 90% probability of being cost-effective.

The analysis by Lam et al. 2016 suggests that chemotherapy may be a cost-effective alternative to palliative care. However the analysis was only partially applicable to the decision problem in the UK setting as they were based on the health care perspective of the United States. Furthermore, some potentially serious limitations were identified in the analysis. The evidence used to inform the analysis was not identified through a systematic literature search and so it is possible that some useful data may have been missed. There were also concerns that the uncertainty around effectiveness estimates may have been underestimated in the probabilistic sensitivity analysis because event probabilities were varied individually (by ± 25%) rather than using evidence based variations in relative effect estimates (such as a relative risk).

The analysis by Meads et al. 2015 suggests that docetaxel is not a cost-effective addition to active symptom control when considering the typical threshold of £20,000 per QALY. If the treatment was deemed to meet the end of life criteria, then the addition of docetaxel may be considered cost-effective at an increased threshold of £50,000 per QALY. However, some

potentially serious limitations were identified in the analysis (including uncertainty around some of the cost estimates).

Overall, the analyses indicate that chemotherapy may be cost-effective in this setting but further research is required before drawing decisive conclusions.

9.3.6 Evidence statements

9.3.6.1 Overall survival

Moderate quality evidence about the effectiveness of second line chemotherapy in terms of overall survival came from 15 randomised trials including 3442 patients and comparing 13 treatments. Almost all treatments appeared to improve overall survival compared to best supportive care alone, though only seven were clinically significant. Docetaxel + fluoropyrimidine was most likely to be the most effective treatment, however, it was only tested on 12 participants.

9.3.6.2 Progression free survival

Moderate quality evidence about the effectiveness of second line chemotherapy in terms of progression free survival came from 11 randomised trials including 2131 patients and comparing 11 treatments. For PFS, results were less clear than for OS as there were slightly fewer studies included and the direct estimates tended to be more imprecise than for OS. The only treatment that appeared to be significantly better than placebo was docetaxel, although fluoropyrimidine and Irinotecan + cisplatin did reasonable effectiveness compared to the other treatments

9.3.6.3 Nausea (grade 3 or greater)

Low quality evidence about the rates of nausea during second line chemotherapy came from 10 randomised trials including 1271 patients and comparing 10 treatments. None of the odds ratios for patients reporting experiencing nausea was clinically significant, and there was considerable uncertainty in results, mainly due to the low event rates.

9.3.6.4 Neutropaenic sepsis (grade 3 or greater)

Low quality evidence about the rates of neutropaenic sepsis during second line chemotherapy came from 12 randomised trials including 1505 patients and comparing 14 treatments. There was very little information for this adverse event due to relatively low event rates. However, placebo / best supportive care was included in this network, and (as expected) it seemed to be better than all other treatments and significantly better than three.

9.3.6.5 Neutropaenia (grade 3 or greater)

Low quality evidence about the rates of neutropaenia during second line chemotherapy came from 18 randomised trials including patients and comparing 10 treatments. Placebo / best supportive care had the lowest risk of neutropenia and this was significant for four treatments. However, paclitaxel had much lower risk than many other treatments whereas docetaxel + oxaliplatin had higher risk than many others

9.3.6.6 Diarrhoea (grade 3 or greater)

Low quality evidence about the rates of diarrhoea during second line chemotherapy came from 9 randomised trials including 1247 patients and comparing 9 treatments. This was a very sparse network here with relatively few events. Although docetaxel performed fairly well

in comparison to the other treatments and fluoropyrimidine quite poorly these results are very uncertain.

9.3.6.7 Treatment related mortality

Low quality evidence about the rates of mortality related to second line chemotherapy came from 10 randomised trials including 1271 patients and comparing 10 treatments. This was a very small network with very few events and as a result there was serious uncertainty about relative effectiveness.

9.3.7 Introduction

There is no consensus on the protocol for follow-up of people with oesophago-gastric cancer and more importantly whether follow-up improves survival and quality of life.

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.

People with oesophago-gastric cancer may gain psychological support from regular follow-up, but other people may suffer additional anxiety caused by planned hospital visits, and few studies have formally evaluated these issues. Regular access to, and support from, cancer nurse specialists, specialist dietitians or other professionals, or patient-led self-referral are promising alternatives for follow-up.

This review aimed to identify the most clinically effective follow-up options for asymptomatic adults who have completed treatment for oesophago-gastric cancer with curative intent and to identify the optimal timing and duration of follow-up.

9.3.8 Evidence to recommendations

9.3.8.1 Relative value placed on the outcomes considered

The most important outcomes considered for this topic were treatment related morbidity and mortality, health-related quality of life and overall survival. Overall survival and health-related quality of life were considered to be important because achieving improvements in these outcomes is the main aim of treatment in this patient group. Treatment related morbidity and mortality are important as chemotherapy is known to have detrimental side-effects.

Taken together, the outcomes characterise the key trade-off between interventions in this patient group. There is the potential for benefits in terms of improved survival and quality of life but this must be weighed against the harms in terms of treatment-related mortality and morbidity and an associated decrease in quality of life.

9.3.8.2 Quality of the evidence

Network meta-analyses (NMA) provided moderate quality evidence that second line chemotherapy improves overall survival compared to best supportive care but low quality evidence about treatment related morbidity and mortality. Second line chemotherapy was associated with an increased risk of neutropaenia compared to best supportive care, but the evidence about nausea, neutropaenic sepsis, diarrhoea and treatment related mortality was uncertain, largely due to low event rates. The group thought here was insufficient evidence to recommend a specific chemotherapy regimen and instead made a general recommendation about second line chemotherapy.

9.3.8.3 Consideration of benefits and harms

The evidence for second-line chemotherapy showed that chemotherapy appeared to improve overall survival compared to supportive care. There was some evidence for increased adverse events such as nausea, neutropaenia and neutropaenic sepsis, although there was some uncertainty around this. The committee agreed the balance of benefits and harms allowed them to recommend second-line palliative chemotherapy but that it should be offered after a discussion of the risks and benefits with the patient.

While the committee agreed that there was enough evidence to recommend second-line chemotherapy, they did not think that the evidence was strong enough to be able to recommend one chemotherapy regimen over another.

The Committee considered that the recommendations are unlikely to significantly change practice and so the primary benefit of the recommendation is that it should encourage shared decision making and ensure that an informed discussion takes place with the patient. The use of second line chemotherapy could potentially improve survival and quality of life in some patients but this must bebalanced against the potential for a diminished quality of life as a result of treatment morbidity. However, it should be noted that the changes in quality of life are hypothesised since there was no evidence identified on this outcome.

There are some patients who may not benefit from treatment. Therefore, the recommendations suggest an individualised approach to treatment selection, which should ensure that the harms and benefits are appropriately balanced for each patient.

9.3.8.4 Consideration of economic benefits and harms

Two relevant studies were identified in a literature review of published cost-effectiveness analyses on this topic; Lam et al. 2016 and Meads et al. 2015. The analysis by Lam et al. 2016 suggests that chemotherapy may be a cost-effective alternative to palliative care. However the analysis was only partially applicable to the decision problem in the UK setting as they were based on the health care perspective of the United States. The analysis by Meads et al. 2015 suggests that docetaxel is not a cost-effective addition to active symptom control when considering the typical threshold of £20,000 per QALY. If the treatment was deemed to meet the end of life criteria, then the addition of docetaxel may be considered cost-effective at an increased threshold of £50,000 per QALY. However, some potentially serious limitations were identified in the analysis (including uncertainty around some of the cost estimates). Overall, the analyses indicate that chemotherapy may be cost-effective in this setting but further research is required before drawing decisive conclusions.

The economic implications of this topic were thought to be negligible as the recommendations largely reflect current clinical practice. The recommendations suggest an emphasis on patient discussion, for which there would be an associated cost. However, the committee anticipate that such discussions should already be taking place in practice and so no additional cost is expected in terms of consultation time.

If there are centres where practice is not currently in line with the recommendations then there could be increased costs associated with the use of chemotherapy (and managing the associated side effects). However, the use of chemotherapy would be expected to be cost-effective as the benefits in terms of overall and disease-free survival would be expected to translate into QALY gains.

9.3.8.5 Other considerations

The Committee were aware of the NICE technology appraisal covering ramicurimab, and since there were already NICE recommendations for ramicurimab, it was excluded from consideration in the evidence review.

9.3.8.6 Key conclusions

The Committee agreed that second line chemotherapy could be a useful treatment modality for some patients and so it should be considered. It was also thought important to make it clear that the potential risks and benefits of the treatment should be discussed with the patient to allow an informed decision to be made. This approach should help to ensure that an individualised treatment approach is taken. As this is an area where further research into emerging treatments is being considered it was also thought important to consider entry into clinical trials as an alternative to second line chemotherapy.

9.3.9 Recommendations

Second-line palliative chemotherapy for locally advanced or metastatic oesophago-gastric cancer

36. Consider second-line palliative chemotherapy for people with oesophago-gastric cancer.

37. Discuss the risks, benefits and treatment consequences of second-line palliative chemotherapy for oesophago-gastric cancer with the person and those who are important to them (as appropriate). Cover:

- how different treatments can have similar effectiveness but different side effects
- how the treatments are given
- if the person has any preference for one treatment over another.

38. Consider a clinical trial (if a suitable one is available) as an alternative to second-line chemotherapy.

9.4 Luminal obstruction

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

9.4.1 Introduction

Many people 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 aimed to evaluate and summarise the efficacy of different interventions to treat luminal obstruction in the palliation of oesophago-gastric cancer and thus identify the most effective treatment option, taking into account important outcomes such as treatment-related and disease-related morbidity and mortality and patient-reported health outcomes.

9.4.2 Description of clinical evidence

A total of 16 studies were included in this review. Evidence for oesophageal and gastric cancers were analysed separately.

9.4.2.1 Interventions for obstructive oesophageal or oesophageo-gastric cancers

Evidence from oesophageal cancers were mainly taken from the Dai 2014 systematic review (SR) which included 53 randomised controlled trials of interventions for dysphagia among patients with unresectable/inoperable oesophageal cancer. However, trials examining interventions such as chemical ablation, thermal ablative therapy, alcohol injection, argon plasma coagulation and bipolar probe electrocoagulation were excluded as they were not included in the review protocol. Apart form the full text articles with Chinese language publication, full text publication for relevant papers were checked for complete details of the outcomes. If the required outcomes were not reported in sufficient details, these studies were also excluded. In total 20 RCTs from Dai 2014 SR were included for analysis. An additional 9 RCTs relevant for obstructive oesophageal cancers were identified from database searches, meaning that a total of 29 RCTs (n=2505) were included in analyses of interventions for obstructive oesophageal or oesophageo-gastric cancers as follows:

1. Self-expanding metallic stent (SEMS) versus plastic tube (data taken from Dai 2014 SR)
    i. De Palma 1996
    ii. Knyrim 1993
    iii. O'Donnell 2002
    iv. Roseveare 1998
    v. Sanyika 1999
    vi. Shenfine 2009
    vii. Siersema 1998
2. SEMS versus laser (data taken from Dai 2014 SR)
    i. Adam 1997
    ii. Dallal 2001
3. Comparison of different types of SEMS
    a. Covered Ultraflex SEMS versus covered Wallstent SEMS (data taken from Dai 2014 SR)
        i. Sabharwal 2003
        ii. Siersema 2001
    b. Irradiation stent versus covered stent
        i. Guo 2008 (data taken from Dai 2014 SR)
        ii. Zhu 2014 (data extracted in Zhu 2014 RCT)
    c. Polyflex stent versus Ultraflex stent
        i. Conio 2007 (data extracted in Conio 2007 RCT)
        ii. Verschuur 2008 (data taken from Dai 2014 SR)
    d. Small-diameter stent versus large-diameter stent
        i. White 2015 (data extracted in White 2015 RCT)
    e. Covered Niti-S stent versus double-layered Niti-S stent
        i. Kim 2009 (data taken from Dai 2014 SR)
4. Stents versus interventions other than stents
    a. SEMS versus oesophageal bypass
        i. Horneaux 2001 (data taken from Dai 2014 SR)
    b. SEMS versus external beam radiotherapy
        i. Turrisi 2002 (data taken from Dai 2014 SR)
    c. SEMS versus SEMS plus external beam radiotherapy
        i. Javed 2012 (data taken from Dai 2014 SR)
    d. SEMS versus laser plus radiotherapy

i. Konigsrainer 2000 (data taken from Dai 2014 SR)

e. SEMS versus laser followed by SEMS
   i. Konigsrainer 2000 (data taken from Dai 2014 SR)

f. SEMS plus brachytherapy versus brachytherapy alone
   i. Amdal 2013 (data taken from Dai 2014 SR)

5. Comparisons of dilatation, intubation, radiation or any combinations

a. Dilatation alone versus dilatation plus laser
   i. Anand 1998 (data extracted in Anand 1998 RCT)

b. Intraluminal radiotherapy (ILRT) versus ILRT plus 5-fluorouracil
   i. Dinshaw 1991 (data extracted in Dinshaw 1991 RCT)

c. Dilatation plus radiotherapy versus dilatation alone
   i. Kharadi 1997 (data extracted in Kharadi 1997 RCT)

d. External beam re-irradiation versus endoscopic dilatation
   i. Teli 2008 (data extracted in Teli 2008 RCT)

e. Different doses of radiotherapy
   i. Sur 1998 (data extracted in Sur 1998 RCT)
   ii. Sur 2002 (data extracted in Sur 2002 RCT)

f. Brachytherapy versus bachytherapy plus external radiotherapy
   i. Rosenblatt 2010 (data taken from Dai 2014 SR)
   ii. Sur 2004 (data taken from Dai 2014 SR)

9.4.2.2 Interventions for obstructive gastric cancers

Evidence for obstructive gastric outlet obstructions were available from 6 different RCTs (n=366). Studies comparing covered and uncovered stents included people with gastric cancers. However, randomised studies examining stents in comparison with bypass surgery were not available and the Committee considered these interventions were of utmost clinical importance for people with gastric cancers. Thus, randomised studies including obstructive gastric outlet obstruction from various nearby structural cancers were considered and the evidence in GRADE was downgraded by one level for indirectness.

6. Covered stent versus uncovered stent

a. Kim 2010 (data extracted in Kim 2010 RCT)

b. Lee 2015 (data extracted in Lee 2015 RCT)

c. Maetani 2014 (data extracted in Maetani 2014 RCT)

d. Shi 2014 (data extracted in Shi 2014 RCT)

7. VII. Stent versus bypass surgery
   i. Fiori 2004 (data extracted in Fiori 2004 RCT)
   ii. Jeurnink 2010 (data extracted in Jeurnink 2010 RCT)

Evidence from these are summarised in the clinical GRADE evidence profile below. See also the study selection flow chart in Appendix K, forest plots in Appendix H, study evidence tables in Appendix F and exclusion list in Appendix J.

9.4.3 Summary of included studies

A summary of the studies that were included in this review are presented in Table 167 to Table 173.

9.4.3.1 Interventions for obstructive oesophageal or oesophageo-gastric cancers

9.4.3.1.1 Self-expanding metal stent versus plastic tubes

Table 167: Summary of included studies: Self-expanding metal stent versus plastic tubes

Study	Country	n	Stent	Plastic tube	Outcomes
De Palma 1996 RCT	Italy	39	Covered Ultraflex SEMS	Wilson Cook plastic tubes	Persistent or recurrent dysphagia; Procedure-related mortality; Any procedure-related morbidity; Perforation; Haemorrhage; Fistula
Knyrim 1993 RCT	Germany	42	Wallstent uncovered stent	Wilson cook plastic tube	Persistent or recurrent dysphagia; Procedure-related mortality; Any procedure-related morbidity; Perforation; Haemorrhage; Sepsis; Fistula
O'Donnell 2002 RCT	UK	50	Covered Ultraflex and Wallstents	Cook plastic tubes	Persistent or recurrent dysphagia; 30-day mortality; any procedure-related mortality; Perforation; Haemorrhage; Fistula; Chest pain; Reflux
Roseveare 1998 RCT	UK	31	SEMS (Gianturco Z-stent)	Atkinson plastic tubes	Persistent or recurrent dysphagia; Procedure-related mortality; Any procedure-related morbidity; Perforation; Haemorrhage; Fistula
Sanyika 1999 RCT*	South Africa	40	SEMS (Wallstents)	Procter Livingstone tubes	Persistent or recurrent dysphagia; Procedure-related mortality; Any procedure-related morbidity; Perforation; Haemorrhage; Fistula; Chest pain; Sepsis; Reflux
Shenfine 2009 RCT	UK	217	SEMS (18 mm or 24 mm)	Atkinson plastic tubes	Dysphagia grade at 4 or more weeks; Persistent or recurrent dysphagia; Procedure-related mortality; any procedure-related morbidity; Perforation; Haemorrhage; Chest pain
Siersema 1998 RCT	Netherlands	75	SEMS	Celestin tubes	Dysphagia grade at 4 or more weeks; Persistent or recurrent dysphagia; Procedure-related mortality; Any procedure-related morbidity; Perforation; Haemorrhage; Fistula; Chest pain; Reflux

**recruited patients with squamous cell carcinoma only*
n=total number of participants; RCT = randomised controlled trial; SEMS=self-expanding metallic stent

Outcomes for time from intervention to recurrence of symptoms, overall survival, re-intervention, and patients' reported outcomes measures (PROMs) were not available or could not be extracted.

9.4.3.1.2 Self-expanding metal stents versus laser

Table 168: Summary of included studies: Self-expanding metal stents versus laser

Study	Country	n	Stent	Laser	Outcomes
Adam 1997 RCT	UK	60	Covered SEMS (Wall) or Strecker uncovered SEMS	Not described in details	Persistent or recurrent dysphagia; Re-intervention; Any procedure-related morbidity; Perforation; Haemorrhage; Sepsis; Fistula; Overall survival; Procedure-related mortality
Dallal 2001 RCT	UK	65	SEMS	Not described in details	Persistent or recurrent dysphagia; Re-intervention; Any procedure-related morbidity; Perforation; Haemorrhage; Sepsis; Fistula; Overall survival; Procedure-related mortality

n=total number of participants; RCT= randomised controlled trials; SEMS = self-expanding metal stents

Outcomes for symptom improvement including time from intervention to improvement of symptoms and dysphagia score, time from intervention to recurrence of symptoms, and patients' reported outcomes measures (PROMs) were not available or could not be extracted.

9.4.3.1.3 Comparisons of different types of stents

Table 169: Summary of included studies: Comparisons of different types of stents

Study	Country	n	Intervention	Comparison	Outcomes
Conio 2007 RCT	Italy, France, Germany	101	Polyflex SEMS	Ultraflex SEMS	Dysphagia score at last follow-up; Body weight at 4 weeks; Major complication; Reflux; Survival days; Days from intervention to symptom recurrence; Re-intervention; Retrosternal pain
Guo 2008 RCT	China	53	Iodine 125(^{125}I) seeds loaded SEMS	Conventional SEMS	Dysphagia score; Overall survival months; Fistula; Haemorrhage; Severe chest pain
Kim 2009 RCT	South Korea	37	Covered Niti-S stent	Double-layered Niti-S stent	Dysphagia score; Any procedure-related complication
Sabharwal 2003 RCT	UK	53	Covered Ultraflex SEMS	Covered wallstent SEMS	Change in dysphagia score; Persistent or recurrent dysphagia; Any procedure-related complication; Perforation; Haemorrhage; Reflux; Procedure-related mortality
Siersema 2001 RCT	Netherlands	100	Covered Ultraflex SEMS	Covered Wallstent SEMS	Change in dysphagia score; Persistent or recurrent dysphagia; Any procedure-related complication; Perforation; Haemorrhage; Reflux; Procedure-related mortality

Study	Country	n	Intervention	Comparison	Outcomes
Verschuur 2008 RCT	Netherlands	125	Polyflex stent	Ultraflex stent	Recurrent dysphagia; Major complication; Reflux; Retrosternal pain; Overall survival
White 2015 RCT	South Africa	100	Small-diameter (18mm shaft/23mm proximal flange) Ultraflex stent	Large-diameter (23mm shaft/28mm proximal flange) Ultraflex stent	Dysphagia score <2; Any immediate procedure-related complication; Any delayed procedure-related complication; Recurrent dysphagia; Haemorrhage; Fistula; New reflux; Overall survival at 6 months
Zhu 2014 RCT	China	160	Iodine 125(^{125}I) seeds loaded SEMS	Conventional SEMS	Dysphagia score; Overall survival; Fistula; Haemorrhage; Severe chest pain

n=total number of participants; RCT=randomised controlled trials; SEMS=self-expanding metal stent

Outcomes for time from intervention to improvement of symptoms and dysphagia score, time from intervention to recurrence of symptoms, and patients' reported outcomes measures (PROMs) were not available or could not be extracted.

9.4.3.1.4 Stents versus Interventions other than stents

Table 170: Summary of included studies: Stents versus interventions other than stents

Study	Country	n	Intervention	Comparison	Outcomes
Amdal 2013 RCT	Norway	41	SEMS+Brachy therapy	Brachytherapy	Number of patients with dysphagia improvement; Procedure-related morbidity
Horneaux 2001 RCT*	Brazil	40	SEMS (Esophacoil)	Posthelwaite surgical bypass	Dysphagia score
Javed 2012 RCT	India	84	Covered Ultraflex stent	Stent+EBRT	Mean dysphagia free interval; Overall survival
Konigsrainer 2000 RCT**	Austria	39	SEMS (Wallstent)	Limited Laser followed by SEMS (or) Laser+EBRT	Dysphagia score; Recurrent dysphagia
Turrisi 2002 RCT	USA	32	Ultraflex SEMS	EBRT	Overall survival days

**Included only people with stage III, IV squamous cell carcinoma of oesophagus; **three-armed study*
n=total number of participants; EBRT=External beam radiotherapy; RCT=randomised controlled trial; SEMS=self-expanding metal stent;

Outcomes for time from intervention to improvement of symptoms and dysphagia score, time from intervention to recurrence of symptoms, re-intervention, procedure-related mortality and patients' reported outcomes measures (PROMs) were not available or could not be extracted.

9.4.3.1.5 Comparisons of dilatation, intubation, radiation or any combinations

Table 171: Summary of included studies: Comparisons of dilatation, intubation, radiation or any combinations

Study	Country	n	Intervention	Comparison	Outcomes
Anand 1998 RCT*	USA	15	Dilatation by "Through The Scope" (TTS) balloons, Savary dilators or both	Dilatation (same as intervention) +Laser therapy by Nd-YAG laser	Re-intervention; Dysphagia score at 2 months; Survival rate at 30 months
Dinshaw 1991 RCT	India	50	ILRT alone (2500 cGy in 13 hours)	ILRT (same as intervention)+ 5 FU (500 mg/m2 for 24 hours)	Complete tumor regression (detected by barium swallow and negative biopsy); Overall survival at 2 years
Kharadi 1997 RCT*	India	104	Dilatation (by Savary dilators)/ Intubation (by Prosthetic tube) + Radiotherapy	Dilatation or Intubation (same as intervention)	Body weight at 6 months; ECOG performance score of 2 or more at one month; Survival months
Rosenblatt 2010 RCT	Austria	219	HDR brachytherapy	HDR brachytherapy+ EBRT	Strictures; Fistula; Dysphagia relief experience
Sur 1998 RCT	South Africa	172	HDR radiotherapy - 16 Gy in 2 fractions**	HDR radiotherapy - 18Gy in 3 fractions**	Dysphagia free survival rate; Overall survival rate at 12 months; Strictures; Persistent dysphagia; Fistula
Sur 2002 RCT	South Africa, Poland and India	232	HDR radiotherapy - 16Gy in 2 fractions ***	HDR radiotherapy - 18Gy in 3 fractions***	Median survival days; Fistula; Strictures; Patients necessitating additional treatment
Sur 2004 RCT	South Africa	60	Brachytherapy (16Gy in 2 fractions over 3 days)	Brachytherapy followed by EBRT (30Gy over 2 weeks)	Strictures; Fistula
Teli 2008 RCT****	India	69	Re-irradiation – depending on ther interval after perious radiotherapy	Dilatation by Savary-Gillard dilatators	Number of people with dysphagia grade 2 or more at 4 weeks; Overall survival; Oeophagitis; Acute chest pain; Chest infection; Hemetemesis; Recurrent chest infection; Fistula; Tumour bleed

**Included only people with squamous cell carcinoma of oesophagus*

***Given one fraction per week*

****Given on alternate day*

*****Included people with history of radical EBRT with a time interval of at least 6 months between initial radical radiotherapy and irradiation treatment protocol*

n=total number of participants; EBRT=external beam radiotherapy; ECOG= Eastern cooperative oncology group; 5FU=5-Fluorouracil; HDR=high dose rate; ILRT=intraluminal radiotherapy; RCT=randomised controlled trial; SEMS=self-expanding metal stent

Outcomes for time from intervention to improvement of symptoms, dysphagia score and procedure-related mortality were unavailable or could not be extracted.

9.4.3.2 Interventions for obstructive gastric cancers

9.4.3.2.1 Covered versus uncovered stents

Table 172. Summary of included studies: Covered versus uncovered stents

Study	Country	n	Covered stent	Uncovered stent	Outcomes
Kim 2010 RCT	Korea	80	Niti-S pyloric stent or Niti-S Comvi pyloric stent	Enteral Wallstents or Wallflex duodenal stents	Clinical success; Patency at follow-up; Major complication;
Lee 2015 RCT	Korea	102	WAVE-covered SEMS*	Uncovered SEMS	Re-intervention; Overall survival
Maetani 2014 RCT	Japan	62	Triple-layered covered ComVi SEMS	Uncovered Niti-S SEMS	Clinical success; Major complication; any procedure related complication; Recurrent obstructive symptoms
Shi 2014 RCT	China	65	GOO-tailored SEMS	Standard uncovered SEMS	Clinical success; Major complication; Re-intervention; Survival days; Change in GOOSS

**Stent with anti-migration design.*
n=total number of participants; GOO=gastric outlet obstruction; GOOSS= gastric outlet obstruction scoring system; RCT=randomised controlled trial; SEMS=self-expanding metal stent

Outcomes for time from intervention to improvement of symptoms and dysphagia score, time form intervention to improvement of symptoms and recurrence of symptoms, overall survival, procedure-related mortality and patients' reported outcomes measures (PROMs) were unavailable or could not be extracted.

9.4.3.2.2 Stent versus bypass surgery

Table 173. Summary of included studies: Stent versus bypass surgery

Study	Country	n	Population	Stent	Bypass surgery	Outcomes
Fiori 2004 RCT	Italy	18	GOO due to adenocarcinoma	Covered Ultraflex SEMS	Gastroenterostomy	Minor complications; Major complications; Mortality; Relief of symptoms after 8 days or 30 days;
Jeurnink 2010 RCT	Netherlands	39	GOO due to pancreatic, biliary or gastroduodenal cancers	Enteral wallflex stent	Open or laparoscopic gastrojejunostomy	Minor complications; Major complications; Peristent or recurrent obstructive symptoms; Re-intervention

n=total number of participants
GOO=gastric outlet obstruction; RCT=randomised controlled trial; SEMS=self-expanding metal stent

Outcomes for time from intervention to recurrence of symptoms, overall survival and patients' reported outcomes measures (PROMs) were unavailable or could not be extracted.

9.4.4 Clinical evidence profile

The clinical evidence profiles for this review question are presented in Table 174 to Table 195.

9.4.4.1 Interventions for obstructive oesophageal or oesophageo-gastric cancers

9.4.4.1.1 Self-expanding metallic stent (SEMS) versus plastic tube

Table 174: Summary clinical evidence profile. Self-expanding metallic stent (SEMS) versus plastic tube

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)
	Assumed risk plastic tube	Corresponding risk SEMS			
Dysphagia improvement		The mean dysphagia improvement in the intervention groups was 0.3 lower (0.69 lower to 0.1 higher)		231 (2 studies)	moderate [1,2]
Persistent or recurrent dysphagia	495 per 1000	297 per 1000 (193 to 450)	RR 0.60 (0.39 to 0.91)	433 (7 studies)	very low [2,3,4]
Procedure mortality	83 per 1000	32 per 1000 (14 to 73)	RR 0.39 (0.17 to 0.88)	433 (7 studies)	low [3,4]
30-day mortality	268 per 1000	198 per 1000 (129 to 305)	RR 0.74 (0.48 to 1.14)	304 (4 studies)	moderate [4,5]
Procedure-related morbidity - Perforation	73 per 1000	17 per 1000 (6 to 52)	RR 0.24 (0.08 to 0.71)	433 (7 studies)	moderate[3]
Fistula	21 per 1000	16 per 1000 (4 to 70)	RR 0.76 (0.17 to 3.28)	277 (6 studies)	very low [3,6]
Procedure-related morbidity - Haemorrhage	115 per 1000	95 per 1000 (57 to 158)	RR 0.83 (0.5 to 1.38)	433 (7 studies)	very low [3,6]
Chest pain	236 per 1000	262 per 1000 (177 to 384)	RR 1.11 (0.75 to 1.63)	326 (4 studies)	very low [5,6]
Procedure-related morbidity - Sepsis	49 per 1000	10 per 1000 (0 to 192)	RR 0.20 (0.01 to 3.93)	82 (2 studies)	very low [5,6]
Reflux	79 per 1000	112 per 1000 (36 to 298)	RR 1.46 (0.43 to 4.92)	126 (3 studies)	very low [5,6]

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)
	Assumed risk plastic tube	Corresponding risk SEMS			

RR=relative risk; CI=confidence interval; SEMS=self-expanding metallic stent
[1] Randomisation with appropriate allocation concealment and blinding of participants and personnels
[2] I^2 > 50%
[3] 2 studies with unclear randomisation and 3 studies with unclear blinding
[4] 95%CI crossed one boundary of default MID
[5] Only one study was conducted in unclear randomisation
[6] 95%CI crossed 2 boundaries of 95% CI

9.4.4.1.2 Self-expanding metallic stent (SEMS) versus laser

Table 175: Summary clinical evidence profile. Self-expanding metallic stent (SEMS) versus laser

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)
	Assumed risk laser	Corresponding risk SEMS			
Persistent or recurrent dysphagia	308 per 1000	228 per 1000 (117 to 440)	RR 0.74 (0.38 to 1.43)	125 (2 studies)	very low [1,2,3]
Need of intervention for recurrent dysphagia	596 per 1000	322 per 1000 (137 to 751)	RR 0.54 (0.23 to 1.26)	125 (2 studies)	very low [1,2,3]
Procedure-related morbidity - Perforation	58 per 1000	11 per 1000 (1 to 95)	RR 0.19 (0.02 to 1.64)	125 (2 studies)	very low [1,3]
Procedure-related morbidity - Fistula	77 per 1000	12 per 1000 (2 to 104)	RR 0.15 (0.02 to 1.35)	125 (2 studies)	very low [1,3]
Procedure-related morbidity - Haemorrhage	0 per 1000	0 per 1000 (0 to 0)	RR 3.91 (0.53 to 28.66)	125 (2 studies)	very low [1,3]
Procedure-related morbidity - Sepsis	19 per 1000	42 per 1000 (7 to 270)	RR 2.2 (0.34 to 14.04)	125 (2 studies)	very low [1,3]
Procedure-related morbidity - All adverse effects	192 per 1000	346 per 1000 (179 to 667)	RR 1.8 (0.93 to 3.47)	125 (2 studies)	low [1,4]
Procedure related mortality	38 per 1000	81 per 1000 (18 to 368)	RR 2.1 (0.46 to 9.57)	125 (2 studies)	very low [1,3]
Overall survival days		The mean overall survival in the		125 (2 studies)	moderate[1]

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)
	Assumed risk laser	Corresponding risk SEMS			
		intervention groups was **7.89 higher** (24.30 lower to 40.07 higher)			

RR=relative risk; CI=confidence interval; SEMS=self-expanding metallic stent
[1] One study with unclear allocation concealment
[2] I2 > 50%
[3] 95%CI crossed 2 boundaries of default MID
[4] 95%CI crossed one boundary of default MID

9.4.4.1.3 Comparisons of different types of stents

9.4.4.1.4 Covered ultraflex SEMS versus covered wallstent SEMS

Table 176: Summary clinical evidence profile. Covered ultraflex SEMS versus covered wallstent SEMS

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)
	Assumed risk covered wallstent SEMS	Corresponding risk covered ultraflex SEMS			
Dysphagia improvement		The mean dysphagia improvement in the intervention groups was 0.15 higher (0.04 lower to 0.33 higher)		120 (2 studies)	moderate[1]
Persistent or recurrent dysphagia	182 per 1000	218 per 1000 (105 to 449)	RR 1.2 (0.58 to 2.47)	120 (2 studies)	very low [1,2]
30-day mortality	145 per 1000	167 per 1000 (73 to 384)	RR 1.15 (0.5 to 2.64)	120 (2 studies)	very low [1,2]
All adverse effects	564 per 1000	462 per 1000 (333 to 643)	RR 0.82 (0.59 to 1.14)	120 (2 studies)	low [1,3]
Adverse effects - Perforation	18 per 1000	23 per 1000 (4 to 126)	RR 1.28 (0.24 to 6.92)	120 (2 studies)	very low [1,2]
Adverse effects - Haemorrhage	73 per 1000	100 per 1000 (30 to 327)	RR 1.37 (0.41 to 4.5)	120 (2 studies)	very low [1,2]
Adverse effects - Reflux	73 per 1000	46 per 1000 (10 to 206)	RR 0.63 (0.14 to 2.83)	120 (2 studies)	very low [1,2]

