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# Chemoradiotherapy versus chemoradiotherapy plus surgery for esophageal cancer (Review)

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[Intervention Review]

# Chemoradiotherapy versus chemoradiotherapy plus surgery for esophageal cancer

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## ABSTRACT

### Background

Please see Appendix 4 for a glossary of terms.

The outcome of patients with esophageal cancer is generally poor. Although multimodal therapy is standard, there is conflicting evidence regarding the addition of esophagectomy to chemoradiotherapy.

### Objectives

To compare the effectiveness and safety of chemoradiotherapy plus surgery with that of chemoradiotherapy alone in people with nonmetastatic esophageal carcinoma.

### Search methods

We performed a computerized search for relevant studies, up to Feburary 2017, on the CENTRAL, MEDLINE, and Embase databases using MeSH headings and keywords. We searched five online databases of clinical trials, handsearched conference proceedings, and screened reference lists of retrieved papers.

### Selection criteria

We included randomized controlled trials (RCTs) comparing chemoradiotherapy plus esophagectomy with chemoradiotherapy alone for localized esophageal carcinoma. We excluded RCTs comparing chemotherapy or radiotherapy alone with esophagectomy.

### Data collection and analysis

Two authors independently selected studies, extracted data, and assessed risk of bias and the quality of the evidence, using standardized Cochrane methodological procedures. The primary outcome was overall survival (OS), estimated with Hazard Ratio (HR). Secondary outcomes, estimated with risk ratio (RR), were local and distant progression-free survival (PFS), quality of life (QoL), treatment-related mortality and morbidity, and use of salvage procedures for dysphagia. Data were analyzed using a random effects model in Review Manager 5.3 software.

### Main results

From 2667 references, we identified two randomized studies, in six reports, that included 431 participants. All participants were clinically staged to have at least T3 and/or node positive thoracic esophageal carcinoma, 93% of which was squamous cell histology. The risk of methodological bias of the included studies was low to moderate.

High-quality evidence found the addition of esophagectomy had little or no difference on overall survival (HR 0.99, 95% CI 0.79 to 1.24; P = 0.92; $I^2$ = 0%; two trials). Neither study reported PFS, therefore, freedom from loco-regional relapse was used as a proxy. Moderate-quality evidence suggested that the addition of esophagectomy probably improved freedom from locoregional relapse (HR 0.55, 95% CI 0.39 to 0.76; P = 0.0004; $I^2$ = 0%; two trials), but low-quality evidence suggested it may increase the risk of treatment-related mortality (RR 5.11, 95% CI 1.74 to 15.02; P = 0.003; $I^2$ = 2%; two trials).

The other pre-specified outcomes (quality of life, treatment-related toxicity, and use of salvage procedures for dysphagia) were reported by only one study, which found very low-quality evidence that use of esophagectomy was associated with reduced short-term QoL (MD 0.93, 95% CI 0.24 to 1.62), and low-quality evidence that it reduced use of salvage procedures for dysphagia (HR 0.52, 95% CI 0.36 to 0.75). Neither study compared treatment-related morbidity between treatment groups.

### Authors' conclusions

Based on the available evidence, the addition of esophagectomy to chemoradiotherapy in locally advanced esophageal squamous cell carcinoma, provides little or no difference on overall survival, and may be associated with higher treatment-related mortality. The addition of esophagectomy probably delays locoregional relapse, however, this end point was not well defined in the included studies. It is undetermined whether these results can be applied to the treatment of adenocarcinomas, tumors involving the distal esophagus and gastro-esophageal junction, and to people with poor response to chemoradiation.

## PLAIN LANGUAGE SUMMARY

### The benefits and side effects of adding surgery to chemoradiotherapy for the treatment of esophageal cancer that can be surgically removed

### Review question

Does the addition of surgery to chemoradiotherapy, improve survival in people with resectable esophageal cancer (cancer that can be surgically removed)?

### Background

Cancer of the esophagus (muscular tube that leads from the mouth through the throat to the stomach) is a lethal condition. It is usually treated with surgery, radiotherapy, chemotherapy, or a combination of these. It is unclear if adding surgery after chemoradiotherapy (chemotherapy plus radiation) adds any benefit for people with esophageal cancer.

### Study characteristics

We included two randomized studies, in six published reports, with 431 participants with locally advanced esophageal cancer. We searched biomedical databases, clinical trial registries, conference proceedings, and reference lists up to 7 February 2017 for studies.

### Quality of the evidence

The quality of evidence ranged from very low to high, depending on the outcome being assessed, because the trials were small and at unclear or high risk of bias (a systematic error or deviation from the truth that affects the results, favouring one treatment over another).

### Key results

We found evidence that adding surgery reduced the risk of the cancer recurring at the primary site, but did not improve overall survival. Moreover, there were more treatment-related deaths in the group of participants who underwent surgery.

**Summary of findings for the main comparison. Chemoradiotherapy versus chemoradiotherapy plus surgery for esophageal cancer**

| Chemoradiotherapy versus chemoradiotherapy plus surgery for esophageal cancer | | | | | |
|---|---|---|---|---|---|
| **Patient or population:** nonmetastatic esophageal cancer<br>**Setting:** hospital<br>**Intervention:** chemoradiotherapy plus surgery<br>**Comparison:** chemoradiotherapy alone | | | | | |
| **Outcomes** | **Anticipated absolute effects* (95% CI)** | | **Relative effect (95% CI)** | **No of participants (studies)** | **Quality of the evidence (GRADE)** |
| | **Risk with chemoradiotherapy alone** | **Risk with chemoradiotherapy plus surgery** | | | |
| Overall survival<br>Follow-up: median 4 to 6 years | 35.4% to 40.0% at 2 years | 34.0% to 39.9% at 2 years | HR 0.99 (95% CI 0.79 to 1.24) | 431<br>(2 RCTs) | ⊕⊕⊕⊕<br>High |
| Freedom from locoregional relapse<br>Follow-up: median 4 to 6 years | 40.7% to 57.0% at 2 years | 64.3% to 66.4% at 2 years | HR 0.55 (95% CI 0.39 to 0.76) | 431<br>(2 RCTs) | ⊕⊕⊕⊖<br>Moderate[1] |
| Quality of Life<br>assessed with: Spitzer QoL index<br>Scale: 0 to10<br>Follow-up: 3 months | the mean Q0L score was 7.52 points in the chemoradiotherapy alone group | the mean QoL score in the chemoradiotherapy plus surgery group was 0.93 points worse (from -1.62 worse to -0.24 worse) | | 165<br>(1 RCT) | ⊕⊖⊖⊖<br>Very Low[2,3,4] |
| Treatment-related mortality<br>Follow-up: median 1 to 3 months | 1.9 per 100 | 9.5 per 100<br>(3.2 to 27.8) | RR 5.11 (95% CI 1.74 to 15.02) | 431<br>(2 RCTs) | ⊕⊕⊖⊖<br>Low[1,2] |
| Use of salvage procedures for dysphagia<br>Follow-up: median 4 years | 46 per 100 | 24 per 100 | RR 0.52 (95% CI 0.36 to 0.75) | 259<br>(1 RCT) | ⊕⊕⊖⊖<br>Low[1,2] |

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
**CI:** Confidence interval; **RR:** Risk ratio; **HR:** Hazard ratio;

**GRADE Working Group grades of evidence**
**High quality:** We are very confident that the true effect lies close to that of the estimate of the effect

**Moderate quality:** We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
**Low quality:** Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
**Very low quality:** We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

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[1] Downgraded one level due to risk of bias (detection bias as investigators were not blinded).
[2] Downgraded one level due to imprecision.
[3] Downgraded two levels due to risk of bias (detection bias as investigators and participants were not blinded).

# BACKGROUND

## Description of the condition

Esophageal cancer accounted for 16,980 new cancer cases and 15,590 cancer deaths in the United States alone in 2015 (Siegal 2015). The incidence rate is highest in Southern Africa and Eastern Asia (Torre 2016).

Esophageal cancer is usually classified histologically as squamous cell carcinoma (SCC) or adenocarcinoma. Squamous cell carcinoma has been increasing in certain Asian countries, such as Taiwan, and decreasing in Western countries, such as North America. Such trends are likely due to differences in the rates of alcohol consumption and tobacco use (Cook 2009; Lu 2010). Interestingly, incidence rates for adenocarcinoma have been increasing in Western countries, probably due to an increase in the prevalence of obesity (El-Serag 2007; Post 2007). Another important risk factor may be chronic gastroesophageal (GE) reflux disease, which leads to Barrett's esophagus, a pre-malignant condition associated with lower esophageal and GE junction adenocarcinoma.

Esophageal cancer remains an aggressive malignancy, despite current treatment modalities. The Surveillance, Epidemiology and End Results (SEER) registry demonstrated a statistically significant, but modest improvement in the five-year relative overall survival (OS) from 5% between 1975 and 1977 to 18.5% from 2001 to 2007 (NCI 2011). Survival is dependent on the stage of disease, with five-year relative OS of 37.3% for localized disease, 18.4% for regional disease, and 3.1% for metastatic disease. Unfortunately, more than half of the people presented with advanced (regional and metastatic) disease at diagnosis (NCI 2011).

## Description of the intervention

The National Comprehensive Cancer Network (NCCN) and European Society for Medical Oncology (ESMO) guidelines established a standard of care for medically fit people with resectable disease (Lordick 2016). While surgery alone is appropriate for early-stage disease (T1N0), combined modality therapy is offered to people with more advanced disease (T2 to T4 and/or node positive disease). Specifically, options include definitive chemoradiotherapy or trimodality treatment (preoperative chemoradiotherapy or chemotherapy followed by surgery; surgery followed by chemoradiotherapy). Treatment options depend on the tumor location, as well as histology.

