Chemoradiotherapy versus chemoradiotherapy plus surgery for esophageal cancer

Review information

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What's new

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Abstract

Background
The outcome of patients with esophageal cancer is generally poor. Although multimodality therapy is standard, there is conflicting evidence regarding the addition of esophagectomy to chemo-radiotherapy

Objectives
To compare the effectiveness and safety of chemoradiotherapy plus surgery with that of chemoradiotherapy alone in non-metastatic esophageal carcinoma patients, in terms of overall survival (OS), progression-free survival (PFS), quality-of-life (QoL), treatment-related mortality and morbidity.

Search methods
A computerized search for relevant trials was performed (up until January 2016) on Cochrane Central Register of Controlled trials (CENTRAL), MEDLINE, EMBASE using MESH headings and keywords. We hand-searched several online databases, conference proceedings and reference lists of retrieved papers.

Selection criteria
Randomized controlled trials (RCTs) comparing chemo-radiotherapy plus esophagectomy with chemo-radiotherapy alone for
localized esophageal carcinoma. RCTs comparing chemotherapy or radiotherapy alone with esophagectomy were excluded.

Data collection and analysis
Trials were selected, data extracted and quality assessed, using standardized methodological procedures expected by The Cochrane Collaboration, by two authors. The primary outcome is overall survival (OS), estimated with Hazard Ratio (HR). Secondary outcomes, estimated with risk ratio (RR), are local and distant progression-free survival, QoL, treatment-related mortality and morbidity and use of salvage procedures for dysphagia. Data was analyzed, employing a random effects model, using Revman 5.3.

Main results
From 2454 results we identified six references, including 431 participants, from two randomized trials. All patients were clinically staged to have at least T3, N0-1 thoracic esophageal carcinoma, of which 93% was squamous-cell histology. The risk of methodological bias of the included trials was low to moderate. Addition of esophagectomy improved loco-regional control (HR 0.55 95% CI 0.39 to 0.76, P= 0.0004, I^2 = 0%, moderate quality evidence), but did not improve survival (HR 0.99 95% CI 0.79 to 1.24, P=0.92 I^2 = 0%, high quality evidence) and increased the risk of treatment-related mortality (RR 5.11 95% CI 1.74 to 15.02, P=0.003, I^2 = 2%, low quality evidence). The other pre-specified outcomes were reported by only one trial, which found that use of esophagectomy was associated with, impaired short term QoL and reduced use of salvage procedures for dysphagia. Neither trial compared treatment-related morbidity between arms.

Authors’ conclusions
Based on the available evidence the addition of esophagectomy to chemo-radiotherapy, in locally advanced esophageal squamous cell carcinoma, improves loco-regional control but not overall survival and was associated with higher treatment related mortality. It is undetermined whether these results can be applied to adenocarcinomas, and to patients with poor response to chemo-radiation.

Plain language summary
The benefits and side effects of adding surgery to chemo-radiotherapy for the treatment of resectable esophageal cancer

Review question
Does the addition of surgery, to chemo-radiotherapy, improve survival in patients with resectable esophageal cancer?

Background
Cancer of the esophagus is a lethal condition. It is usually treated with surgery, radiotherapy, chemotherapy or a combination of these. It is unclear if adding surgery to patients who have undergone chemo-radiotherapy adds benefit.

Study characteristics
This review included information from two published randomized studies and combined results from 431 participants to answer our question regarding survival.

Key results
The review of trials, which included patients with locally advanced esophageal cancer, found evidence that adding surgery reduces the risk of the cancer recurring at the primary site, but did not improve the survival of these patients. Moreover, there were more treatment-related deaths in the group of patients who underwent surgery.

Quality of the evidence
This review used information from randomized studies that is considered to represent the highest quality of evidence.

Background
Description of the condition
Esophageal cancer accounted for 482,300 new cancer cases and 406,800 cancer deaths in 2008 worldwide (Jemal 2011). The incidence rate is highest in Southern Africa and Eastern Asia and lowest in Western and Middle Africa (Jemal 2011).

Esophageal cancer is usually classified histologically as squamous cell carcinoma (SCC) or adenocarcinoma. SCC 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 difference 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 increase in prevalence of obesity (El-Serag 2007; Post 2007). Another important risk factor may be chronic gastroesophageal (GE) reflux disease, which leads to Barrett esophagus, a premalignant 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% in the years of 1975 to 1977 to 18.5% in the years 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) guidelines establish a standard-of-care for medically fit people with resectable disease (www.nccn.org). While surgery alone is appropriate for early-stage disease (T1N0), combined modality therapy – consisting of chemotherapy or chemoradiation pre-, peri- or postoperatively – is offered to people with more advanced disease (T2-4N\text{any} or N+ disease). Specifically, options include: definitive chemoradiotherapy, preoperative chemoradiotherapy or chemotherapy followed by surgery (along with postoperative chemoradiotherapy for people with GE junction adenocarcinomas treated with preoperative chemotherapy) or surgery followed by chemoradiotherapy. Treatment options depend on the tumor location, as well as histology.