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)
	Assumed risk covered wallstent SEMS	Corresponding risk covered ultraflex SEMS			
Procedure related mortality	18 per 1000	18 per 1000 (1 to 271)	RR 0.97 (0.06 to 14.88)	120 (2 studies)	very low [1,2]

RR=relative risk; CI=confidence interval; SEMS=self-expanding metallic stent
[1] One study with unclear randomisation
[2] 95%CI crossed 2 boundaries of default MID
[3] 95%CI crossed one boundary of default MID
95%CI = 95% confidence interval; SEMS=self-expanding metal stent

9.4.4.1.5 Irradiation SEMS versus Conventional SEMS

Table 177: Summary clinical evidence profile. Irradiation SEMS versus conventional SEMS

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)
	Assumed risk conventional SEMS	Corresponding risk irradiation SEMS			
Dysphagia score		The mean dysphagia score in the intervention groups was 0.12 higher (0.05 lower to 0.30 higher)		201 (2 studies)	moderate [1,2]
Overall survival	-	-	HR 0.59 (0.41 to 0.86)	148 (1 study)	moderate[2]
Severe chest pain	218 per 1000	248 per 1000 (150 to 412)	RR 1.14 (0.69 to 1.89)	201 (2 studies)	low[3]
Fistula formation	50 per 1000	69 per 1000 (24 to 200)	RR 1.39 (0.48 to 4.03)	201 (2 studies)	low[3]
Haemorrhage	119 per 1000	137 per 1000 (69 to 272)	RR 1.15 (0.58 to 2.29)	201 (2 studies)	low[3]
Overall survival months		The mean overall survival months in the intervention groups was 3.76 higher (3.19 to 4.33 higher)		53 (1 study)	high

95%CI = 95% confidence interval; SEMS=self-expanding metal stent; RR=relative risk; HR=hazard ratio
[1] appropriate randomisation with proper allocation concealment

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)
	Assumed risk conventional SEMS	Corresponding risk irradiation SEMS			

[2] 95%CI crossed one boundary of default MID
[3] 95%CI crossed 2 boundaries of default MID

9.4.4.1.6 Polyflex SEMS versus ultraflex SEMS

Table 178: Summary clinical evidence profile. Polyflex SEMS versus ultraflex SEMS

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)
	Assumed risk ultraflex SEMS	Corresponding risk polyflex SEMS			
Dysphagia score at last follow-up		The mean dysphagia score at last follow-up in the intervention groups was 0.2 higher (0.25 lower to 0.65 higher)		101 (1 study)	low [1,2]
Retrosternal pain	192 per 1000	81 per 1000 (35 to 188)	RR 0.42 (0.18 to 0.98)	105 (2 studies)	low [1,2]
Body weight at 4 weeks in kg		The mean body weight at 4 weeks in the intervention groups was 1 lower (5.3 lower to 3.3 higher)		101 (1 study)	low [1,2]
Major complications (</= 7 days)	42 per 1000	80 per 1000 (24 to 261)	RR 1.91 (0.58 to 6.27)	184 (1 study)	very low [1,3]
Major complications (> 7 days)	250 per 1000	338 per 1000 (203 to 565)	RR 1.35 (0.81 to 2.26)	184 (2 studies)	very low [1,3]
Gastro-oesophageal reflux (within a week)	31 per 1000	7 per 1000 (0 to 146)	RR 0.23 (0.01 to 4.66)	184 (2 studies)	very low [1,3]
Survival days		The mean survival days in the intervention groups was 12 higher (4.56 to 19.44 higher)		101 (1 study)	low [1,2]
Days from intervention to		The mean days from intervention to recurrence of		101 (1 study)	low [1,2]

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)
	Assumed risk ultraflex SEMS	Corresponding risk polyflex SEMS			
recurrence of symptoms		symptoms in the intervention groups was 12.86 lower (38.49 lower to 12.77 higher)			
Re-intervention rate	37 per 1000	43 per 1000 (6 to 290)	RR 1.15 (0.17 to 7.84)	101 (1 study)	very low [1,3]
Overall survival	881 per 1000	836 per 1000 (683 to 943)	HR 0.85 (0.54 to 1.35)	83 (1 study)	low[3]
Recurrent dysphagia	524 per 1000	367 per 1000 (225 to 602)	RR 0.70 (0.43 to 1.15)	83 (1 study)	moderate[2]

95%CI = 95% confidence interval; SEMS=self-expanding metal stent; kg=kilograms; RR=relative risk; HR=hazard ratio
[1] appropriate randomisation with unclear allocation concealment
[2] 95%CI crossed one boundary of default MID
[3] 95%CI crossed 2 boundaries of default MID

9.4.4.1.7 Small diameter SEMS versus Large diameter SEMS

Table 179: Summary clinical evidence profile. Small diameter SEMS vs large diameter SEMS

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)
	Assumed risk large-diameter stent	Corresponding risk Small-diameter stent			
Dysphagia score < 2	940 per 1000	940 per 1000 (855 to 1000)	RR 1 (0.91 to 1.1)	100 (1 study)	high
Immediate adverse effects (chest/back pain requiring hospitalisation, persistent dysphagia, dyspnoea, GI haemorrhage, Arrhythmia)	0 per 1000	0 per 1000 (0 to 0)	RR 5 (0.25 to 101.58)	100 (1 study)	low[1]
Recurrent dysphagia	420 per 1000	500 per 1000 (328 to 769)	RR 1.19 (0.78 to 1.83)	100 (1 study)	low[1]

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)
	Assumed risk large-diameter stent	Corresponding risk Small-diameter stent			
GI haemorrhage	120 per 1000	60 per 1000 (16 to 227)	RR 0.5 (0.13 to 1.89)	100 (1 study)	low[1]
ER fistula	100 per 1000	40 per 1000 (8 to 197)	RR 0.4 (0.08 to 1.97)	100 (1 study)	low[1]
New GERD	240 per 1000	259 per 1000 (132 to 514)	RR 1.08 (0.55 to 2.14)	100 (1 study)	low[1]
Any delayed adverse events	580 per 1000	597 per 1000 (435 to 829)	RR 1.03 (0.75 to 1.43)	100 (1 study)	low[1]
Overall survival at 6 months	300 per 1000	501 per 1000 (300 to 828)	RR 1.67 (1 to 2.76)	100 (1 study)	moderate[2]

95%CI = 95% confidence interval; SEMS=self-expanding metal stent; kg=kilograms; RR=relative risk; GERD=gastrooesophageal reflux disease; ER=oesophageo-respiratory; GI =gastrointestinal
[1] 95% CI crossed 2 boundaries of default MID
[2] 95%CI crossed one boundary of default MID

9.4.4.1.8 Covered Niti-S SEMS versus double-layered Niti-S SEMS

Table 180: Summary clinical evidence profile. Covered Niti-S SEMS versus double-layered Niti-S SEMS

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)
	Assumed risk Double-layered Niti-S stent	Corresponding risk Covered Niti-S stent			
Dysphagia score		The mean dysphagia score in the intervention groups was 0.10 higher (0.27 lower to 0.47 higher)		37 (1 study)	very low [1,2]
Procedure-related complications	118 per 1000	579 per 1000 (149 to 1000)	RR 4.92 (1.27 to 19.12)	36 (1 study)	low[1]

95%CI = 95% confidence interval; SEMS=self-expanding metal stent; RR=relative risk; MD=mean difference
[1] Randomisation method was not reported in details
[2] 95%CI crossed 2 boundaries of default MID

9.4.4.1.9 Stents versus interventions other than stents

9.4.4.1.10 SEMS versus oesophageal bypass

Table 181: Summary clinical evidence profile. SEMS versus oesophageal bypass

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)
	Assumed risk oesophageal bypass	Corresponding risk SEMS			
Dysphagia score		The mean dysphagia score in the intervention groups was 0.60 higher (0.15 to 1.05 higher)		40 (1 study)	very low [1,2]

95%CI = 95% confidence interval; SEMS=self-expanding metal stent
[1] Randomisation was not reported in details
[2] 95%CI crossed one boundary of default MID

9.4.4.1.11 SEMS versus External beam radiotherapy

Table 182: Summary clinical evidence profile. SEMS versus external beam radiotherapy

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)
	Assumed risk external beam radiotherapy	Corresponding risk SEMS			
Overall survival days		The mean overall survival days in the intervention groups was 77.13 lower (116.71 to 37.55 lower)		64 (1 study)	very low [1,2]

95%CI = 95% confidence interval; SEMS=self-expanding metal stent
[1] Unclear randomisation and no blinding
[2] 95%CI crossed one boundary of default MID

9.4.4.1.12 SEMS versus SEMS plus external beam radiotherapy

Table 183: Summary clinical evidence profile. SEMS versus SEMS plus external beam radiotherapy

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)
	Assumed risk SEMS plus external beam RT	Corresponding risk SEMS			
Mean dysphagia free survival		The mean dysphagia free survival in the intervention groups was 21.80 lower (43.63 lower to 0.03 higher)		79 (1 study)	moderate[1]
Overall survival	690 per 1000	897 per 1000 (749 to 976)	HR 1.94 (1.18 to 3.18)	79 (1 study)	moderate[1]

95%CI = 95% confidence interval; SEMS=self-expanding metal stent ; HR=hazard ratio
[1] 95%CI crossed one boundary of default MID

9.4.4.1.13 SEMS versus laser plus radiotherapy

Table 184: Summary clinical evidence profile. SEMS versus laser plus radiotherapy

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)
	Assumed risk laser plus radiotherapy	Corresponding risk SEMS			
Dysphagia score		The mean dysphagia score in the intervention groups was 0.08 higher (0.01 lower to 0.17 higher)		31 (1 study)	very low [1,2]
Recurrent dysphagia	429 per 1000	99 per 1000 (13 to 686)	RR 0.23 (0.03 to 1.60)	31 (1 study)	very low [1,3]

95%CI = 95% confidence interval; SEMS=self-expanding metal stent; RR=relative risk
[1] Unclear randomisation plus no blinding
[2] 95%CI crossed one boundary of default MID
[3] 95%CI crossed 2 boundaries of default MID

9.4.4.1.14 SEMS versus laser followed by SEMS

Table 185: Summary clinical evidence profile. SEMS versus laser followed by SEMS

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)
	Assumed risk Laser followed by SEMS	Corresponding risk SEMS			
Recurrent dysphagia	375 per 1000	101 per 1000 (11 to 787)	RR 0.27 (0.03 to 2.10)	18 (1 study)	very low [1,2]

95%CI = 95% confidence interval; SEMS=self-expanding metal stent; RR=relative risk
[1] Unclear randomisation and no blinding
[2] 95%CI crossed 2 boundaries of default MID

9.4.4.1.15 SEMS plus brachytherapy versus brachytherapy alone

Table 186: Summary clinical evidence profile. SEMS plus brachytherapy versus brachytherapy alone

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)
	Assumed risk brachytherapy alone	Corresponding risk SEMS plus brachytherapy			
Number of patients with dysphagia improvement	389 per 1000	708 per 1000 (366 to 1000)	RR 1.82 (0.94 to 3.50)	35 (1 study)	low [1,2]
Procedure-related morbidity			RR 8.59 (0.49 to 150)	41 (1 study)	very low [1,3]

95%CI = 95% confidence interval; SEMS=self-expanding metal stent; RR=relative risk
[1] Appropriate randomisation with no blinding
[2] 95%CI crossed one boundary of default MID
[3] 95%CI crossed 2 boundaries of default MID

9.4.4.1.16 Comparisons of dilatation, intubation, radiation or any combinations

9.4.4.1.17 Dilatation alone versus dilatation plus laser

Table 187: Summary clinical evidence profile. Dilatation alone versus dilatation plus laser

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)
	Assumed risk dilatation plus laser	Corresponding risk dilatation			
Number of re-intervention		The mean number of re-intervention in the intervention groups was 0.5 higher (0.45 lower to 1.45 higher)		15 (1 study)	very low [1,2]
Dysphagia score at 2 months		The mean dysphagia score at 2 months in the intervention groups was 0.1 higher (0.1 lower to 0.3 higher)		15 (1 study)	very low [1,2]
Survival rate at 30 months	250 per 1000	142 per 1000 (15 to 1000)	RR 0.57 (0.06 to 5.03)	15 (1 study)	very low [1,2]

95%CI = 95% confidence interval; SEMS=self-expanding metal stent; RR=relative risk
[1] RCT with unclear randomisation and blinding
[2] 95%CI crossed 2 boundaries of MID

9.4.4.1.18 Intraluminal radiotherapy (ILRT) versus ILRT plus 5-fluorouracil

Table 188: Summary clinical evidence profile. ILRT versus ILRT plus 5-fluorouracil

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk ILRT+5FU	Corresponding risk ILRT			
Overall survival at 2 years	240 per 1000	161 per 1000 (50 to 499)	RR 0.67 (0.21 to 2.08)	50 (1 study)	low1,2
Complete regression (on barium swallow and -ve biopsy)	1000 per 1000	880 per 1000 (750 to 1000)	RR 0.88 (0.75 to 1.04)	50 (1 study)	low1,3

95%CI = 95% confidence interval; SEMS=self-expanding metal stent; RR=relative risk; 5FU=5-fluorouracil; ILRT=intraluminal radiotherapy;
[1] unclear randomisation with appropriate concealment and unclear outcome of interest
[2] 95%CI crossed 2 boundaries of default MID
[3] 95%CI crossed one default MID

9.4.4.1.19 Dilatation plus radiotherapy versus dilatation alone

Table 189: Summary clinical evidence profile. Dilatation plus radiotherapy versus dilatation alone

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)
	Assumed risk dilatation alone	Corresponding risk dilatation plus radiotherapy			
Body weight at 6 months in kg		The mean body weight at 6 months in the intervention groups was 8.27 higher (3.81 to 12.73 higher)		39 (1 study)	low[1]
ECOG performanc escore of 2 or more at 1 month (lower, better)	659 per 1000	316 per 1000 (198 to 514)	RR 0.48 (0.3 to 0.78)	88 (1 study)	low[1]
Survival months		The mean survival months in the intervention groups was 0.34 higher (1.93 lower to 2.61 higher)		14 (1 study)	very low [1,2]

95%CI=95%confidence interval; ECOG=Eastern cooperative oncology group; RR=relative risk; MD=mean difference; kg=kilograms
[1] Unclear randomisation and blinding
[2] 95%CI crossed 2 boundaries of default MID

9.4.4.1.20 External beam re-irradiation versus Endoscopic dilatation

Table 190: Summary clinical evidence profile. External beam re-irradiation versus endoscopic dilatation

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)
	Assumed risk endoscopic dilatation	Corresponding risk external beam re-irradiation			
Dysphagia grade 2 or more at 4 weeks	914 per 1000	411 per 1000 (274 to 622)	RR 0.45 (0.3 to 0.68)	69 (1 study)	low[1]
Overall survival at the end of study	-	-	HR 0.54 (0.28 to 1.03)	69 (1 study)	low [1,2]

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)
	Assumed risk endoscopic dilatation	Corresponding risk external beam re-irradiation			
Oesophagitis within 4 weeks	257 per 1000	589 per 1000 (314 to 1000)	RR 2.29 (1.22 to 4.29)	69 (1 study)	very low [1,2]
Acute chest pain (within 24 hours of dilatation)	1000 per 1000	10 per 1000 (0 to 230)	RR 0.01 (0 to 0.23)	69 (1 study)	low[1]
Chest infection within 4 weeks	200 per 1000	118 per 1000 (38 to 366)	RR 0.59 (0.19 to 1.83)	69 (1 study)	very low [1,3]
Hemetemesis within 4 weeks	0 per 1000	0 per 1000 (0 to 0)	RR 3.09 (0.13 to 73.21)	69 (1 study)	very low [1,3]
Recurrent chest infection after 6-10 weeks	86 per 1000	236 per 1000 (68 to 813)	RR 2.75 (0.79 to 9.49)	69 (1 study)	very low [1,3]
Tracheooesophageal fistula after 6-10 weeks	171 per 1000	14 per 1000 (0 to 231)	RR 0.08 (0 to 1.35)	69 (1 study)	very low [1,3]
Tumour bleed after 6-10 weeks	143 per 1000	117 per 1000 (34 to 401)	RR 0.82 (0.24 to 2.81)	69 (1 study)	very low [1,3]

95%CI=95%confidence interval; RR=relative risk; HR=hazard ratio
[1] Randomisation method was not reported in details
[2] 95%CI crossed one boundary of default MID
[3] 95%CI crossed 2 boundaries of default MID

9.4.4.1.21 Different doses of radiotherapy

Table 191: Summary clinical evidence profile. 16Gy per 2 fractions within 3 days versus 18 Gy per 3 fractions within 5 days

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)
	Assumed risk 18 Gy per 3 fractions within 5 days	Corresponding risk 16Gy per 2 fractions within 3 days			
Tracheo-oesophageal fistula	115 per 1000	93 per 1000 (43 to 202)	RR 0.81 (0.37 to 1.75)	222 (1 study)	very low [1,2]
Fibrous strictures	125 per 1000	101 per 1000 (49 to 213)	RR 0.81 (0.39 to 1.7)	222 (1 study)	very low [1,2]

Patients necessitation additional treatment	900 per 1000	738 per 1000 (612 to 891)	RR 0.82 (0.68 to 0.99)	100 (1 study)	very low [1,3]

95%CI =95% confidence interval; RR=relative risk
[1] inappropriate randomisation with unclear allocation concealment and blinding
[2] 95%CI crossed two boundaries of default MID
[3] 95%CI crossed one boundary of default MID

Table 192: Summary clinical evidence profile. 16Gy per 2 fractions versus 18Gy per 3 fractions (delivered one fraction per week)

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)
	Assumed risk 18Gy /3fract weekly	Corresponding risk 16Gy/2fract weekly			
Overall survival rate at 12 months	345 per 1000	235 per 1000 (131 to 418)	RR 0.68 (0.38 to 1.21)	115 (1 study)	very low [1,2]
Dysphagia free survival rate	382 per 1000	248 per 1000 (145 to 435)	RR 0.65 (0.38 to 1.14)	115 (1 study)	very low [1,2]
Strictures	418 per 1000	251 per 1000 (146 to 427)	RR 0.6 (0.35 to 1.02)	115 (1 study)	very low [1,2]
Persistent disease	73 per 1000	67 per 1000 (17 to 254)	RR 0.92 (0.24 to 3.49)	115 (1 study)	very low [1,3]
Fistula	109 per 1000	34 per 1000 (7 to 158)	RR 0.31 (0.06 to 1.45)	115 (1 study)	very low [1,3]

CI=confidence interval; RR=relative risk
[1] Inappropriate randomisation and no blinding
[2] 95%CI crossed one boundary of default MID
[3] 95%CI crossed 2 boundaries of default MID

9.4.4.1.22 Brachytherapy versus brachytherapy plus radiotherapy

Table 193: Summary clinical evidence profile. Brachytherapy versus brachytherapy plus radiotherapy

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)
	Assumed risk brachytherapy plus radiotherapy	Corresponding risk brachytherapy			
Adverse effects - Stricture	58 per 1000	82 per 1000 (10 to 653)	RR 1.43 (0.18 to 11.34)	277 (2 studies)	very low [1,2,3]
Adverse effects - Fistula	72 per 1000	78 per 1000 (19 to 313)	RR 1.09 (0.27 to 4.35)	277 (2 studies)	very low [1,3]

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)
	Assumed risk brachytherapy plus radiotherapy	Corresponding risk brachytherapy			

95%CI=95%Confidence interval; RR=relative risk
[1] Both studies with no clear randomisation and no blinding
[2] I2> 50%
[3] 95%CI crossed 2 boundaries of default MID

9.4.4.2 Interventions for obstructive gastric cancers

9.4.4.2.1 Covered stent versus uncovered stent

Table 194: Summary clinical evidence profile. Covered stent versus uncovered stent

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)
	Assumed risk uncovered stent	Corresponding risk covered stent			
Clinical success	922 per 1000	922 per 1000 (849 to 996)	RR 1 (0.92 to 1.08)	207 (3 studies)	low[1]
Clinical success - GOO-tailored stent vs Standard uncovered stent	938 per 1000	938 per 1000 (825 to 1000)	RR 1 (0.88 to 1.13)	65 (1 study)	low[2]
Clinical success - Covered pyloric stent vs uncovered pyloric stent	915 per 1000	915 per 1000 (824 to 1000)	RR 1 (0.9 to 1.11)	142 (2 studies)	moderate[3]
Patency at final follow-up	361 per 1000	451 per 1000 (253 to 809)	RR 1.25 (0.7 to 2.24)	67 (1 study)	very low [4,5]
Major complication	29 per 1000	118 per 1000 (38 to 362)	RR 4.06 (1.32 to 12.44)	207 (3 studies)	low[1]
Major complication - GOO-tailored covered stent vs Standard uncovered stent	62 per 1000	333 per 1000 (80 to 1000)	RR 5.33 (1.28 to 22.2)	65 (1 study)	low[2]
Major complication - Covered pyloric stent vs	14 per 1000	33 per 1000 (5 to 217)	RR 2.33 (0.35 to 15.42)	142 (2 studies)	very low [3,5]

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)
	Assumed risk uncovered stent	Corresponding risk covered stent			
Uncovered pyloric stent					
Reintervention rate	304 per 1000	119 per 1000 (58 to 240)	RR 0.39 (0.19 to 0.79)	144 (2 studies)	low[6]
Reintervention rate - WAVE-covered SEMS vs Uncovered SEMS	378 per 1000	144 per 1000 (61 to 333)	RR 0.38 (0.16 to 0.88)	79 (1 study)	low [4,7]
Reintervention rate - GOO-tailored stent vs uncovered stent	219 per 1000	92 per 1000 (26 to 322)	RR 0.42 (0.12 to 1.47)	65 (1 study)	very low [5,8]
Adverse events	323 per 1000	194 per 1000 (81 to 468)	RR 0.6 (0.25 to 1.45)	62 (1 study)	very low [5,9]
Overall survival	676 per 1000	502 per 1000 (318 to 723)	HR 0.62 (0.34 to 1.14)	79 (1 study)	low [4,7]
Recurrent obstructive symptoms	290 per 1000	32 per 1000 (3 to 241)	RR 0.11 (0.01 to 0.83)	62 (1 study)	low [7,9]
Survival days		The mean survival days in the intervention groups was 19 higher (8.06 to 29.94 higher)		65 (1 study)	very low [7,8]
Gastric outlet obstruction score (GOOSS) change		The mean gastric outlet obstruction score (goos) change in the intervention groups was 0.1 higher (0.12 lower to 0.32 higher)		65 (1 study)	very low [7,8]

95%CI=95%confidence interval; GOO=Gastric outlet obstruction; GOOSS=Gastric outlet obstruction scoring system; SEMS=self-expanding metal stent; RR=relative risk; HR=Hazard ratio

[1] All 3 studies unclear or inappropriate randomization and unclear blinding

[2] RCT with inappropriate randomisation and unclear blinding

[3] One study unclear randomisation and another study with unclear allocation concealment

[4] One study with unclear allocation concealment and unclear blinding

[5] 95%CI crossed 2 boundaries of default MID

[6] one study with unclear randomization, one study with inappropriatre randomisation and unclear blinding

[7] 95%CI crossed one boundary of MID

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)
	Assumed risk uncovered stent	Corresponding risk covered stent			

[8] *one study with inappropriate randomisation*
[9] *One study with unclear randomisation and blinding*

9.4.4.2.3 Stent versus bypass surgery

Table 195: Summary clinical evidence profile. Stent versus bypass surgery

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)
	Assumed risk gastroenter-ostomy	Corresponding risk stent			
Mortality at 3-month follow-up			No event in either arm	18 (1 study)	Very low[1,2,6]
Minor complications	222 per 1000	162 per 1000 (58 to 469)	RR 0.73 (0.26 to 2.11)	57 (2 studies)	very low [2,3,4]
Major complication	37 per 1000	125 per 1000 (21 to 737)	RR 3.37 (0.57 to 19.9)	57 (2 studies)	very low [2,3,4]
Relief of symptoms after 8 days	667 per 1000	887 per 1000 (533 to 1000)	RR 1.33 (0.8 to 2.23)	18 (1 study)	very low [1,3,4]
Persistent obstructive symptoms	167 per 1000	143 per 1000 (33 to 622)	RR 0.86 (0.2 to 3.73)	39 (1 study)	very low [3,4,5]
Recurrent obstructive symptom	56 per 1000	238 per 1000 (31 to 1000)	RR 4.29 (0.55 to 33.38)	39 (1 study)	very low [3,4,5]
Re-intervention	111 per 1000	333 per 1000 (79 to 1000)	RR 3 (0.71 to 12.66)	39 (1 study)	very low [3,4,5]
Mean time for oral intake		The mean time for oral intake in the intervention groups was 4.20 lower (5.53 to 2.87 lower)		18 (1 study)	very low [1,3]

95%CI =95%confidence interval; RR=relative risk;
[1] *Inappropriate randomisation and no blinding*
[2] *Only one study with inappropriate randomisation but no blinding in both studies*
[3] *Majority people with gastric outlet obstruction from non-gastric origin*
[4] *95%CI crossed 2 boundaries of default MID*
[5] *appropriate randomisation but no blinding*
[6] *no event in either arm*

9.4.5 Economic evidence

One relevant study was identified in a literature review of published cost-effectiveness analyses on this topic; Rao et al. 2009 (see table 4 in Appendix L). The analysis considered the cost-effectiveness of stents in patients with oesophageal cancer that is unsuitable for curative resection. The base case results of Rao et al. 2009 showed that covered self-expanding metal stents were cost-effective and indeed dominant (i.e. loss costly and more effective) in comparison to uncovered self-expanding metal stents and plastic stents. Probabilistic sensitivity analysis showed that at all thresholds below $200,000 per QALY, there was a 97% probability that covered SEMS were more cost-effective than uncovered SEMS.

The analysis was deemed to be directly applicable to the decision problem in the UK setting as it was based on the health care perspective of the NHS. However, costs were converted from UK pound sterling (£) and presented in US dollars ($). Some potentially serious limitations were identified in the analysis including the absence of deterministic sensitivity analyses and a potential conflict of interest for one of the study authors. There was also a concern that uncertainty had been underestimated in the probabilistic sensitivity analysis since triangular distributions were used for all parameters and effectiveness esitmates were parameterised using variations in absolute effects rather than relative effects. Most notably, the clinical effectiveness estimates on which the analysis was based were drawn from a meta-analysis of randomised and non-randomised data. Given the lack of randomised data in this area, it is likely that the meta-analysis was primarily informed by non-randomised data thereby limiting the validity of the effectiveness estimates.

Overall, the analysis can be considered to show the potential cost-effectiveness of self-expanding metal stents over plastic stents. Furthermore the analysis suggested that covered self-expanding stents were preferable (in cost-effectiveness terms) to uncovered self-expanding stents. However, given the potential limitations of the analysis, it is difficult to draw decisive conclusions.

9.4.6 Evidence statements

9.4.6.1 Interventions for obstructive oesophageal or oesophageo-gastric cancers

9.4.6.1.1 Self-expanding metallic stent (SEMS) versus plastic tube

Dysphagia improvement

Moderate quality evidence from 2 RCTs with 231 people with obstructive oesophageal cancer showed that there was no clinically significant difference between SEMS and plastic tube for dysphagia improvement identified by dysphagia score.

Persistent or recurrent dysphagia

Very low quality evidence from 7 RCTs with 433 people with obstructive oesophageal cancer showed that there was a clinically significant beneficial effect of SEMS in comparison with plastic tube for preventing persistent or recurrent dysphagia.

Procedure-related mortality

Moderate quality evidence from 7 RCTs with 433 people with obstructive oesophageal cancer showed that there was a clinically significant beneficial effect of SEMS in comparison with plastic tube for decreasing procedure-related mortality.

30-day mortality

Moderate quality evidence from 4 RCTs with 304 people with obstructive oesophageal cancer showed that there was no clinically significant difference between SEMS and plastic tube for 30-day mortality rate.

Procedure-related morbidities (perforation, fistula, haemorrhage, chest pain, sepsis, migration, reflux, stent malfunction)

Moderate quality evidence from 7 RCTs with 433 people with obstructive oesophageal cancer showed that there was a clinically significant beneficial effect of SEMS in comparison with plastic tube for reducing the risk of all procedure-related morbidities. Moreover, subgroup analyses of procedure-related morbidities suggested that SEMS was clinically effective in reducing the risks of perforation (7 RCTs, n=433) and migration (7 RCTs, n=431) but the effects was found to have no difference in the risks of fistula formation (6 RCTs, n=277), haemorrhage (7 RCTs, n=433), sepsis (2 RCTs, n=82) and stent malfunction (7 RCTs, n=433) compared to plastic tube and the evidence was of very low quality.

Patient Reported Outcome Measures (PROMs): chest pain and gastro-oesophageal reflux

Very low quality evidence from 4 RCTs with 326 people and 3 RCTs with 126 people with obstructive oesophageal cancer showed that there was no clinically significant difference between SEMS and plastic tube for PROMs such as chest pain and reflux, respectively.

9.4.6.1.2 Self-expanding metallic stents versus laser

Persistent or recurrent dysphagia

Very low quality evidence from 2 RCTs with 125 people with obstructive oesophageal cancer showed that there was no clinically significant difference between SEMS and laser for preventing persistent or recurrent dysphagia.

Need for intervention for recurrent dysphagia

Very low quality evidence from 2 RCTs with 125 people with obstructive oesophageal cancer showed that there was no clinically significant difference between SEMS and laser for necessitating interventions for recurrent dysphagia.

Procedure-related morbidity (perforation, fistula, haemorrhage, sepsis)

Very low quality evidence from 2 RCTs with 125 people with obstructive oesophageal cancer showed that there was no clinically significant difference between SEMS and laser for preventing the risk of perforation or haemorrhage or sepsis although there may be a clinically significant beneficial effect of SEMS compared to laser for reducing the risk of fistula formation, however, there is an uncertainty around the estimate. In addition, low quality evidence also suggested that there may be a clinically significant beneficial effect of SEMS compared with laser for preventing all procedure-related morbidities, but there was an uncertainty around the estimate.

Procedure-related mortality

Very low quality evidence from 2 RCTs with 125 people with obstructive oesophageal cancer showed that there was no clinically significant difference between SEMS and laser for preventing procedure-related mortality.

Overall survival days

Moderate quality evidence from 2 RCTs with 125 people with obstructive oesophageal cancer showed that there was no clinically significant difference between SEMS and laser for the number of overall survival days.

9.4.6.1.3 Comparisons of different types of stents

9.4.6.1.4 Covered ultraflex SEMS versus covered wallstent SEMS

Dysphagia improvement

Moderate quality evidence from 2 RCTs with 120 people with obstructive oesophageal cancer reported that there was no clinically significant difference between covered ultraflex SEMS and covered wallstent SEMS for improving dysphagia mean scores.

Persistent or recurrent dysphagia

Very low quality evidence from 2 RCTs with 120 people with obstructive oesophageal cancer reported that there was no clinically significant difference between covered ultraflex SEMS and covered wallstent SEMS for preventing the risk of persistent or recurrent dysphagia.

Mortality

Very low quality evidence from 2 RCTs with 120 people with obstructive oesophageal cancer reported that there was no clinically significant difference between covered ultraflex SEMS and covered wallstent SEMS for the risk of procedure-related mortality or 30-day mortality.

All adverse effects

Very low to low quality evidence from 2 RCTs with 120 people with obstructive oesophageal cancer reported that there was no clinically significant difference between covered ultraflex SEMS and covered wallstent SEMS for preventing the risk of unspecified procedure-related morbidity or perforation or haemorrhage.

Reflux

Very low quality evidence from 2 RCTs with 120 people with obstructive oesophageal cancer reported that there was no clinically significant difference between covered ultraflex SEMS and covered wallstent SEMS for preventing the risk of reflux.

9.4.6.1.5 Irradiation stent versus covered stent

Dysphagia score

Moderate quality evidence from 2 RCTs with 201 people with obstructive oesophageal cancer reported that there was no clinically significant difference between irradiation SEMS and conventional SEMS for dysphagia score.

Overall survival

Moderate quality evidence from 1 RCT with 148 people with obstructive oesophageal cancer reported that there was a clinically significant beneficial effect of irradiation SEMS compared with conventional SEMS for improving overall survival.

High quality evidence from 1 RCT with 53 people with obstructive oesophageal cancer reported that there was a clinically significant beneficial effect of irradiation SEMS compared with conventional SEMS for improving overall survival months.

Procedure-related morbidity (fistula formation, haemorrhage)

Low quality evidence from 2 RCTs with 201 people with obstructive oesophageal cancer reported that there was no clinically significant difference between irradiation SEMS and conventional SEMS for reducing the risk of fistula formation or haemorrhage.

PROMs: Severe chest pain

Low quality evidence from 2 RCTs with 201 people with obstructive oesophageal cancer reported that there was no clinically significant difference between irradiation SEMS and conventional SEMS for decreasing the patients' report on severe chest pain.