### Surgery alone

The type of approach for esophagectomy, such as transhiatal or thoracoabdominal, is dependent on the size, stage, and location of the primary tumor, surgeon's experience, and patient preference. Studies have demonstrated a five-year survival rate of 20% with surgery alone (Altorki 2002; Bosset 1997; Hulscher 2002; Kelsen 1998; Orringer 1999). Survival postesophagectomy is not dependent on the type of surgical approaches or histology. Muller and colleagues reviewed the outcomes of various types of esophagectomy and did not find any significant differences in postesophagectomy survival (Muller 1990). Salazar and colleagues reported similar cumulative postoperative survival rates for people with SCC and adenocarcinoma (Salazar 1998).

### Definitive chemoradiotherapy

The Radiation Therapy Oncology Group (RTOG) 85-01 study demonstrated that concurrent chemoradiotherapy improved OS significantly in people with medically operable SCC when compared with radiotherapy alone (Cooper 1999). In this study, 121 people were randomized to receive four cycles of cisplatin plus 5-fluorouracil with concurrent radiotherapy (50 Gy in 25 fractions), or radiotherapy (64 Gy in 32 fractions) alone. About 88% of the participants had SCC. People who received combined modality treatment had a significant improvement in five-year OS (27% versus 0%) and median survival (14 months versus 9 months) compared with radiotherapy alone. The incidence of local failure (local recurrence or persistent disease) at one year was also lower in the combined modality arm (47% versus 65%). The results of this study have established definitive chemoradiotherapy as the standard of care for people with SCC who are not surgical candidates.

### Trimodality treatment

Numerous phase II and III studies have compared preoperative chemoradiotherapy followed by surgery versus surgery alone. The use of pre- or perioperative chemotherapy and surgery has also been evaluated. One updated meta-analysis of randomized studies, comparing the efficacy of preoperative chemoradiotherapy or chemotherapy followed by surgery with surgery alone, reported a significant survival benefit with preoperative treatment over surgery alone in people with resectable esophageal carcinoma (Sjoquist 2011). The hazard ratio (HR) for all-cause mortality for preoperative chemoradiotherapy was 0.78 (95% confidence interval (CI) 0.70 to 0.88, P value < 0.0001), and for preoperative chemotherapy was 0.87 (95% CI 0.79 to 0.96, P = 0.005). Based on their findings, a clear advantage of preoperative chemoradiotherapy over chemotherapy could not be established. Moreover, this meta-analysis did not directly address the question of definitive versus preoperative chemoradiotherapy.

The seminal randomized study that supported the use of surgery plus postoperative chemoradiotherapy is the US Intergroup 0116 study (Macdonald 2001). In this study, 556 people with resected adenocarcinoma of the stomach or GE junction were randomized to surgery alone or surgery plus postoperative chemoradiotherapy. Twenty per cent of the participants had a tumor at the esophagogastric junction. People who received postoperative chemoradiotherapy had significant improvement in three-year survival (50% versus 41%), and median survival (36 months versus 27 months). A major criticism of this study was that 54% of the participants underwent less than a group 1 lymph node dissection (i.e. D1 dissection), raising the possibility that radiation may be compensating for inadequate surgery. Nevertheless, this study suggested that postoperative chemoradiotherapy was a reasonable option for people with GE junction adenocarcinoma. A subsequent randomized study from China investigated the role of perioperative chemoradiotherapy in locally advanced (Stage II to III) thoracic esophageal squamous cell carcinoma (Jin 2010). Two hundred and thirty-eight participants were randomized into surgery alone (80 participants), preoperative chemoradiotherapy (80 participants), and postoperative chemoradiotherapy (78 participants). Progression-free survival (PFS) and OS were improved with either preoperative (PFS: $Chi^2$ 6.81, P = 0.009; OS: $Chi^2$ 7.85, P = 0.005) or postoperative (PFS: $Chi^2$ 5.38, P = 0.02; OS: $Chi^2$ 5.33 P = 0.021) chemoradiotherapy, compared to surgery

alone. There were no significant differences in PFS ($Chi^2$ 0.14, P = 0.71) or OS ($Chi^2$ 0.46, P = 0.50) between pre- and postoperative chemoradiotherapy.

Compared to trimodality treatment, the role of definitive chemoradiotherapy alone is uncertain. This is particularly so, given the high local failure rate with chemoradiotherapy, the inability to predict a pathologic complete response even with repeat imaging or endoscopy (or both), and lack of data for non-surgical management of people with adenocarcinoma.

### Why it is important to do this review

The benefits of adding surgery to chemoradiotherapy when compared to chemoradiotherapy alone for nonmetastatic esophageal cancer are unclear. Definitive chemoradiotherapy alone has been shown to provide a five-year OS in up to 27% of people with SCC (Cooper 1999). This result is similar to that achieved with preoperative chemoradiotherapy followed by surgery alone (O'Reilly 1995; Urba 2001; Walsh 1996). There was also no clear consensus from the NCCN guidelines on whether a trimodality approach was preferred over chemoradiotherapy alone, in people with resectable disease (www.nccn.org). We were unable to locate any systematic reviews or meta-analyses that specifically addressed the efficacy of a trimodality approach when compared to chemoradiotherapy alone.

However, we did find several narrative reviews that addressed the management of people with locally advanced esophageal cancer (Ku 2009; Mariette 2007; Wolf 2011). Most authors concluded that definitive chemoradiotherapy has become a reasonable treatment option, especially for people with SCC. Performing surgery on people who respond to initial chemoradiotherapy may improve local control, but may not clearly impact OS. While the overall conclusion was similar in these studies, they lacked explicit methodology in their review, which limited interpretation of the data and valid conclusions.

Hence, we conducted a systematic review and meta-analysis to compare the efficacy and safety of surgery plus chemoradiotherapy with chemoradiotherapy alone in people with nonmetastatic esophageal cancer.

## OBJECTIVES

To compare the effectiveness and safety of chemoradiotherapy plus surgery with that of chemoradiotherapy alone in people with nonmetastatic esophageal carcinoma, in terms of overall survival (OS), progression-free survival (PFS), quality–of-life (QoL), treatment-related mortality and morbidity, and the use of salvage procedures for dysphagia.

## METHODS

### Criteria for considering studies for this review

#### Types of studies

We only included randomized studies in this review. The nature of the intervention made it difficult for blinding to be part of the study design, and therefore, was not a requirement for study inclusion. We included published and unpublished studies, full articles, and abstracts satisfying the criteria listed below, without any language restriction.

#### Types of participants

People with nonmetastatic carcinoma (stage I to III) of the esophagus, who had been treated with curative intent.

#### Types of interventions

The control arm of the study was chemoradiotherapy alone. The intervention arm was the group that underwent chemoradiotherapy plus surgery. Treatment had to be given with curative intent. The timing of the chemotherapy and radiotherapy could be sequential or concomitant; surgery may have been performed pre- or post-chemoradiotherapy.

#### Types of outcome measures

##### *Primary outcomes*

The primary outcome was overall survival (OS) — time from randomization to death from any cause.

##### *Secondary outcomes*

- Local progression-free survival (PFS) — time from randomization to disease progression at initially treated site by radiotherapy, or death;
- Distant PFS — time from randomization to disease progression at sites not treated by radiotherapy, or death;
- Quality of life (QoL) — measured using a validated scale;
- Treatment-related mortality;
- Treatment-related toxicity (both acute and chronic). Toxicity resulting from treatment is typically classified as acute (that which occurs within 90 days of treatment) or chronic (that which occurs after 90 days of treatment);
- Use of salvage procedures for dysphagia.

### Search methods for identification of studies

We sought papers in all languages and carried out translations if necessary.

#### Electronic searches

We performed the search for studies with the assistance of the Cochrane Upper Gastrointestinal and Pancreatic Diseases Group. The electronic search strategy searched the following databases from its date of inception to 7 February 2017:

- Cochrane Central Register of Controlled Trials (CENTRAL; 2017, Issue 1) in the Cochrane Library (searched 7 February 2017; Appendix 2);
- MEDLINE OVIDSP (1966 to 7 February 2017; Appendix 3);
- Embase OVIDSP (1988 to 7 February 2017; Appendix 4).

We used a search strategy to identify randomized controlled studies performed in humans. We used MeSH headings, subject headings, and additional free-text words.

##### *Unpublished and grey literature*

We identified prospective and ongoing studies by searching the prospective study registers (February 2017):

- International Standard Randomized Controlled Trial Number Registry (www.controlled-trials.com);
- US National Institutes of Health (www.clinicaltrials.gov);

- U.S. National Cancer Institute (www.cancer.gov/clinicaltrials/search);
- International Clinical Trials Registry Platform (www.who.int/trialsearch);
- Australian New Zealand Clinical Trials Registry (www.anzctr.org.au).

#### Searching other resources

##### *Handsearching*

We handsearched the citation lists of included studies, key textbooks, and previous systematic reviews, and contacted experts in the field to identify further reports of studies. We handsearched reports of conferences in the following sources:

- annual meeting of the American Society of Clinical Oncology (2006 to 2016);
- annual meeting of the American Society for Therapeutic Radiology and Oncology (2006 to 2016);
- annual meeting of the European Society of Medical Oncology (2006 to 2016);
- annual Gastrointestinal Cancers Symposium (2006 to 2016).

### Data collection and analysis

#### Selection of studies

We downloaded all titles and abstracts obtained by electronic searches to a reference management database (Microsoft Excel) and removed duplicates. Four review authors (BAV, YYS, CNL, JCST) independently reviewed the remaining titles and abstracts. They excluded studies that clearly did not meet the inclusion criteria. We obtained full-text articles of the remaining articles, and four review authors independently determined the eligibility of the retrieved papers.

We resolved disagreements by consensus, or by consulting a fifth review author (JJL) if necessary. We documented reasons for exclusion during this process. We did not blind the review authors to the source of the document for article selection or data extraction.