9.4.6.1.6 Polyflex stent versus ultraflex stent

Dysphagia score at last follow-up

Low quality evidence from 1 RCT with 101 people with obstructive oesophageal cancer reported that there was no clinically significant difference between polyflex SEMS and ultraflex SEMS for mean dysphagia score at last follow-up.

Recurrent dysphagia

Moderate quality evidence from 1 RCT with 83 people with obstructive oesophageal cancer reported that there was no clinically significant difference between polyflex SEMS and ultraflex SEMS for the risk of recurrent dysphagia.

Body weight at 4 weeks

Low quality evidence from 1 RCT with 101 people with obstructive oesophageal cancer reported that there was no clinically significant difference between polyflex SEMS and ultraflex SEMS for improving body weight at 4 weeks.

Major complications

Very low quality evidence from 2 RCTs with 184 people with obstructive oesophageal cancer reported that there was no clinically significant difference between polyflex SEMS and ultraflex SEMS for preventing early major complications (<7 days) or late major complications (>7 days).

Re-intervention rate

Very low quality evidence from 1 RCT with 101 people with obstructive oesophageal cancer reported that there was no clinically significant difference between polyflex SEMS and ultraflex SEMS for preventing the risk of re-intervention.

PROMs: retrosternal pain and gastro-oesophageal reflux

Very low to low quality evidence from 2 RCTs with 184 people with obstructive oesophageal cancer reported that although there was a clinically significant beneficial effect of polyflex SEMS compared with ultraflex SEMS for decreasing patients' reports of retrosternal pain, there was no clinically significant difference between these two groups for patients' reports of gastrooesophageal reflux.

Survival

Low quality evidence from 1 RCT with 101 people with obstructive oesophageal cancer reported that there was a clinically significant beneficial effect of polyflex SEMS compared with ultraflex SEMS for improving survival days. However, low quality evidence from another RCT with 83 people with obstructive oesophageal cancer show no clinically significant difference between these two stents for overall survival.

9.4.6.1.7 Small-diameter stent versus large-diameter stent

Dysphagia score < 2

High quality evidence from 1 RCT with 100 people with obstructive oesophageal cancer showed that there was no clinically significant difference between small-diameter stent and large-diameter stent for the number of patients with dysphagia score <2.

Immediate adverse effects (chest/back pain requiring hospitalisation, persistent dysphagia, dyspnoea, GI haemorrhage, arrhythmias)

Low quality evidence from 1 RCT with 100 people with obstructive oesophageal cancer showed that there was no clinically significant difference between small-diameter stent and large-diameter stent for the number of patients with immediate procedure-related complications.

PROMs: new gastro-oesophageal reflux disease

Low quality evidence from 1 RCT with 100 people with obstructive oesophageal cancer showed that there was no clinically significant difference between small-diameter stent and large-diameter stent for the number of patients with new gastro-oesophageal reflux disease.

Any delayed adverse effect (GI haemorrhage, oesophago-respiratory fistula)

Low quality evidence from 1 RCT with 100 people with obstructive oesophageal cancer showed that there was no clinically significant difference between small-diameter stent and large-diameter stent for the number of patients with unspecified procedure-related morbidities or GI haemorrhage or oesophago-respiratory fistula.

Recurrent dysphagia

Low quality evidence from 1 RCT with 100 people with obstructive oesophageal cancer showed that there was no clinically significant difference between small-diameter stent and large-diameter stent for the number of patients with recurrent dysphagia.

Overall survival at 6 months

Moderate quality evidence from 1 RCT with 100 people with obstructive oesophageal cancer showed that there was no clinically significant difference between small-diameter stent and large-diameter stent for overall survival at 6 months.

9.4.6.1.8 Covered Niti-S stent versus double-layered Niti-S stent

Dysphagia score

Very low quality evidence from 1 RCT with 37 people with obstructive oesophageal cancer showed that there was no clinically significant difference between covered Niti-S stent and double-layered Niti-S stent for mean dysphagia score.

Procedure-related complications

Low quality evidence from 1 RCT with 37 people with obstructive oesophageal cancer showed that there was a clinically significant harmful effect of covered Niti-S stent compared with double-layered Niti-S stent for increased procedure-related complications such as tumour overgrowth, stent migration, gastro-oesophageal reflux and haemorrhage.

9.4.6.1.9 Stents versus interventions other than stents

9.4.6.1.10 SEMS versus oesophageal bypass

Dysphagia score

Very low quality evidence from 1 RCT with 40 people with obstructive oesophageal cancer showed that there was a clinically significant harmful effect of SEMS compared with oesophageal bypass for worsening dysphagia score.

9.4.6.1.11 SEMS versus external beam radiotherapy

Overall survival days

Very low quality evidence from 1 RCT with 64 people with obstructive oesophageal cancer showed that there was a clinically significant harmful effect of SEMS compared with external beam radiotherapy for decreasing mean overall survival days.

9.4.6.1.12 SEMS versus SEMS plus external beam radiotherapy

Mean dysphagia free survival

Moderate quality evidence from 1 RCT with 79 people with obstructive oesophageal cancer showed that there may be a clinically significant harmful effect of SEMS compared with SEMS plus external beam radiotherapy for decreasing mean dysphagia free survival, however, there was an uncertainty around the estimate.

Overall survival

Moderate quality evidence from 1 RCT with 79 people with obstructive oesophageal cancer showed that there is a clinically significant harmful effect of SEMS compared with SEMS plus external beam radiotherapy for decreasing overall survival.

9.4.6.1.13 SEMS versus laser plus radiotherapy

Dysphagia score

Very low quality evidence from 1 RCT with 31 people with obstructive oesophageal cancer showed that there was no clinically significant difference between SEMS and laser plus radiotherapy for dysphagia score.

Recurrent dysphagia

Very low quality evidence from 1 RCT with 31 people with obstructive oesophageal cancer showed that there was no clinically significant difference between SEMS and laser plus radiotherapy for risk of recurrent dysphagia.

9.4.6.1.14 SEMS versus laser followed by SEMS

Recurrent dysphagia

Very low quality evidence from 1 RCT with 18 people with obstructive oesophageal cancer showed that there was no clinically significant difference between SEMS and laser followed by SEMS for risk of recurrent dysphagia.

9.4.6.1.15 SEMS plus brachytherapy versus brachytherapy alone

Number of patients with dysphagia improvement

Low quality evidence from 1 RCT with 41 people with obstructive oesophageal cancer showed that there was a clinically significant beneficial effect of SEMS plus brachytherapy compared with brachytherapy alone for the number of patients with dysphagia improvement.

Procedure-related morbidity

Low quality evidence from 1 RCT with 41 people with obstructive oesophageal cancer showed that there was no clinically significant difference between SEMS plus brachytherapy and brachytherapy alone for the risk of procedure-related morbidity.

9.4.6.2 Comparisons of dilatation, intubation, radiation or any combinations

9.4.6.2.1 Dilatation alone versus dilatation plus laser

Number of re-interventions

Very low quality evidence from 1 RCT with 15 people with obstructive oesophageal cancer reported that there was no clinically significant difference between dilatation alone and dilatation plus laser therapy for reducing the number of re-interventions.

Dysphagia score at 2 months

Very low quality evidence from 1 RCT with 15 people with obstructive oesophageal cancer reported that there was no clinically significant difference between dilatation alone and dilatation plus laser therapy for improving dysphagia score at 2 months.

Survival rate at 30 months

Very low quality evidence from 1 RCT with 15 people with obstructive oesophageal cancer reported that there was no clinically significant difference between dilatation alone and dilatation plus laser therapy for improving survival rate at 30 months.

9.4.6.2.2 Intraluminal radiotherapy (ILRT) versus ILRT plus 5-fluorouracil

Overall survival at 2 years

Low quality evidence from 1 RCT with 50 people with obstructive oesophageal cancer reported that there was no clinically significant difference between ILRT and ILRT plus 5-fluorouracil for overall survival at 2 years.

Complete regression

Low quality evidence from 1 RCT with 50 people with obstructive oesophageal cancer reported that there was no clinically significant difference between ILRT and ILRT plus 5-fluorouracil for complete regression determined by barium swallow and negative biopsy.

9.4.6.2.3 Dilatation plus radiotherapy versus dilatation alone

Body weight at 6 months

Low quality evidence from 1 RCT with 39 people with obstructive oesophageal cancer reported that there was a clinically significant beneficial effect of dilatation plus radiotherapy compared with dilatation alone for improving mean body weight at 6 months.

ECOG performance score of 2 or more at 1 month

Low quality evidence from 1 RCT with 88 people with obstructive oesophageal cancer reported that there was a clinically significant beneficial effect of dilatation plus radiotherapy compared with dilatation alone for decreasing the number of people with ECOG performance score of 2 or more at 1 month.

Survival months

Very low quality evidence from 1 RCT with 14 people with obstructive oesophageal cancer showed that there was no clinically significant difference between dilatation plus radiotherapy compared with dilatation alone for improving survival months.

9.4.6.2.4 External beam re-irradiation versus endoscopic dilatation

Dysphagia grade 2 or more at 4 weeks

Low quality evidence from 1 RCT with 69 people with obstructive oesophageal cancer showed that there was a clinically significant beneficial effect of external beam re-irradiation compared with endoscopic dilatation alone for the number of patients with dysphagia score 2 or more at 4 weeks.

Overall survival at the end of the study

Low quality evidence from 1 RCT with 69 people with obstructive oesophageal cancer showed that there may be a clinically significant beneficial effect of external beam re-irradiation compared with endoscopic dilatation alone for overall survival at the end of the study but there is an uncertainty around the estimate.

Procedure-related morbidity (oesophagitis, chest infection, haematemesis within 4 weeks)

Very low quality evidence from 1 RCT with 69 people with obstructive oesophageal cancer showed that there was a clinically significant harmful effect of external beam re-irradiation compared with endoscopic dilatation alone for the number of patients with oesophagitis at 4 weeks follow-up.

Low quality evidence from 1 RCT with 69 people with obstructive oesophageal cancer showed that there was no clinically significant beneficial effect of external beam re-irradiation compared with endoscopic dilatation alone for the number of patients with chest infection or haematemesis within 4 weeks.

Acute chest pain (within 24 hours of dilatation)

Low quality evidence from 1 RCT with 69 people with obstructive oesophageal cancer showed that there was a clinically significant beneficial effect of external beam re-irradiation compared with endoscopic dilatation alone for the number of patients with acute chest pain within 24 hours of dilatation.

Recurrent chest infection or tumour bleed after 6 – 10 weeks

Very low quality evidence from 1 RCT with 69 people with obstructive oesophageal cancer showed that there was no clinically significant difference between external beam re-irradiation and endoscopic dilatation alone for the number of patients with recurrent chest infection or tumour bleed after 6-10 weeks of procedure.

Tracheo-oesophageal fistula after 6 – 10 weeks

Very low quality evidence from 1 RCT with 69 people with obstructive oesophageal cancer showed that there was no clinically significant difference between external beam re-irradiation and endoscopic dilatation alone for the number of patients with tracheo-oesophageal fistula after 6-10 weeks of procedure

9.4.6.2.5 Different doses of radiotherapy (RT)

16Gy per 2 fractions within 3 days versus 18 Gy per 3 fractions within 5 days

Tracheo-oesophageal fistula

Very low quality evidence from 1 RCT with 222 people with obstructive oesophageal cancer showed that there was no clinically significant difference between 16 Gy per 2 fractions within 3 days and 18 Gy per 3 fractions within 5 days for decreasing the risk of trachea-oesophageal fistula.

Fibrous strictures

Very low quality evidence from 1 RCT with 222 people with obstructive oesophageal cancer showed that there was no clinically significant difference between 16 Gy per 2 fractions

within 3 days and 18 Gy per 3 fractions within 5 days for decreasing the risk of fibrous strictures.

Patients necessitating additional treatment

Very low quality evidence from 1 RCT with 100 people with obstructive oesophageal cancer showed that there was a clinically significant beneficial effect of 16 Gy per 2 fractions within 3 days compared with 18 Gy per 3 fractions within 5 days for decreasing the number of patients necessitating additional treatment.

16Gy/2 fractions weekly versus 18Gy/3 fractions weekly

Dysphagia free survival rate at 12 months

Very low quality evidence from 1 RCT with 115 people with obstructive oesophageal cancer showed that there was no clinically significant difference between 16 Gy per 2 fractions weekly and 18 Gy per 3 fractions weekly for dysphagia free survival rate at 12 months.

Persistent disease

Very low quality evidence from 1 RCT with 115 people with obstructive oesophageal cancer showed that there was no clinically significant difference between 16 Gy per 2 fractions weekly and 18 Gy per 3 fractions weekly for persistent disease.

Procedure-related complication: fistula or strictures

Very low quality evidence from 1 RCT with 115 people with obstructive oesophageal cancer showed that there was no clinically significant difference between 16 Gy per 2 fractions weekly and 18 Gy per 3 fractions weekly for fistula although there may be a clinically significant beneficial effect of 16 Gy per 2 fractions weekly compared with 18 Gy per 3 fractions weekly for decreased risk of strictures.

Overall survival rate at 12 months

Very low quality evidence from 1 RCT with 115 people with obstructive oesophageal cancer showed that there was no clinically significant difference between 16 Gy per 2 fractions weekly and 18 Gy per 3 fractions weekly for overall survival rate at 12 months.

9.4.6.2.6 Brachytherapy versus brachytherapy plus radiotherapy

Procedure-related morbidity (stricture, fistula)

Very low quality evidence from 2 RCTs with 106 people with obstructive oesophageal cancer reported that there was no clinically significant difference between brachytherapy and brachytherapy plus radiotherapy for preventing the risk of stricture or fistula.

9.4.6.3 Interventions for obstructive gastric cancers

9.4.6.3.1 Covered versus uncovered stent

Clinical success

Low quality evidence from 3 RCTs with 207 people with gastric outlet obstruction (GOO) from gastric cancer showed that there was no clinically significant difference between covered stent (or GOO-tailored covered stent; 1 RCT with 65 patients) and standard uncovered stent for clinical success rate.

Patency at final follow-up

Very low quality evidence from 1 RCT with 207 people with gastric outlet obstruction from gastric cancer showed that there was no clinically significant difference between covered pyloric stent and standard uncovered pyloric stent for patency of final follow-up.

Major complications

Low quality evidence from 3 RCTs with 207 people with gastric outlet obstruction from gastric cancer showed that there was a clinically significant harmful effect of covered stent compared with standard uncovered stent for increasing major complication rate.

Subgroup analyses according to type of stent

Low quality evidence from 1 RCT with 65 people with gastric outlet obstruction from gastric cancer showed that there was a clinically significant harmful effect of GOO-tailored covered stent compared with standard uncovered stent for increasing major complication rate whereas very low quality evidence from 2 RCTs with 142 people with gastric outlet obstruction from gastric cancer showed that there was no clinically significant difference between unspecified covered stent and standard uncovered stent for major complication rate.

Re-intervention rate

Low quality evidence from 2 RCTs with 144 people with gastric outlet obstruction from gastric cancer showed that there was a clinically significant beneficial effect of covered stent compared with standard uncovered stent for decreasing the risk of re-intervention.

Subgroup analyses according to type of stent

Low quality evidence from 1 RCT with 79 people with gastric outlet obstruction from gastric cancer showed that there was a clinically significant beneficial effect of WAVE-covered stent compared with standard uncovered stent for decreasing the risk of re-intervention whereas very low quality evidence from 1 RCT with 65 people with gastric outlet obstruction from gastric cancer showed that there was no clinically significant difference between GOO-tailored covered stent and standard uncovered stent for re-intervention risk.

Adverse events

Very low quality evidence from 1 RCT with 62 people with gastric outlet obstruction from gastric cancer showed that there was no clinically significant difference between covered pyloric stent compared with standard uncovered pyloric stent for risk of adverse events such as occlusion, migration and stent fracture.

Survival (overall survival or survival days)

Low quality evidence from 1 RCT with 79 people with gastric outlet obstruction from gastric cancer showed that there was no clinically significant beneficial effect of WAVE-covered stent and standard uncovered stent for overall survival.

Very low quality evidence from 1 RCT with 65 people with gastric outlet obstruction from gastric cancer showed that there was a clinically significant harmful effect of GOO-tailored covered stent compared with standard uncovered stent for decreasing survival days.

Change in GOO scoring system

Very low quality evidence from 1 RCT with 65 people with gastric outlet obstruction from gastric cancer showed that there was no clinically significant difference between GOO-tailored covered stent and standard uncovered stent for change in GOO scoring system.

9.4.6.3.2 Stent versus bypass surgery

Time for oral intake

Low quality evidence from 1 RCT with 187 people with gastric outlet obstruction from gastric cancer showed that there was a clinically significant beneficial effect of stent compared with bypass surgery for earlier gain of oral intake after intervention.

Minor complications

Very low quality evidence from 2 RCTs with 57 people with gastric outlet obstruction from gastric cancer showed that there was no clinically significant difference between stent and bypass surgery for minor complications.

Major complications

Very low quality evidence from 2 RCTs with 57 people with gastric outlet obstruction from gastric cancer showed that there was no clinically significant difference between stent and bypass surgery for major complications.

Gastric emptying time after 8 days

Very low quality evidence from 1 RCT with 18 people with gastric outlet obstruction from gastric cancer showed that there was no clinically significant difference between stent and bypass surgery for gastric emptying time after 8 days of intervention.

Persistent or recurrent obstructive symptoms

Very low quality evidence from 1 RCT with 39 people with gastric outlet obstruction from gastric cancer showed that there was no clinically significant difference between stent and bypass surgery for persistent or recurrent obstructive symptoms.

Re-intervention

Very low quality evidence from 1 RCT with 39 people with gastric outlet obstruction from gastric cancer showed that there was no clinically significant difference between stent and bypass surgery for re-intervention rate.

Mortality at 3-months follow-up

Low quality evidence from 1 RCT with 18 people with gastric outlet obstruction from gastric cancer showed that there was no event of death in either endoscopic stent or gastroenterostomy arm.

9.4.7 Evidence to recommendations

9.4.7.1 Relative value placed on the outcomes considered

Management of luminal obstruction is a palliative procedure, and thus the critical outcomes considered by the Committee for this topic were symptom improvement (which was primarily a reflection of dysphagia), time to symptom recurrence and procedure-related morbidity.

Important outcomes were overall survival, procedure-related mortality and re-intervention rates. As dysphagia and the inability to eat or drink can have a serious impact on quality of life, the Committee were also interested in patient reported outcomes such as health-related quality of life. However, no evidence that reported this as an outcome was identified for inclusion in the review.

9.4.7.2 Quality of the evidence

The clinical evidence for this review comprises 35 randomised controlled studies which were assessed using GRADE and the overall quality of the evidence ranged from very low to moderate.

The Committee noted that some of the trials included comparisons between interventions that had been included in the protocol but were seldom used in routine clinical practice (such as dilation, rigid plastic stents, laser therapy and photodynamic therapy, PDT) which made comparisons with currently used interventions (such as expanding metal stents) more difficult to interpret. The Committee therefore focussed their review of the evidence on the comparisons of interventions for luminal obstruction that they regarded as treatment options in current practice. These included radiotherapy and the use of self-expanding metal stents (SEMSs). The quality of the studies comparing SEMS and external beam radiotherapy were of very low quality, the combination of SEMS and external beam radiotherapy compared to SEMS alone was from moderate quality studies, and the use of different doses of external beam radiotherapy was also from very low quality studies.

For gastric outlet obstruction, the Committee focused on the evidence for the use of covered versus uncovered stents, where all the evidence was of low quality (for clinical success, complications, or overall survival) or very low (patency and adverse events), and the evidence for bypass surgery where it was of low quality (time for oral intake, mortality at 3 months) or very low (all other outcomes).

9.4.7.3 Consideration of benefits and harms

In oesophageal cancer, the use of expanding metal stents and radiotherapy were shown to lead to significant symptom improvement, with the possibility of improved survival, with radiotherapy or the combination of stents and radiotherapy. Although not included in the evidence available for this review, the Committee knew from their clinical experience that a proactive approach to stenting would reduce emergency admissions for dysphagia and improve quality of life in patients who were receiving palliative treatment only.

The Committee agreed that the potential harms of their recommendations included the risk of complications associated with stenting, and the potential adverse effects due to additional radiotherapy. However, the Committee agreed that the potential benefits outweighed the risks and stenting and/or radiotherapy were likely to lead improved overall outcomes for patients.

For gastric outflow obstruction, the comparisons available from the evidence were for covered and uncovered stents. There was no difference in the clinical success or patency with uncovered versus covered, there was no difference in overall survival, but major complication rates were higher with covered stents and re-intervention rates were higher with uncovered stents.

In the comparison of stents with bypass surgery, stenting led to earlier gain of oral intake, and there was no difference in the complication rates, recurrent symptoms or re-intervention rates.

The Committee agreed that either stenting or surgery would offer benefits to patients and that any potential adverse effects of the procedures would be outweighed by the benefits of relieving the gastric outflow obstruction.

9.4.7.4 Consideration of economic benefits and harms

One relevant UK study was identified in a literature review of published cost-effectiveness analyses on oesophageal stenting; Rao et al. 2009. The analysis suggested that self-expanding metal stents were cost-effective in comparison to plastic stents. Furthermore the analysis suggested that covered self-expanding stents were preferable (in cost-effectiveness terms) to uncovered self-expanding stents.However, some potentially serious limitations were identified in the analysis, which limited the validity of the conclusions that could be drawn from the analysis. Most notably, the clinical effectiveness estimates on which the analysis was based were drawn from a meta-analysis of randomised and non-randomised data. Given the lack of randomised data in this area, it is likely that the meta-analysis was primarily informed by non-randomised data thereby limiting the validity of the effectiveness estimates. Furthermore, while the probabilistic sensitivity analysis suggested that the probability of covered self-expanding stents being cost-effective was very high, there were concerns that uncertainty had not been fully captured. Triangular distributions were used for all parameters in the probabilistic sensitivity analysis and effectiveness esitmates were parameterised using variations in absolute effects rather than relative effects.

The resource implications of this recommendations were considered but not thought to be substantial as they reflect current clinical practice where radiotherapy or stenting are typically used to manage luminal obstruction. There is the potential for additional costs if there are centres not currently offering these interventions. In such cases, the Committee considered that the additional costs of stenting and radiotherapy would be offset, at least partially, by a reduction in emergency admissions due to dysphagia.

9.4.7.5 Other considerations

The Committee agreed that their recommendations would lead to a minimal change in practice, as plastic stents, dilatation, laser therapy and PDT were no longer widely used in clinical practice, and that luminal obstruction was already treated in most centres using expanding metal stents and radiotherapy.

9.4.7.6 Key conclusions

Among people with oesophageal cancers, expanding metal stents showed reduced overall survival (mean difference -77.13 days, 95% confidence interval -116.71 to -37.55 days) compared to external beam radiotherapy but the Committee discussed the fact that placement of a stent led to immediate relief of dysphagia, whereas radiotherapy led to a temporary worsening of dysphagia, and therefore although radiotherapy may be the preferred option in terms of survival, where immediate relief of dysphagia was required, it was preferable to use a stent. They agreed that the decision of which modality to use should therefore be based on the degree of dysphagia and its impact on nutrition and quality of life.

The combination of an expanding metal stent and then external beam radiotherapy led to improved overall survival and dysphagia-free survival compared to stenting alone so the Committee were able to recommend this combination as an option.

Although there was no clinical data comparing covered and uncovered stents for oesophageal obstruction, the economic evidence suggested that covered stents might be more cost-effective. However, the Committee knew from their clinical experience that ucovered stents allowed a degress of tissue growth around the mesh of the stent which helped retain it in place. This did not happen with covered oesophageal stents, and thus they were more likely to slip out of position and cause a lower obstruction.

The Committee considered the use of stents and surgery to manage gastric outflow obstruction in gastric cancer separately. Although there was no difference in the rates of clinical success for covered and uncovered stents, rates of major complications were lower with uncovered stents and so these were recommended by the Committee. Stenting led to a

faster resumption of oral intake compared to bypass surgery, with similar rates of major and minor complications. However, the Committee knew from their clinical experience that some patients would require palliative surgery with obstructions that could not be relieved by stent insertion and so recommended both options, with the choice to be made following consideration of disease-related and patient-related factors.

9.4.8 Recommendations

Luminal obstruction in oesophageal and oesophageal-gastric junctional cancer

39. Offer self-expanding stents to people who need immediate relief of dysphagia.

40. Offer self-expanding stents or radiotherapy as primary treatment, depending on the degree of dysphagia and its impact on nutrition and quality of life, performance status and prognosis.

41. Consider external beam radiotherapy after stenting, for long-term disease control.

Outflow obstruction in gastric cancer

42. Offer uncovered self-expanding metal stents or palliative surgery, depending on fitness to undergo surgery, prognosis and extent of disease.

10 Nutritional support

10.1 Curative treatment

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

10.1.1 Introduction

Nutrition plays an important role in the management of people with oesophago-gastric cancer. Weight loss and poor nutritional status is associated with increased post-operative morbidity, mortality, longer hospital stays, increased treatment-relataed toxicity 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, and treatments also can adversely impact on nutritional status. Resection of the oesophago-gastric cancer 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 can 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 aimed to evaluate which nutritional interventions improve outcomes for adults with oesophago-gastric cancer undergoing curative treatment. In addition, since nutritional needs depend on tumour site, symptoms and previous or planned treatments, this review also aimed to investigate the patient groups most likely to benefit from nutritional interventions.

10.1.2 Description of clinical evidence

32 randomised trials were included in the review (Carey 2013, Barlow 2011, Bowrey 2015, Cong 2015, Faber 2015, Farreras 2005, Froghi 2016, Fujita 2012, Fujitani 2012, Gavazzi 2016, Ida 2017, Imamura 2016, Klek 2017, Liu 2012, Lobo 2006, Marano 2013, Miyata 2012, Miyata 2017, Okada 2017, Okamoto 2009, Page 2002, Rajabi 2015, Ryan 2009, Sakurai 2007, Sand 1997, Senkal 1997, Sultan 2012, Sunpaweravong 2014, Swails 1995, Takesu 2015, Wei 2014 and Yildiz 2016). Evidence from these are summarised in the clinical GRADE evidence profiles below. See also the study selection flow chart in Appendix K, forest plots in Appendix H, study evidence tables in Appendix F and exclusion list in Appendix J.

The studies were organised into five categories for analysis:

- Enteral nutrition versus parenteral nutrition or IV support immediately after surgery
- Immunonutrition versus standard nutrition in the perioperative period
- Oral supplements
- Additional nutritional support to mitigate toxicity during chemotherapy or chemoradiotherapy
- Continued routine nutritional support after discharge from hospital

Studies were most commonly carried out in Japan (Fujita 2012, Fujitani 2012, Ida 2017, Imamura 2016, Miyata 2012, Miyata 2017, Okada 2017, Okamoto 2009, Sakurai 2007, and Takesu 2015), Europe (Barlow 2011, Bowrey 2015, Faber 2015, Farreras 2005, Froghi 2016, Lobo 2006, Marano 2013, Page 2002, Ryan 2009, Sand 1997, Senkal 1997 and Sultan 2012) or China (Cong 2015, Liu 2012 and Wei 2014)

Studies with mixed populations were included if at least 70% of the participants had oesophago-gastric cancer (Barlow 2011, Carey 2013, Lobo 2006, Senkal 1997 and Yildiz 2016). These studies included a minority of patients with pancreatic cancer.

10.1.3 Summary of included studies

Summaries of the included studies are presented in Table 196 to Table 200.

Table 196: Summary of included studies: Trials comparing early enteral nutrition with parenteral nutrition or IV fluids after surgery

Study	Country	Diagnosis	Enteral nutrition approach	Parenteral nutrition / IV	Duration of nutrition support
Barlow 2011	UK	Oesophageal (45%), gastric (31%) or pancreatic cancer (24%)	Jejunostomy, n=64	IV fluids, n=57	POD 1-12
Fujita 2012	Japan	Oesophageal cancer	Nasojejunal feeding tube, n=76	IV, n=88	POD 1-6
Page 2002	UK	Oesophageal cancer	Nasojejunal feeding tube, n=20	IV, n=20	POD 1-6
Rajabi 2015	Iran	Oesophageal cancer	Jejunostomy, n=20	PN, n=20	POD 1-7
Sand 1997	Finland	Gastric cancer	Nasojejunal feeding tube, n=13	PN, n=16	NR
Swails 1995	USA	Oesophageal cancer	Jejunostomy, n=13	No feeding, n=12	NR
Takesu 2015	Japan	Oesophageal cancer	Jejunostomy, n=24	Central vein PN, n=23	POD 1-7

Abbreviations: EN enteral nutrition; IV intravenous; NR not reported; PN parenteral nutrition; POD post-operative day; n=number of participants

Table 197: Summary of included studies: Trials comparing immunonutrition with standard nutrition in the perioperative period

Study	Country	Diagnosis	Nutrition approach	Additional Immuno-elements	Comparison	Timing and duration
Farreras 2005	Spain	Gastric cancer	NR	Arginine, Omega-3 fatty acids and RNA, n=30	Isocaloric, isonitrogenous n=30	POD 1-7
Fujitani 2012	Japan	Gastric cancer	Oral	Arginine, Omega-3 fatty acids and RNA, n=120	Regular diet, n=111	Preop 5 days
Ida 2017	Japan	Gastric cancer	Oral	Eicosapentaenoic acid (ProSure) n=63	Regular diet, n=60	Preop 7 days, Postop 21 days

Study	Country	Diagnosis	Nutrition approach	Additional Immuno-elements	Comparison	Timing and duration
Klek 2016	Poland	Gastric cancer	Enteral (NR)	Reconvan, n=76	Peptisorb, n=69	POD 1-7
Liu 2012	China	Gastric cancer	Nasojejunal tube	Glutamine, Arginine, n=28	Standard EN, n=24	POD 1-7
Lobo 2006	UK	Oesophageal (59%), gastric (27%) and pancreatic (14%) cancer	Jejunostomy	Glutamine, Arginine (Stresson), n=54	Isocaloric, isonitrogenous (Nutrison high protein) n=54	POD 10-14
Marano 2013	Italy	Gastric cancer	Jejunostomy	Arginine, Omega-3 fatty acids and RNA, n=54	Isocaloric, isonitrogenous n=55	POD 1-7
Okamoto 2009	Japan	Gastric cancer	Oral	Arginine, Omega-3 fatty acids and RNA, n=30	Isocaloric, n=14	Preop 7 days
Ryan 2009	Ireland	Oesophageal cancer	Oral(preop), jejunostomy	Omega-3 fatty acid, n=28	Isocaloric, isonitrogenous n=25	Preop 5 days, POD 1-21
Sakurai 2007	Japan	Oesophageal cancer	Oral (preop), jejunostomy	Arginine, Omega-3 fatty acids and RNA, n=16	Isocaloric, n=14	Preop 3 days, POD 14
Senkal 1995	Germany	Oesophageal (19%), gastric (51%) and pancreatic (30%) cancer	Jejunostomy	Arginine, Omega-3 fatty acids and RNA, n=78	Isocaloric nutrition, n=76	POD 1-5
Sultan 2012	UK	Gastric cancer	Oral (preop), jejunostomy or nasojejunal tube	Omega-3 fatty acid supplemented EN, n=66	Standard EN (Osmolite), n=63	Preop 7 days, POD 1-7
Wei 2014	China	Gastric cancer	Peripheral or central vein PN	Omega-3 fatty acid supplemented PN, n=26	Standard PN, n=26	POD 1-6
Yildiz 2016	Turkey	Oesophageal (24%), gastric (59%) and pancreatic (17%) cancer	Oral (preop), nasojejunal tube	HMB, Arginine and Glutamine + high protein, n=21	Standard EN, n=20	Preop 7 days, POD 1-7

Abbreviations: EN enteral nutrition; HMB β-Hydroxy β-Methylbutyrate; IV intravenous; NR not reported; PN parenteral nutrition; POD postoperative day; RNA ribonucleic acid; n=number of participants

Table 198: Summary of included studies: Trials of oral nutrition supplements

Study	Country	Diagnosis	Oral supplement	Comparison	Timing and duration
Imamura 2016	Japan	Gastric cancer	Elemental diet supplement (Elental), n=53	Regular diet alone, n=47	Post gastrectomy, as soon as soft food was tolerated and lasting 6-8 weeks
Faber 2015	Netherlands	Oesophageal or gastro-oesophageal junctional cancer	Energy dense nutritionally complete supplement (FortiCare), n=24	Placebo or isocaloric product if weight loss >5%, n=23	Starting soon after diagnosis and lasting 4 weeks

n=number of participants

Table 199: Summary of included studies: Trials of additional nutritional support during chemotherapy or chemoradiotherapy

Study	Country	Diagnosis	Nutrition approach	Intervention	Comparison	Timing and duration
Cong 2015	China	Oesophageal cancer	Nutritional support included diet counselling ONS, EN, and PN	Nutrition support team: nutrition risk screening, nutrition assessment, nutrition intervention, nutrition monitoring, and evaluation via standardised clinical nutrition process. n=25	Nutrition supervised by radiotherapy team n=25	During chemo-radiotherapy, for 28 days
Miyata 2012	Japan	Oesophageal cancer	Oral, or transnasal tube	Omega-3 fatty acid rich enteral supplement plus parenteral nutrition, n=47	Parenteral nutrition only, n=44	During chemotherapy for 14 days
Miyata 2017	Japan	Oesophageal cancer	Oral, or transnasal tube	Omega-3 fatty acid rich enteral supplement plus parenteral nutrition n=31	Omega-3 fatty acid poor enteral supplement plus parenteral nutrition, n=30	During chemotherapy for 12 days
Okada 2017	Japan	Oesophageal cancer	Oral	Elemental diet supplement	Regular diet, n=10	During chemotherapy for 14 days

Study	Country	Diagnosis	Nutrition approach	Intervention	Comparison	Timing and duration
				(Elental), n=10		
Sunpaweravong 2014	Thailand	Oesophageal cancer	Percutaneous endoscopic gastrostomy	Arginine, glutamine and Omega-3 fatty acid EN, n=35	isocaloric and isonitrogenous EN, n=36	During chemo-radiotherapy for 28 days

Abbreviations: EN enteral nutrition; IV intravenous; NR not reported; ONS oral nutritional supplements; PN parenteral nutrition; n=number of participants

Table 200: Summary of included studies: Trials of continued nutritional support after discharge from hospital

Study	Country	Diagnosis	Intervention	Comparison	Timing and duration
Bowrey 2015	UK	Oesophageal (66%) or gastric (34%) cancer	Enteral feeds (50 % of energy and protein requirements) via jejunostomy at home n=20	Discontinuation of jejunostomy feeds (restarted only if deemed necessary) n=21	Starting at discharge from hospital, for at least six weeks
Carey 2013	Australia	Oesophageal (37%), gastric (37%) or pancreatic (26%) cancer	Regular phone review by the clinical dietitian on a fortnightly basis for the following 6 months, and face-to-face follow-up if needed, n=14	No dietician follow-up, n=13	Starting at discharge from hospital, for six months
Froghi 2016	UK	Oesophageal (73%) or gastric (27%) cancer	Enteral feeds (600 kcal/day) via jejunostomy, n=20	Discontinuation of jejunostomy feeds (restarted only if deemed necessary) n=21	Starting at discharge from hospital, for six weeks
Gavazzi 2016	Italu	Oesphagus (17%), pancreas (12%), gastric (63%) and biliary tract (7%) cancer	Home enteral feeds via jejunostomy, n=38	Discontinuation of jejunostomy feeds (restarted only if deemed necessary) n=41	Starting at discharge from hospital, for at least 2 months

n=number of participants

10.1.4 Clinical evidence profile

The clinical evidence profiles for this review are presented in Table 201 to Table 205.

Table 201: Summary clinical evidence profile. Early enteral nutrition versus parenteral nutrition or IV support after surgery

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)
	Risk with parenteral nutrition or IV fluids	Risk with Enteral nutrition			
Pneumonia follow up: Typically during hospital stay	147 per 1,000	77 per 1,000 (44 to 134)	RR 0.52 (0.30 to 0.91)	441 (6 RCTs)	LOW [a,b]
Surgical site infections follow up: Typically during hospital stay	152 per 1,000	123 per 1,000 (70 to 216)	RR 0.81 (0.46 to 1.42)	441 (6 RCTs)	VERY LOW [a,c]
Anastomotic leaks follow up: Typically during hospital stay	137 per 1,000	59 per 1,000 (30 to 116)	RR 0.43 (0.22 to 0.85)	429 (6 RCTs)	LOW [a]
Sarcopenia - not reported	-	-	-	-	-
Short term mortality follow up: Typically during hospital stay	19 per 1,000	20 per 1,000 (5 to 75)	RR 1.08 (0.29 to 4.00)	419 (6 RCTs)	VERY LOW [a,c]
Overall survival - not reported	-	-	-	-	-
Length of hospital stay (days)	The mean length of hospital stay (days) ranged from 13.4 to 40 days	The mean length of hospital stay (days) in the intervention group was 0.96 days lower (2.54 lower to 0.61 higher)	-	231 (4 RCTs)	LOW [a,d]
Hospital admission - not reported	-	-	-	-	-
Weight change (%) assessed with: Percentage change from baseline weight follow up: 14 days	The mean weight change (%) was -5.05 %	The mean weight change (%) in the intervention group was 2.11 % higher (0.15 higher to 4.07 higher)	-	47 (1 RCT)	MODERATE [a]

RCT =randomised controlled trials; RR=relative risk; CI=confidence interval
[a]. Randomisation and allocation concealment unclear in most cases. Blinding either unclear or not present.
[b].95% CI of the effect estimate includes one MID threshold [0.80, 1.25]
[c].95% CI of the effect estimate includes both MID thresholds [0.80, 1.25]
[d].95% CI of the effect estimate includes both the MID (1 day) and no effect

Table 202: Summary clinical evidence profile. Immunonutrition versus standard nutrition in the perioperative period

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)
	Risk with standard nutrition	Risk with Immunonutrition			
Pneumonia follow up: during hospital stay	143 per 1,000	136 per 1,000 (102 to 181)	RR 0.95 (0.71 to 1.26)	1073 (12 RCTs)	VERY LOW [a,b]
Surgical site infections follow up: during hospital stay	98 per 1,000	82 per 1,000 (55 to 122)	RR 0.84 (0.56 to 1.25)	1073 (12 RCTs)	VERY LOW [a,b]
Anastomotic leaks follow up: during hospital stay	70 per 1,000	49 per 1,000 (29 to 85)	RR 0.71 (0.41 to 1.22)	858 (8 RCTs)	VERY LOW [a,b]
Sarcopenia - not reported	-	-	-	-	-
Short term mortality follow up: Typically during hospital stay	33 per 1,000	31 per 1,000 (15 to 63)	RR 0.93 (0.46 to 1.90)	931 (9 RCTs)	VERY LOW [a,b]
Overall survival – follow up 5 years	Median OS 1.7 years	Median OS 1.5 years	HR 0.91 (0.57 to 1.45)	99 (1 RCT)	LOW [c]
Length of hospital stay (days)	The mean length of hospital stay (days) ranged from 15 to 31 days	The mean length of hospital stay (days) in the intervention group was 2.09 days lower (3.22 lower to 0.97 lower)	-	933 (9 RCTs)	LOW [a,d]
Length of hospital stay (days) – gastric cancer subgroup		The mean length of hospital stay (days) in the intervention group was 1.24 days lower (3.03 lower to 0.56 higher)	-	512 (5 RCTs)	LOW[a,e]
Length of hospital stay (days) – oesophageal cancer subgroup		The mean length of hospital stay (days) in the intervention group was 3.61 days lower (4.47 lower to 2.75 lower)	-	184 (2 RCTs)	MODERATE[a]
Length of hospital stay (days) – oesophageoga		The mean length of hospital stay (days) in the intervention group was 2.96 days lower	-	237 (2 RCTs)	MODERATE[a]

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)
	Risk with standard nutrition	Risk with Immunonutrition			
stric cancer subgroup		(3.94 lower to 1.97 lower)			
Hospital admission - not reported	-	-	-	-	-
Weight change - not reported	-	-	-	-	-

RCT =randomised controlled trials; RR=relative risk; HR=hazard ratio; OS=overall survival; CI=confidence interval
[a]. *Allocation concealment unclear in most cases.*
[b].*95% CI of the effect estimate includes both MID thresholds [0.80, 1.25]*
[c].*32% of patients not included in survival analysis and no ITT analysis*
[d].I^2=*70%*
[e].I^2=*76%*

Table 203: Summary clinical evidence profile. Oral nutritional supplements

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)
	Risk with standard diet	Risk with Oral nutritional supplements			
Pneumonia - not reported	-	-	-	-	-
Adverse events (grade 2 or more) follow up: range 4 weeks to 6 weeks	189 per 1,000	258 per 1,000 (128 to 525)	RR 1.37 (0.68 to 2.78)	111 (1 RCT)	VERY LOW [a,b]
Anastomotic leaks - not reported	-	-	-	-	-
Sarcopenia - not reported	-	-	-	-	-
Short term mortality follow up: range 4 weeks to 6 weeks	0 per 1,000	0 per 1,000 (0 to 0)	RR 2.75 (0.11 to 65.98)	111 (1 RCT)	LOW [a,c]
Overall survival - not reported	-	-	-	-	-
Length of hospital stay - not reported	-	-	-	-	-
Hospital admission - not reported	-	-	-	-	-
Weight change (%)	The mean weight change (%)	The mean weight change (%) in the	-	146 (2 RCTs)	MODERATE [d]

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)
	Risk with standard diet	Risk with Oral nutritional supplements			
assessed with: change from baseline follow up: range 4 weeks to 6 weeks	ranged from -4.1 to 0.4 %	intervention group was 1.03 % higher (0.23 higher to 1.82 higher)			

RCT =randomised controlled trials; RR=relative risk; CI=confidence interval
[a]. No blinding, unclear allocation concealment
[b].95%CI includes both MID thresholds [0.80, 1.25]
[c].95%CI includes both MID thresholds [0.80, 1.25], but the absolute risk difference is small
[d]. No blinding in one trial, unclear allocation concealment in both

Table 204: Summary clinical evidence profile. Additional nutritional support during chemotherapy or chemoradiotherapy

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)
	Risk with placebo	Risk with extra nutritional support during CRT			
Treatment related adverse effects - Oral mucositis (grade 3 or more) follow up: during chemo(radio)therapy	134 per 1,000	79 per 1,000 (23 to 273)	RR 0.59 (0.17 to 2.03)	242 (4 RCTs)	VERY LOW [a,b]
Treatment related adverse effects - Oesophagitis (grade 3 or more) follow up: during chemo(radio)therapy	28 per 1,000	29 per 1,000 (2 to 439)	RR 1.03 (0.07 to 15.81)	71 (1 RCT)	VERY LOW [a,b]
Treatment related adverse effects - Diarrhea (grade 3 or more) follow up: during chemo(radio)therapy	155 per 1,000	85 per 1,000 (40 to 176)	RR 0.55 (0.26 to 1.14)	223 (3 RCTs)	VERY LOW [a,b]
Treatment related adverse effects - Nausea (grade 3 or more) follow up: during chemo(radio)therapy	391 per 1,000	297 per 1,000 (219 to 407)	RR 0.76 (0.56 to 1.04)	223 (3 RCTs)	LOW [a,c]
Treatment related adverse effects - Vomiting (grade 3 or more) follow up: during chemo(radio)therapy	27 per 1,000	27 per 1,000 (5 to 142)	RR 0.98 (0.19 to 5.22)	223 (3 RCTs)	VERY LOW [a,b]

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)
	Risk with placebo	Risk with extra nutritional support during CRT			
Treatment related adverse effects - complication related infection follow up: during chemo(radio)therapy	440 per 1,000	119 per 1,000 (40 to 378)	RR 0.27 (0.09 to 0.86)	50 (1 RCT)	LOW [a,b]
Completion of planned chemotherapy	889 per 1,000	916 per 1,000 (844 to 996)	RR 1.03 (0.95 to 1.12)	273 (4 RCTs)	LOW [a,b]
Sarcopenia - not reported	-	-	-	-	-
Short term mortality follow up: during chemo(radio)therapy	83 per 1,000	57 per 1,000 (10 to 322)	RR 0.69 (0.12 to 3.86)	71 (1 RCT)	VERY LOW [a,b]
Overall survival - not reported	-	-	-	-	-
Hospital admission - not reported	-	-	-	-	-
Length of hospital stay (days)	The mean length of hospital stay (days) was 50 days	The mean length of hospital stay (days) in the intervention group was 4.48 days lower (7.08 lower to 1.88 lower)	-	50 (1 RCT)	MODERATE [a]
Weight change (%) assessed with: change from baseline follow up: during chemo(radio)therapy	The mean weight change (%) ranged from -0.1 to -4.3 %	The mean weight change (%) in the intervention group was 0.89 % higher (1.77 lower to 3.55 higher)	-	276 (4 RCTs)	VERY LOW [a,d]

RCT =randomised controlled trials; RR=relative risk; CI=confidence interval
[a]. No blinding or blinding unclear. Allocation concealment unclear
[b].95% CI of the effect estimate includes both MID thresholds [0.8, 1.25]
[c].95% CI of the effect estimate includes one MID threshold [0.8, 1.25]
[d].I^2=86%

Table 205: Summary clinical evidence profile. Continued nutritional support after discharge from hospital

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)
	Risk with placebo	Risk with Post discharge nutrition support			
Jejunostomy complications - In hospital complications follow up:	304 per 1,000	499 per 1,000 (237 to 1,000)	RR 1.64 (0.78 to 3.46)	45 (1 RCT)	VERY LOW [a,b]

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)
	Risk with placebo	Risk with Post discharge nutrition support			
during hospital stay					
Jejunostomy complications - Post discharge (out of hospital) complications follow up: range 6 weeks to 6 months	357 per 1,000	296 per 1,000 (182 to 482)	RR 0.83 (0.51 to 1.35)	85 (2 RCTs)	VERY LOW [a]
Pneumonia	304 per 1,000	228 per 1,000 (85 to 609)	RR 0.75 (0.28 to 2.00)	45 (1 RCT)	VERY LOW [a]
Surgical site infections	261 per 1,000	318 per 1,000 (128 to 798)	RR 1.22 (0.49 to 3.06)	45 (1 RCT)	VERY LOW [a]
Anastomotic leak	261 per 1,000	136 per 1,000 (39 to 480)	RR 0.52 (0.15 to 1.84)	45 (1 RCT)	VERY LOW [a]
Sarcopenia assessed with: change in grip strength from baseline follow up: range 6 weeks to 6 months	Mean sarcopenia ranged from -2 to 2.9 kg	The mean sarcopenia in the intervention group was 1.02 kg higher (0.11 to 1.93k g higher)	-	143 (3 RCTs)	MODERATE [a]
Short term mortality	0 per 1,000	0 per 1,000 (0 to 0)	RR 3.13 (0.13 to 72.99)	45 (1 RCT)	LOW [a,c]
Overall survival - not reported	-	-	-	-	-
Length of hospital stay - not reported	-	-	-	-	-
Hospital admission - not reported	-	-	-	-	-
QOL - Change in QOL from baseline to 6 months assessed with: change in EORTC QLQ-C30 from baseline Scale from: -	The mean QOL - Change in QOL from baseline to 6 months was -7	The mean QOL - Change in QOL from baseline to 6 months in the intervention group was 2 higher (12.57 lower to 16.57 higher)	-	36 (1 RCT)	VERY LOW [a,d]

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)
	Risk with placebo	Risk with Post discharge nutrition support			
100 to 100 follow up: mean 6 months					
QOL - QOL at the end of follow up assessed with: EORTC QLQ-C30 Scale from: 0 to 100 follow up: range 6 weeks to 6 months	The mean QOL - QOL at the end of follow up ranged from 64 to 73	The mean QOL - QOL at the end of follow up in the intervention group was 4.81 lower (15.52 lower to 5.89 higher)	-	63 (2 RCTs)	LOW [a,e]
Weight change (kg) assessed with: change from baseline follow up: range 6 weeks to 6 months	The mean weight change (kg) ranged from -10.1 to -3.2 kg	The mean weight change (kg) in the intervention group was 2.37 kg higher (0.48 to 4.27 kg higher)	-	143 (3 RCTs)	LOW [a,f]

RCT =randomised controlled trials; RR=relative risk; CI=confidence interval; QOL=quality of life; EORTC = European Organisation for Research and Treatment of Cancer

[a.] *No blinding*

[b.] *95% CI of the effect estimate includes both MID thresholds [0.80, 1.25]*

[c.] *95% CI of the effect estimate includes both MID thresholds [0.80, 1.25] - but absolute risk difference is small*

[d.] *95% CI of the effect estimate includes both MID thresholds [-9, +9] - based on 0.5 SD of the control group*

[e.] *95% CI of the effect estimate includes one MID threshold [-9, +9] - based on 0.5 SD of the control group*

[f.] *95% CI of the effect estimate includes one MID thresholds [-4, +4] - based on 0.5 SD of the control group*

10.1.5 Economic evidence

A systematic review of the economic literature was conducted but no relevant studies were identified which were applicable to this review question. Economic modelling was not undertaken for this question because other topics were agreed as higher priorities for economic evaluation.

10.1.6 Evidence statements

10.1.6.1 Enteral nutrition versus parenteral nutrition or IV support immediately after surgery

Low quality evidence from 6 randomised trials including 441 patients indicated that early enteral nutrition after oesophagectomy or gastrectomy led to a clinically important reduction in the risk of pneumonia compared to parenteral nutrition or IV fluids alone.

Low quality evidence from 5 randomised trials including 390 patients indicated that early enteral nutrition after oesophagectomy or gastrectomy led to a clinically important reduction in the risk of anastomotic leak compared to parenteral nutrition or IV fluids alone.

Very low quality evidence from 6 randomised trials including 419 patients indicated no clinically important difference in short term mortality or surgical site infections with early

enteral nutrition compared to parenteral nutrition or IV support. Similarly no clinically important difference in the length of hospital stay of the two groups was observed in four randomised trials including 231 patients.

Moderate quality evidence from 1 trial including 47 patients indicated that patients who received early enteral nutrition lost less weight than those who received parenteral nutrition only.

10.1.6.2 Immunonutrition versus standard nutrition in the perioperative period

Very low to moderate quality evidence indicated no clinically important differences in the risk of pneumonia (12 RCTs, 1073 patients), surgical site infections (12 RCTs, 1073 patients), anastomotic leak (8 RCTs, 858 patients), overall survival (1 RCT, 99 patients) or short term mortality (9 RCTs, 931 patients) in patients receiving immunonutrition compared to those receiving standard nutrition.

Low quality evidence from 9 RCTs including 933 patients indicated that patients receiving immunonutrition had shorter hospital stays (on average 2.7 days shorter) than those receiving standard nutrition.

Subgroup analysis according to the type of cancer

i) Although low quality evidence from 5 RCTs including 512 people with gastric cancers suggested that there was no clinically significant difference, moderate quality evidence from 2 RCTs including 184 people with oesophageal cancers or 237 people with oesophageogastric cancers revealed a clinically significant beneficial effect of immunonutrition in people receiving immunonutrition in comparison with standard nutrition for reduction in length of hospital stay.

10.1.6.3 Oral supplements

Moderate quality evidence from 2 RCTs including 146 patients indicated that patients receiving oral supplements experienced reduced weight loss (of the order of 1% of their baseline weight) when compared with those on a standard diet, but no differences in adverse events or short term mortality were observed.

10.1.6.4 Additional nutritional support to mitigate toxicity during chemotherapy or chemoradiotherapy

Low to very low quality evidence from 4 RCTs including 242 patients did not indicate an effect of additional nutritional support interventions when compared to standard care on the rates of chemotherapy or chemoradiotherapy related toxicity, completion of planned chemotherapy, weight change or short term mortality.

Moderate quality evidence from 1 RCT including 50 patients indicated a clinically significant reduction in the length of hospital stay when patients had their nutrition managed by an interdisciplinary nutrition support team compared to management by radiotherapy practitioners.

10.1.6.5 Continued routine nutritional support after discharge from hospital

Low to moderate from 3 RCTs including 143 patients suggested a clinically important effect in favour of home enteral nutrition or fortnightly dietetic follow-up after discharge from hospital when compared to standard nutritional support in terms of weight change and sarcopenia.

Very low to moderate quality evidence from 4 RCTs including 183 patients suggested no clinically important effect of home enteral nutrition or fortnightly dietetic follow-up after

discharge from hospital when compared to standard nutritional support in terms of quality of life, jejunostomy or complications.

10.1.7 Evidence to recommendations

10.1.7.1 Relative value placed on the outcomes considered

As this review was focused on patients undergoing curative treatment, the critical outcomes considered by the Committee for this topic were overall survival, health-related quality of life and treatment-related morbidity. However, overall survival was not reported in any of the evidence identified for this review. Other important outcomes were length of stay, treatment-related mortality, sarcopenia and nutritional status and these were reported in some of the studies.

10.1.7.2 Quality of the evidence

Thirty-two randomised controlled trials were included in the evidence review and quality, assessed by GRADE, was rated very low to moderate. The Committee were very concerned about the poor quality of some of the studies, including a poor description of the interventions – for example intravenous fluids were described as parenteral nutrition and the studies of immunonutrition included a variety of different formulations. There was also concern over the lack of blinding in trials comparing enteral and parenteral nutrition, unclear allocation concealment, and unclear inclusion and exclusion criteria. Some of the clinical studies were also conducted in countries (such as Japan and China) where the nutritional support team configuration is different to that in the UK, and the parenteral and enteral nutrition practices are not comparable to UK practice. Therefore the results of these studies may not be directly applicable to the UK population. Finally, the Committee agreed that the safety of parenteral nutrition in the UK is likely to have improved with the establishment of nutrition support teams following the 2006 NICE guidance on Nutrition Support in Adults. Many of the papers looked at were from other countries which do not have the same practice or they predate this guidance.

10.1.7.3 Consideration of benefits and harms

The interventions covered by the evidence review included enteral versus parenteral nutrition, oral supplements versus a standard diet, immunonutrition versus standard nutrition, nutritional support, and nutritional support on discharge versus standard care. There were some benefits seen with some interventions, such as reduced weight loss with enteral nutrition and oral supplements and nutritional support, and decreased sarcopenia with support on discharge. There was also some very low to low quality evidence that suggested that nutritional interventions could reduce the risk of events such as anastamotic leaks and surgical site infections. There was no evidence of any harms or adverse effects from the nutriotional interventions included.

The Committee agreed that the recommendations should lead to patients undergoing curative treatment receiving dietetic assessment and monitoring, and a tailored approach to their nutritional support. This may lead to a reduced risk of complications and therefore a reduced length of hospital stay. People with a better nutritional status are more likely to complete their treatment (such as surgery or chemotherapy) and have an improved quality of life.

The recommendation to provide parenteral nutrition or enteral nutrition, particularly via a jejunal tube, may lead to an increased risk of complications in some patients, but the Committee agreed that it was likely that benefits of tailored nutritional support outweighed these possible risks.

10.1.7.4 Consideration of economic benefits and harms

No health economic evidence was identified and no health economic model was built for this topic.

The recommendations were not thought to require any major change to clinical practice. Therefore the cost impact of the recommendations is likely to be minimal. In centres not currently offering nutritional assessment and interventions, there could be increased costs as a result of the recommendations. However, the assessments should lead to more appropriate use of interventions, tailored to the individual needs of the patient. This, in turn, could lead to potential savings from reduced post-operative complications and length of hospital stay.

10.1.7.5 Other considerations

The Committee was unable to make a definitive recommendation between enteral and parenteral nutrition in this population, or to make a recommendation on the best method of administration or type of enteral nutrition. This was due to the lack of good quality evidence available on nutrition in this population. The Committee therefore made a series of research recommendations on this particular topic.

The Committee agreed that their recommendations would lead to a minimal change in practice but that some centres may need to increase dietetic input for this group of people.

10.1.7.6 Key conclusions

Results from one study found that the use of a nutritional support team for patients undergoing chemoradiotherapy led to a reduced length of stay (although this was on a long baseline length of stay). In a number of studies (which were of low or very low quality) looking at nutritional support, there was no difference in the rates of completion of planned therapy, short term mortality or weight change. However, the Committee agreed that, in their experience, the input of a dietitian was important in managing the complex nutritional needs of patients undergoing radical treatment. For example, maximizing nutrional input prior to and during treatment may enable patients to tolerate treatment better, and may lead to better rates of treatment completion. In addition, after curative treatment, patients required support to adjust to their diet as their tolerance improved, make suitable food choices, and to maximize their input by adjusting the size and frequency of meals. While the Committee felt that the role of a specialist dietitian in supporting these patients was part of current best practice, and that it should be provided in all units, they recognised that there was little evidence to support this and were therefore unable to make a strong recommendation.

Oral supplements were shown to improve weight gain with no difference in the rates of adverse effects. Based on their clinical experience the Committee agreed that nutritional assessment and support, tailored to the needs of individual people would lead to benefit in people undergoing curative surgery, but also agreed that well designed, prospective randomised studies were needed to elucidate these benefits further.

There was no difference between enteral and parenteral nutrition in terms of short-term mortality and length of stay, nor in surgical site infections. There was evidence for reduced rates of pneumonia and anastomotic leaks with enteral nutrition compared to parenteral nutrition, but due to concerns with the quality of evidence detailed above, the Committee agreed that they could not make a specific recommendation for either enteral or parenteral nutrition. However, based on their clinical experience, the Committee agreed that one form of nutrition should be offered in the immediate post-operative period.

Immunonutrition was shown only to reduce length of hospital stay compared to standard nutrition, with no difference in short term mortality or complications such as anastomotic leak,

surgical site infections or pneumonia, and the Committee therefore did not recommend this as an option in people undergoing curative surgery.

10.1.8 Recommendations

Radical treatment

43. Consider nutritional assessment and tailored support from a specialist oesophago-gastric dietitian to people with oesophago-gastric cancer before, during and after radical treatments.

44. Offer immediate enteral or parenteral nutrition after surgery to people who are having radical surgery for oesophageal and oesophago-gastric junction cancers.

45. Follow the recommendations in the NICE guideline on nutrition support for adults

10.1.9 Research recommendations

7. What is the optimal method of delivering nutritional support to adults after surgery with curative intent for oesophago-gastric cancer?

Why this is important?

People who have surgery for oesophago-gastric cancer have a prolonged period without adequate oral intake after surgery. Oral, enteral and parenteral nutrition support strategies are used to support people during this time. Evidence suggests that providing some form of nutrition support improves surgical outcomes. However, which of these methods is the safest and most effective has not been determined and because of this, practice in this field varies nationally. A study to identify the best method of delivering safe and effective nutritional support interventions which aim to reduce post-operative complications in this population would help guide future clinical practice.

Table 206: Research recommendation rationale

Research question	What is the optimal method of delivering nutritional support to adults after surgery with curative intent for oesophago-gastric cancer?
Importance to 'patients' or the population	Nutritional support after surgery for oesophago-gastric cancer improves post-surgical outcomes, and helps people recover and get out of hospital quicker. Nutrition support can be delivered either parenterally or enterally. Practice varies across the surgical centres, and the choice of method is usually determined by the experience of the centre or surgeon preference. Both methods carry a risk of morbidity and mortality. Being able to determine which is safer and more effective would improve the overall risk associated with this surgery.
Relevance to NICE guidance	It was not possible to determine which method of nutrition support is safer and more effective. Future NICE guidelines would benefit from the identification of the most appropriate method of nutrition support to adults after surgery for oesophago-gastric cancer.
Relevance to the NHS	Evidence shows that providing nutritional support post-operative has a benefit on surgical outcomes, but which intervention is safer and more effective has yet to be elucidated. Both methods have an associated risk of morbidity and mortality, and parenteral nutrition is more costly to the NHS. Since the NICE 2006 Nutrition Support in Adults guidance, and consequently the establishment of nutrition support teams, the delivery of parenteral nutrition is

Research question	What is the optimal method of delivering nutritional support to adults after surgery with curative intent for oesophago-gastric cancer?
	safer, and so there is a need for more up to date studies comparing parenteral and enteral nutrition support in the setting. Also, the impact of enhanced recovery programmes, and consequently earlier resumption of oral intake post-surgery, on post-operative outcomes, alongside nutrition support interventions, also warrants investigation.
National priorities	There is a national drive to improve post-surgical outcomes. Centralisation of services resulted in significant improvements, along with the establishment of enhanced recovery and the emergence of preoperative optimisation and prehabilitiation. However, determining which nutrition support intervention is safer and more effective, may offer a modifiable strategy to improve outcomes further.
Current evidence base	There is evidence to support providing nutrition support after surgery. However, evidence comparing both methods show them to be equivocal. More up to date, well designed studies would elucidate this further.
Equality	Adults with oesophago-gastric cancer undergoing surgery will receive different nutrition support interventions depending on where they are having surgery. It would be beneficial to offer all patients an intervention which has been shown to be safer and more effective for their recovery.

Table 207: Research recommendation statements

Criterion	Explanation
Population	Adults with oesophago-gastric cancer who are undergoing oesophagectomy.
Intervention	Enteral nutrition Parenteral nutrition
Comparator (without the risk factor)	Each other
Outcome	• Postoperative complications • Length of hospital stay • Morbidity and mortality • Readmissions • Patient-reported outcome measures • Quality of life • Cost effectiveness • Nutritional status • Sarcopenia
Study design	Multicentre randomised controlled trial or prospective cohort study
Timeframe	2 years

8. What is the effectiveness of long-term jejunostomy support compared to intensive dietary counselling and support along with symptom management for people having radical surgery for oesophago-gastric cancer?

Why is it important?

People who have had surgery for oesophago-gastric cancer have nutritional difficulties as a result of problems eating, ongoing symptoms, and side-effects related to the surgery. It is well recognised that they have a poor quality of life (QoL). Most patients have adjuvant treatment, however their nutritional status may negatively impact on their ability to tolerate this, meaning treatment can be stopped early or not received. Jejunostomy feeding tubes are often used to provide nutrition support after discharge from hospital after surgery. Some small studies have shown a benefit in terms of weight preservation, but none have shown

that this leads to better recovery, tolerance of treatment or quality of life. Practice in this area varies greatly, with some centres placing jejunostomy tubes and continuing enteral feeding after discharge, some placing the jejunostomy tubes and not using them routinely and others not placing jejunostomy tubes at all. Studies should aim to identify if jejunostomy placement leads to clinical benefit in adults who have had surgery for oesophago-gastric cancer.

Table 208: Research recommendation rationale

Research question	What is the effectiveness of long-term jejunostomy support compared to intensive dietary counselling and support along with symptom management for people having radical surgery for oesophago-gastric cancer?
Importance to 'patients' or the population	Oesophagectomy has a major impact on people's nutritional status. Eating is difficult, and this is confounded by adverse side effects of the surgery. This results in weight loss and poor nutritional status, and leads to slower recovery after surgery, poor QoL and may limit the amount of treatment people can tolerate. People who have had this surgery may have jejunostomy feeding tubes placed to support them, however this practice varies and is usually determined by the experience of the centre or surgeon preference. Jejunostomy tubes carry a risk of morbidity and mortality. Being able to determine the safest and most effective way to support people's nutrition after surgery would improve benefit outcomes for patients.
Relevance to NICE guidance	Some small studies show longer term jejunostomy feeding tubes results in better weight stability in people after surgery for oesophago-gastric cancer. However, whether this impacts of recovery, tolerance of further treatments and QoL has yet to be elucidated. Future NICE guidelines would benefit from the identification of the most appropriate nutritional support interventions after surgery, following discharge from hospital.
Relevance to the NHS	High priority Jejunostomy feeding tubes are often used to provide longer term nutrition support in people following surgery for oesophago-gastric cancer. They have an associated risk of morbidity and mortality, but may be beneficial in improving longer term. However, practice varies nationally; some centre will place jejunostomy feeding tubes, whilst others will not. In recent years, there have been advancements in the management of post- operative symptoms, which may have a positive impact on nutritional status and could potentially reduce the need for artificial nutrition support. Whether jejunostomy feeding improves longer term outcomes compared to dietary advice and counselling and symptom management warrants investigation.
National priorities	There is a national drive to improve the recovery and QoL after treatment for cancer (survivorship). The National Cancer Survivorship Initiative and the recent Cancer Strategy highlights the need to deliver improvement in the coming years. QoL after surgery for oesophago-gastric cancer is poor, and this is well highlighted in the literature. However, little evidence exists on strategies to improve QoL in this group of people. Determining which nutrition support interventions are safer and more effective, will offer a strategy to improve longer term outcomes.
Current evidence base	Few studies exist. Poor level of evidence.
Equality	Adults with oesophago-gastric cancer undergoing surgery will receive different nutrition support interventions depending on where they are had their surgery. It would be beneficial to offer all patients interventions which have been shown to be safer and more effective to improve survivorship.

Table 209: Research recommendation statements

Criterion	Explanation
Population	Adults with oesophago-gastric cancer who have undergone oesophagectomy.

Criterion	Explanation
Intervention	Jejunostomy feeding
Comparator (without the risk factor)	Intensive dietary advice and counselling with symptom management
Outcome	• Patient-reported outcome measures • Quality of life • Completion of treatment • Hospital admissions • Survival • Cost effectiveness • Nutritional status • Sacropenia
Study design	Multicentre randomised controlled trial Prospective cohort study
Timeframe	5 years

9. What is the benefit of artificial nutritional support in people undergoing gastrectomy?

Why this is important?

People who undergo total gastrectomy for gastric cancer have a prolonged period without adequate oral intake after surgery. Oral, enteral and parenteral nutrition are used to support people during this time. However, which of these methods is the safest and most effective is not clear from the evidence, and consequently clinical practice varies. Studies should aim to identify safe and effective nutrition support interventions which aim to reduce post-operative complications in people with gastric cancer undergoing curative intent surgery.