#### Data extraction and management

Four review authors (BAV, YYS, CNL, JCST) independently extracted data on characteristics of participants and interventions, risk of bias, duration of follow-up, outcomes and deviations from the protocol to a data abstraction form especially designed for the review. We resolved differences between review authors by discussion or by consulting with a fifth review author if necessary.

We extracted the following participant data: age, gender, performance status, clinical pretreatment staging (American Joint Committee on Cancer), location of primary tumor (upper, middle, or lower third, or GE junction), histopathological subtype (SCC versus adenocarcinoma), and pathological staging (if available). If documented, we noted modalities used for pretreatment clinical staging, such as barium studies, endoscopy, endoscopic ultrasound, computed tomography, and positron emission tomography.

We extracted the following data on types of intervention:

- radiotherapy: the total dose and dose fractionation, treatment target volume, beam arrangement, beam energy, modality (photons, electrons, or both), treatment planning (two-dimensional, three-dimensional), treatment delivery (conventional, intensity modulated, or brachytherapy), and compliance to the recommended protocol;
- chemotherapy: chemotherapeutic agents, biologics, schedule, route of administration, dose intensity, and compliance to the recommended protocol.

The type of surgery was to have a curative intent, and consist of esophagectomy to resect all gross and microscopic disease. We documented the type of surgery (transhiatal or transthoracic, two- or three-staged resection).

We extracted these data for outcomes:

- For time-to-event (OS and PFS) data, we extracted the log of the hazard ratio (log (HR)) and its standard error; if these were not reported, we attempted to estimate the log (HR) and its standard error using the methods from Parmar (Parmar 1998).
- For dichotomous outcomes (e.g. adverse events or deaths, if it was not possible to use an HR), we extracted the number of participants in each treatment arm who experienced the outcome of interest, and the number of participants originally randomized, in order to estimate a risk ratio (RR).
- For continuous outcomes (e.g. QoL measures), we extracted the final value and standard deviation of the outcome of interest, and the number of participants assessed at the end point in each treatment arm at the end of follow-up, in order to estimate the mean difference between treatment arms and its standard deviation.

We extracted both unadjusted and adjusted statistics. We used the data extracted in an intention-to-treat analysis, in which participants were analyzed in the groups to which they were assigned. We noted the time points at which outcomes were reported.

#### Assessment of risk of bias in included studies

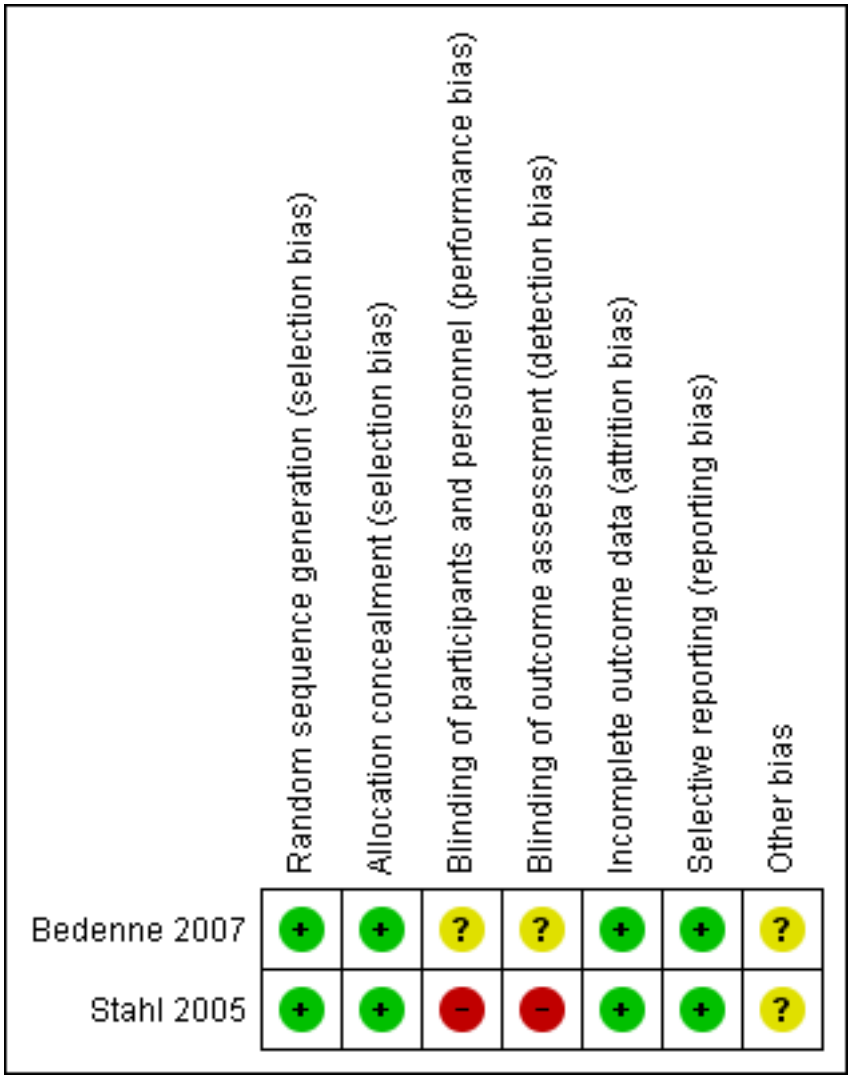
Four review authors (BAV, YYS, CNL, JCST) independently used the 'Risk of bias' tool to assess the risk of bias for each study, using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). They resolved disputes by consensus, and consulted with a fifth author (LLJ) if necessary. We assessed the risk of bias according to the following domains:

- random sequence generation;
- allocation concealment;
- blinding of participants and personnel;
- blinding of outcome assessment;
- incomplete outcome data;
- selective outcome reporting;
- other bias.

We graded each potential source of bias as high, low, or unclear risk, and provided a quote from the study report, together with a justification for our judgement, in the 'Risk of bias' table. We summarized the 'Risk of bias' judgements across different studies for each of the domains listed in a 'Risk of bias' summary table

(Figure 1). We interpreted the results of meta-analyses with respect to the risk of overall bias.

**Figure 1. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.**




***Assessment of bias in conducting the systematic review***

We conducted the review according to the published protocol, and reported any deviations from it in the 'Differences between protocol and review' section of the systematic review (Vellayappan 2013).

**Measures of treatment effect**

We used the following measures of the effect of treatment:

- for time-to-event data, we used hazard ratio (HR), if possible;
- for dichotomous outcomes, we used the risk ratio (RR);
- for continuous outcomes, we used the mean difference (MD) between treatment arms.

**Unit of analysis issues**

The unit of analysis was the individual participant. We did not find any cross-over or cluster-randomized studies.

**Dealing with missing data**

We were not able to contact the study corresponding authors to obtain missing numerical outcome data. We did not impute any missing data.

**Assessment of heterogeneity**

We assessed heterogeneity between studies by visually inspecting the forest plots (L'Abbé 1987), estimating the percentage heterogeneity between studies that could not be attributed to sampling variation (Higgins 2003), formally applying a statistical test of significance of the heterogeneity (Deeks 2001), and if possible, by conducting a subgroup analysis.

**Assessment of reporting biases**

Given that we only included two studies, we did not perform a funnel plot assessment.

### Data synthesis

If sufficient studies were available, we had planned to pool their data in a meta-analysis. For time-to-event data, we pooled HRs using the generic inverse variance function in RevMan 5 (RevMan 2014). For dichotomous outcomes, we calculated a pooled RR. For continuous outcomes, we calculated a pooled mean difference between the two arms at the end of follow-up, if all studies measured the outcome on the same scale. If different scales were used, used a standardized mean difference.

If any studies had multiple treatment groups, we divided the 'shared' comparison group into the number of treatment groups, and treated comparisons between each treatment group and the split comparison group as independent comparisons.

We used a random-effects model with inverse variance weighting for all meta-analyses (DerSimonian 1986). If possible, we synthesized studies making different comparisons using the methods of Bucher (Bucher 1997).

### Subgroup analysis and investigation of heterogeneity

We had planned to perform subgroup analysis, grouping the studies by:

1. concomitant versus sequential chemoradiotherapy;
2. use of targeted therapies (e.g. cetuximab, transtuzumab, and bevacizumab) versus none;
3. type of chemotherapy used (5-fluorouracil-based versus cisplatin-based versus others);
4. histological subtype (SCC versus adenocarcinoma);
5. type of surgery (transhiatal versus transthoracic versus two- or three-stage resections);
6. type of radiation delivery techniques (intensity modulated versus conventional versus brachytherapy);
7. sequencing of intervention in the experimental arm (chemoradiotherapy followed by surgery versus surgery followed by chemoradiotherapy).

We considered factors such as age, clinical staging of esophageal cancer, radiation dose, length of follow-up, and adjusted and unadjusted analysis in interpretation of heterogeneity.

### Sensitivity analysis

We had planned to perform sensitivity analysis for the following:

1. exclusion of studies at high risk of bias;
2. using a fixed-effect model in place of a random-effects model.

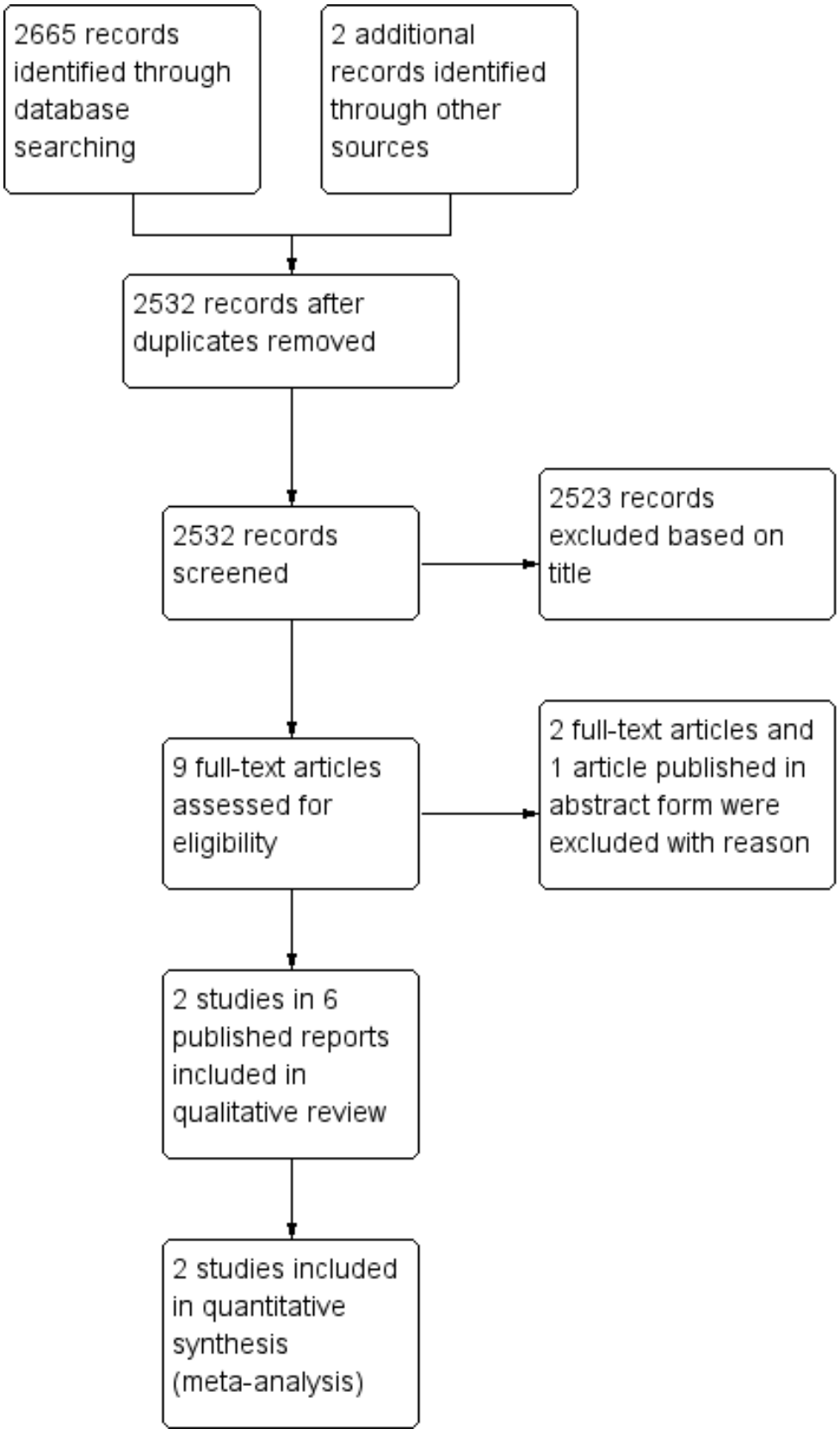
## RESULTS

## Description of studies

### Results of the search

We identified 2665 records from the search results, and two records from other sources. Once we removed duplicates, we screened 2532 titles and abstracts, excluding 2523 that were obviously not eligible. We obtained the full-text copy of nine reports and included two randomized controlled studies (Bedenne 2007; Stahl 2005), in six reports (Bedenne 2007; Bonnetain 2006; Burtin 2008; Crehange 2007; Stahl 2005; Vincent 2015), which included 431 participants (Figure 2).

**Figure 2. PRISMA flow diagram.**



### Included studies

Both included studies were published as full journal articles (Bedenne 2007; Stahl 2005). Sample size in the included studies ranged from 172 to 259. Of the 431 included participants, only 29 had adenocarcinoma histology; the remainder had squamous cell cancer.

Bedenne 2007 included participants with operable T3N0 thoracic esophageal cancer. There was no restriction for histology or tumor location. All registered participants (N = 444) received induction chemoradiation, however, only participants who showed objective response were randomized (N = 259).

Chemotherapy consisted of fluorouracil 800 mg/m² and cisplatin 15 mg/m², given on days one to five, every three weeks. All participants received two cycles prior to randomization; the non-surgical arm received three more cycles, together with radiation.

Radiotherapy was given by conventional fraction or split-course, until January 1999, when the split-course arm was discontinued due to inferior results. Radiotherapy volumes included the gross tumor and lymph nodes, with a 3 cm superior-inferior margin, and 2 cm axial margin. Split-course radiotherapy was delivered in daily fractions of 3 Gy, in two sequences of five days each (15 Gy each, two weeks apart) prior to randomization, and one sequence after (total 45 Gy). Conventional radiotherapy was delivered to 46 Gy (2 Gy per fraction, five fractions per week) prior to randomization, and 20 Gy after (total 66 Gy).

Surgery was performed between days 50 and 60 in the surgical arm, however, no particular type of surgery was recommended.

The primary outcome was overall survival; secondary outcomes included duration of hospital stay, quality of life, type of recurrence, and procedures against dysphagia. The primary and selected secondary outcomes were reported in Bedenne 2007. Quality of life outcomes were reported in Bonnetain 2006. The results of split-course versus conventionally-fractionation were reported in Crehange 2007. Outcome of the registered, but non-randomized, participants were published by Vincent 2015

Stahl 2005 included locally advanced (T3 to T4, and/or node positive) squamous cell cancers of the upper or mid-thoracic esophagus. Participants were randomized to induction chemotherapy followed by chemoradiotherapy and surgery versus induction chemotherapy followed by chemoradiotherapy alone. Induction chemotherapy, in both arms, consisted of 3 cycles of bolus flurouracil 500 mg/m², leucovorin 300 mg/m², etoposide 100 mg/m², and cisplatin 30 mg/m² on days one to three, every three weeks.

The surgical arm received chemoradiotherapy consisting of cisplatin 50 mg/m² on days two to eight, and etoposide 80 mg/m² on days three to five with 40 Gy of radiation (2 Gy per fraction, over four weeks). The volume of irradiation, included the gross tumor with 5 cm superior-inferior margin and 2 cm axial margin, as well as the supraclavicular, infraclavicular, and lower cervical nodal regions. This was followed by esophagectomy, two weeks later, involving a right thoracic and abdominal approach (e.g. Ivor-Lewis procedure) and excision of para-esophageal, paracardial, left gastric, and celiac lymph nodes (two-field lymphadenectomy).

Participants in the non-surgical arm were treated with chemoradiotherapy involving the same chemotherapeutic agents and radiation volumes (to 40 Gy). This was followed by a sequential radiation boost. For T4 or obstructing T3 tumors, the gross tumor with a 2 cm superior-inferior margin and 1 cm axial margin (CTV boost) was treated with 50 Gy, followed by a hyperfractionated boost to 65 Gy (1.5 Gy twice a day, six hours apart, over one week). Non-obstructing tumors were treated with 60 Gy (CTV boost), followed by two fractions of high-dose rate brachytherapy boost (4 Gy to 5 mm depth).

The primary outcome was overall survival. Secondary outcomes, although not stated explicitly, were assumed to be local progression-free survival, and treatment-related mortality.

We extracted time-to-event data for OS (primary outcome) from both studies. However, secondary outcomes were inconsistently reported, therefore, were only combined where adequate information was available (Effects of interventions).

### Excluded studies

We excluded ISRCTN 89052791 after review of the study protocol, as the study arms were not in line with our inclusion criteria. This is an ongoing randomized controlled study in esophageal squamous cell cancer, between induction chemotherapy followed by chemoradiotherapy versus surgery.

We excluded Nomura 2015, which is available only in abstract form. This study is a secondary analysis from two randomised controlled studies. The authors compared neoadjuvant chemotherapy followed by surgery to definitive chemoradiotherapy. This study was excluded as randomization was not performed between chemoradiotherapy plus surgery versus chemoradiotherapy alone.

We excluded Wang 2007, as a process of randomization was not described. Participants were prospectively assigned to neo-adjuvant chemoradiotherapy, followed by surgery or definitive chemoradiotherapy, followed by consolidation chemotherapy in a non-randomized fashion.

## Risk of bias in included studies

We have summarized the risk of bias of the included studies under Characteristics of included studies and Figure 1.

### Allocation

The risk of bias in random sequence generation was low in both studies. Bedenne 2007 used a minimization algorithm, whereas Stahl 2005 used computer-generated randomization. The risk of bias from allocation concealment was also low in both studies, as they were performed centrally.

### Blinding

Blinding of participants and personnel was only reported by Stahl 2005. This was an unblinded study, and risk of bias from lack of blinding was high for subjective outcomes, such such as local progression-free survival and treatment-related mortality, and low for objective outcomes, such as overall survival. Bedenne 2007 did not describe blinding, so the risk of bias is unclear. Similar to the other study, it is expected that risk of bias would be low for objective outcomes (OS) and high for subjective outcomes (such as quality

of life, treatment-related morbidity, and salvage procedures for dysphagia).

### Incomplete outcome data

The risk of bias from incomplete outcome data was low for both studies. Neither of the included studies had missing data. Both studies followed an intention-to-treat principle in the analysis of survival data.

### Selective reporting

Risk of bias from selective reporting was low in both studies. Stahl 2005 reported on the pre-specified primary outcome (OS), and Bedenne 2007 reported on the pre-specified primary outcome (OS), and secondary outcomes (duration of hospital stay, quality of life, type of recurrence, and procedures against dysphagia).

### Other potential sources of bias

We did not find any other potential sources of bias in the included studies. Although a funnel plot was initially planned to examine possible publication bias, due to the small number of included studies, a funnel plot analysis was deemed not useful and therefore, not performed.