Table 210: Research recommendation rationale

Research question	What is the benefit of artificial nutritional support in people undergoing gastrectomy?
Importance to 'patients' or the population	Nutritional support after surgery for gastric cancer improves post-surgical outcomes, and helps people recover and leave hospital earlier. Nutritional support can be delivered either parenterally, enterally or orally. Practice varies across the surgical centres, and the choice of method is usually determined by the experience of the centre or surgeon preference. All artificial nutrition support methods carry risk of morbidity and mortality. Being able to determine which is safer and more effective would improve the overall risk associated with this surgery.
Relevance to NICE guidance	It was not possible to determine which method of nutrition support is safer and more effective. Future NICE guidelines would benefit from the identification of the most appropriate method of nutrition support to adults after total gastrectomy for gastric cancer.
Relevance to the NHS	Evidence shows that providing nutritional support postoperatively has a benefit on surgical outcomes, but which intervention is safer and more effective has yet to be determined. Artificial nutrition support methods have an associated risk of morbidity and mortality, and parenteral nutrition is more costly to the NHS. Since the NICE 2006 Nutrition Support in Adults guidance, and consequently the establishment of nutrition support teams, the delivery of parenteral nutrition is safer, and so there is a need for more up to date studies comparing parenteral and enteral nutrition support in the setting. Also, the impact of enhanced recovery programmes and earlier resumption of oral intake post-surgery, on postoperative outcomes, in conjunction with nutrition support interventions, also warrants investigation.

Research question	What is the benefit of artificial nutritional support in people undergoing gastrectomy?
National priorities	There is a national drive to improve post-surgical outcomes. Centralisation of services resulted in significant improvements, along with the establishment of enhanced recovery and the emergence of preoperative optimisation and prehabilitiation. However, determining which nutrition support intervention is safer and more effective, may offer a modifiable strategy to improve outcomes further.
Current evidence base	There is evidence to support providing nutrition support after surgery. However, evidence comparing both methods show them to be equivocal. More up to date, well designed studies would elucidate this further.
Equality	Adults with gastric cancer undergoing total gastrectomy will receive different nutrition support interventions depending on where they are having surgery. It would be beneficial to offer all patients an intervention which has been shown to be safer and more effective for their recovery.

Table 211: Research recommendation statements

Criterion	Explanation
Population	Adults with gastric cancer who are undergoing total gastrectomy.
Intervention	Enteral nutrition Parenteral nutrition Oral nutrition support alone
Comparator (without the risk factor)	• Each other
Outcome	• Postoperative complications • Morbidity and mortality • Length of hospital stay • Readmissions • Patient-reported outcome measures • Quality of life • Cost effectiveness • Nutritional status • Sarcopenia
Study design	Multicentre randomised controlled trial or prospective cohort study
Timeframe	2 years

10. What is the role of prophylactic gastrostomy placement in people undergoing radical chemoradiotherapy for oesophageal cancer?

Why this is important?

People who undergo radical chemoradiotherapy for oesophageal cancer often have a poor nutritional status at presentation, which is confounded further by the side effects of treatment. Dysphagia is common, and radiotherapy can result in worsening dysphagia, leading to hospital admission and commencement of nasogastric feeding. This can lead to interruptions or delays in further treatment. Prophylactic gastrostomy tubes may improve pre-treatment nutritional status and offer an enteral access that is more acceptable to patients for the duration of their treatment. However, gastrostomy tubes have associated risks of morbidity and mortality, and there is little evidence to demonstrate their overall benefits and harms.

1 **Table 212: Research recommendation rationale**

Research question	What is the role of prophylactic gastrostomy placement in people undergoing radical chemoradiotherapy for oesophageal cancer?
Importance to 'patients' or the population	Weight loss and poor nutritional status is common at diagnosis of oesophago-gastric cancer and chemoradiothery can further impact on nutritional status. Poor nutritional status has a negative impact on tolerance of treatment, recovery after treatment and quality of Life. Dysphagia is a common presenting symptom, and can be exacerbated by the side effects of radiotherapy, leading to nutritional difficulties requiring hospital admissions for nasogastric feeding. Prophylactic gastrostomy tubes may offer a more acceptable enteral feeding route for people, reduce the need for hospital admissions, and improve the rates of treatment completion.
Relevance to NICE guidance	There is little evidence on which to base recommendations relating to nutrition support during chemoradiotherapy. Future NICE guidelines would benefit from the identification of the most appropriate method of nutrition support to adults during and after chemoradiotherapy for oesophageal cancer.
Relevance to the NHS	Practice varies nationally and placement of prophylactic gastrostomy tubes will depend on centre experience and/or oncologist preference. Gastrostomy tubes may deliver benefits to patients but also have risks of increasing morbidity and mortality.
National priorities	Increasingly, chemoradiotherapy is used to treat oesophageal cancer, either as a definitive treatment or as part of a multimodal pathway. Symptom burden associated with chemoradiotherapy is high, impacting on nutritional status, quality of life and completion of treatment.
Current evidence base	There is currently very little evidence on the risks and benefits of prophylactic gastrostomy placement.
Equality	No special considerations required.

2 **Table 213: Research recommendation statements**

Criterion	Explanation
Population	People with oesophageal cancer undergoing radical chemoradiotherapy
Intervention	Prophylactic gastrostomy tube placed pre-treatment, in addition to dietetic advice, counselling and symptom management
Comparator (without the risk factor)	• Dietetic advice, counselling and symptom management, with nasogastric feeding tube insertion as indicated during treatment
Outcome	• Completion of chemoradiotherapy treatment • Hospital admissions • Morbidity and mortality • Overall and disease free survival • Quality of Life • Acceptability of feeding tube • Nutritional status • Sarcopenia
Study design	Prospective multicentre cohort study or randomised controlled trial
Timeframe	2 years

10.2 Palliative care

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

10.2.1 Introduction

Advanced oesophago-gastric cancer is complicated by a higher incidence of symptoms and morbidity, and the side effects of chemotherapy can also 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 interventions in people 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 the patient's wishes, relative's wishes and the patient's quality of life.

This review aimed to evaluate which nutritional interventions improve outcomes for adults with oesophago-gastric cancer who are being managed with palliative intent, as well as identifying the patient groups most likely to benefit from nutritional interventions.

10.2.2 Description of clinical evidence

This review involved evaluating the evidence for nutritional interventions to improve outcomes for people with oesophago-gastric cancer who are being managed with palliative intent. Evidence for nutritional interventions in this population was sparse and the majority of the evidence evaluated perioperative nutritional interventions which was not the focus of this review question.

No evidence was found to meet the inclusion criteria for this review.

Full details of the review protocol are reported in Appendix D. Study selection flow chart is reported in Appendix K and exclusion list in Appendix J.

10.2.3 Clinical evidence profile

No clinical evidence was found to meet the inclusion criteria for this review

10.2.4 Economic evidence

A systematic review of the economic literature was conducted but no relevant studies were identified which were applicable to this review question. Economic modelling was not undertaken for this question because other topics were agreed as higher priorities for economic evaluation.

10.2.5 Evidence statements

No clinical evidence was found to meet the inclusion criteria for this review

10.2.6 Evidence to recommendations

10.2.6.1 Relative value placed on the outcomes considered

As this review was concerned with pallitive care the critical outcomes considered by the Committee for this topic were treatment-related morbidity, health-related quality of life and patient-reported outcome measures. Other important outcomes of interest were treatment-related mortality, weight change and nutritional status.

10.2.6.2 Quality of the evidence

No evidence was identified for this question, but the Committee made recommnedations based on their clinical experience.

10.2.6.3 Consideration of benefits and harms

Despite the absence of clinical evidence, the Committee agreed that dietetic support remains important to people affected by oesophago-gastric cancer in the palliative setting, and their carers.

The involvement of a multidisciplinary team and the tailored approach to meeting the nutritional and dietetic support needs of people living with oesophago-gastric cancer receiving palliative treatment and care is likely to increase patients' sense of wellbeing.

The Committee noted that not recommending a specific nutritional intervention, such as enteral or parenteral nutrition, could contribute to anxiety and harms experienced by this group of people, their carers and healthcare professionals working with this group of people.

The Committee thought that providing dietetic support, involving the multi-disciplinary team (MDT) and tailoring dietetic support needs to the person affected by oesophago-gastric cancer may limit the potential harms associated with providing incorrect or inappropriate nutritional advice and/or interventions.

Further research in this area is required to assess what dietetic and nutrition support interventions benefit this group of people and is in their best interests and/or in keeping with their wishes.

The Committee agreed, based on their clinical experience, that for patients receiving palliative care, the dietitian providing the advice should be specialised in cancer-care, but would not necessarily need to be a specialist oesophago-gastric dietitian.

10.2.6.4 Consideration of economic benefits and harms

No health economic evidence was identified and no health economic model was built for this topic.

Variation in current practice makes assessment of potential costs and savings difficult.

Currently, large proportions of people with oesophago-gastric cancer who are receiving palliative treatment and/or care do not receive assessment of their nutritional support needs. The recommendations could highlight a resource need for the assessment and thus provision of specialist cancer-specific dietetic support. Given the current limitations to dietetic services offered to this group of people, it may be costly to establish a service which meets their needs.

Potential costs of improving access to specialist dietetic services and meeting the nutritional needs of this group of people could include:

- The additional costs of consultations with the specialist dietitians, the MDT and/or community team to assess and tailor nutritional and dietetic support to individual needs.
- The costs of nutritional and dietetic support interventions, such as supplements. However, specialist dietetic advice may actually reduce the prescribing of inappropriate nutritional products so may decrease expenditure.

10.2.6.5 Other considerations

The Committee noted that guidance or research that provides insight and clarity to the role of dietetic support in the palliative setting would benefit people living with oesophago-gastric cancer receiving palliative treatment and/care, their carers and healthcare professionals working with this group. The Committee therefore made a research rcommendation.

Provision of support varies across the country. It is therefore difficult to assess the extent of change in practice.

10.2.6.6 Key conclusions

Despite the lack of evidence, the Committee agreed that, in their experience, the input of a dietitian was important in managing the nutritional needs of patients with oesophago-gastric cancer receiving palliative care. For example, helping patients make suitable food choices, and to maximize their input by adjusting the size and frequency of meals. While the Committee felt that the role of a specialist cancer-specific dietitian in supporting these patients was part of current best practice, and that it should be provided in all units, they recognised that there was little evidence to support this and were therefore unable to make a strong recommendation.

10.2.7 Recommendations

Palliative care

46. Consider support from a specialist cancer-specific dietitian for people with oesophago-gastric cancer receiving palliative care.

47. Together with members of the multidisciplinary team and the hospital and community palliative care teams, tailor dietetic support to the person with oesophago-gastric cancer and their clinical situation.

48. Follow the recommendations in the NICE guidelines on improving supportive and palliative care for adults with cancer.

10.2.8 Research recommendations

11. What is the effectiveness of nutritional interventions in adults with oesophago-gastric cancer being treated palliatively?

Why this is important?

Weight loss and nutritional difficulties are common in people with oesophago-gastric cancer who are suitable only for palliative treatment, and poor nutritional status impacts negatively on treatment outcomes and quality of life. The inherent difficulties with eating associated with this disease impact on family life, impair social interactions and can be a significant burden to people with life-limiting disease. However, it is not known what nutritional interventions are safe and effective in this group of people, whether they improve outcomes, or how they should be delivered. Research in this area should aim to identify safe and

effective nutritional interventions which improve tolerance of treatment, and preserve quality of life.

Table 214: Research recommendation rationale

Research question	What is the effectiveness of nutritional interventions in adults with oesophago-gastric cancer being treated palliatively?
Importance to 'patients' or the population	A significant proportion of people will be diagnosed with oesophago-gastric cancer not suitable for curative treatment, and nutritional problems are common in people with oesophago-gastric cancer undergoing palliative management, as a result of the mechanical and systemic consequences of the disease. Poor nutrition and difficulty eating can have a profound impact on their quality of life, and these people would benefit from nutrition support strategies to improve their quality of life.
Relevance to NICE guidance	No evidence was found to support nutritional interventions in people with oesophago-gastric cancer undergoing palliative management. Future NICE guidelines would benefit from the identification of the most appropriate nutritional support interventions for adults with life-limiting disease.
Relevance to the NHS	Providing safe and effective nutritional support interventions in this group of people may reduce emergency hospital admissions. There is also a drive to develop more effective and efficient models of delivering care led by non-medical, trained professionals such as dietitians and clinical nurse specialists.
National priorities	There is a national drive to improve the recovery and quality of life after treatment for cancer (Survivorship). The National Cancer Survivorship Initiative and the recent Cancer Strategy highlights the need to deliver improvement in the coming years.
Current evidence base	No evidence currently available
Equality	Not all people with oesophago-gastric cancer receiving palliative care have access to specialist nutrition advice or support.

Table 215: Research recommendation statements

Criterion	Explanation
Population	People with oesophago-gastric cancer who are being managed palliatively.
Intervention	Tailored dietetic management: Nutrition support Dietary counselling and advice Symptom management Service model – access to clinical nurse specialist and dietitian for support
Comparator (without the risk factor)	• No dietetic input unless referred
Outcome	• Completion of treatment • Emergency hospital admissions • Patient-reported outcome measures • Quality of life • Cost effectiveness • Nutritional status • Sarcopenia
Study design	Prospective randomised study or cohort study
Timeframe	1 year recruitment

11 Follow-up

11.1 Routine follow-up

Review question: 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?

11.1.1 Description of clinical evidence

43 publications (N= 13706) were included in the review. Two types of evidence were considered for this review: studies reporting the diagnostic accuracy of tests used to detect recurrent disease in asymptomatic people treated for oesophagogastric cancer and prognostic studies of the underlying risk of recurrence according to disease characteristics and treatment received. Details of the included studies of summarised below. See also the study selection flow chart in Appendix K, forest plots in Appendix H, study evidence tables in Appendix F and exclusion list in Appendix J.

11.1.1.1 Diagnostic Accuracy

Imaging for gastric cancer

13 studies (N=979) that reported on the diagnostic accuracy of positron emission tomography/computed tomography (PET/CT) or PET/CT and CT were included in the review. All studies included were retrospective cohort design. All studies included a population of gastric cancer patients post-surgery. Most studies were conducted in an Eastern setting. There were 7 studies from Korea (Kim 2011, Lee 2011, Lee 2014, Lee 2016, Park 2009, Sim, 2009, Yun 2005). There was 1 study each from Tukey (Bilici 2011), Belgium (De Potter, 2003), China (Sun 2008), Japan (Nakamoto 2009), Italy (Sharma, 2012) and Italy (Graziosi, 2011). All studies but one (Lee, 2016) were included a systematic review identified in this area that was used to assist in data extraction (Li, 2016).

Tumour antigens for gastric cancer

Seven studies (N= 2012) reported on the diagnostic accuracy of serum carcinogenic embryonic antigen (CEA), cancer antigen 19-9 (CA19-9) or both. Five studies were retrospective cohort studies (Kim 2014b, Lee 2014b, Marelli 2001, Ohtsuka 2008, Qui 2009) and two were prospective cohort studies (Cazin 1998, Joypaul 1995). All studies included a population of gastric cancer patients post-surgery. There were 2 studies from Korea (Kim 2011b, Lee 2014b) and 1 study each from France (Cazin 1998), UK (Joypaul, 1995), Italy (Marrelli, 2001), Japan (Ohtsuka, 2008) and China (Qui, 2009).

Imaging for oesophageal cancer

Three studies (N= 143) reported on the diagnostic accuracy of PET/CT or CT. Two studies were retrospective cohort (Kato 2004 and Roedl 2008). One study was prospective cohort (Teyton 2010). All studies included a population of oesophageal cancer patients post-surgery. One study was conducted in the each of: the US (Roedl, 2008), France (Teyton, 2010) and Japan (Kato, 2004).

Tumour antigens for oesophageal cancer

Three studies (N= 433) reported on the diagnostic accuracy of CEA, serum or mRNA. All 3 studies were prospective cohort design. All studies included a population of oesophageal cancer patients post-surgery. Two studies were conducted in Japan (Setoyama 2006 and Tanaka 2010) and 1 study was conducted in the US (Clark, 1995).

11.1.1.2 Prognostic Studies

15 studies (N=10644) reported on prognostic factors and the follow-up of people with oesophago-gastric cancer. There were two reports of different analysis on one database population (D'Angelica 2005 and Bennett 2005).

Five studies reported on a population of people with gastric cancer after curative gastrectomy (D'Angelica 2004, Dittmar 2015, Jin 2015, Moorcraft 2016 and Spolverato 2014). All studies were retrospective cohort design. Three studies were from the US (D'Angelica 2004, Jin 2005). Other studies were from Germany (Dittmar 2015) and the UK (Moorcraft 2016), respectively.

Six studies reported on a population of people with early gastric cancer after endoscopic mucosal resection (Abe 2015, Kato 2013, Lee 2012, Hahn 2016, Nakajima 2006 and Min 2015). All studies were retrospective cohort design. All studies were from an Eastern setting. Three studies were from Japan (Abe 2015, Kato 2013, Nakajima 2006) and 3 were from Korea (Lee, 2012, Hahn 2016 and Min, 2015).

Four studies reported on a population of people with oesophageal or gastric oesophageal junction cancer after curative oesophagectomy (Lou 2013, Mariette 2003, Moorcraft 2016 and Yoon 2010). All studies were retrospective cohort design. Studies were conducted in the US (Lou 2013 and Yoon 2010), France (Mariette 2003) and UK (Moorcraft 2016).

One study reported on a population of people with oesophageal cancer after definitive chemoradiotherapy (Versteijne 2015). This study was retrospective cohort design and was conducted in the Netherlands.

11.1.2 Summary of included studies

A summary of the studies that were included in this review are presented in Table 216 to Table 220.

Table 216: Summary of included studies: Imaging diagnostic studies for gastric cancer

Study	Population	Index Test	Reference Standard	Notes
Bilici 2011 Setting: Turkey Design: Retrospective cohort	N= 34 Age= 58.5 (32-79) years Stage: 1-4 Histology: adenocarcinoma, signet ring carcinoma	CT Chest and abdomen/pelvis diagnostic CT imaging were performed using the MS CT scanner (Siemens Somatom Sensation, 40-slice CT system). Images with 40×0.72 mm collimation were obtained 18F-FDG PET/CT Using a Siemens Biograph Duo PET/CT	Histological and clinical follow-up	Some data extracted from Li 2016 systematic review

Study	Population	Index Test	Reference Standard	Notes
		scanner with lutetium orthosilicate (LSO) detectors.		
De Potter 2002 Setting: Belgium Design: Retrospective cohort	N= 33 Age= 60 years Stage: NA Histology: adenocarcinoma, signet ring carcinoma,	18F-FDG PET Imaging was performed with a CTI-Siemens 931 or an HR+ scanner (Knoxville, Tenn.), with an axial field of view of 10.1 cm or 15 cm, and a spatial resolution of 8 or 6 mm. The raw imaging data were reconstructed in a 128×128 matrix.	Histological and clinical follow-up	Some data extracted from Li 2016 systematic review
Graziosi 2011 Setting: Italy Design: Retrospective cohort study	N= 50 Age= 68.4 years Stage: 1-4 Histology: NA	18F-FDG PET/CT Integrated Positron Emission Tomography and CT scan system (Discovery ST, GE Healthcare, Chalfont St. Giles, United Kingdom; General Electric Company, Fairfield, CT, USA). CT scan was performed after the PET with 5-millimeters-thick sections, at 350-380 mA and 140 Kw, from the neck to the perineum.	Histological and clinical follow-up	Some data extracted from Li 2016 systematic review
Kim 2011 Setting: Korea Design: Retrospective cohort	N= 139 Age= 61.5 years Stage: NA Histology: adenocarcinoma, signet ring carcinoma, mucinous cell carcinoma	CT All follow-up CECT scans were performed with multi-detector row CT scanners (Somatom Volume Zoom, Siemens AG, Enlan- gen, Germany). A slice collimation of 1.2 mm and a table pitch of 1:1 were used. Images were reconstructed at 5 mm intervals. 18F-FDG PET/CT Using an integrated PET/ CT system (Biograph Sensation 16, Siemens Medical Systems, Munich, Germany). The	Histological and clinical follow-up	Some data extracted from Li 2016 systematic review

Study	Population	Index Test	Reference Standard	Notes
		following parameters were used: tube rotation time 0.5 sec per revolution, 120 kV, 140 mAs, reconstructed slice thickness 5 mm.		
Lee 2011 Setting: Korea Design: Retrospective cohort	N= 89 Age= 56.4 years Stage: 1-4 Histology: adenocarcinoma, signet ring carcinoma, mucinous cell carcinoma	CT Scanning from above the diaphragm to the greater trochanter was performed using a 16-row multi-slice CT unit (Sensation 16; Siemens Medical Solutions, Erlangen, Germany), with 120 kVp, 300 mA, and 5 mm section thickness at 7 mm/sec table speed. 18F-FDG PET/CT Data acquisition was done by an integrated PET/CT system (Philips Gemini, DA Best, the Netherlands).	Histological and clinical follow-up	Some data extracted from Li 2016 systematic review
Lee 2014 Setting: Korea Design: Retrospective cohort	N= 46 Age= 60.6 years Stage: 1-3 Histology: adenocarcinoma, signet ring carcinoma, mucinous cell carcinoma	18F-FDG PET/CT Discovery STE (GE Healthcare, Milwaukee, WI, USA), Discovery 690 (GE Healthcare), Biograph Sensation16 (Siemens, Knoxville, TN, USA), or Biograph TruePoint 40 scanners (Siemens) were used.	Histological and clinical follow-up	Some data extracted from Li 2016 systematic review
Lee 2016 Setting: Korea Design: retrospective cohort study	N= 190 Underwent curative surgical resection for histopathologically confirmed gastric cancer.	18F-FDG PET/CT Scans were performed with using a Gemini PET/CT scanner (Philips, Milpitas, CA, USA) or a Biograph mCT 128 scanner (Siemens Healthcare, Knoxville, TN, USA). At first, a CT scan was performed without contrast enhancement. Subsequently, a PET scan was performed in the three-	Follow-up examinations, histopathological confirmation or clinical follow-up for more than 12 months with tumour markers and imaging studies.	

Study	Population	Index Test	Reference Standard	Notes
		dimensional (3D) mode. PET images were reconstructed with an iterative reconstruction algorithm with attenuation correction.		
Nakamoto 2009 Setting: Japan Design: Retrospective cohort	N= 92 Age= 67 (31-87) years Stage: NA Histology: adenocarcinoma, signet ring carcinoma, mucinous cell carcinoma	18F-FDG PET/CT Scanner (Advance, GE Healthcare), a BGO PET/CT scanner (Discovery LS/ST, GE Healthcare), an LSO PET/CT scanner (Biograph, CTI/Siemens) and a GSO PET/ CT scanner (Gemini, Philips Medical Systems). PET images were reconstructed with attenuation correction by the ordered-subsets expectation maximization algorithm, but specific parameters for image reconstruction were dependent on each institutional method	Histological and clinical follow-up	Some data extracted from Li 2016 systematic review
Park 2009 Setting: Korea Design: Retrospective cohort	N= 105 Age= 58 (34-83) years Stage: NA Histology: adenocarcinoma, signet ring carcinoma, mucinous cell carcinoma	18F-FDG PET/CT Image acquisition was performed with an integrated PET/CT device (Discovery LS; GE Medical Systems, Milwaukee, Wis) that consisted of a PET scanner (Advance NXi; GE Medical Systems) and an eight-slice helical CT thickness of 5.0 mm which corresponded to the PET image section thickness.	Clinical follow-up	Some data extracted from Li 2016 systematic review
Sharma 2012 Setting: India Design: retrospective cohort	N= 72 Age= 52.8 (28-86) years Stage: NA Histology: NA	18F-FDG PET/CT Dedicated PET-CT scanner (Biograph 2, Siemens). CT acquisition was performed on a spiral dual slice CT with 130 kV, 60 mAs, slice thickness of 4 mm using a matrix of 512x512. 3D PET	Histological and clinical follow-up	Some data extracted from Li 2016 systematic review

Study	Population	Index Test	Reference Standard	Notes
		acquisition was performed for 2-3 min per bed position. PET data were acquired using a matrix of 128X128.		
Sim 2009 Setting: Korea Design: Retrospective cohort	N= 52 Age= 55.4 (27-84) years Stage: 1-4 Histology: adenocarcinoma, signet ring carcinoma,	All scans were performed by PET/CT system (Philips Gemini, DA best, Netherlands) CT 5mm thick sections were obtained at 50 mA (but adjusted for body thickness) and 120 kVp from the skull base to the mid-thigh. 18F-FDG PET/CT 5-min emission acquisition per imaging level and the images were reconstructed.	Histological and clinical follow-up	Some data extracted from Li 2016 systematic review
Sun 2008 Setting: China Design: retrospective cohort	N= 23 Age= 55.4 (27-84) years Stage: NA Histology: NA	18F-FDG PET/CT Data acquisition by an integrated PET/CT system (Discovery STE; GE Medical Systems, Milwaukee, WI, USA). CT scanning was first performed, from the head to the pelvic floor, with 110 kV, 110 mA, a tube rotation time of 0.5 s, and a 3.3-mm section thickness which was matched to the PET section thickness.	Histological and clinical follow-up	Some data extracted from Li 2016 systematic review
Yun 2005 Setting: Korea Design: Retrospective cohort study	N= 30 Age= 58.3 (27-80) years Stage: 1-4 Histology: adenocarcinoma, signet ring carcinoma,	18F-FDG PET/CT Images were obtained on either an Advance PET scanner (GE Healthcare) or an Allegro PET system (Philips- ADAC Medical Systems). The Advance obtained images in 2 dimensional mode, and the Allegro in 3 dimensional mode.	Histological and clinical follow-up	Some data extracted from Li 2016 systematic review

N=total number of participants; NA=Not applicable; 18F-FDG = 18F-fluorodeoxyglucose; PET=Positron Emission Tomography; CT= computerised tomography;

Table 217: Summary included studies: Tumour antigen studies of gastric cancer

Study	Population	Index Test	Reference Standard	Notes
Cazin 1998 Setting: France Design= prospective cohort study	N=38 Clinical diagnosis of localized or metastatic, histologically confirmed primary gastric carcinoma	Blood drawn by venepuncture 1 week prior to surgery and then 3, 7 and 14 days after gastrectomy and every 3 months during clinical follow-up. Serum Antigen levels: 29.4 U/mL for CA 19.9 and 10.6 U/mL for CEA	Clinical follow-up as appropriate	
Joypaul 1995 Setting: UK Design= prospective cohort study	N=52 Patients who had undergone surgery for primary gastric adenocarcinomas were also assessed.	Outpatient visits were scheduled every 3 months for the first year and every 6 months thereafter. The recommended cut-off points for CA 19-9 was 22 kU/L.	Recurrence was diagnosed based on the evaluation of symptoms, signs of recurrence, and the results of the investigations	
Kim 2011b Setting: Korea Design= retrospective cohort study	N=479 Patients who had been diagnosed as gastric cancer and underwent surgery from January 2003 to June 2005	Tests were performed repeated every year after surgery The normal values of CEA, CA 19-9, were set at less than 7 ng/ml, 35 U/ml, respectively.	Recurrences were evaluated by physical examination, ultrasonic inspection, chest radiography, CT, PET-CT, MRI, endoscopy, or histological biopsy.	
Lee 2014b Setting: Korea Design= Retrospective cohort study	N=1304 Patients who underwent curative (R0) gastric cancer surgery from January 1, 2005 to December 31, 2006 at Seoul National University Hospital.	Measurement of serum CEA and CA19-9 levels, conducted every 6 months. Cut-off values were 5.0 ng/ml for CEA and 37 U/ml for CA19-9	Recurrence confirmed by imaging or pathology.	
Marrelli 2001 Setting: Italy Design= Retrospective cohort study	N=133 Patients resected for primary cancer of the stomach.	Blood samples were taken from patients upon admission to the hospital, 1 week after surgery, and	Diagnosis of recurrence based on clinical follow-up	

Study	Population	Index Test	Reference Standard	Notes
		at every follow-up examination. Pathological cut-off levels were established as 5 ng/mL for CEA, 37 U/mL for CA 19-9.		
Ohtsuka 2008 Setting: Japan Design= Retrospective cohort study	N=161 Patients who underwent curative resection for gastric cancer. All patients showed no residual cancer macroscopically as well as histologically.	Follow-up schedule of the tumour markers after the operation were: every 1–3 months during the initial 6 months after the operation, every 3–6 months from 6 months to 2 years, and every 6–12 months during 2–5 years after the operation. Serum antigen levels: CEA > 5 ng/mL; CA 19-9 > 37 ng/mL	Clinical follow-up as appropriate.	Data extracted only for gastric cancer (not colorectal)
Qiu 2009 Setting: China Design= Retrospective cohort study	N=181 Patients admitted for radical surgery for gastric adenocarcinoma	Every 3 months after surgery. To exclude false elevation of tumour markers, a rise in CEA and CA19-9 was confirmed 2 weeks later. Cut-offs: CEA 5 ng/mL and CA 19-9 35 U/mL	Clinical follow-up.	

N=total number of participants; NA=Not applicable; 18F-FDG = 18F-fluorodeoxyglucose; PET=Positron Emission Tomography; CT= computerised tomography; MRI=magnetic resonance imagine; CEA= Chorioembryonic antigen

Table 218: Summary of included studies: Imaging diagnostic studies for oesophageal cancer

Study	Population	Index Test	Reference Standard	Notes
Kato 2004 Setting: Japan Design: Retrospective cohort study	N=55 Patients who had undergone oesophageal resection were studied	CT All patients underwent CT of the neck, chest and abdomen. Ten-millimetre continuous scans were obtained	Recurrent disease was assessed by physical examination, histological findings, clinical	

Study	Population	Index Test	Reference Standard	Notes
		from the neck to the bottom of the liver. CT was performed after administration of intravenous contrast medium. PET PET images were obtained with a SET 2400Wscanner (Shimadzu Corporation, Kyoto, Japan) with a 59·5-cm transaxial field of view and a 20-cm axial field of view. This produced 63 image planes spaced 3·125 mm apart.	follow-up and specific imaging.	
Roedl 2008 Setting: USA Design: retrospective cohort study	N=47 Consecutive patients with squamous cell carcinoma and adenocarcinoma of the oesophagus who underwent neoadjuvant chemoradiotherapy followed by surgery were included in the study	PET/CT Using an integrated PET-CT system (Biograph 16; Siemens Medical Solutions, Erlangen Germany). Low-dose CT for attenuation correction was performed first with the 16- slice multi-detector CT component of the combined PET-CT then PET was performed in 3D mode.	Suspicious sites of recurrence and tumour progression (suspected on PET-CT) were proved by biopsy. A tumour/ recurrence-free status at the 18 month follow-up PET-CT scan was confirmed by EUS and follow-up.	
Teyton Setting: France Design= prospective cohort study	N=41 Consecutive patients with oesophageal cancer were included in the present study after they underwent oesophagectomy with curative intention.	PET Performed using an Allegro dedicated PET scanner (Philips Medical Systems). Images were reconstructed both with and without attenuation correction using a previously optimized 3D	Regional and distant recurrences were established by biopsy, if feasible, or by clinical follow-up and repeated examinations.	

Study	Population	Index Test	Reference Standard	Notes
		RAMLA reconstruction protocol.		