## Effects of interventions

See: **Summary of findings for the main comparison** Chemoradiotherapy versus chemoradiotherapy plus surgery for esophageal cancer

### Overall survival

Overall survival was reported in both the included studies (N = 431; Bedenne 2007; Stahl 2005). We used HRs as published, or estimated indirectly from published data, for the calculation of summary statistics. The data appeared homogenous ($Chi^2 = 0.18$; P = 0.67; $I^2$ = 0%). Pooled data showed little or no difference with the addition of esophagectomy (HR 0.99, 95% confidence interval (CI) 0.79 to 1.24; Analysis 1.1).

### Progression-free survival (PFS)

#### *Local PFS*

We had defined local progression-free survival as a secondary outcome in the initial protocol, but neither of the studies reported these data. Bedenne 2007 reported higher locoregional relapse without esophagectomy (HR 1.63, 95% CI 1.04 to 2.55, P = 0.03). Stahl 2005 reported freedom from local progression favouring esophagectomy (HR 2.1, 95% CI 1.3 to 3.5, P = 0.003).

We pooled the data from the two studies (N = 431) and found an improved freedom from locoregional relapse favouring esophagectomy (HR 0.55, 95% CI 0.39 to 0.76; Analysis 1.2). The data appeared homogenous ($Chi^2 = 0.5$; P = 0.48; $I^2$ = 0%).

#### *Distant PFS*

This outcome was reported by neither study, and could not be included in a summary statistic calculation.

Bedenne 2007 reported a two-year metastatic probability of 39.1% (SE 5.3) for trimodality therapy and 29% (SE 4.7; P = 0.24) for chemoradiation alone.

### Quality of life

Quality of life (QoL) was only reported by the FFCD 9102 study (Bedenne 2007). As such, a pooled estimate could not be estimated. In this study, QoL was assessed using the Spitzer QoL index (scored 0 to10), where a higher score indicated a worsening of quality of life. At three-month follow-up, only 165 participants had reported QoL scores. Mean difference was worse with trimodality therapy (MD -0.93, 95% CI -1.62 to -0.24; Analysis 1.3). However, subsequent follow-up did not show any difference between treatment groups (P = 0.26).

### Treatment-related mortality

Death due to acute treatment toxicities in both arms were analyzed. This may be classified as grade 5 toxicity, according to the Common Toxicity Criteria for Adverse Events (CTCAE 2006). Perioperative mortality (within 90 days of surgery) was also analyzed under this outcome.

Both studies reported this outcome,allowing us to obtain a pooled estimate (N = 431; Bedenne 2007; Stahl 2005). The pooled estimate for treatment-related mortality favoured chemoradiation alone (RR 5.11, 95% CI 1.74 to 15.02; P = 0.003; Analysis 1.4). The data appeared homogenous ($Chi^2 = 1.02$; P = 0.31; $I^2$ = 2%).

### Treatment-related toxicity (acute or chronic)

Toxicity was reported according to the organ systems, and was to be graded according to the intensity of these symptoms. We considered grade 3 and grade 4 toxicities to be severe, and grouped them together. Grade 1 and grade 2 toxicities, if reported, were considered mild (Cox 1995). Acute and chronic treatment-related toxicities were analyzed separately.

Treatment-related toxicity was not reported uniformly, and we were unable to combine data in a meta-analysis. Stahl 2005 reported acute toxicity after induction chemotherapy, prior to starting chemoradiation. The data on acute toxicity for the individual arms were not presented, and we assumed them to be equal, since identical induction chemotherapy was used for both arms. Bedenne 2007 only presented the incidence of acute toxicity (Grade 3/4) for the chemoradiation arm, as a per-protocol analysis, and made no comparison with surgery.

### Use of salvage procedures for dysphagia

This outcome was measured quantitatively to objectively determine the difference between the two groups. Procedures may have included balloon dilation, endoscopic stent insertion, laser debulking of tumor, or tube insertion for enteral nutrition. The outcome was only reported by Bedenne 2007. A higher proportion of participants undergoing chemoradiotherapy alone required salvage procedures, either dilation or stent placement, for dysphagia (46.2% versus 24%; P < 0.001), with a RR of 0.52 (95% CI 0.36 to 0.75; Analysis 1.5).

# DISCUSSION

## Summary of main results

Moderate-quality evidence found that the addition of esophagectomy to chemoradiotherapy probably improved freedom from locoregional relapse. However, low-quality evidence found there may be increased treatment-related mortality, and

high-quality evidence found little or no improvement in overall survival (OS). The impact of esophagectomy on quality of life (QoL), treatment-related morbidity, and use of salvage procedures for dysphagia was only reported by one study, and hence, remains undetermined.

## Overall completeness and applicability of evidence

Despite our systematic and extensive search, we only found two eligible studies to include in the meta-analysis. From the standpoint of the individual studies, both were only powered to show equivalence, and therefore, any difference in survival may have been deemed not significant. A meta-analysis provides the ideal statistical tool to increase the power of these comparisons.

We judged that the included studies provided sufficient evidence to draw reliable conclusions for overall survival, freedom from locoregional relapse, and treatment-related mortality. The other outcomes of interest, which were determined a priori, were only reported by one of the two studies (Bedenne 2007).

### Stage and location of the disease

Multimodal treatment is generally considered necessary for advanced esophageal cancers. No restrictions were placed on stage during our selection of studies. However, it is important to note that these studies included only locally advanced, resectable, cancers and therefore, the applicability should be restricted to this group i.e. T3 to T4, node positive, or both. Stahl 2005 used both endoscopic ultrasound and computed tomography (CT), whereas Bedenne 2007 relied solely on CT. With regards to T classification, it is possible that a portion of participants were incorrectly-staged, as CT alone has been shown to be a poor assessor for depth of tumor infiltration (Kim 2009). It remains unclear if the inclusion of a minority of participants with potentially Stages I or II disease would have changed our findings. Stahl 2005 only included participants with upper and middle esophageal tumors, whereas Bedenne 2007 included all thoracic esophageal tumors. It is unclear how many participants with distal esophageal cancers were included in the latter study, although most squamous cell carcinomas occur in the proximal two-thirds of the esophagus. As such, these results may not be applicable to distal esophageal and gastroesophageal junction tumors.

### Effect of histology

There were no restrictions imposed during the search for the studies. However, Stahl 2005 included only squamous cell carcinoma (SCC) participants and Bedenne 2007 included participants with both SCC and a minority with adenocarcinoma. Overall, 93% of the included participants had squamous cell carcinoma (SCC). It is widely regarded that SCC and adenocarcinoma are considered two separate disease entities, with individual treatment strategies. Therefore, these results should not be applied to people with adenocarcinomas.

### Responders versus non-responders

For ethical reasons, Bedenne 2007 only randomized participants who responded to induction chemoradiation. In a recent publication by Vincent and colleagues, the non-responding participants were reported to have much poorer outcomes; however, the addition of salvage surgery in these participants improved OS (hazard ratio (HR) 0.39, 95% confidence interval (CI) 0.25 to 0.61, P < 0.0001; Vincent 2015). Stahl 2005 randomized all participants, regardless of their response to induction multi-agent chemotherapy. However, subgroup analysis corroborated the findings that participants who responsed to induction therapy fared better. These results should not be applied to people who do not respond to induction chemoradiation, i.e. those who had progressive or residual primary tumors. Salvage surgery remains a strong consideration for such people.

### Chemotherapy and radiotherapy dose and design

A landmark practice changing study (CROSS) published impressive results for the use of neoadjuvant chemoradiotherapy prior to surgery (Van Hagen 2012). Many centers have adopted this regimen of weekly carboplatin and paclitaxel with a reduced dose of radiotherapy (41.4 Gy in 23 fractions) prior to surgery. However, for people who are treated with chemoradiotherapy alone, the standard of care remains 50 Gy with platinum and flurouracil-based chemotherapy, based on the INT 0123 study (Minsky 2002). This study was closed early due to mortalities in the dose-escalated arm (64 Gy).

Stahl 2005 used different radiotherapy regimens in both intervention groups. Participants undergoing surgery had 40 Gy of external beam radiotherapy, whereas participants who received chemoradiation alone, received a total dose of 65 Gy, or more. Notably, all participants in the chemoradiation arm received a coned-down boost, either with hyper-fractionated external beam radiotherapy (70%) or high-dose rate brachytherapy (30%). Bedenne 2007 allowed for both conventionally fractioned radiotherapy and split-course radiotherapy. However, the split-course strategy was disallowed midway due to an increased number of deaths. Like Stahl 2005, participants in the surgical arm received chemoradiation (46 Gy), while participants treated with chemoradiation alone received an additional 20 Gy (total 66 Gy). Based on our findings, the addition of surgery did not confer a survival benefit compared to high-dose chemoradiotherapy alone (more than 65 Gy). However, it remains unclear if surgery may have conferred a survival advantage compared to standard dose chemoradiotherapy alone (50 Gy).

Considering that all participants in the Stahl 2005 study received induction multi-agent chemotherapy, which in itself has been shown to reduce mortality by 13% (HR 0.87, 95% CI 0.79 to 0.96; Sjoquist 2011), these results may not be applicable to people treated without induction therapy.

## Quality of the evidence

We assessed the quality of the evidence for all reported outcomes, including those whose results could not be pooled.

We determined the quality of evidence using the guideline development tool developed by the GRADE Working Group (GRADEpro 2015; Ryan 2016)

Overall survival (two studies): high-quality evidence. Absence of blinding is unlikely to have influenced this objective outcome.

Freedom from locoregional relapse (two studies): moderate-quality evidence. Downgraded one level due to risk of bias from the absence of blinding.

Treatment-related mortality (two studies): low-quality evidence. Downgraded one level due to risk of bias from the absence of blinding and imprecision (large confidence interval).

Quality of life (one study): very low-quality evidence. Downgraded two levels due to risk of bias (absence of blinding and loss to follow-up), downgraded one level due to imprecision (small effect size with overlapping confidence interval) and publication bias.

Use of salvage procedures (one study): low-quality evidence. Downgraded one level due to risk of bias from absence of blinding, imprecision and publication bias.

Quality of evidence for treatment-related toxicity could not be judged as it was reported by neither study.

Please refer to Summary of findings for the main comparison.

### Potential biases in the review process

The strengths of this review are that it addresses a clinically relevant and pragmatic question. In addition, this is the first published quantitative review for this specific question

A limitation of this review was that we used published results rather than individually updated patient data (IPD). Although these results may overestimate the benefits of additional upfront surgery, it is unlikely that an IPD meta-analysis would alter the conclusions. This stands to reason, as the effects of upfront surgery on locoregional control and treatment-related mortality are likely to remain significant, whereas the effects on OS are likely to remain non-significant.

We did not perform a funnel-plot analysis, as we only identified two studies. Although publication bias may exist, it is unlikely that a large unpublished randomized controlled study exists that would alter our findings. For the same reasons of limited studies, sensitivity and subgroup analysis (as stated in the protocol) were not performed, as they would not have been meaningful.

We had not specified, a priori, a subgroup analysis of outcomes between responders and non-responders to induction treatment. Bedenne 2007 did not randomize participants who failed to respond to induction chemoradiotherapy, and Stahl 2005 did not provide sufficient information on non-responders. As such, a quantitative subgroup analysis could not be performed.

As mentioned above, both studies were in concordance that non-responding participants had inferior survival outcomes. Vincent 2015 suggested that the survival of non-responders from the FFCD 9102 study who underwent upfront surgery, was comparable to that of responders having surgery in the randomized arms (median survival 17.3 to 17.7 months). This corroborated with information provided by Stahl's commentary, where a salvage esophagectomy improved the survival in non-responders.

Another limitation of this study was the inability to summarize the data on local and distant progression-free survival using the Kaplan-Meier method, as stated in the protocol. Stahl 2005 reported two-year freedom from local progression, whereas Bedenne 2007 reported two-year recurrence probability and locoregional relapses. Deviating from the protocol, we combined the available data to formulate a hazard ratio for freedom from locoregional relapse. Although not stated a priori, this provided a close and reliable estimate of local progression-free survival.

A further limitation was the heterogeneity in reporting outcomes, such as distant progression-free survival, treatment-related morbidity, use of salvage procedures, and QoL. We thought these outcomes were clinically relevant, so we included them in our protocol. However, only Bedenne 2007 reported on them, so we were unable to perform quantitative analyses.

### Agreements and disagreements with other studies or reviews

Best 2016 performed a similar systematic review comparing the benefits and harms of non-surgical treatment with surgical treatment approaches for esophageal cancer. Besides including randomized studies of chemoradiotherapy, with or without esophagectomy, Best 2016 also included randomized studies that compared radiotherapy or chemoradiotherapy with esophagectomy alone. Best 2016 performed a subgroup analysis that pooled the overall survival results of Bedenne 2007 and Stahl 2005. It showed that there was no survival benefit when esophagectomy was added to chemo-radiotherapy, similar to the findings of this review.

We acknowledge that while there was some overlap between this review and the review by Best 2016, there are important differences as well. First, our review's question was more specific, as we were only interested in knowing if there was any clinical benefit for people who had undergone chemoradiotherapy for esophageal cancer if esophagectomy was added, whereas Best 2016 was more interested in comparing the effects of a non-surgical approach with a surgical approach for treatment of esophageal cancer. The definitions of non-surgical and surgical approaches in Best 2016 review were extremely varied. Non-surgical approaches could include radiotherapy alone or chemoradiotherapy treatment, and surgical approaches included esophagectomy alone or esophagectomy plus chemoradiotherapy. Second, we examined the effects of adding esophagectomy to chemoradiotherapy more thoroughly than Best 2016, who only pooled the effects of adding esophagectomy for overall survival. Besides overall survival, we also pooled the effects of additional esophagectomy on freedom from locoregional relapse, and treatment-related mortality.

In addition, prospective non-randomized studies corroborated our findings. Wang 2007 conducted a prospective non-randomized study comprising 50 participants with esophageal cancer, 67% of whom had adenocarcinoma histology, and comparing carboplatin and paclitaxel and radiotherapy to 45 Gy, followed by esophagectomy versus carboplatin and paclitaxel and radiotherapy to 50.4 Gy, followed by consolidation chemotherapy alone. The survival outcomes were not difference between the two groups (three-year survival 60% in each group). A single institution retrospective series similarly found no difference in survival outcomes with the addition of surgery (Rawat 2013).

Both of our included studies were conducted in the 1990's, therefore one has to re-examine the effect of increased treatment-related mortality with esophagectomy, which may have negated any potential survival advantage (Finks 2011; Jafari 2013). Could there be a potential survival benefit with improved modern surgical techniques and post-operative care? As such, the applicability

of these results to modern day treatment techniques (surgery, radiotherapy) may be questioned.

Practice guidelines from NCCN (Version 3.2015) are in line with our findings. These guidelines recommend surveillance in people with SCC undergoing definitive chemoradiation, unless there is evidence of persistent local disease, for which salvage esophagectomy should be undertaken. Similarly, ESMO guidelines recommend either chemoradiation with planned surgery, or close surveillance with salvage surgery, for people with locally advanced SCC (Stahl 2013).

## AUTHORS' CONCLUSIONS

### Implications for practice

There is moderate-quality evidence that adding surgery to chemoradiation probably increases the time to locoregional relapse. However, based on the available evidence, this may be at the cost of increased treatment-related morality and little or no improvement in overall survival. People who do not respond to chemoradiation, or who have persistent local disease, warrant upfront surgery. In addition, in people where surgery is deferred, they should undergo close surveillance and surgical salvage upon local recurrence.

### Implications for research

Large scale randomized studies with homogenous treatment arms, using modern techniques, and including participants with adenocarcinoma histology (which is now the dominant histology in the U.S., Western Europe, and parts of Australasia), may be warranted, to re-assess the impact of upfront surgery on survival.

Furthermore, participant selection using advanced functional imaging (e.g. PET or CT), or predictive biomarkers may help select participant groups who may benefit from upfront surgery after definitive chemoradiation.

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**Muller 1990**

Muller JM, Erasmi H, Stelzner M, Zieren U, Pichlmaier H. Surgical therapy of oesophageal carcinoma. *British Journal of Surgery* 1990;**77**:845-57.

**O'Reilly 1995**

O'Reilly S, Forastiere AA. Is surgery necessary with multimodality treatment of oesophageal cancer. *Annals of Oncology* 1995;**6**:519-22.

**Orringer 1999**

Orringer MB, Marshall B, Iannettoni MD. Transhiatal esophagectomy: clinical experience and refinements. *Annals of Surgery* 1999;**230**:392-403.

**Parmar 1998**

Parmar MK, Torri V, Stewart L. Extracting summary statistics to perform meta-analyses of the published literature for survival endpoints. *Statistics in Medicine* 1998;**17**(24):2815-34.

**Post 2007**

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**Rawat 2013**

Rawat S, Kumar G, Kakria A, Sharma MK, Chauhan D. Chemoradiotherapy in the management of locally advanced squamous cell carcinoma esophagus: Is surgical resection required?. *Journal of Gastrointestinal Cancer* 2013;**44**:277-84.

**RevMan 2014 [Computer program]**

The Nordic Cochrane Centre, The Cochrane Collaboration. Review Manager 5 (RevMan 5). Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014.

**Ryan 2016**

Ryan R, Hill S. How to GRADE the quality of the evidence. Cochrane Consumers and Communication Group cccrg.cochrane.org/author-resources (accessed 10 December 2016).

**Salazar 1998**

Salazar JD, Doty JR, Lin JW, Dyke MC, Roberts J, Heitmiller ES, et al. Does cell type influence post-esophagectomy survival in patients with esophageal cancer. *Diseases of the Esophagus* 1998;**11**:168-71.

**Siegal 2015**

Siegel RL, Miller KD, Jemal A. Cancer statistics, 2015. *CA: A Cancer Journal for Clinicians* 2015;**65**(1):5-29. [DOI: 10.3322/caac.21254]

## CHARACTERISTICS OF STUDIES

### Characteristics of included studies *[ordered by study ID]*

**Sjoquist 2011**

Sjoquist KM, Burmeister BH, Smithers BM, Zalcberg JR, Simes RJ, Barbour A, et al. Survival after neoadjuvant chemotherapy or chemoradiotherapy for resectable esophageal carcinoma: an updated meta-analysis. *Lancet Oncology* 2011;**12**:681-92.

**Stahl 2013**

Stahl M, Mariette C, Haustermans K, Cervantes A, Arnold D. Oesophageal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Annals of Oncology* 2013;**24**:51-6.

**Torre 2016**

Torre LA, Siegel RL, Ward EM, Jemal A. Global cancer incidence and mortality rates and trends: an update. *Cancer Epidemiology, Biomarkers & Prevention* 2016;**25**(1):16-27.

**Urba 2001**

Urba SG, Orringer MB, Turrisi A, Iannettoni M, Forastiere A, Strawderman M. Randomized trial of preoperative chemoradiation versus surgery alone in patients with locoregional esophageal carcinoma. *Journal of Clinical Oncology* 2001;**19**:305-13.

**Van Hagen 2012**

Van Hagen P, Hulshof MCCM, Van Lanschot JJB, Steyerberg EW, Van Berge Henegouwen MI, Wijnhoven BPL, et al. Preoperative Chemoradiotherapy for Esophageal or Junctional Cancer. *New England Journal of Medicine* 2012;**366**:2074-84.

**Vellayappan 2013**

Vellayappan BA, Soon YY, Ku GY, Leong CN, Lu JJ, Tey JCS. Chemoradiotherapy versus chemoradiotherapy plus surgery for esophageal cancer. *Cochrane Database of Systematic Reviews* 2013, Issue 5. [DOI: 10.1002/14651858.CD010511]

**Vincent 2015**

Vincent J, Mariette C, Pezet D, Huet E, Bonnetain F, Bouché O, et al. Early surgery for failure after chemoradiation in operable thoracic oesophageal cancer. Analysis of the non-randomised patients in FFCD 9102 phase III trial: Chemoradiation followed by surgery versus chemoradiation alone. *European Journal of Cancer* 2015;**51**(13):1683-93.