N=total number of participants; NA=Not applicable; PET=Positron Emission Tomography; CT= computerised tomography;

Table 219: Summary of included studies: Tumour antigen studies for oesophageal cancer

Study	Population	Index Test	Reference Standard	Notes
Clark 1995 Setting: US Design= prospective cohort study	N=83 Patient follow-up after surgical resection of oesophageal cancer.	Levels >5 ng/mL were considered to be elevated for the purpose of this study	Objective evidence of recurrence was determined in the presence of biopsy-positive findings on endoscopy, en-larging abdominal or thoracic nodes on sequential CT scans, or unequivocal systemic metastases on roentgenogram or CT	
Setoyama 2006 Setting: Japan Design= prospective cohort study	N=106 Patients with oesophageal squamous cell carcinoma who underwent R0 resection	Blood samples were obtained from the peripheral vein every 3 months. Serum CEA cut-off > 5 ng/mL; mRNA CEA cut-off > 9 ng/mL.	Diagnosis of recurrence based on clinical follow-up and imaging	

N=total number of participants; CT= computerised tomography; CEA = choriembryonic antigen

Table 220: Summary of included studies: Prognostic studies

Study	Population	Outcomes	Notes
Abe 2015 Setting: japan Design: Retrospective cohort	N=1526 Patients with early gastric cancer lesions underwent curative resection by ESD Median follow-up period of 82.2 months.	Recurrence rate	
D'Angelica 2004 Setting: US Design: Retrospective cohort study	N=1172 Utilizing a prospectively maintained gastric cancer database, all patients from July 1985 to June 2000 who underwent a curative gastrectomy at Memorial Sloan-Kettering Cancer Center were identified.	Recurrence rate Disease-free survival	Some data extracted from additional analysis (Bennett 2005)

Study	Population	Outcomes	Notes
	Patients who had involved histologic margins (R1) or who had gross disease left behind during surgery (R2) were excluded. Median follow-up time not reported. Follow-up was at least 4 years.		
Dittmar 2015 Setting: Germany Design: retrospective cohort study	N= 228 Patients who underwent elective gastric resection for gastric adenocarcinoma with curative intent, had no evidence of lymph node metastases, as well as clear resection margins. Duration of follow-up ranged from 1 to 212 months, with a median follow-up time of 59 months.	Overall survival Disease-free survival Recurrence rate	
Hahn 2016 Setting: Korea Design: Retrospective cohort study	N= 1347 Patients with initial-onset gastric cancers who underwent endoscopic submucosal dissection. The mean follow-up period after ESD was 32.12 months (interquartile range, 14.60-44.73).	Overall survival Disease-free survival Recurrence rate	
Jin 2005 Setting: USA Design: Retrospective cohort study	N=317 Patients who underwent resection for gastric adenocarcinoma via an abdominal approach with lymph-node negative disease. Median follow-up was 68 months after resection.	Overall survival Recurrence rate	
Kato 2013 Setting: Japan Design: Retrospective cohort	N= 1258 Patients with gastric cancer who underwent curative ESD Mean observation period 27 months.	Recurrence rate Overall survival	
Lee 2012 Setting: Korea Design= retrospective cohort	N= 372 Patients with early gastric cancer who underwent endoscopic resection. Median follow-up period of 48 months.	Recurrence rate	
Lou 2013 Setting: US Design= retrospective cohort	N=1147 Patients who had undergone esophagectomy for pathologic stage I to III esophageal adenocarcinoma or squamous cell carcinoma The median follow-up for those alive and without recurrence at study end was 46 months (range, 0–192 months).	Recurrence rate Disease-free survival	
Mariette 2003	N= 439	Recurrence rate	

Study	Population	Outcomes	Notes
Setting: France Design: Retrospective cohort study	Patients receiving R0 oesophagectomy with 2-field lymphadenectomy at one institution. Adenocarcinoma and squamous cell carcinoma included. Followed for evidence of recurrence over a mean interval of 37.3 (range, 1–207) months.	Overall survival Disease-free survival	
Min 2015 Setting: Korea Design= retrospective cohort	N=1306 Patients who underwent their first ESD for differentiated-type early gastric cancer (well or moderately differentiated early gastric cancer or papillary early gastric cancer) During median 47 months of follow-up.	Overall survival Recurrence rate	
Moorcraft 2016 Setting: UK Design: Retrospective cohort study	N= 360 Patients with a diagnosis of oesophageal, gastro-oesophageal junction (GOJ) or gastric adenocarcinoma who had undergone surgery with radical intent. Median follow-up of 61.7 months.	Recurrence rate Status at recurrence	
Nakajima 2006 Setting: Japan Design: Retrospective cohort	N= 633 Patients who underwent treatment with endoscopic resection for gastric cancer for gastric cancer. The average follow-up period after ER for the 633 study patients was 4.4 ± 2.8 years (range, 1.0–13.9 years).	Recurrence rate	
Spolverato 2014	N=817 Patients undergoing curative intent resection for gastric cancer at 1 of 7 major academic institutions participating in the US Gastric Cancer Collaborative Median follow-up of 28.9 months.	Overall survival Disease-free survival Recurrence rate	
Versteijne 2015 Setting: The Netherlands Design: Retrospective cohort study	N= 184 Patients undergoing definitive chemoradiotherapy. Patients had tumours that were unresectable or inoperable when co-morbidity excluded them from surgery. Mean follow up of 22.8 months (range 0.4–89.8 months, median follow-up 15 months).	Recurrence rate Overall survival Disease-free survival	
Yoon 2010 Setting: USA Design: Retrospective cohort study	N=796 Patient who underwent surgery with curative intent for tissue-confirmed adenocarcinoma of the oesophagus, GOJ or gastric cardia.	Overall survival Disease-free survival	

Study	Population	Outcomes	Notes
	Median follow-up for vital status and disease recurrence was 12.8 and 5.8 years respectively.		

N=total number of participants; ER = endoscopic resection; ESD = endoscopic submucosal dissection ; GOJ =gastro-oesophageal junction

11.1.3 Clinical evidence profile

The clinical evidence profiles for this review are presented in Table 221 to Table 233.

Table 221: Summary clinical evidence profile. PET/CT for gastric cancer

No of studies	n	Risk of bias[a]	Inconsistency[b]	Indirectness[c]	Imprecision[d]	Other considerations	Sens % (95% CI)	Spec % (95% CI)	LR+ (95% CI)	LR- (95% CI)	Quality
Recurrence- any site (all studies)											
13 studies	979	Serious risk of bias[1]	Very serious inconsistency[2]	No serious indirectness	Serious imprecision[3]	None	82% (71 % - 89 %)	82 % (76%- 87 %)	4.6 (3.2 - 6.6)	0.22 (0.13- 0.37)	VERY LOW
Recurrence- any site (excluding studies from China, Japan or Korea)											
4 studies	214	Serious risk of bias[1]	Very serious inconsistency[2]	No serious indirectness	Serious imprecision[3]	None	91% (77% - 97%)	80% (69% - 88%)	4.7 (2.7 – 7.97)	0.11 (0.04 – 0.31)	VERY LOW
Recurrence- any site (routine follow-up PET/CT)											
4 studies	481	Serious risk of bias[1]	Very serious inconsistency[2]	No serious indirectness	Very serious imprecision[5]	None	83% (67%- 92%)	86% (80%- 91%)	6.0 (3.9 – 9.4)	0.20 (0.10- 0.41)	VERY LOW
Recurrence- any site (routine follow-up PET/CT and Western study setting)											
1 study	50	Serious risk of bias1	No serious inconsistency	No serious indirectness	Very serious imprecision[5]	None	89% (72% - 98%)	82% (60%- 95%)	4.91 (2.01- 12.03)	0.13 (0.04- 0.39)	VERY LOW
Local recurrence											
1 study	46	Serious risk of bias[1]	No serious inconsistency	No serious indirectness	Very serious imprecision[5]	None	100% (3% to 100)	93 % (82% to 99 %)	15.00 (5.03 to 44.76)	NC	VERY LOW
Distant recurrence											
1 study	46	Serious risk of bias[1]	No serious inconsistency	No serious indirectness	Very serious imprecision[5]	None	100% (29% to 100%)	93 % (81% to 99%)	14.33 (4.81 to 42.69)	NC	VERY LOW

NC= not calculable; CI=confidence interval; n=total number of participants; Sens = sensitivity; Spec=specificity; LR = likelihood ratio; PET = Positron Emission Tomography; CT=computerised tomography

[a] *Risk of bias was assessed using the QUADAS-2 checklist.*
[b] *Inconsistency was assessed by inspection of the 95% prediction region in a HSROC plot if a diagnostic meta-analysis was conducted.*
[c] *Indirectness was assessed using the QUADAS-2 checklist items referring to applicability.*
[d] *The judgement of precision was based on the confidence interval of test sensitivity as this was considered to be the primary measure of interest. For this review the Committee agreed the following definition: 95% CI crosses either 75% or 90%, the result was judged to be seriously imprecise (90% was considered to be the cut-off for the test to be highly sensitive and if the sensitivity was less than 75% the test was considered to be of low sensitivity). If the 95% CI crosses both 75% and 90%, the results was judged to be very seriously imprecise.*
[1] *Reference test varied depending on index test for all studies. All patients did not receive the same reference test. Flow and timing of patient unclear for all studies.*
[2] *95% prediction region very wide*
[3] *95% CI for sensitivity crosses 75%*
[4] *95% CI for sensitivity crosses 90%*
[5] *Sensitivity crosses 75% and 90%*

Table 222: Summary clinical evidence profile: CT for gastric cancer

No of studies	n	Risk of bias[a]	Inconsistency[b]	Indirectness[c]	Imprecision[d]	Other considerations	Sens % (95% CI)	Spec % (95% CI)	LR+ (95% CI)	LR- (95% CI)	Quality
Recurrence- any site (By individual study[f])											
Study 1 (non-Eastern)	34	Serious risk of risk[1]	No serious inconsistency	No serious indirectness	Serious imprecision[2]	None	63 % (41% to 81%)	10% (0 % to 45 %)	0.69 (0.48 to 1.01)	3.75 (0.54 to 25.83)	LOW
Study 2	139	Serious risk of risk[1]	No serious inconsistency	No serious indirectness	Serious imprecision[2]	None	64 % (44% to 81 %)	86 % (79% to 92%)	4.76 (2.76 to 8.21)	0.41 (0.25 to 0.68)	LOW
Study 3	92	Serious risk of risk[1]	No serious inconsistency	No serious indirectness	Very serious imprecision[3]	None	86 % (64 % to 97 %)	87 % (77 % to 94 %)	6.76 (3.58 to 12.76)	0.16 (0.06 to 0.47)	VERY LOW
Study 4	52	Serious risk of risk[1]	No serious inconsistency	No serious indirectness	Serious imprecision[4]	None	89 % (75 % to 97%)	64 % (35% to 87%)	2.51 (1.23 to 5.10)	0.16 (0.06 to 0.45)	LOW

CI=confidence interval; n=total number of participants; Sens = sensitivity; Spec=specificity; LR = likelihood ratio; CT=computerised tomography
[a] *Risk of bias was assessed using the QUADAS-2 checklist.*
[b] *Inconsistency was assessed by inspection of the 95% prediction region in a HSROC plot if a diagnostic meta-analysis was conducted.*
[c] *Indirectness was assessed using the QUADAS-2 checklist items referring to applicability.*

[d] The judgement of precision was based on the confidence interval of test sensitivity as this was considered to be the primary measure of interest. For this review the Committee agreed the following definition: if the 95% CI crosses either 75% or 90%, the result was judged to be seriously imprecise (90% was considered to be the cut-off for the test to be highly sensitive and if the sensitivity was less than 75% the test was considered to be of low sensitivity). If the 95% CI crosses both 75% and 90%, the results was judged to be very seriously imprecise.
[f] reported by individual study due to very serious heterogeneity
[1] Serious risk of bias due to: Reference test varied depending on index test for all studies. All patients did not receive the same reference test. Flow and timing of patient unclear for all studies.
[2] Sensitivity crosses 75% threshold
[3] Sensitivity cross 75 and 90% threshold
[4] Sensitivity crosses 90% threshold
[5] 95% prediction region very wide.

Table 223: Summary clinical evidence profile: CEA for gastric cancer

No of studies	n	Risk of bias[a]	Inconsistency[b]	Indirectness[c]	Imprecision[d]	Other considerations	Sens % (95% CI)	Spec % (95% CI)	LR+ (95% CI)	LR- (95% CI)	Quality
Recurrence- any site (all studies)											
6 studies	2050	Very serious risk of bias [1,2]	Very serious inconsistency3	No serious indirectness	No serious imprecision	None	40% (33% - 47%)	92% (82% - 97%)	4.9 (2.3 – 10.2)	0.66 (0.60-0.72)	VERY LOW
Recurrence- any site (CEA cut off > 5 ng/mL only)											
4 studies	1545	Serious risk of bias[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	42% (36% - 37%)	89% (87%-90%)	3.7 (3.0-4.6)	0.66 (0.60-0.73)	MODERATE
Recurrence- any site (non-Eastern studies)											
Study 1	26	Very serious risk of bias [1,2]	No serious inconsistency	No serious indirectness	Serious imprecision[5]	None	55% (23% - 83%)	87% (60%-98%)	4.09 (1.01-16.56)	0.52 (0.27-1.03)	VERY LOW
Study 2	133	Serious risk of bias[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	44% (33%-56%)	79% (67% - 89%)	2.13 (1.21 to 3.74)	0.71 (0.56 to 0.90)	MODERATE
Local recurrence											
1 study	479	Serious risk of bias[4]	No serious inconsistency	No serious indirectness	No serious imprecision	None	0 % (0% - 71%)	96% (94% - 98%)	NC	1.04 (1.02 -1.06)	MODERATE

No of studies	n	Risk of bias[a]	Inconsistency[b]	Indirectness[c]	Imprecision[d]	Other considerations	Sens % (95% CI)	Spec % (95% CI)	LR+ (95% CI)	LR- (95% CI)	Quality
Distant lymph node recurrence											
1 study	479	Serious risk of bias[4]	No serious inconsistency	No serious indirectness	Serious imprecision[5]	None	40% (5%-85%)	97% (95% - 98%)	12.6 (3.9-41.3)	0.62 (0.30 - 1.27)	LOW

NC= not calculable; CI=confidence interval; n=total number of participants; Sens = sensitivity; Spec=specificity; LR = likelihood ratio; CEA = chorioembryonic antigen
[a] Risk of bias was assessed using the QUADAS-2 checklist.
[b] Inconsistency was assessed by inspection of the 95% prediction region in a HSROC plot if a diagnostic meta-analysis was conducted.
[c] Indirectness was assessed using the QUADAS-2 checklist items referring to applicability.
[d] The judgement of precision was based on the confidence interval of test sensitivity as this was considered to be the primary measure of interest. For this review the Committee agreed the following definition: if the 95% CI crosses either 75% or 90%, the result was judged to be seriously imprecise (90% was considered to be the cut-off for the test to be highly sensitive and if the sensitivity was less than 75% the test was considered to be of low sensitivity). If the 95% CI crosses both 75% and 90%, the results was judged to be very seriously imprecise.
[1] Serious risk of bias due to: Reference test varied depending on index test for all studies. All patients did not receive the same reference test. Flow and timing of patient unclear for all studies.
[2] Cazin 1998: unclear eligibility criteria, 12 patients missing from analysis- explanation not provided
[3] Very wide 95% prediction region
[4] Kim 2011b: serious risk of bias due to patients receiving different reference standard, unclear patient flow, study excludes patients with less than 4 years follow-up data
[5] Sensitivity crosses 75% threshold

Table 224: Summary clinical evidence profile: CA 19-9 for gastric cancer

No of studies	n	Risk of bias[a]	Inconsistency[b]	Indirectness[c]	Imprecision[d]	Other considerations	Sens % (95% CI)	Spec % (95% CI)	LR+ (95% CI)	LR- (95% CI)	Quality
Recurrence- any site (all studies)											
7 studies	2012	Very serious risk of bias [1,2]	Serious inconsistency[3]	No serious indirectness	No serious imprecision	None	43 % (33% - 53%)	87% (77% - 93%)	3.2 (2.1 – 4.9)	0.66 (0.58-0.74)	VERY LOW
Recurrence- any site (cut off 35-37 U/mL only)											
5 studies	1956	Serious risk of bias[1]	Serious inconsistency[3]	No serious indirectness	No serious imprecision	None	38% (30% - 47%)	90% (84% - 94%)	4.0 (2.7-5.9)	0.68 (0.61-0.76)	LOW
Recurrence- any site (non-Eastern setting)											

No of studies	n	Risk of bias[a]	Inconsistency[b]	Indirectness[c]	Imprecision[d]	Other considerations	Sens % (95% CI)	Spec % (95% CI)	LR+ (95% CI)	LR- (95% CI)	Quality
Study 1e	26	Very serious risk of bias [1,2]	No serious inconsistency	No serious indirectness	Serious imprecision[6]	None	45% (17%-77%)	73% (45%-92%)	1.70 (0.59-4.92)	0.74 (0.40-1.38)	VERY LOW
Study 2e	52	Serious risk of bias[1]	No serious inconsistency	No serious indirectness	Very serious imprecision[5]	None	69% (39% - 91%)	59% (33% - 82%)	1.68 (0.86 - 3.30)	0.52 (0.21 -1.30)	VERY LOW
Study 3e	133	Serious risk of bias[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	56% (44% to 67%)	74% (61% to 85%)	2.17 (1.34 to 3.50)	0.59 (0.44 to 0.80)	MODE RATE
Local recurrence											
1 study	479	Serious risk of bias[4]	No serious inconsistency	No serious indirectness	No serious imprecision	None	0% (0%-71%)	92% (89% - 94%)	NC	1.09 (1.06-1.12)	MODE RATE
Distant lymph node recurrence											
1 study	479	Serious risk of bias[4]	No serious inconsistency	No serious indirectness	No serious imprecision	None	20 % (0%-72%)	92% (89% - 94%)	2.43 (0.41-14.39)	0.87 (0.56 - 1.35)	MODE RATE

NC= not calculable; CI=confidence interval; n=total number of participants; Sens = sensitivity; Spec=specificity; LR = likelihood ratio;
[a] Risk of bias was assessed using the QUADAS-2 checklist.
[b] Inconsistency was assessed by inspection of the 95% prediction region in a HSROC plot if a diagnostic meta-analysis was conducted.
[c] Indirectness was assessed using the QUADAS-2 checklist items referring to applicability.
[d] The judgement of precision was based on the confidence interval of test sensitivity as this was considered to be the primary measure of interest. For this review the Committee agreed the following definition: if the 95% CI crosses either 75% or 90%, the result was judged to be seriously imprecise (90% was considered to be the cut-off for the test to be highly sensitive and if the sensitivity was less than 75% the test was considered to be of low sensitivity). If the 95% CI crosses both 75% and 90%, the results was judged to be very seriously imprecise.
[e] Unable to conduct meta-analysis in STATA with less than 4 studies
[1] Serious risk of bias due to: Reference test varied depending on index test for all studies. All patients did not receive the same reference test. Flow and timing of patient unclear for all studies.
[2] Cazin 1998: unclear eligibility criteria, 12 patients missing from analysis- explanation not provided
[3] wide 95% confidence interval
[4] Kim 2011b: serious risk of bias due to patients receiving different reference standard, unclear patient flow, study excludes patients with less than 4 years follow-up data
[5] Sensitivity 95% CI crosses 75% and 90%
[6] Sensitivity crosses 75% threshold

Table 225: Summary clinical evidence profile: CEA and CA19-9 for gastric cancer

No of studies	n	Risk of bias[a]	Inconsistency[b]	Indirectness[c]	Imprecision[d]	Other considerations	Sens % (95% CI)	Spec % (95% CI)	LR+ (95% CI)	LR- (95% CI)	Quality
Recurrence- any site											
1 study	1064	Very serious risk of bias[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	19 % (13 %-27%)	98% (97%-99%)	12.06 (6.47-22.47)	0.82 (0.75-0.90)	LOW

NC= not calculable; CI=confidence interval; n=total number of participants; Sens = sensitivity; Spec=specificity; LR = likelihood ratio; CEA=chorioembryonic antigen
[a] Risk of bias was assessed using the QUADAS-2 checklist.
[b] Inconsistency was assessed by inspection of the 95% prediction region in a HSROC plot if a diagnostic meta-analysis was conducted.
[c] Indirectness was assessed using the QUADAS-2 checklist items referring to applicability.
[d] The judgement of precision was based on the confidence interval of test sensitivity as this was considered to be the primary measure of interest. For this review the Committee agreed the following definition: if the 95% CI crosses either 75% or 90%, the result was judged to be seriously imprecise (90% was considered to be the cut-off for the test to be highly sensitive and if the sensitivity was less than 75% the test was considered to be of low sensitivity). If the 95% CI crosses both 75% and 90%, the results was judged to be very seriously imprecise.
[1] Lee 2014b: patients received different reference standards, unclear patient flow, 201 lost to follow-up

Table 226: Summary clinical evidence profile: CEA or CA19-9 for gastric cancer

No of studies	n	Risk of bias[a]	Inconsistency[b]	Indirectness[c]	Imprecision[d]	Other considerations	Sens % (95% CI)	Spec % (95% CI)	LR+ (95% CI)	LR- (95% CI)	Quality
Recurrence- any site											
1 study	1008	Very serious risk of bias[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	54% (45% - 63%)	84% (81%-86%)	3.39 (2.72-4.23)	0.54 (0.45-0.66)	LOW

NC= not calculable; CI=confidence interval; n=total number of participants; Sens = sensitivity; Spec=specificity; LR = likelihood ratio; CEA=chorioembryonic antigen
[a] Risk of bias was assessed using the QUADAS-2 checklist.
[b] Inconsistency was assessed by inspection of the 95% prediction region in a HSROC plot if a diagnostic meta-analysis was conducted.
[c] Indirectness was assessed using the QUADAS-2 checklist items referring to applicability.
[d] The judgement of precision was based on the confidence interval of test sensitivity as this was considered to be the primary measure of interest. For this review the Committee agreed the following definition: if the 95% CI crosses either 75% or 90%, the result was judged to be seriously imprecise (90% was considered to be the cut-off for the test to be highly sensitive and if the sensitivity was less than 75% the test was considered to be of low sensitivity). If the 95% CI crosses both 75% and 90%, the results was judged to be very seriously imprecise.
[1] Lee 2014b: patients received different reference standards, unclear patient flow, 201 lost to follow-up

Table 227: Summary clinical evidence profile: PET/CT for oesophageal cancer

No of studies	n	Risk of bias[a]	Inconsistency[b]	Indirectness[c]	Imprecision[d]	Other considerations	Sens % (95% CI)	Spec % (95% CI)	LR+ (95% CI)	LR- (95% CI)	Quality
Recurrence- any site (2 studies)											
Study 1 e (Eastern setting)	55	Serious risk of bias[1]	No serious inconsistency	No serious indirectness	Serious imprecision[2]	None	96% (81% - 100%)	68% (48% - 84%)	3.00 (1.74 - 5.16)	0.05 (0.01 - 0.38)	LOW
Study 2 e (non-Eastern setting)	47	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious imprecision[3]	None	89% (71%-98%)	75% (51%-91%)	3.56 (1.65-7.68)	0.15 (0.05-0.44)	LOW
Locoregional recurrence											
1 Study	55	Serious risk of bias[1]	No serious inconsistency	No serious indirectness	Serious imprecision[2]	None	100% (82%-100%)	75% (58% - 88%)	4.00 (2.27-7.04)	NC	LOW
Distant recurrence											
1 Study	55	Serious risk of bias[1]	No serious inconsistency	No serious indirectness	Very serious imprecision[3]	None	87% (60% - 98%)	95% (83% - 99%)	17.33 (4.43-67.90)	0.14 (0.04 - 0.51)	LOW

NC= not calculable; CI=confidence interval; n=total number of participants; Sens = sensitivity; Spec=specificity; LR = likelihood ratio; CT=computerised tomography; PET=positron emission tomography

[a] Risk of bias was assessed using the QUADAS-2 checklist.

[b] Inconsistency was assessed by inspection of the 95% prediction region in a HSROC plot if a diagnostic meta-analysis was conducted.

[c] Indirectness was assessed using the QUADAS-2 checklist items referring to applicability.

[d] The judgement of precision was based on the confidence interval of test sensitivity as this was considered to be the primary measure of interest. For this review the Committee agreed the following definition: if the 95% CI crosses either 75% or 90%, the result was judged to be seriously imprecise (90% was considered to be the cut-off for the test to be highly sensitive and if the sensitivity was less than 75% the test was considered to be of low sensitivity). If the 95% CI crosses both 75% and 90%, the results was judged to be very seriously imprecise.

[e] unable to conduct meta-analysis (minimum 4 studies needed)

[1] Kato 2004: reference test not the same for all patients- clinical follow-up as indicated

[2] Sensitivity crosses 90% threshold

[3] Sensitivity crosses 75% and 90% threshold

Table 228: Summary clinical evidence profile: CT for oesophageal cancer

No of studies	n	Risk of bias[a]	Inconsistency[b]	Indirectness[c]	Imprecision[d]	Other considerations	Sens % (95% CI)	Spec % (95% CI)	LR+ (95% CI)	LR- (95% CI)	Quality
Recurrence- any site											
1 study (Eastern setting)	55	Serious risk of bias1	No serious inconsistency	No serious indirectness	Serious imprecision[2]	None	89% (71% - 98%)	79% (59% - 91%)	4.15 (2.02 - 8.54)	0.14 (0.05 – 0.42)	LOW
Locoregional recurrence											
1 study	55	Serious risk of bias[1]	No serious inconsistency	No serious indirectness	Very serious imprecision[3]	None	84% (60% - 97%)	86% (71%-95%)	6.06 (2.63-13.99)	0.18 (0.06 -0.52)	VERY LOW
Distant recurrence											
1 study	55	Serious risk of bias[1]	No serious inconsistency	No serious indirectness	Very serious imprecision[3]	None	87 % (60%-99%)	98% (87%-100%)	34.67 (4.95-242.57)	0.14 (0.04 - 0.50)	VERY LOW

NC= not calculable; CI=confidence interval; n=total number of participants; Sens = sensitivity; Spec=specificity; LR = likelihood ratio; CT=computerised tomography
a Risk of bias was assessed using the QUADAS-2 checklist.
b Inconsistency was assessed by inspection of the 95% prediction region in a HSROC plot if a diagnostic meta-analysis was conducted.
c Indirectness was assessed using the QUADAS-2 checklist items referring to applicability.
d The judgement of precision was based on the confidence interval of test sensitivity as this was considered to be the primary measure of interest. For this review the Committee agreed the following definition: if the 95% CI crosses either 75% or 90%, the result was judged to be seriously imprecise (90% was considered to be the cut-off for the test to be highly sensitive and if the sensitivity was less than 75% the test was considered to be of low sensitivity). If the 95% CI crosses both 75% and 90%, the results was judged to be very seriously imprecise.
1 Kato 2004: reference test not the same for all patients- clinical follow-up as indicated
2 Sensitivity crosses 90% threshold
3 Sensitivity crosses 75% and 90% thresholds

Table 229: Summary clinical evidence profile: Serum CEA for oesophageal cancer

No of studies	n	Risk of bias[a]	Inconsistency[b]	Indirectness[c]	Imprecision[d]	Other considerations	Sens % (95% CI)	Spec % (95% CI)	LR+ (95% CI)	LR- (95% CI)	Quality
Recurrence- any site (2 studies)											

No of studies	n	Risk of bias[a]	Inconsistency[b]	Indirectness[c]	Imprecision[d]	Other considerations	Sens % (95% CI)	Spec % (95% CI)	LR+ (95% CI)	LR- (95% CI)	Quality
Study 1e (Non-Eastern setting)	83	Serious risk of bias[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	46% (33%-59%)	90% (73% - 98%)	4.60 (1.52-13.92)	0.60 (0.46-0.78)	MODERATE
Study 2e (Eastern setting)	106	Serious risk of bias[2]	No serious inconsistency	No serious indirectness	No serious imprecision	None	35% (20% - 53%)	79% (68%-88%)	1.69 (0.89-3.21)	0.82 (0.62 - 1.08)	MODERATE

NC= not calculable; CI=confidence interval; n=total number of participants; Sens = sensitivity; Spec=specificity; LR = likelihood ratio; CEA=chorioembryonic antigen
a Risk of bias was assessed using the QUADAS-2 checklist.
b Inconsistency was assessed by inspection of the 95% prediction region in a HSROC plot if a diagnostic meta-analysis was conducted.
c Indirectness was assessed using the QUADAS-2 checklist items referring to applicability.
d The judgement of precision was based on the confidence interval of test sensitivity as this was considered to be the primary measure of interest. For this review the Committee agreed the following definition: if the 95% CI crosses either 75% or 90%, the result was judged to be seriously imprecise (90% was considered to be the cut-off for the test to be highly sensitive and if the sensitivity was less than 75% the test was considered to be of low sensitivity). If the 95% CI crosses both 75% and 90%, the results was judged to be very seriously imprecise.
e unable to conduct meta-analysis with less than 4 studies
1 Clark 1995: patients received different reference standard- clinical follow-up as needed; unclear whether a consecutive sample was used
2 Setoyama 2006: patients received different reference standard- imaging or histopathology as needed; unclear eligibility criteria

Table 230: Summary clinical evidence profile: Prognostic studies in gastric cancer

Study	n	Risk of Bias[a]	Indirectness[b]	Overall Survival	Disease-free Survival	Disease stage at recurrence	Quality[c]
Follow-up post gastrectomy							
D'Angelica 2004/ Bennett 2005	1172	Serious risk of bias[1]	No serious risk of indirectness	NR	median time to recurrence= 11.8 months for those with recurrence (n=382) Recurrence at 2 years: 290/1172 Recurrence at 4 years: 345/ 1172	NR	VERY LOW
Dittmar 2015	207	Serious risk of bias[5]	No serious indirectness	Overall survival 5-year	Disease-free survival 5-year	NR	VERY LOW

Study	n	Risk of Bias[a]	Indirectness[b]	Overall Survival	Disease-free Survival	Disease stage at recurrence	Quality[c]
				Events= 35, n= 207 10-year Events= 51, n= 207 15-year Events= 56, n=207	Events= 46, n= 207 10-year Events= 56, n= 207 15-year Events= 56, n=207 Recurrence rate Overall 43/207 Local recurrence: 16/207 Peritoneal recurrence: 14/207 Distance recurrence: 9/207 1-year 16/207 2-year 27/207 5-year 37/207		
Jin 2015	317	No serious risk of bias	No serious indirectness	5-year: Events= 149, n=317 Of those with recurrence: Events= 46, n=54 Of those without recurrence: Events= 82, n=263	Recurrence rate Overall: 54/317 2-year: 36/317 5-year: 48/317 Local recurrence: 18/317 Regional recurrence: 16/317 Distant recurrence: 38/317	NR	LOW
Moorcraft 2016	360 (146 gastric)	No serious risk of bias	No serious indirectness	NR	Recurrence rate overall: 47/ 146 1 year: 22/146 2 year: 34/146 3 year: 41/146 Local recurrence: 4/146 Distant recurrence: 37/146	ECOG performance status at relapse: 0=3; 1=7; 2=2; 3-4=4; unknown=31	LOW

Study	n	Risk of Bias[a]	Indirectness[b]	Overall Survival	Disease-free Survival	Disease stage at recurrence	Quality[c]
					Both local and distant recurrence: 6/146		
Spolverato 2014	817	No serious risk of bias	No serious indirectness	Overall survival 1-year Events= 154, n=817 3-year Events= 401, n=817 5-year Events= 496, n=817	Disease-free survival Median overall: 27.7 months (IQR 23.2-35.5) Median time to recurrence= 10.8 (IQR 8.9-12.8), among those experiences recurrence. Overall recurrence rate 244/817 Hematogenous recurrence: n= 57 Peritoneal recurrence: n=47 Locoregional recurrence: n=59 Multiple site reccurence: n=81	NR	LOW
Follow-up post endoscopic mucosal resection							
Abe 2015	1526	No serious risk of bias	Serious risk of indirectness[2]	NR	Metachronous lesions Overall rate: 228/1526 5-year: n=145 cumulative incidence= 9.5% 10-year: n=346 cumulative incidence= 22.7%	NR	VERY LOW
Hahn 2016	1347	No serious risk of bias	Serious risk of indirectness[2]	5-year Recurrent group: 94.0% Non-recurrent group: 91.5%	5-year Disease-free survival Recurrent group: 100% Non-recurrent group: 98.2% Overall recurrence rate 141/ 1347 39= recurrence at ESD site 102= synchronous or metachronous lesions	NR	VERY LOW

Study	n	Risk of Bias[a]	Indirectness[b]	Overall Survival	Disease-free Survival	Disease stage at recurrence	Quality[c]
Kato 2013	1258	No serious risk of bias	Serious risk of indirectness[2]	3-year: Events= 37, n=1258	Local recurrence: n=5 cumulative incident rate= 0.40% Metachronous cancers: 2-year: n=43 cumulative incident rate= 3.7% 3-year: n=80 cumulative incident rate= 6.9% 5-year: n= 185 cumulative incident rate= 16%	NR	VERY LOW
Lee 2012	372	Serious risk of bias[3]	Serious risk of indirectness[2]	NR	The 5-years cumulative recurrence rate was 4.8%. Recurrence was found in 12 of the 17 cases of local recurrence (71%) within 12 months, while local recurrence was detected in the other five cases (29%) after 12 months (range: 17-49 months).	NR	VERY LOW
Min 2015	1306	Serious risk of bias[4]	Serious risk of indirectness[2]	5-year: Events=38, n=1306	Recurrence rate Local recurrence: 1/1306 Metachronous recurrence: 47/1306 44 early gastric cancer 3 advanced gastric cancer Distant recurrence: 2/1306	NR	VERY LOW
Nakajima 2006	633	Serious risk of bias[6]	Serious risk of indirectness[2]	NR	Overall recurrence rate 52/633 (8.2%) 3-year recurrence rate 5.9%	NR	VERY LOW

NR= not reported by the study; n=total number of participants; ECOG = Eastern Cooperative Oncology Group
[a] Assessed using NICE manual checklist for prognostic studies

[b] *Assessed using GRADE principle for assessing indirectness*
[c] *Based on GRADE methodology- observational studies start as low quality. Quality assessed using risk of bias and indirectness alone (Inconsistency and imprecision not applicable)*
[1] *D'Angelica 2004: Loss to follow-up not clearly reported*
[2] *Eastern population only- query relevance to UK setting*
[3] *Lee 2012: 23 patients with follow-up less than 6 months excluded*
[4] *Min 2015: 154 patients with inadequate follow-up excluded*
[5] *Dittmar 2015: patients with inadequate follow-up excluded- numbers not reported.*
[6] *Nakajima 2006: 180 patients excluded based on follow-up < 1 year; unclear inclusion criteria*

Table 231: Summary clinical evidence profile: Prognostic studies in oesophageal cancer

Study	n	Risk of Bias[a]	Indirectness[b]	Overall Survival	Disease-free Survival	Diseaes stage at Recurrence	Quality[c]
Follow-up post oesophagectomy							
Lou 2013	1147	No serious risk of bias	No serious indirectness	Only reported graphically.	Recurrence rate Overall recurrence: 435/1147 Distant and locoregional: 73/1147 Distant: 241/1147 Locoregional: 121/1147 Disease-free survival 2 year recurrence rate: 326/1147 The median time to recurrence was 5.5 years (95% confidence interval [CI], 3.8–8.1 years)	NR	LOW
Mariette 2003	439	No serious risk of bias	No serious indirectness	1-year overall survival: Events= 39, n=439 3-year overall survival: Events= 202, n=439	1-year disease-free survival: Events= 39, n=439 3-year disease-free survival: Events= 206, n=439 5-year disease-free survival: Events= 277, n=439 Recurrence rate at 1 year: 105/439	NR	LOW

Study	n	Risk of Bias[a]	Indirectness[b]	Overall Survival	Disease-free Survival	Diseaes stage at Recurrenc e	Quality[c]
				5-year overall survival: Events= 259, n= 439	Overall recurrence rate: 230/439 Local recurrence: 53/439 Regional recurrence: 90/439 Distant metastasis: 87/439		
Moorcraft 2016	360 (oeso=214)	No serious risk of bias	No serious indirectness	NR	Recurrence rate Oeso/junction cancer overall: 100/214 1 year: 53/214 2 year: 82/214 3 year: 94/214 Local recurrence: 7/214 Distant recurrence: 79/214 Both local and distant recurrence: 14/214	ECOG performanc e status at relapse: Oeso/junction cancer 0= 12; 1=13; 2=4; 3-4= 8; unknown=63	LOW
Yoon 2010	796	No serious risk of bias	No serious indirectness	Overall survival 1-year Events= 183; n=796 3-year Events= 462; n=796 5-year Events= 549; n=796	Disease-free survival 1-year Events= 310; n=796 3-year Events= 517; n=796 5-year Events= 573; n=796	NR	LOW
Follow-up post definitive chemoradiotherapy							
Versteijne 2015	184	No serious risk of bias	Serious indirectness[1]	Median= 16.8 months for all patients. 1-year:	Locoregional recurrence free rate: 1-year Events= 65, n=184 3-year	NR	VERY LOW

Study	n	Risk of Bias[a]	Indirectness[b]	Overall Survival	Disease-free Survival	Diseaes stage at Recurrenc e	Quality[c]
				Events= 64, n=184 3-year: Events= 132, n= 184 5-year: Events= 145, n=184	Events= 101, n= 184 AC group Events= 64, n=81 SCC group Events= 51, n=103 5-year Events= 109, n=184 Overall locoregional recurrence rate 76/184 Overall distant recurrence rate 76/184 Combination locoregional and distant recurrence rate 37/184		

NR= not reported by the study; n=total number of participants; ECOG = Eastern Cooperative Oncology Group
[a] Assessed using NICE manual checklist for prognostic studies
[b] Assessed using GRADE principle for assessing indirectness
[c] Based on GRADE methodology- observational studies start as low quality. Quality assessed using risk of bias and indirectness alone (Inconsistency and imprecision not applicable)
[1]Versteijne 2015: 11% of population underwent dCRT for recurrence

Table 232: Absolute estimates for 1000 gastric cancer patients with no residual disease

Diagnostic Method	Prevalence of Recurrence Estimate[a]	Expected TP (95% CI)	Expected FN (95% CI)	Expected FP (95% CI)	Expected TN (95% CI)	Quality of Diagnostic Evidence
Post-gastrectomy population						
PET/CT	Mean overall recurrence rate= 26.5%	217 (188 – 236)	48 (29 - 77)	132 (96 – 176)	603 (559 – 639)	VERY LOW
CT[b]		167-234 (109- 257)	31-98 (8-156)	96- 662 (44-735)	73- 639 (0-691)	VERY LOW
CEA[c]		111 (95 – 125)	154 (140 –170)	81 (73 - 96)	654 (639 – 662)	MODERATE
CA 19-9		114 (87- 140)	151 (125-178)	96 (51- 169)	639 (566 – 684)	VERY LOW
CEA and CA 19-9[d]		50	215	15	720	LOW

Diagnostic Method	Prevalence of Recurrence Estimate[a]	Expected TP (95% CI)	Expected FN (95% CI)	Expected FP (95% CI)	Expected TN (95% CI)	Quality of Diagnostic Evidence
		(34 – 71)	(194- 213)	(7- 22)	(713 – 728)	

TP= true positive; FP= false positive; FN= true negative; TN= true negative; CI=confidence interval; PET=positron emission tomography; CT=computerised tomography; CEA=chorioembryonic antigen

[a] *Estimated with mean overall recurrence rate from 5 studies reporting on follow-up of gastrectomy patients. Quality of evidence= low to very low*

[b] *Based on range of 4 studies*

[c] *Based on meta-analysis of 5ng/mL only due to lower heterogeneity and higher quality*

[d] *Based on one study alone*

If 1000 people treated with gastrectomy were followed up we could expect:

- With PET/CT: 217 true positives, 48 false negatives, 132 false positives, 603 true negatives.
- With CT: 167-234 true positives, 31-98 false negatives, 96- 662 false positives, 73- 639 true negatives.
- With CEA: 111 true positives, 154 false negatives, 81 false positives, 654 true negatives.
- With CA19-9: 114 true positives, 151 false negatives, 96 false positives, 639 true negatives.
- With CEA and CA19-9: 50 true positives, 215 false negatives, 15 false positives, 720 true negatives.

Table 233: Absolute estimates for 1000 oesophageal cancer patients with no residual disease

Diagnostic Method	Prevalence of Recurrence Estimate	Expected TP (95% CI)	Expected FN (95% CI)	Expected FP (95% CI)	Expected TN (95% CI)	Quality of Diagnostic Evidence
Post-oesophagectomy population						
PET/CT	Mean overall recurrence rate= 45.7%[a]	407-439[d] (324-457)	18- 50 (0- 133)	127- 174 (49 - 282)	369-407[d] (261- 494)	LOW
CT		407 (324-448)	50 (2-133)	114 (49 - 223)	429 (320- 494)	LOW
Serum CEA		160- 210[d] (91- 270)	247 – 297 (187 - 366)	54 – 105 (11- 174)	429-489[d] (369 – 532)	MODERATE
mRNA CEA		347 (270 – 407)	110 (50 - 187)	81 (43 - 141)	462 (402 – 500)	LOW
Post-definitive chemotherapy population[b]						
PET/CT	5-year locoregional recurrence rate= 59%[c]	525- 566[d] (419 – 590)	24 – 65 (0 – 171)	102 – 131 (37 - 213)	279 – 308[d] (197 – 373)	LOW
CT		525 (419 – 578)	65 (12-171)	86 (37-168)	324 (242-373)	LOW
Serum CEA		207 – 271[d] (118 – 348)	319 - 383 (242 - 472)	41- 176 (8-131)	324 – 369[d] (279 – 402)	MODERATE
mRNA CEA		448 (348 – 525)	142 (65 – 242)	62 (33- 107)	348 (303 – 377)	LOW

TP= true positive; FP= false positive; FN= false negative; *TN= true negative; CI=confidence interval; PET=positron emission tomography; CT=computerised tomography; CEA=chorioembryonic antigen*

[a] *Estimated with 3 studies reporting on follow-up of oesophagectomy patients. Quality of evidence= low.*

[b] *Diagnostic accuracy from post-gastrectomy studies extrapolated to post-dCRT population*

[c] *Estimated with 1 study reporting on follow-up of dCRT patients with oesophageal cancer. Overall recurrence not reported. Quality of evidence= very low.*
[d] *Range of 2 studies reporting*

If 1000 people treated with oesophagectomy were followed up we could expect:

- With PET/CT: 407-439 true positives, 18- 50 false negatives, 127- 174 false positives, 369-407 true negatives.
- With CT: 407 true positives, 50 false negatives, 114 false positives, 429 true negatives.
- With serum CEA: 160- 210 true positives, 247 – 297 false negatives, 54 – 105 false positives, 429-489 true negatives.
- With mRNA CEA: 347 true positives, 110 false negatives, 81 false positives, 462 true negatives.

11.1.4 Economic evidence

A systematic review of the economic literature was conducted but no relevant studies were identified which were applicable to this review question. Economic modelling was not undertaken for this question because other topics were agreed as higher priorities for economic evaluation.

11.1.5 Evidence Statements

11.1.5.1 Diagnostic accuracy

No studies reported on patient anxiety as an outcome

11.1.5.1.1 PET/CT for gastric cancer

Very low quality evidence from 13 studies with 979 people found PET/CT to have moderate sensitivity and moderate specificity in detecting recurrence (any site). LR+ indicated that PET/CT is less useful in 'ruling in' recurrence and LR- indicated that PET/CT is less useful in 'ruling out' recurrence.

This meta-analysis showed high heterogeneity, therefore, possible reasons for heterogeneity were explored and subgroup analysis was conducted when possible. Studies where PET/CT was conducted for suspicion of recurrence were excluded. The subgroup analysis with 4 studies (N=481) including studies where PET/CT was conducted routinely only showed no considerable change in the results or heterogeneity. The quality of the evidence was very low.

Subgroup analysis was also conducted for non-Eastern setting and routinely conducted PET/CT. Very low quality evidence from 1 study with 50 people found PET/CT to have moderate sensitivity and moderate specificity in detecting recurrence. LR+ indicated that PET/CT is less useful in 'ruling in' and LR- moderately using in 'ruling out' recurrence.

Very low quality evidence from 1 study with 46 people found PET/CT to have high sensitivity and high specificity in detecting local recurrence however the confidence interval around sensitivity is very wide. LR+ indicated that PET/CT is very useful in 'ruling in' local recurrence and LR- was not calculable.

Very low quality evidence from 1 study with 46 people found PET/CT to have high sensitivity and high specificity in detecting distant recurrence however the confidence interval around sensitivity is wide. LR+ indicated that PET/CT is very useful in 'ruling in' distant recurrence and LR- was not calculable.

11.1.5.1.2 CT for gastric cancer

Low to very low quality evidence from 4 studies with 34 to 139 people each found CT to have low to moderate sensitivity and low to moderate specificity in detecting recurrence (any site). LR+ indicated that CT is less useful to moderately useful in 'ruling in' recurrence. LR- indicated that CT is less useful to moderately useful in 'ruling out' recurrence.

Results are described by individual study as meta-analysis for this area showed very high heterogeneity and was not considered to be valid.

Subgroup analysis was conducted for non-Eastern setting. Low quality evidence from 1 study with 34 people found CT to have low sensitivity and low specificity in detecting recurrence. LR+ indicated that CT is less useful in 'ruling in' recurrence and LR- indicated that CT is less useful in 'ruling out' recurrence.

11.1.5.1.3 CEA for gastric cancer

Very low quality evidence from 6 studies with 2050 people found serum CEA to have low sensitivity and high specificity in detecting recurrence (any site). LR+ indicated that CEA is less useful in 'ruling in' recurrence. LR- indicated that CEA is less useful in 'ruling out' recurrence.

This meta-analysis showed high heterogeneity, therefore, possible reasons for heterogeneity were explored and subgroup analysis was conducted when possible. Studies with CEA cut-off other than 5 ng/mL were excluded. The subgroup analysis with 4 studies (N=1545) including studies with cut offs of 5 ng/mL only showed no considerable change in the results in terms of sensitivity, specificity and LR+ and LR- estimates. There was less heterogeneity of sensitivity. The quality of the evidence was moderate.

Subgroup analysis was conducted for non-Eastern setting. Low quality evidence from 2 studies with 26 and 133 people each found CEA to have moderate sensitivity and low specificity in detecting recurrence. LR+ indicated that CEA is less useful in 'ruling in' recurrence and LR- indicated that CEA is less useful in 'ruling out' recurrence.

Moderate quality evidence from 1 study with 479 people found serum CEA to have low sensitivity and high specificity in detecting local recurrence however the confidence interval around sensitivity is very wide. LR+ was not calculable. LR- indicated that CEA is not useful in 'ruling out' local recurrence.

Low quality evidence from 1 study with 479 people found serum CEA to have low sensitivity and high specificity in detecting distant recurrence however the confidence interval around sensitivity is very wide. LR+ indicated that CEA is very useful in 'ruling in' distant recurrence. LR- indicated that CEA is not useful in 'ruling out' distant recurrence.

11.1.5.1.4 CA19-9 serum antigen for gastric cancer

Very low quality evidence from 7 studies with 2012 people found serum CA19-9 to have low sensitivity and moderate specificity in detecting recurrence (any site). LR+ indicated that CA19-9 is less useful in 'ruling in' recurrence. LR- indicated that CA19-9 is less useful in 'ruling out' recurrence.

This meta-analysis showed high heterogeneity, therefore, possible reasons for heterogeneity were explored and subgroup analysis was conducted when possible. Studies with CA 19-9 cut-off other than 35 or 37 U/mL were excluded. The subgroup analysis with 5 studies (N=1956) including studies with cut offs of 35 or 37 U/mL showed no considerable change in the results or heterogeneity. The quality of the evidence was low.

Subgroup analysis was conducted for non-Eastern setting. Low quality evidence from 3 studies with 26, 52, 133 people each found CA19-9 to have low sensitivity and low specificity in detecting recurrence. LR+ indicated that CA19-9 is less useful in 'ruling in' recurrence and LR- indicated that CA19-9 is less useful in 'ruling out' recurrence.

Moderate quality evidence from 1 study with 479 people found serum CA19-9 to have low sensitivity and high specificity in detecting local recurrence however the confidence interval around sensitivity is very wide. LR+ was not calculable. LR- indicated that CEA is not useful in 'ruling out' local recurrence.

Moderate quality evidence from 1 study with 479 people found serum CA19-9 to have low sensitivity and high specificity in detecting distant recurrence however the confidence interval around sensitivity is very wide. LR+ indicated that CA19-9 is less useful in 'ruling in' distant recurrence. LR- indicated that CA19-9 is less useful in 'ruling out' distant recurrence.

11.1.5.1.5 CEA and CA19-9 combination for gastric cancer

Low quality evidence from 1 study with 1064 people found serum CEA and CA19-9 in combination to have low sensitivity and high specificity in detecting recurrence (any site). LR+ indicated that CA19-9 and CEA combination is very useful in 'ruling in' recurrence. LR- indicated that CA19-9 and CEA combination is less useful in 'ruling out' recurrence.

Low quality evidence from 1 study with 1008 people found either serum CEA or CA19-9 to have low sensitivity and moderate specificity in detecting recurrence (any site). LR+ indicated that either CA19-9 or CEA is less useful in 'ruling in' recurrence. LR- indicated that either CA19-9 or CEA is less useful in 'ruling out' recurrence.

11.1.5.1.6 PET/CT for oesophageal cancer

Low quality evidence from 2 studies with 55 and 47 people each found PET/CT to have moderate to high sensitivity and low to moderate specificity in detecting recurrence (any site). LR+ indicated that PET/CT is less useful in 'ruling in' recurrence. LR- indicated that PET/CT is moderately to very useful in 'ruling out' recurrence.

Subgroup analysis was conducted for non-Eastern setting. Low quality evidence from 1 study with 55 people found PET/CT to have high sensitivity and low specificity in detecting recurrence. LR+ indicated that PET/CT is less useful in 'ruling in' recurrence and LR- indicated that PET/CT is very useful in 'ruling out' recurrence.

Low quality evidence from 1 study with 55 people found PET/CT to have high sensitivity and moderate specificity in detecting locoregional recurrence. LR+ indicated that PET/CT is less useful in 'ruling in' locoregional recurrence and LR- was not calculable.

Low quality evidence from 1 study with 55 people found PET/CT to have moderate sensitivity and high specificity in detecting distant recurrence. LR+ indicated that PET/CT is very useful in 'ruling in' distant recurrence. LR- indicated that PET/CT is moderately in 'ruling out' distant recurrence.

11.1.5.1.7 CT for oesophageal cancer

Low quality evidence from 1 study with 55 people found CT to have moderate sensitivity and moderate specificity in detecting recurrence (any site). LR+ indicated that CT is less useful in 'ruling in' recurrence. LR- indicated that CT is moderately useful in 'ruling out' recurrence.

Low quality evidence from 1 study with 55 people found CT to have moderate sensitivity and moderate specificity in detecting locoregional recurrence. LR+ indicated that CT is moderately useful in 'ruling in' locoregional recurrence. LR- indicated that CT is moderately useful in 'ruling out' locoregional recurrence.

Low quality evidence from 1 study with 55 people found CT to have moderate sensitivity and high specificity in detecting distant recurrence. LR+ indicated that CT is very useful in 'ruling in' distant recurrence. LR- indicated that CT is moderately in 'ruling out' distant recurrence.

11.1.5.1.8 CEA for oesophageal cancer

Moderate quality evidence from 2 studies with 83 and106 people each found serum CEA to have low sensitivity and moderate to high specificity in detecting recurrence (any site). LR+ indicated that serum CEA is less useful in 'ruling in' recurrence. LR- indicated that CEA is less useful in 'ruling out' recurrence.

Subgroup analysis was conducted for non-Eastern setting. Low quality evidence from 1 study with 83 people found CEA to have low sensitivity and high specificity in detecting recurrence. LR+ indicated that CEA is less useful in 'ruling in' recurrence and LR- indicated that CEA is less useful in 'ruling out' recurrence.

11.1.5.1.9 CA19-9 for oesophageal cancer

No studies reporting.

11.1.5.2 Prognostic studies

No studies reported on additional test consequential to results or health-related quality of life. Evidence for overall survival and progression-free survival including recurrence rates in described below.

11.1.5.2.1 Post-gastrectomy

Overall survival

Low quality evidence from 1 study reported that the 1-year survival rate was 77.9%. Low quality evidence from 1 study reported that the 3-year survival rate was 50.9%. Very low to low quality evidence from 3 studies with 207 to 817 people each reported that the 5-year survival rate was 39.3%, 53.0% and 83.0% respectively.

Progression-free survival

Low to very low quality evidence from 5 studies with 207 to 1172 people each reported an overall recurrence rate of 17.0%, 20.8%, 29.9%, 32.2% and 32.6%. Low to very low quality evidence from 2 studies with 817 and 1172 people each reported that the median time to recurrence was 11.8 months and 10.8 months among those experiencing recurrence.

Low to very low quality evidence from 2 studies with 207 and 360 people each reported that the 1-year recurrence rate was 7.7% and 15.1%. Low to very low quality evidence from 4 studies with 207 to 1172 people reported that the 2-year recurrence rate was 11.4%, 13.0%, 23.3% and 24.7%. Low to very low quality evidence from 2 studies with 207 and 317 people each reported that the 5-year recurrence rate was 15.1% to 17.9%.

Very low quality evidence from 1 study with 207 people reported that the 5-year disease free survival rate was 77.9%.

Disease stage at recurrence

Although no studies reported on this critical outcome there was low quality evidence from 1 study with 146 people reported that the ECOG performance status at recurrence was 0 in 3 people, 1 in 7 people, 2 in 2 people, 3-4 in 4 people and unknown in 31 people.

11.1.5.2.2 Post-endoscopic mucosal resection

No studies reported on endoscopic resection for oesophageal cancer.

Overall survival

Very low quality evidence from 1 study with 1258 people reported that the 3-year survival rate was 97.1%. Very low quality evidence from 1 study with 1306 people reported that the 5-year survival rate was 97.1%.

Progression-free survival

Very low quality evidence from 5 studies with 372 to 1526 people each reported an overall recurrence rate of 3.8%, 4.6%, 8.2%, 10.5% and 14.9% respectively. Very low quality evidence from 1 study with 1258 people reported that the 2-year recurrence rate was 3.7%. Very low quality evidence from 1 study with 633 people reported that the 3-year recurrence

rate was 5.9%. Very low quality evidence from 3 studies with 372 to 1526 people each reported that the 5-year recurrence rate was 4.8%, 9.5%, and 14.7%.

Disease stage at recurrence

No studies reported on this critical outcome.

11.1.5.2.3 Post-oesophagectomy

Overall survival

Low quality evidence from 2 studies with 439 and 796 people each reported that the 1-year overall survival were 77% and 91%. Low quality evidence from 2 studies with 439 and 796 people each reported that the 3-year overall survival were 42% and 54%. Low quality evidence from 2 studies with 439 and 796 people each reported that the 5-year overall survival were 31% and 41%.

Progression-free survival

Low quality evidence from 3 studies with 214 to 1147 people each reported that the overall recurrence rate was 37.9%, 46.7% and 52.4%. Low quality evidence from 2 studies with 214 and 439 people each reported that the 1-year recurrence rate was 23.9% and 24.8%. Low quality evidence from 2 studies with 214 and 1147 people each reported that the 2-year recurrence rate was 28.4% and 38.3%.

Low quality evidence from 2 studies with 439 and 796 people each reported that the 1-year disease-free survival rate was 61.1% and 91.1%. Low quality evidence from 2 studies with 439 and 796 people each reported that the 3-year disease-free survival rate was 35.1% and 53.1%. Low quality evidence from 2 studies with 439 and 796 people each reported that the 5-year disease-free survival rate was 28.0% and 36.9%.

Disease stage at recurrence

Low quality evidence from 1 study with 214 people reported that the ECOG performance status at recurrence was 0 in 12 people, 1 in 13 people, 2 in 4 people, 3-4 in 8 people and unknown in 63 people.

11.1.5.2.4 Post-definitive chemoradiotherapy

No studies reported on definitive chemoradiotherapy for gastric cancer.

Overall Survival

Very low quality evidence from 1 study with 184 people reported that the 1-year overall survival rate was 65%. Very low quality evidence from 1 study with 184 people reported that the 3-year overall survival rate was 28%. Very low quality evidence from 1 study with 184 people reported that the 5-year overall survival rate was 21%.

Progression-free survival

Very low quality evidence from 1 study with 184 people reported that the 1-year locoregional recurrence rate was 34%. Very low quality evidence from 1 study with 184 people reported that the 3-year locoregional recurrence rate was 55%. Very low quality evidence from 1 study with 184 people reported that the 5-year locoregional recurrence rate was 59%.

Very low quality evidence from 1 study with 184 people reported that the distant recurrence rate was 41.3%.

Disease stage at recurrence

No studies reported on this critical outcome.

11.1.6 Evidence to recommendations

11.1.6.1 Relative value placed on the outcomes considered

The outcomes the Committee considered criticalfor this review were overall survival, stage of disease at recurrence and progression free survival. However, no studies that evaluated the method of follow-up and provided outcome data ('test and treat') studies were identified so a combination of diagnostic studies and prognostic studies were used. For the diagnostic methods of follow-up (investigations, scans) the Committee considered the sensitivity, specificity, positive and negative predictive values and positive and negative likelihood ratios were important. In addition, the Committee had identified that disease stage at recurrence, patient anxiety and health-related quality of life were important but these outcomes were not reported in the evidence. However, recurrence rates were reported in the evidence and so this outcome was considered by the Committee when making their recommendations.

11.1.6.2 Quality of the evidence

The quality of the individual studies included in the evidence review was assessed using QUADAS-2 to determine the risk of bias and the quality of individual outcomes was assessed using modified GRADE. Overall the quality of the evidence was graded very low to low, with a high risk of bias being found in the diagnostic studies.

The Committee noted that a number of the studies included were from an Asian population and that data from these populations might not be applicable to the UK population due to differences in the disease presentation and the approach to treatment. In addition, it was not clear from some of the studies whether the patients were symptom-free with no evidence of residual disease, as defined in the population of interest.

Finally, there was a lack of clinical evidence on endoscopic surveillance, where no studies were identified for inclusion in the review, and very little evidence on the role of CT and tumour markers. The Committee therefore reviewed the evidence but also used their clinical experience to draft the recommendations.

11.1.6.3 Consideration of benefits and harms

Diagnostic accuracy data was available for PET-CT and CT scans for both gastric and oesophageal cancer, and for the tumour markers carcinoembryonic antigen (CEA) and cancer antigen 19-9 (CA19-9).

A bivariate analysis of sensitivity and specificity of PET-CT for any site recurrence of gastric cancer gave a pooled sensitivity of 0.82 (95% CI 0.71 to 0.89) and a pooled specificity of 0.82 (95% CI 0.76 to 0.87) with a positive likelihood ratio of 4.6, and a negative likelihood ratio of 0.22, and the Committee concluded therefore that PET-CT did not provide useful information on recurrence.

Similar results were seen for CT for any site recurrence with evidence from individual studies providing not useful or only moderately useful positive and negative likelihood ratios and so the Committee also concluded that CT did not provide useful information on recurrence of gastric cancer.

A number of tumour antigen studies in gastric cancer were reviewed with a combined bivariate analysis for CEA giving a sensitivity of 0.43 (95% CI 0.33 to 0.53) and a specificity of 0.87 (95% CI 0.77 to 0.93) and both positive and negative likelihood ratios giving only

moderately useful information. As a result the Committee concluded that CEA did not provide useful information on recurrence of gastric cancer.

Again, similar results were seen for CA19-9 in gastric cancer, with pooled positive and negative likelihood ratios of 3.2 and 0.66 respectively not providing any robust information on the recurrence of gastric cancer and so the Committee could not recommend routine use of this test.

One study looked at the combination of CEA and CA19-9 with a positive result being defined as elevated levels of both tumour markers. The combination only had sensitivity of 0.19 (95% CI 0.13 to 0.27) but had high specificity of 0.98 (95% CI 0.97 to 0.99), and a very useful positive likelihood ratio of 12.06, suggesting that it would be useful to rule in recurrence of gastric cancer. However, these data were taken from a single Korean study and the Committee did not feel the weight of this evidence in an eastern population would allow them to make a recommendation.

A review of the corresponding evidence for oesophageal cancer showed that PET-CT and CT provided very useful or moderately useful negative likelihood ratios to rule out recurrence, but not useful positive likelihood ratios. The Committee could not therefore recommend the use of PET-CT to detect recurrence of oesophageal cancer at follow-up.

Tumour antigen studies for CEA were available for oesophageal cancer (no studies were available for CA19-9) but did not provide useful positive and negative likelihood ratios and therefore again could not be recommended by the Committee to detect recurrence.

A number of prognostic studies were examined to determine the 1-year, 3-year and 5-year survival rates after gastrectomy and after oesophagectomy, as well as the 1-year, 2-year and 5-year recurrence rates. Combining these data with the results from the diagnostic tests produced estimates of the number of true and false positives and true and false negatives for different diagnostic tests.

From the diagnostic accuracy evidence the Committee evaluated the role of PET-CT, CT, CEA and CA19-9 (and the combination) for detecting gastric cancer recurrence but found the evidence from different studies to be contradictory with no clear indication if these imaging techniques or tests were reliable enough to rule-in or rule-out recurrent disease.

From the similar review of PET-CT, CT or CEA for oesophageal cancer there was also conflicting evidence about the usefulness of these techniques or tests with no clear indication if they could be used to reliably rule-in or rule-out recurrent disease.

The combination of this information with the prognostic data provided an estimate of the number of true and false positives and negatives that could be expected with the diagnostic tests, but the wide variability in these figures confirmed to the Committee that they could not recommend specific imaging techniques or tests to detect the recurrence of oesopago-gastric cancer.

The Committee agreed that the main benefit of their recommendations would be likely to be a reduction in anxiety in people who had undergone curative treatment and had no residual symptoms, as many patients find hospital appointments, tests and scans a stressful and worrying experience. The Committee also recognised that false positive results may lead to additional stress and anxiety for patients.

The Committee also agreed that their recommendations clarified the role of follow-up in asymptomatic people, and would reduce unnecessary investigations and their associated morbidity. By educating patients to seek follow-up if they develop symptoms or have concerns, the Committee also stated that the recommendation would empower patients.

The Committee agreed that there was a small proportion of people who seek regular tests and scans as reassurance that their disease has not recurred and for this group anxiety might be increased by not having access to routine and ongoing follow-up.

The Committee stated that the recommendations might also lead to a small number of patients who would otherwise have had early recurrence of their disease detected, allowing them to receive repeat curative treatment, being 'missed', but this was likely to be a very small number of patients and that there was no evidence of improved survival or outcomes to back up this approach.

The Committee were in agreement that the majority of patients would be picked up when they presented symptomatically, but this approach did necessitate rapid patient-initiated access to specialist services, and they therefore made a recommendation to this effect.

11.1.6.4 Consideration of economic benefits and harms

A systematic review of the economic literature was conducted but no relevant studies were identified which were applicable to this review question.

The 'do not offer' recommendations aim to reduce the intensity of medically-led follow-up and are anticipated to result in cost savings. In particular, the recommendation to not offer routine clinical follow-up is likely to represent a significant change in clinical practice and lead to substantial cost savings. The recommendation to not offer routine radiological surveillance is largely already followed in clinical practice but there will be cost savings for those centres currently offering radiological surveillance.

The recommendation to offer rapid access to the specialist team would be a change in practice in some places with a possible increase in cost. However, it is expected that any increased costs here would be offset by the cost savings resulting from the "do not offer" recommendations.

The recommendations to reduce the intensity of medically led follow-up should also allow resources to be redeployed to provide quality of life directed follow up.

11.1.6.5 Other considerations

The Committee made recommendations based on their clinical experience, and agreed that in many units this reflected current clinical practice. However, the Committee identified the lack of clinical evidence on the role of CT scans or tumour markers in the identification of recurrent disease in asymptomatic people. The Committee therefore made a research recommendation as there may still be uncertainty and variation of practice across the UK.

11.1.6.6 Key conclusions

The Committee agreed that the evidence did not allow them to make recommendations to use specific scans or blood tests to identify recurrence in oesophageal or gastric cancer. Instead they recommended that people should be educated to identify symptoms that may indicate disease recurrence, and that rapid access should be available for these people to receive specialist review.

11.2 Recommendations

49. For people who have no symptoms or evidence of residual disease after treatment for oesophago-gastric cancer with curative intent:

- provide information about the symptoms of recurrent disease, and what to do if they develop these symptoms

- offer rapid access to the oesophago-gastric multidisciplinary team for review, if symptoms develop.

50. For people who have no symptoms or evidence of residual disease after treatment for oesophago-gastric cancer with curative intent, do not offer:

- routine clinical follow-up solely for the detection of recurrent disease
- routine radiological surveillance solely for the detection of recurrent disease.

11.3 Research recommendations

12. Is the routine use of CT and tumour markers effective in detecting recurrent disease suitable for radical treatment in asymptomatic people who have had treatment for oesophago-gastric cancer with curative intent?

Why this is important?

There is no clearly defined follow-up protocol for people with oesophago-gastric cancer treated radically. Detection of early recurrence potentially suitable for radical treatment offers the possibility of increased survival but the best methods of detecting recurrence are unclear, and there is no evidence to show whether early detection leads to improved overall survival. The alternative strategy is to wait until symptoms reoccur and then re-evaluate the further treatment options available. Studies examining the role of screening in this scenario would define whether routine follow-up in asymptomatic people was effective at detecting recurrence and improving overall survival.

Table 234: Research recommendation rationale

Research question	Is the routine use of CT and tumour markers effective in detecting recurrent disease suitable for radical treatment in asymptomatic people who have had treatment for oesophago-gastric cancer with curative intent?
Importance to 'patients' or the population	Many patients seek the reassurance of regular check-ups (including scans and blood tests) to inform them whether their disease has been cured or if it is returning. Likewise, a number of patients find routine check-ups and tests when they feel well and have no symptoms to be alarming and unnecessary. While detection of early recurrence and consequent treatment may lead to improved survival there is no evidence to demonstrate this and so clinical practices may vary, which can also lead to confusion amongst patients
Relevance to NICE guidance	Research in this area could lead to more appropriate recommendations on the role of post-operative imaging and tumour markers in patient follow up
Relevance to the NHS	More appropriate use of post-operative imaging and tumour markers could reduce costs, morbidity due to excessive testing, and potentially improve survival.
National priorities	NHS Outcomes Framework for 2016-17: Improved 1-year and 5-year survival for all cancers
Current evidence base	There is currently no available evidence which links the use of CT and tumour markers to survival outcomes in patients who have undergone radical treatment.
Equality	No issues

Table 235: Research recommendation statements

Criterion	Explanation
Population	People who have undergone radical treatment for oesophago-gastric cancer
Intervention	Routine imaging, routine tumour marker analysis, clinical review on re-presentation with symptoms
Comparator (without the risk factor)	• Each other
Outcome	• Overall survival • Early detection of recurrence • Further radical intervention • Quality of Life • Patient-reported outcomes
Study design	Randomised controlled trial
Timeframe	5 years

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13 Glossary and Abbreviations

Term	Definition
Abstract	Summary of a study, which may be published alone or as an introduction to a full scientific paper.
Adenocarcinoma (AC)	Adenocarcinomas are cancers that develop in the gland cells that produce mucous in the lining of the oesophagus. Adenocarcinomas are the most common type of oesophageal cancer in the UK.
Arm (of a clinical study)	Subsection of individuals within a study who receive one particular intervention, for example placebo arm.
Association	Statistical relationship between 2 or more events, characteristics or other variables. The relationship may or may not be causal.
Attrition bias	Systematic differences between comparison groups for withdrawal or exclusion of participants from a study.
Available case analysis (ACA)	Analysis of data that is available for participants at the end of follow-up.
Baseline	The initial set of measurements at the beginning of a study (after run-in period where applicable) with which subsequent results are compared.
Bias	Influences on a study that can make the results look better or worse than they really are. Bias can occur by chance, deliberately or as a result of systematic errors in the design and execution of a study. It can also occur at different stages in the research process, for example during the collection, analysis, interpretation, publication or review of research data. For examples see Confounding factor, Performance bias, Publication bias Selection bias.
Cancer antigen 19-9 (CA19-9)	Cancer antigen 19-9 is a type of glycosphingolipid that can be measured by radioimmunometric assay and may be elevated in people with upper gastrointestinal cancers.
Carcinoembryonic antigen (CEA)	Carcinoembryonic antigen is a glycosylphosphatidylinositol-cell surface anchored glycoprotein that can be measured in the plasma and may be elevated in people with various gastrointestinal cancers.
Carer	Someone who looks after family, partners or friends in need of help because they are ill, frail or have a disability.
Case-control study	A study to find out the cause(s) of a disease or condition. This is done by comparing a group of patients who have the disease or condition (cases) with a group of people who do not have it (controls) but who are otherwise as similar as possible (in characteristics thought to be unrelated to the causes of the disease or condition). This means the researcher can look for aspects of their lives that differ to see if they may cause the condition. Such studies are retrospective because they look back in time from the outcome to the possible causes of a disease or condition.
Case series	Report of a number of cases of a given disease, usually covering the course of the disease and the response to treatment. There is no comparison (control) group of patients.
Chemotherapy (CT)	The use of drugs to treat cancer
Chemoradiotherapy (CRT)	A combination of chemotherapy and radiotherapy for the treatment of oesophago-gastric cancer
Computed tomography (CT)	A CT scan uses computer-processed combinations of X-ray images taken from different angles to produce cross-sectional images of specific areas of the body.