**Walsh 1996**

Walsh TN, Noonan N, Hollywood D, Kelly A, Keeling N, Hennessy TPJ. A comparison of multimodal therapy and surgery for esophageal adenocarcinoma. *New England Journal of Medicine* 1996;**335**:462-7.

**Wolf 2011**

Wolf MC, Stahl M, Krause BJ, Bonavina L, Bruns C, Belka C, et al. Curative treatment of oesophageal carcinoma: current options and future developments. *Radiation Oncology* 2011;**26**(6):55.

**Bedenne 2007**

| | |
|---|---|
| Methods | Randomized controlled study |
| Participants | Histologically proven epidermoid or adenocarcinoma of the thoracic esophagus. T3N0-N1M0 (International Union Against Cancer criteria, 1987) ; Clinical and biologic eligibility for surgery or chemoradiation; no age limit; Feburary 1993 to December 2000; France (multi-center)<br><br>Participants with tumors within 18 cm from dental ridge or infiltrating gastric cardia, tracheobronchial involvement, visceral metastasis or supraclavicular nodes, weight loss more than 15%, symptomatic coronary heart disease, liver cirrhosis Child-Pugh B/C or respiratory insufficieny were excluded.<br><br>444 participants eligible for the study, 259 of whom were randomized (242 male, 17 female)<br><br>Participants randomized/analysed in this meta-analysis: 259/259<br><br>Median follow-up time was 47.4 months. |
| Interventions | All participants received induction chemoradiation initially.<br><br>Participants who responded to induction chemoradiation (day 38 to day 41), were randomized to surgery versus further chemoradiation.<br><br>Initially, split-course and conventional radiotherapy were allowed (investigator's choice). From January 1999, only conventional radiotherapy was permitted.<br><br>Radiotherapy treatment volumes included macroscopic tumor and lymph nodes, with a 3 cm proximal/distal margin and 2 cm radial margin. (3 or 4 fields, and treating all fields daily)<br><br>Split-course: 3 Gy per day (days 1 to 5, then days 22 to 26) to a total dose of 30 Gy. After randomization to further chemoradiation, 3 Gy per day (days 43 to 47) to a total dose of 45 Gy.<br><br>Conventional: 2 Gy per fraction, 5 fractions per week to a total dose of 46 Gy. After randomization to further chemoradiation, 2 Gy per fraction, 5 fractions per week to a total dose of 66 Gy.<br><br>Chemotherapy (arm B): 2 cycles of chemotherapy were delivered before random assignment, on day1 and day 22. After random assignment, three cycles were administered (day 43, day 64, day 92).<br><br>Chemotherapy consisted of cisplatin 15 mg/m$^2$ (days 1 to 5), and continuous infusion flurouracil 800 mg/m$^2$ daily (days 1 to 5)<br><br>Surgery (arm A): no particular type of surgery was required. Surgery was to be performed between days 50 and 60. |
| Outcomes | overall survival. Duration of hospital stay, quality of life, type of recurrence, procedures against dysphagia |
| Notes | |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Sequence was generated using a minimization program. |
| Allocation concealment (selection bias) | Low risk | Allocation was done at a central site (FFCD Data center) |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Unclear risk | The risk of bias for the primary outcome (overall survival) is objective and therefore low. However, the risk of bias from lack of blinding was high for subjective outcomes such as quality of life, use of salvage procedures for dysphagia, duration of hospital stay, and type of recurrence. |

**Bedenne 2007** *(Continued)*

| | | |
|---|---|---|
| Blinding of outcome assessment (detection bias) All outcomes | Unclear risk | The risk of bias for the primary outcome (overall survival) is objective and therefore low. However, the risk of bias from lack of blinding was high for subjective outcomes such as quality of life, use of salvage procedures for dysphagia, duration of hospital stay, and type of recurrence. |
| Incomplete outcome data (attrition bias) All outcomes | Low risk | No missing outcome data |
| Selective reporting (reporting bias) | Low risk | All pre-specifed primary and secondary outcomes were reported |
| Other bias | Unclear risk | Quality assurance of radiotherapy planning and delivery were not reported.<br>Type and quality of surgeries performed were not audited or reported. |

**Stahl 2005**

| | |
|---|---|
| Methods | Randomized controlled study |
| Participants | Histologically proven squamous cell carcinoma of the upper and mid-third esophagus (no exact definition given on tumor location from dental ridge); age < 70 years, WHO performance status 0 to 1. Locally advanced disease (T3-4, N0-1, M0 according to endoscopic ultrasound and computed tomography); June 1994 to May 2002; Germany (multi-center)<br>172 participants (138 male, 34 female)<br>Median observation time: 6 years<br>Participants randomized/analysed in this meta-analysis: 172/172 |
| Interventions | Induction chemotherapy, followed by preoperative chemoradiation versus induction chemotherapy, followed by chemoradiation alone.<br>Both groups received induction chemotherapy, consisting of three courses of bolus fluorouracil (500 mg/m$^2$), leucovarin (300 mg/m$^2$), etoposide (100 mg/m$^2$), cisplatin(30 mg/m$^2$) days 1 to 3 every 3 weeks.<br>Intervention group: After induction chemotherapy, preoperative concomitant chemoradiotherapy was given as detailed below.<br>Chemotherapy: Cisplatin (50 mg/m$^2$) , etoposide(80 mg/m$^2$) on days 2 to 8<br>Radiotherapy: 2 Gy per fraction, 5 fractions per week to a total dose of 40 Gy.<br>Radiotherapy clinical target volume included gross tumor with 5 cm craniocaudal margin and 2 cm transverse margin. Supra-, infraclavicular, and lower cervical lymph nodes were included for upper thoracic tumors.<br>AP and PA fields were used in conjunction with three-dimensional planning.<br>Surgery: transthoracic esophagacteomy was performed 3 to 4 weeks after chemoradiation. Resection included para-esophageal, paracardial, left gastric, and celiac nodes (two-field lymphadenectomy)<br>Control group: after induction chemotherapy, definitive chemoradiotherapy was given.<br>Chemotherapy: Cisplatin (50 mg/m$^2$), etoposide(80 mg/m$^2$) on days 2 to 8.<br>Radiotherapy: 2 Gy per fraction, 5 fractions per week to a total dose of 50 Gy initially. Following which, a boost was delivered. |

**Stahl 2005** *(Continued)*

| | |
|---|---|
| | Radiotherapy boost to reduced volume:<br><br>For T4 and obstructing T3 tumors, a total external beam dose of 65 Gy was delivered. (i.e. 15 Gy delivered using 1.5 Gy twice a day, 6-hour intervals, over 5 days)<br><br>For T3 and non-obstructing tumors, external beam dose to a total of 60 Gy, followed by intracavitary brachytherapy (two fractions of 4 Gy high dose rate administered with a 4 to 7 day interval; prescribed to 5 mm depth from applicator to pre-radiotherapy tumor length and 5 mm superior and inferior margin)<br><br>Radiotherapy clinical target volume for the initial phase included gross tumor with 5 cm craniocaudal margin and 2 cm transverse margin. Supra-, infraclavicular, and lower cervical lymph nodes were included for upper thoracic tumors.<br><br>Radiotherapy clinical target volume (external beam) for the boost phase included gross tumor with 2 cm craniocaudal margin and 1 cm transverse margin.<br><br>AP, PA, and oblique fields were used in conjunction with three-dimensional planning. |
| Outcomes | overall survival, local progression free survival, treatment-related mortality |
| Notes | |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Sequence was generated using a computerized randomization program. |
| Allocation concealment (selection bias) | Low risk | Allocation was done at a central site (Institute for Medical Informatics, Biometry and Epidemiology, University Clinics Essen) |
| Blinding of participants and personnel (performance bias)<br>All outcomes | High risk | The risk of bias for the primary outcome (overall survival) is objective and therefore low. However, the risk of bias from lack of blinding was high for local progression-free survival. |
| Blinding of outcome assessment (detection bias)<br>All outcomes | High risk | The risk of bias for the primary outcome (overall survival) is objective and therefore low. However, the risk of bias from lack of blinding was high for local progression-free survival. |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | No missing outcome data |
| Selective reporting (reporting bias) | Low risk | The prespecified primary outcome was reported |
| Other bias | Unclear risk | Quality assurance of radiotherapy planning and delivery were not reported.<br><br>Type and quality of surgeries performed were not audited or reported. |

Key: AP = anterior-posterior ; PA = posterior-anterior

**Characteristics of excluded studies** *[ordered by study ID]*

| Study | Reason for exclusion |
|---|---|
| ISRCTN 89052791 | Study arms not in line with our inclusion criteria. This is an ongoing randomized controlled study investigating induction chemotherapy followed by chemoradiotherapy versus induction chemotherapy followed by surgery. |
| Nomura 2015 | This is a secondary analysis of a randomized controlled study and a single-arm prospective study. This study was excluded as randomization was not performed between chemoradiotherapy plus surgery versus chemoradiotherapy alone. |
| Wang 2007 | Process of randomization was not described, therefore presumed to be a prospective non-randomized study |

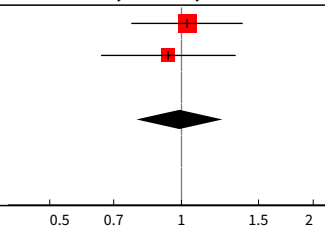
## DATA AND ANALYSES

### Comparison 1. Chemoradiotherapy (CRT) plus surgery versus chemoradiotherapy alone

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1 Overall survival | 2 | 431 | Hazard Ratio (Random, 95% CI) | 0.99 [0.79, 1.24] |
| 2 Freedom from locoregional relapse | 2 | 431 | Hazard Ratio (Random, 95% CI) | 0.55 [0.39, 0.76] |
| 3 Quality of Life (at 3 months) | 1 | | Mean Difference (IV, Random, 95% CI) | Subtotals only |
| 4 Treatment-related mortality | 2 | 431 | Risk Ratio (M-H, Random, 95% CI) | 5.11 [1.74, 15.02] |
| 5 Use of salvage procedures for dysphagia | 1 | | Risk Ratio (M-H, Random, 95% CI) | Subtotals only |

### Analysis 1.1. Comparison 1 Chemoradiotherapy (CRT) plus surgery versus chemoradiotherapy alone, Outcome 1 Overall survival.

| Study or subgroup | CRT plus surgery N | CRT alone N | log[Hazard Ratio] (SE) | Hazard Ratio IV, Random, 95% CI | Weight | Hazard Ratio IV, Random, 95% CI |
|---|---|---|---|---|---|---|
| Bedenne 2007 | 129 | 130 | 0 (0.15) | | 59.02% | 1.03[0.77,1.38] |
| Stahl 2005 | 86 | 86 | -0.1 (0.18) | | 40.98% | 0.93[0.66,1.33] |
| **Total (95% CI)** | | | | | **100%** | **0.99[0.79,1.24]** |
| Heterogeneity: Tau²=0; Chi²=0.18, df=1(P=0.67); I²=0% | | | | | | |
| Test for overall effect: Z=0.1(P=0.92) | | | | | | |



### Analysis 1.2. Comparison 1 Chemoradiotherapy (CRT) plus surgery versus chemoradiotherapy alone, Outcome 2 Freedom from locoregional relapse.

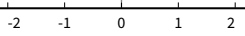
| Study or subgroup | CRT plus surgery N | CRT alone N | log[Hazard Ratio] (SE) | Hazard Ratio IV, Random, 95% CI | Weight | Hazard Ratio IV, Random, 95% CI |
|---|---|---|---|---|---|---|
| Bedenne 2007 | 86 | 86 | -0.5 (0.23) | | 54.16% | 0.61[0.39,0.96] |
| Stahl 2005 | 129 | 130 | -0.7 (0.25) | | 45.84% | 0.48[0.3,0.79] |
| **Total (95% CI)** | | | | | **100%** | **0.55[0.39,0.76]** |
| Heterogeneity: $Tau^2$=0; $Chi^2$=0.5, df=1(P=0.48); $I^2$=0% | | | | | | |
| Test for overall effect: Z=3.54(P=0) | | | | | | |




Favours CRT plus surgery — Favours CRT alone

### Analysis 1.3. Comparison 1 Chemoradiotherapy (CRT) plus surgery versus chemoradiotherapy alone, Outcome 3 Quality of Life (at 3 months).

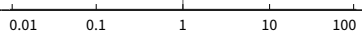
| Study or subgroup | CRT plus surgery N | Mean(SD) | CRT alone N | Mean(SD) | Mean Difference Random, 95% CI | Weight | Mean Difference Random, 95% CI |
|---|---|---|---|---|---|---|---|
| Bedenne 2007 | 73 | 7.5 (2.5) | 92 | 8.5 (1.9) | | 0% | -0.93[-1.62,-0.24] |




Favours CRT plus surgery — Favours CRT alone

### Analysis 1.4. Comparison 1 Chemoradiotherapy (CRT) plus surgery versus chemoradiotherapy alone, Outcome 4 Treatment-related mortality.

| Study or subgroup | CRT plus surgery n/N | CRT alone n/N | Risk Ratio M-H, Random, 95% CI | Weight | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|
| Bedenne 2007 | 12/129 | 1/130 | | 27.85% | 12.09[1.6,91.65] |
| Stahl 2005 | 11/86 | 3/86 | | 72.15% | 3.67[1.06,12.68] |
| **Total (95% CI)** | **215** | **216** | | **100%** | **5.11[1.74,15.02]** |
| Total events: 23 (CRT plus surgery), 4 (CRT alone) | | | | | |
| Heterogeneity: $Tau^2$=0.02; $Chi^2$=1.02, df=1(P=0.31); $I^2$=2.43% | | | | | |
| Test for overall effect: Z=2.97(P=0) | | | | | |




Favours CRT plus surgery — Favours CRT alone

### Analysis 1.5. Comparison 1 Chemoradiotherapy (CRT) plus surgery versus chemoradiotherapy alone, Outcome 5 Use of salvage procedures for dysphagia.

| Study or subgroup | CRT plus surgery n/N | CRT alone n/N | Risk Ratio M-H, Random, 95% CI | Weight | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|
| Bedenne 2007 | 31/129 | 60/130 | | 0% | 0.52[0.36,0.75] |


Favours CRT plus surgery — Favours CRT alone

# APPENDICES

## Appendix 1. Glossary

Adenocarcinoma: cancer arising from glandular cells.

Chemoradiotherapy: a treatment plan that combines chemotherapy and radiotherapy.

Dysphagia: difficulty in swallowing.

Esophagectomy: excision of a portion of the esophagus.

Induction chemotherapy: starting with chemotherapy before proceeding to another planned treatment.

Locoregional relapse: cancer recurrence at the primary site, or nearby lymph nodes.

Metastases: cancer spread from site of origin to other parts of the body.

Morbidity: a diseased condition or state.

Mortality: death.

Multimodality: involving more than one method of treatment.

Nodes: lymph glands.

Nonmetastatic: without evidence of cancer spread to distant organs.

Resectable: amenable to surgical removal.

Squamous cell carcinoma: cancer arising from squamous cells.

Transhiatal: resection of the esophagus from above through the neck and below through the diaphragm.

Thoraco-abdominal: resection of the esophagus through an approach through the chest and abdomen.

Trimodality: involving the use of surgery, radiotherapy and chemotherapy.

## Appendix 2. CENTRAL search strategy

1. (carcin$ or cancer$ or neoplas$ or tumour$ or tumor$ or cyst$ or growth$ or adenocarcin$ or malig$).mp.
2. (esophagus or oesophagus or esophageal or oesophageal).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
3. 1 and 2
4. Neoadjuvant Therapy/
5. Chemotherapy, Adjuvant/
6. Radiotherapy, Adjuvant/
7. chemoradiotherap*.tw.
8. chemo-radiotherap*.tw.
9. radiochemotherap*.tw.
10. radio-chemotherap*.tw.
11. or/4-10
12. 3 and 11

## Appendix 3. MEDLINE search strategy

1. (carcin$ or cancer$ or neoplas$ or tumour$ or tumor$ or cyst$ or growth$ or adenocarcin$ or malig$).mp.
2. (esophagus or oesophagus or esophageal or oesophageal).mp. [mp=protocol supplementary concept, rare disease supplementary concept, title, original title, abstract, name of substance word, subject heading word, unique identifier]
3. 1 and 2
4. Neoadjuvant Therapy/
5. Chemotherapy, Adjuvant/
6. Radiotherapy, Adjuvant/
7. chemoradiotherap*.tw.

8. chemo-radiotherap*.tw.
9. radiochemotherap*.tw.
10. radio-chemotherap*.tw.
11. or/4-10
12. 3 and 11
13. randomized controlled trial.pt.
14. controlled clinical trial.pt.
15. randomized.ab.
16. placebo.ab.
17. drug therapy.fs.
18. randomly.ab.
19. trial.ab.
20. groups.ab.
21. or/13-20
22. exp animals/ not humans.sh.
23. 21 not 22
24. 12 and 23
25. case report*.tw.
26. case report*.pt.
27. (systematic adj (review* or overview*)).tw.
28. Review.pt.
29. or/25-28
30. 24 not 29

### Appendix 4. Embase search strategy

1. (carcin$ or cancer$ or neoplas$ or tumour$ or tumor$ or cyst$ or growth$ or adenocarcin$ or malig$).mp.
2. (esophagus or oesophagus or esophageal or oesophageal).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
3. 1 and 2
4. chemoradiotherap*.tw.
5. chemo-radiotherap*.tw.
6. radiochemotherap*.tw.
7. radio-chemotherap*.tw.
8. adjuvant therapy/
9. adjuvant chemotherapy/
10. multimodality cancer therapy/
11. chemoradiotherapy/
12. or/4-11
13. 3 and 12
14. random:.tw. or placebo:.mp. or double-blind:.tw.
15. 13 and 14

## CONTRIBUTIONS OF AUTHORS

Conception and design: BAV, YYS, GYK, JCST.
Protocol writing: BAV, YYS.
Final approval of protocol: BAV, YYS, GYK, CNL, JJL, JCST.
Manuscript writing: BAV, YYS.
Final approval of manuscript: BAV, YYS, GYK, CNL, JJL, JCST.

## DECLARATIONS OF INTEREST

BAV: none known.
YYS: none known.
GYK: none known.

CNL: none known.
JJL: none known.
JCST: none known.

## DIFFERENCES BETWEEN PROTOCOL AND REVIEW

In our protocol, we stated that we intended to perform subgroup and sensitivity analyses. However, this was not carried out, due to limited available information and the presence of only two RCTs.

## INDEX TERMS

### Medical Subject Headings (MeSH)

*Chemoradiotherapy [adverse effects] [mortality]; *Esophagectomy [mortality]; Carcinoma [mortality] [pathology] [surgery] [therapy]; Carcinoma, Squamous Cell [mortality] [pathology] [surgery] [*therapy]; Cisplatin; Combined Modality Therapy [adverse effects] [methods] [mortality]; Deglutition Disorders [therapy]; Esophageal Neoplasms [mortality] [pathology] [surgery] [*therapy]; Fluorouracil [administration & dosage]; Neoplasm Recurrence, Local; Quality of Life; Randomized Controlled Trials as Topic

### MeSH check words

Humans