Term	Definition
Confidence in the Evidence from Reviews of Qualitative Research (CERQual)	A tool that looks of four components of qualitative evidence to assess it and provide a measure of confidence in the research
Critical Appraisal Skills Programme (CASP)	A tool comprising 11 questions that assess the validity, results, and applicability of a randomised control trial.
Clinical audit	A systematic process for setting and monitoring standards of clinical care. Whereas 'guidelines' define what the best clinical practice should be, 'audit' investigates whether best practice is being carried out. Clinical audit can be described as a cycle or spiral. Within the cycle there are stages that follow a systematic process of establishing best practice, measuring care against specific criteria, taking action to improve care and monitoring to sustain improvement. The spiral suggests that as the process continues, each cycle aspires to a higher level of quality.
Clinical effectiveness	How well a specific test or treatment works when used in the 'real world' (for example when used by a doctor with a patient at home), rather than in a carefully controlled clinical trial. Trials that assess clinical effectiveness are sometimes called management trials. Clinical effectiveness is not the same as efficacy.
Clinical efficacy	The extent to which an intervention is active when studied under controlled research conditions.
Clinical nurse specialist (CNS)	An advanced practice nurse who can provide expert advice related to a specific condition such as oesophago-gastric cancer.
Clinician	A healthcare professional who provides patient care. For example a doctor, nurse or physiotherapist.
Cochrane Review	The Cochrane Library consists of a regularly updated collection of evidence-based medicine databases including the Cochrane Database of Systematic Reviews (reviews of RCTs prepared by the Cochrane Collaboration).
Cohort study	A study with 2 or more groups of people – cohorts – with similar characteristics. One group receives a treatment, is exposed to a risk factor or has a particular symptom and the other group does not. The study follows their progress over time and records what happens.
Comorbidity	A disease or condition that someone has in addition to the health problem being studied or treated.
Concealment of allocation	The process used to ensure that the person deciding to enter a participant into an RCT does not know the comparison group into which that individual will be allocated. This is distinct from blinding and is aimed at preventing selection bias. Some attempts at concealing allocation are more prone to manipulation than others and the method of allocation concealment is used as an assessment of the quality of a trial.
Confidence interval (CI)	There is always some uncertainty in research. This is because a small group of patients is studied to predict the effects of a treatment on the wider population. The confidence interval is a way of expressing how certain we are about the findings from a study, using statistics. It gives a range of results that is likely to include the 'true' value for the population. The CI is usually stated as '95% CI', which means that the range of values has a 95 in 100 chance of including the 'true' value. For example, a study may state that "based on our sample findings, we are 95% certain that the 'true' population blood pressure is not higher than 150 and not lower than 110". In such a case the 95% CI would be 110 to 150. A wide confidence interval indicates a lack of certainty about the true effect of the test or treatment – often because a small group of patients has been studied. A narrow confidence interval indicates a more precise estimate (for example if a large number of patients have been studied).

Term	Definition
Confounding factor	Something that influences a study and can result in misleading findings if it is not understood or appropriately dealt with. For example, a study of heart disease may look at a group of people who exercise regularly and a group who do not exercise. If the ages of the people in the 2 groups are different, then any difference in heart disease rates between the 2 groups could be because of age rather than exercise. Therefore age is a confounding factor.
Continuous outcome	Data with a potentially infinite number of possible values within a given range. Height, weight and blood pressure are examples of continuous variables.
Control group	A group of people in a study who do not receive the treatment or test being studied. Instead, they may receive the standard treatment (sometimes called 'usual care') or a dummy treatment (placebo). The results for the control group are compared with those for a group receiving the treatment being tested. The aim is to check for any differences. Ideally, the people in the control group should be as similar as possible to those in the treatment group, to make it as easy as possible to detect any effects due to the treatment.
Cost–benefit analysis (CBA)	Cost-benefit analysis is one of the tools used to carry out an economic evaluation. The costs and benefits are measured using the same monetary units (for example UK pounds) to see whether the benefits exceed the costs.
Cost–consequence analysis (CCA)	Cost-consequence analysis is one of the tools used to carry out an economic evaluation. This compares the costs (such as treatment and hospital care) with the consequences (such as health outcomes) of a test or treatment with a suitable alternative. Unlike cost–benefit analysis or cost-effectiveness analysis, it does not attempt to summarise outcomes in a single measure (such as the quality adjusted life year) or in financial terms. Instead, outcomes are shown in their natural units (some of which may be monetary) and it is left to decision-makers to determine whether, overall, the treatment is worth carrying out.
Cost-effectiveness analysis (CEA)	Cost-effectiveness analysis is one of the tools used to carry out an economic evaluation. The benefits are expressed in non-monetary terms related to health, such as symptom-free days, heart attacks avoided, deaths avoided or life years gained (that is, the number of years by which life is extended as a result of the intervention).
Cost-effectiveness model	An explicit mathematical framework which is used to represent clinical decision problems and incorporate evidence from a variety of sources in order to estimate the costs and health outcomes.
Cost–utility analysis (CUA)	Cost–utility analysis is one of the tools used to carry out an economic evaluation. The benefits are assessed in terms of both quality and duration of life, and expressed as quality adjusted life years (QALYs). See also Utility.
COX proportional hazard model	In survival analysis, a statistical model that asserts that the effect of the study factors (for example the intervention of interest) on the hazard rate (the risk of occurrence of an event) in the study population is multiplicative and does not change over time.
Credible interval (CrI)	The Bayesian equivalent of a confidence interval.
Dissection stage (D-stage) resections in gastrectomy	D-stage resections in gastrectomy: **D0 resection** refers to removal of the tumour but no resection of the surrounding lymph nodes **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

Term	Definition
	D3 dissection refers to the removal of more distant nodes (stations 12-15) in addition to D1/2 nodes.
Decision analysis	An explicit quantitative approach to decision-making under uncertainty, based on evidence from research. This evidence is translated into probabilities, and then into diagrams or decision trees which direct the clinician through a succession of possible scenarios, actions and outcomes.
Dichotomous outcomes	Outcome that can take one of 2 possible values, such as dead/alive, smoker/non-smoker, present/not present (also called binary data).
Discounting	Costs and perhaps benefits incurred today have a higher value than costs and benefits occurring in the future. Discounting health benefits reflects individual preference for benefits to be experienced in the present rather than the future. Discounting costs reflects individual preference for costs to be experienced in the future rather than the present.
Dominance	A health economics term. When comparing tests or treatments, an option that is both less effective and costs more is said to be 'dominated' by the alternative.
Drop-out	A participant who withdraws from a trial before the end.
Dysphagia	Difficulty swallowing
Economic evaluation	An economic evaluation is used to assess the cost effectiveness of healthcare interventions (that is, to compare the costs and benefits of a healthcare intervention to assess whether it is worth doing). The aim of an economic evaluation is to maximise the level of benefits – health effects – relative to the resources available. It should be used to inform and support the decision-making process; it is not supposed to replace the judgement of healthcare professionals. There are several types of economic evaluation: cost–benefit analysis, cost–consequence analysis, cost-effectiveness analysis, cost-minimisation analysis and cost–utility analysis. They use similar methods to define and evaluate costs, but differ in the way they estimate the benefits of a particular drug, programme or intervention.
Effect (as in effect measure, treatment effect, estimate of effect, effect size)	A measure that shows the magnitude of the outcome in 1 group compared with that in a control group. For example, if the absolute risk reduction is shown to be 5% and it is the outcome of interest, the effect size is 5%. The effect size is usually tested, using statistics, to find out how likely it is that the effect is a result of the treatment and has not just happened by chance.
Effectiveness	How beneficial a test or treatment is under usual or everyday conditions.
Efficacy	How beneficial a test, treatment or public health intervention is under ideal conditions (for example in a laboratory).
Endoscopic mucosal resection (EMR)	Endoscopic mucosal resection involves removing abnormal areas in the lining of the oesophagus, using an endoscopic technique (a camera passed through the mouth).
Endoscopic submucosal dissection (ESD)	Endoscopic submucosal dissection involves removing superficial gastrointestinal cancers by injecting fluid into the submucosa to elevate the lesion, cutting the surrounding mucosa of the lesion, and dissecting the submucosa beneath the lesion.
Epidemiological study	The study of a disease within a population, defining its incidence and prevalence and examining the roles of external influences (for example infection, diet) and interventions.
EQ-5D (EuroQol 5 dimensions)	A standardised instrument used to measure health-related quality of life. It provides a single index value for health status.

Term	Definition
Equivalence study	A trial designed to determine whether the response to two or more treatments differs by an amount that is clinically unimportant. This is usually demonstrated by showing that the true treatment difference is likely to lie between a lower and an upper equivalence level of clinically acceptable differences.
Evidence	Information on which a decision or guidance is based. Evidence is obtained from a range of sources including RCTs, observational studies, expert opinion (of clinical professionals or patients).
Exclusion criteria (clinical study)	Criteria that define who is not eligible to participate in a clinical study.
Exclusion criteria (literature review)	Explicit standards used to decide which studies should be excluded from consideration as potential sources of evidence.
Extended dominance	If Option A is both more clinically effective than Option B and has a lower cost per unit of effect when both are compared with a do-nothing alternative, then Option A is said to have extended dominance over Option B. Option A is therefore more cost effective and should be preferred, other things remaining equal.
Extrapolation	An assumption that the results of studies of a specific population will also hold true for another population with similar characteristics.
False negative	A diagnostic test result that incorrectly indicates that an individual does not have the disease of interest, when they do actually have it.
False positive	A diagnostic test result that incorrectly indicates that an individual has the disease of interest, when they actually do not have it.
Fixed-effect model	In meta-analysis, a model that calculates a pooled effect estimate using the assumption that all observed variation between studies is caused by random sample variability. Studies are assumed to estimating the same overall effect.
5-fluorouracil (5-FU)	A chemotherapy agent used in the treatment of oesophago-gastric cancer
Follow-up	Observation over a period of time of an individual, group or initially defined population whose appropriate characteristics have been assessed in order to observe changes in health status or health-related variables.
Forest plot	A graphical representation of the individual results of each study included in a meta-analysis together with the combined meta-analysis result. The plot also allows readers to see the heterogeneity among the results of the studies. The results of individual studies are shown as squares centred on each study's point estimate. A horizontal line runs through each square to show each study's confidence interval. The overall estimate from the meta-analysis and its confidence interval are shown at the bottom, represented as a diamond. The centre of the diamond represents the pooled point estimate, and its horizontal tips represent the confidence interval.
Generalisability	The extent to which the results of a study hold true for groups that did not participate in the research.
Gold standard	A method, procedure or measurement that is widely accepted as being the best available to test for or treat a disease.
GRADE, GRADE profile	A system developed by the GRADE Working Group to address the short-comings of present grading systems in healthcare. The GRADE system uses a common, sensible and transparent approach to grading the quality of evidence. The results of applying the GRADE system to clinical trial data are displayed in a table known as a GRADE profile.
Harms	Adverse effects of an intervention.

Term	Definition
Hazard ratio	A hazard is the rate at which events happen, so that the probability of an event happening in a short time interval is the length of time multiplied by the hazard. Although the hazard may vary with time, the assumption in proportional hazard models for survival analysis is that the hazard in one group is a constant proportion of the hazard in the other group. This proportion is the hazard ratio.
Health economics	Study or analysis of the cost of using and distributing healthcare resources.
Health-related quality of life (HRQoL)	A measure of the effects of an illness to see how it affects someone's day-to-day life.
Heterogeneity	The term is used in meta-analyses and systematic reviews to describe when the results of a test or treatment (or estimates of its effect) differ.
Holistic care	Holistic care includes physical, emotional, social, financial and spiritual issues that may be important to people.
Intraluminal radiotherapy (ILRT)	Delivery of radiotherapy treatment directly into the body – such as via the oesophagus.
Imprecision	Results are imprecise when studies include relatively few patients and few events and thus have wide confidence intervals around the estimate of effect.
Improving Outcomes in Upper Gastro-intestinal Cancers (IOG)	A document published by the NHS Executive in 2001. The full title was: *Guidance on Commissioning Cancer Services* *Improving Outcomes in Upper Gastro-intestinal Cancers* *The Manual* This document defines the model of care and organisation of services for the treatment of oesophago-gastric cancers.
Incidence	The incidence of a disease is the rate at which new cases occur in a population during a specified period.
Inclusion criteria (clinical study)	Specific criteria that define who is eligible to participate in a clinical study.
Inclusion criteria (literature review)	Explicit criteria used to decide which studies should be considered as potential sources of evidence.
Incremental cost	The extra cost linked to using one test or treatment rather than another. Or the additional cost of doing a test or providing a treatment more frequently.
Incremental cost-effectiveness ratio (ICER)	The difference in the mean costs in the population of interest divided by the differences in the mean outcomes in the population of interest for one treatment compared with another.
Incremental net benefit (INB)	The value (usually in monetary terms) of an intervention net of its cost compared with a comparator intervention. The INB can be calculated for a given cost-effectiveness (willingness to pay) threshold. If the threshold is £20,000 per QALY gained then the INB is calculated as: (£20,000×QALYs gained) minus incremental cost.
Indirectness	The available evidence is different to the review question being addressed, in terms of population, intervention, comparison and outcome (PICO).
Intention-to-treat analysis (ITT)	An assessment of the people taking part in a clinical trial, based on the group they were initially (and randomly) allocated to. This is regardless of whether or not they dropped out, fully complied with the treatment or switched to an alternative treatment. Intention-to-treat analyses are often used to assess clinical effectiveness because they mirror actual practice: that is, not everyone complies with treatment and the treatment people receive may be changed according to how they respond to it.
Intervention	In medical terms this could be a drug treatment, surgical procedure, diagnostic or psychological therapy. Examples of public health

Term	Definition
	interventions could include action to help someone to be physically active or to eat a more healthy diet.
Intraperitoneal chemotherapy (IPC)	The administration of chemotherapy drugs directly into the peritoneal (abdominal) cavity.
Kappa statistic	A statistical measure of inter-rater agreement that takes into account the agreement occurring by chance
Length of stay	The total number of days a patient stays in hospital.
Leucovorin (LV)	Leucovorin is another name for folinic acid. It may be used in combination with 5-fluorouracil to treat certain cancers.
Licence	See Product licence.
Life years gained	Mean average years of life gained per person as a result of the intervention compared with an alternative intervention.
Likelihood ratio	The likelihood ratio combines information about the sensitivity and specificity. It tells you how much a positive or negative result changes the likelihood that a patient would have the disease. The likelihood ratio of a positive test result (LR+) is sensitivity divided by (1 minus specificity).
Loss to follow-up	Patients who have withdrawn from the clinical trial at the point of follow-up.
Lymphadenectomy resections in oesophagectomy	Lymphadenectomy resections in 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
Magnetic resonance imaging (MRI)	Magnetic resonance imaging (MRI) is a technique that uses a magnetic field and radio waves to create detailed images of the organs and tissues within a body.
Markov model	A method for estimating long-term costs and effects for recurrent or chronic conditions, based on health states and the probability of transition between them within a given time period (cycle).
Mean	An average value, calculated by adding all the observations and dividing by the number of observations.
Mean difference	In meta-analysis, a method used to combine measures on continuous scales (such as weight), where the mean, standard deviation and sample size in each group are known. The weight given to the difference in means from each study (for example how much influence each study has on the overall results of the meta-analysis) is determined by the precision of its estimate of effect.
Median	The value of the observation that comes half-way when the observations are ranked in order.
Meta-analysis	A method often used in systematic reviews. Results from several studies of the same test or treatment are combined to estimate the overall effect of the treatment.
Minimal important difference (MID)	Threshold for clinical importance which represents the minimal important difference for benefit or for harm; for example the threshold at which drug A is less effective than drug B by an amount that is clinically important to patients.
Minimally invasive oesophagectomy (MIO)	Minimally invasive oesophagectomy (MIO) is used for operations

Term	Definition
	involving thoracoscopic mobilisation of the oesophagus and laparoscopic mobilisation of the stomach
Monte Carlo	A technique used to approximate the probability of certain outcomes by running multiple simulations using random variables.
Multidisciplinary team (MDT)	A team within a healthcare organisation comprising a number of different healthcare professionals.
Multidisciplinary meeting (MDM)	A meeting of a multidisciplinary team, usually formed to agree appropriate management plans for individual patients. (See also 'Specialist MDM')
Multivariate model	A statistical model for analysis of the relationship between 2 or more predictors, (independent) variables and the outcome (dependent) variable.
National Oesophago-Gastric Cancer Audit (NOGCA)	The National Oesophago-Gastric Cancer Audit covers the quality of care given to patients with oesophago-gastric cancer, and is usually conducted every year. Results are published on the website of the Association of Upper Gastrointestinal Surgeons.
Negative predictive value (NPV)	Negative predictive value is the probability that subjects with a negative screening test do not have the disease being tested for.
Net monetary benefit (NMB)	The value (usually in monetary terms) of an intervention net of its cost. The NMB can be calculated for a given cost-effectiveness (willingness to pay) threshold. If the threshold is £20,000 per QALY gained then the NMB is calculated as: (£20,000×QALYs gained) minus cost.
Network meta-analysis (NMA)	Meta-analysis in which multiple treatments (that is, 3 or more) are being compared using both direct comparisons of interventions within RCTs and indirect comparisons across trials based on a common comparator.
Non-inferiority trial	A trial designed to determine whether the effect of a new treatment is not worse than a standard treatment by more than a pre-specified amount. A one-sided version of an equivalence trial.
Number needed to treat (NNT)	The average number of patients who need to be treated to get a positive outcome. For example, if the NNT is 4, then 4 patients would have to be treated to ensure 1 of them gets better. The closer the NNT is to 1, the better the treatment. For example, if you give a stroke prevention drug to 20 people before 1 stroke is prevented, the number needed to treat is 20.
Observational study	Individuals or groups are observed or certain factors are measured. No attempt is made to affect the outcome. For example, an observational study of a disease or treatment would allow 'nature' or usual medical care to take its course. Changes or differences in one characteristic (for example whether or not people received a specific treatment or intervention) are studied without intervening. There is a greater risk of selection bias than in experimental studies.
Odds ratio (OR)	Odds are a way to represent how likely it is that something will happen (the probability). An odds ratio compares the probability of something in one group with the probability of the same thing in another. An odds ratio of 1 between 2 groups would show that the probability of the event (for example a person developing a disease, or a treatment working) is the same for both. An odds ratio greater than 1 means the event is more likely in the first group. An odds ratio less than 1 means that the event is less likely in the first group. Sometimes probability can be compared across more than 2 groups – in this case, one of the groups is chosen as the 'reference category' and the odds ratio is calculated for each group compared with the reference category. For example, to compare the risk of dying from lung cancer for non-smokers, occasional smokers and regular smokers, non-smokers could be used as the reference category. Odds ratios would be worked

Term	Definition
	out for occasional smokers compared with non-smokers and for regular smokers compared with non-smokers. See also Confidence interval, Relative risk.
Oesophageal adenocarcinoma (OAC)	An adenocarcinoma of the oesophagus
Oesophago-gastric (OG) cancer	Cancer affecting the oesophagus, stomach, or junction between the oesophagus and the stomach
Opportunity cost	The loss of other healthcare programmes displaced by investment in or introduction of another intervention. This may be best measured by the health benefits that could have been achieved had the money been spent on the next best alternative healthcare intervention.
Outcome	The impact that a test, treatment, policy, programme or other intervention has on a person, group or population. Outcomes from interventions to improve the public's health could include changes in knowledge and behaviour related to health, societal changes (for example a reduction in crime rates) and a change in people's health and wellbeing or health status. In clinical terms, outcomes could include the number of patients who fully recover from an illness or the number of hospital admissions, and an improvement or deterioration in someone's health, functional ability, symptoms or situation. Researchers should decide what outcomes to measure before a study begins.
p value	The p value is a statistical measure that indicates whether or not an effect is statistically significant. For example, if a study comparing 2 treatments found that one seems more effective than the other, the p value is the probability of obtaining these results by chance. By convention, if the p value is below 0.05 (that is, there is less than a 5% probability that the results occurred by chance) it is considered that there probably is a real difference between treatments. If the p value is 0.001 or less (less than a 1% probability that the results occurred by chance), the result is seen as highly significant. If the p value shows that there is likely to be a difference between treatments, the confidence interval describes how big the difference in effect might be.
Palliative management	Management of oesophago-gastric cancer that is non curative, but where the focus is on alleviation of symptoms and ensuring the greatest quality of life for the longest possible time.
Patient-reported outcome measures (PROMs)	Patient Reported Outcome Measures (PROMs) assess the quality of care delivered to NHS patients from the patient perspective, generally using surveys before and after procedures or interventions.
Percutaneous endoscopic gastrostomy (PEG)	Percutaneous endoscopic gastrostomy is an endoscopic procedure in which a tube (PEG tube) is passed into a patient's stomach through the abdominal wall, most commonly to provide a means of feeding when oral intake is not adequate.
Performance bias	Systematic differences between intervention groups in care provided apart from the intervention being evaluated. Blinding of study participants (both the recipients and providers of care) is used to protect against performance bias.
Placebo	A fake (or dummy) treatment given to participants in the control group of a clinical trial. It is indistinguishable from the actual treatment (which is given to participants in the experimental group). The aim is to determine what effect the experimental treatment has had over and above any placebo effect caused because someone has received (or thinks they have received) care or attention.
Placebo effect	A beneficial (or adverse) effect produced by a placebo and not due to any property of the placebo itself.

Term	Definition
Positive predictive value	Positive predictive value is the probability that subjects with a positive screening test truly have the disease being tested for.
Positron emission tomography (PET)	A PET scan uses radiation to produce 3-D, colour images of the organs. It works be detecting radiation that is emitted by a radiotracer (usually a radioactive glucose injection, F-18 FDG) which is injected into the body. Areas of high metabolic activity show up as 'bright' areas on the scan.
Positron emission tomography – computed tomography (PET-CT)	A combination of a PET scan and a CT scan, which allows the areas of high metabolic activity seen in the PET scan to be correlated with the exact location in the body, as seen on the CT scan.
Post-hoc analysis	Statistical analyses that are not specified in the trial protocol and are generally suggested by the data.
Power (statistical)	The ability to demonstrate an association when one exists. Power is related to sample size; the larger the sample size, the greater the power and the lower the risk that a possible association could be missed.
Prevalence	The prevalence of a disease is the proportion of a population that are cases at a point in time.
Primary care	Healthcare delivered outside hospitals. It includes a range of services provided by GPs, nurses, health visitors, midwives and other healthcare professionals and allied health professionals such as dentists, pharmacists and opticians.
Primary outcome	The outcome of greatest importance, usually the one in a study that the power calculation is based on.
Product licence	An authorisation from the Medicines and Healthcare Products Regulatory Agency (MHRA) to market a medicinal product.
Prognosis	A probable course or outcome of a disease. Prognostic factors are patient or disease characteristics that influence the course. Good prognosis is associated with low rate of undesirable outcomes; poor prognosis is associated with a high rate of undesirable outcomes.
Prospective study	A research study in which the health or other characteristic of participants is monitored (or 'followed up') for a period of time, with events recorded as they happen. This contrasts with retrospective studies.
Protocol (review)	A document written prior to commencing a review that details exactly how evidence to answer a review question will be obtained and synthesised. It defines in detail the population of interest, the interventions, the comparators/controls and the outcomes of interest (PICO).
Publication bias	Publication bias occurs when researchers publish the results of studies showing that a treatment works well and don't publish those showing it did not have any effect. If this happens, analysis of the published results will not give an accurate idea of how well the treatment works. This type of bias can be assessed by a funnel plot.
Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2)	QUADAS-2 is a tool that is used to assess the quality of diagnostic accuracy studies
Quality of life	See Health-related quality of life.
Quality adjusted life year (QALY)	A measure of the state of health of a person or group in which the benefits, in terms of length of life, are adjusted to reflect the quality-of-life. One QALY is equal to 1 year of life in perfect health. QALYS are calculated by estimating the years of life remaining for a patient following a particular treatment or intervention and weighting each year with a quality-of-life score (on a scale of 0 to 1). It is often measured in terms of

Term	Definition
	the person's ability to perform the activities of daily life, and freedom from pain and mental disturbance.
Radical treatment	A treatment for oesophago-gastric cancer which aims to remove or destroy the cancer completely; curative treatment.
Radiotherapy (RT)	The use of high-energy rays, usually x-rays, to treat disease. It destroys cancer cells, but normal cells can also be damaged by radiotherapy.
Random effect model	In meta-analysis, a model that calculates a pooled effect estimate using the assumption that each study is estimating a different true treatment effect due to real differences between studies. Observed variation in effects are therefore caused by a combination of random sample variability (within-study variation) and heterogeneity between studies (between-study variation). The overall effects is an average of the estimated true study effects.
Randomisation	Assigning participants in a research study to different groups without taking any similarities or differences between them into account. For example, it could involve using a random numbers table or a computer-generated random sequence. It means that each individual (or each group in the case of cluster randomisation) has the same chance of receiving each intervention.
Randomised controlled trial (RCT)	A study in which a number of similar people are randomly assigned to 2 (or more) groups to test a specific drug or treatment. One group (the experimental group) receives the treatment being tested, the other (the comparison or control group) receives an alternative treatment, a dummy treatment (placebo) or no treatment at all. The groups are followed up to see how effective the experimental treatment was. Outcomes are measured at specific times and any difference in response between the groups is assessed statistically. This method is also used to reduce bias.
Reference standard	The test that is considered to be the best available method to establish the presence or absence of the outcome – this may not be the one that is routinely used in practice.
Relative risk (RR)	The ratio of the risk of disease or death among those exposed to certain conditions compared with the risk for those who are not exposed to the same conditions (for example the risk of people who smoke getting lung cancer compared with the risk for people who do not smoke). If both groups face the same level of risk, the relative risk is 1. If the first group had a relative risk of 2, subjects in that group would be twice as likely to have the event happen. A relative risk of less than 1 means the outcome is less likely in the first group. Relative risk is sometimes referred to as risk ratio.
Reporting bias	See Publication bias.
Resource implication	The likely impact in terms of finance, workforce or other NHS resources.
Retrospective study	A research study that focuses on the past and present. The study examines past exposure to suspected risk factors for the disease or condition. Unlike prospective studies, it does not cover events that occur after the study group is selected.
Review question	The plan or set of steps to be followed in a study. A protocol for a systematic review describes the rationale for the review, the objectives and the methods that will be used to locate, select and critically appraise studies, and to collect and analyse data from the included studies.
Secondary care	Care provided in hospitals.
Secondary outcome	An outcome used to evaluate additional effects of the intervention deemed a priori as being less important than the primary outcomes.
Selection bias	Selection bias occurs if:

Term	Definition
	• The characteristics of the people selected for a study differ from the wider population from which they have been drawn; or • There are differences between groups of participants in a study in terms of how likely they are to get better.
Sensitivity	How well a test detects the thing it is testing for. If a diagnostic test for a disease has high sensitivity, it is likely to pick up all cases of the disease in people who have it (that is, give a 'true positive' result). But if a test is too sensitive it will sometimes also give a positive result in people who don't have the disease (that is, give a 'false positive'). For example, if a test were developed to detect if a woman is 6 months pregnant, a very sensitive test would detect everyone who was 6 months pregnant but would probably also include those who are 5 and 7 months pregnant. If the same test were more specific (sometimes referred to as having higher specificity), it would detect only those who are 6 months pregnant and someone who was 5 months pregnant would get a negative result (a 'true negative'). But it would probably also miss some people who were 6 months pregnant (that is, give a 'false negative'). Breast screening is a 'real-life' example. The number of women who are recalled for a second breast screening test is relatively high because the test is very sensitive. If it were made more specific, people who don't have the disease would be less likely to be called back for a second test but more women who have the disease would be missed.
Sensitivity analysis	A means of representing uncertainty in the results of an analysis. Uncertainty may arise from missing data, imprecise estimates or methodological controversy. Sensitivity analysis also allows for exploring the generalisability of results to other settings. The analysis is repeated using different assumptions to examine the effect on the results. • One-way simple sensitivity analysis (univariate analysis) – each parameter is varied individually in order to isolate the consequences of each parameter on the results of the study. • Multi-way simple sensitivity analysis (scenario analysis) – 2 or more parameters are varied at the same time and the overall effect on the results is evaluated. • Threshold sensitivity analysis – the critical value of parameters above or below which the conclusions of the study will change are identified. • Probabilistic sensitivity analysis – probability distributions are assigned to the uncertain parameters and are incorporated into evaluation models based on decision analytical techniques (for example Monte Carlo simulation).
Significance (statistical)	A result is deemed statistically significant if the probability of the result occurring by chance is less than 1 in 20 ($p<0.05$).
Specialist cancer care dietitian	A specialist dietitian who spends a significant amount of time working in cancer care and has experience, insight and understanding into the complex issues around nutrition in this setting (Level 3)
Specialist oesophago-gastric cancer dietitian	A senior specialist dietitian who has expert knowledge and experience, working solely with people who have oesophago-gastric cancer (Level 4)
Specialist multidisciplinary meeting (SMDM)	A multidisciplinary meeting which includes specialists in the treatment of oesophago-gastric cancer.
Specificity	The proportion of true negatives that are correctly identified as such. For example, in diagnostic testing the specificity is the proportion of non-cases correctly diagnosed as non-cases. In terms of literature searching a highly specific search is generally narrow and aimed at picking up the key papers in a field and avoiding a wide range of papers.

Term	Definition
	See also Sensitivity.
Squamous cell carcinoma (SCC)	Squamous-cell carcinoma arises from the epithelial cells that line the oesophagus, and is less common in the UK than adenocarcinoma.
Stakeholder	An organisation with an interest in a topic on which NICE is developing a clinical guideline or piece of public health guidance. Organisations that register as stakeholders can comment on the draft scope and the draft guidance. Stakeholders may be: • manufacturers of drugs or equipment • national patient and carer organisations • NHS organisations • organisations representing healthcare professionals.
Standard deviation (SD)	A measure of the spread or dispersion of a set of observations, calculated as the average difference from the mean value in the sample.
Subgroup analysis	An analysis in which the intervention effect is evaluated in a defined subset of the participants in a trial, or in complementary subsets.
Submucosal 1 (SM1) (and SM2, SM3)	Submucosal oesophageal adenocarcinomas (T1b) can be further described by the degree of invasion into the submucosal layer. • Submucosal 1 (SM1) invades the upper third of the submucosal layer • Submucosal 2 (SM2) invades the middle third of the submucosal layer • Submucosal 3 (SM3) invades the lower third of the submucosal layer.
Systematic review	A review in which evidence from scientific studies has been identified, appraised and synthesised in a methodical way according to predetermined criteria. It may include a meta-analysis.
Tetrahydafolic acid (THF)	Tetrahydrofolic acid is synthesized in cells from folic acid by the enzyme, folic acid reductase. Inhibition of this process (by certain chemotherapy agents) leads to impairment of cell division.
Time horizon	The time span over which costs and health outcomes are considered in a decision analysis or economic evaluation.
Treatment allocation	Assigning a participant to a particular arm of a trial.
True negative	A diagnostic test result that correctly indicates that an individual does not have the disease of interest when they actually do not have it.
True positive	A diagnostic test result that correctly indicates that an individual has the disease of interest when they do actually have it.
Univariate	Analysis which separately explores each variable in a data set.
Utility	In health economics, a utility is the measure of the preference or value that an individual or society places upon a particular health state. It is generally a number between 0 (representing death) and 1 (perfect health). The most widely used measure of benefit in cost-utility analysis is the quality-adjusted life year, but other measures include disability-adjusted life years (DALYs) and healthy year equivalents (HYEs).

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14 Appendices

See separate documents as follows:

Appendix A: Scope

Appendix B: Stakeholders

Appendix C: Committee declarations of interest

Appendix D: Review protocols

Appendix E: Search strategies

Appendix F: Evidence tables

Appendix G: GRADE profiles

Appendix H: Forest plots

Appendix I: Cost-effectiveness analyses

Appendix J: Excluded studies

Appendix K: Included studies

Appendix L: Health economic evidence review

Appendix M: Network meta-analysis