The type of approach for esophagectomy such as transhiatal, 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 (\text{Altorki 2002}; \text{Bosset 1997}; \text{Hulscher 2002}; \text{Kelsen 1998}; \text{Orriinger 1999}). Survival post esophagectomy is not dependent on the type of surgical approaches or histology. Muller et al. reviewed the outcomes of various types of esophagectomy and did not find any significant differences in postesophagectomy survival (\text{Muller 1990}). Salazar et al. reported similar cumulative postoperative survival rates for people with SCC and adenocarcinoma (\text{Salazar 1998}).

The Radiation Therapy Oncology Group (RTOG) 85-01 trial demonstrated that concurrent chemoradiotherapy improved OS significantly in people with medically operable SCC when compared with radiotherapy alone (\text{Cooper 1999}). In this trial, 121 people were randomized to received 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 trial have established definitive chemoradiotherapy as the standard-of-care for people with SCC who are not surgical candidates.

Since that time, numerous phase II and III trials 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 trials 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 (\text{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 value = 0.005). However, a clear advantage of preoperative chemoradiotherapy over chemotherapy could not be established.

However, this meta-analysis did not directly address the question of definitive versus preoperative chemoradiotherapy. The role of definitive chemoradiotherapy alone is uncertain, 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 nonsurgical management of people with adenocarcinoma.

The only randomized trial that support the use of surgery plus postoperative chemoradiotherapy is the US Intergroup 0116 study (\text{Macdonald 2001}). In this trial, 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% vs. 41%) and median survival (36 months vs. 27 months). A major criticism of this trial is that 54% of the participants underwent less than a D1 lymph node dissection, raising the possibility that radiation may be compensating for inadequate surgery. Nevertheless, this study suggests that postoperative chemoradiotherapy is a reasonable option for people with GE junction 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 (\text{Cooper 1999}). This result is similar to that achieved with preoperative chemoradiotherapy followed by surgery alone (\text{O'Reilly 1995}; \text{Urba 2001}; \text{Walsh 1996}). There was also no clear consensus from the NCCN guidelines on whether a trimodality approach should be 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 (\text{Ku 2009}; \text{Mariette 2007}; \text{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 on OS. While the overall conclusion was similar in these studies, they lacked explicit methodology in their review and therefore limit interpretation of the data and valid conclusions.

Hence we proposed to conduct 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 patients with nonmetastatic esophageal carcinoma in terms of OS, progression-free survival (PFS), quality–of-life (QoL), treatment-related mortality and morbidity.

**Methods**

**Criteria for considering studies for this review**

**Types of studies**

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

**Types of participants**

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

**Types of interventions**

The control arm of the study was chemoradiotherapy alone group. The intervention arm was the group that undergoes 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 be performed pre-or post-chemoradiotherapy.

**Types of outcome measures**

**Primary outcomes**

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

The intention to treat principle was used for analysis. This outcome measures time from randomization to death from any cause including causes directly related to the malignancy or toxicity of therapy, as well as other causes.

As mentioned earlier, blinding between the two groups will be difficult to achieve. In the absence of blinding, an outcome such as OS would be the least influenced by observer bias.

**Secondary outcomes**

Secondary outcomes included:

- Local PFS (time from randomization to disease progression at initial treated site by radiotherapy or death);
- Distant PFS (time from randomization to disease progression at sites not treated by radiotherapy or death).

The above survival outcomes (OS and PFS) were reported using HRs.

- QoL (measured using a validated scale).

The difference in QoL between the two arms were evaluated.

- 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 (Adverse Event Criteria). Perioperative mortality (within 90 days of surgery) were also analyzed under this outcome.

- 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).

Toxicity was reported according to the organ systems, and were 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. (RTOG Criteria)

Acute and chronic treatment-related toxicities were analyzed separately.

- use of salvage procedures for dysphagia.

This outcome was measured quantitatively to determine the difference between the two groups objectively. Procedures may include balloon dilation, endoscopic stent insertion, laser debulking of tumor or tube insertion for enteral nutrition.

**Search methods for identification of studies**

Papers in all languages were sought and translations carried out 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 present:

- Cochrane Central Register of Controlled Trials, Issue 1, 2016 (Appendix 1);
- MEDLINE 1966 to January 2016 (Appendix 2);
- EMBASE 1988 to January 2016 (Appendix 3).
We used a search strategy to identify randomized controlled trials performed in humans. We used MeSH headings, subject headings and additional free-text words.

Unpublished and grey literature
We identified prospective and ongoing trials by searching the prospective trials registers:

- 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
The citation lists of included studies, key textbooks, and previous systematic reviews were checked through handsearching and experts in the field contacted to identify further reports of trials. Reports of conferences were handsearched in the following sources:

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

Data collection and analysis
Selection of studies
All titles and abstracts obtained by electronic searches were downloaded to a reference management database (Microsoft Excel) and duplicates removed. Four review authors (BAV, YYS, CNL, JCST) reviewed the short-listed articles independently. The studies that clearly do not meet the inclusion criteria were excluded. Full-text articles of the remaining articles were obtained, and four review authors determined the eligibility of the retrieved papers independently. Disagreements were resolved by consensus, or by a fifth review author (LJJ) if necessary. Reasons for exclusion were documented during this process. The review authors were not blinded to the source of the document for article selection or data extraction.

Data extraction and management
For included studies, data on characteristics of participants and interventions (see below), risk of bias, duration of follow-up, outcomes and deviations from protocol were abstracted independently by four review authors (BAV, YYS, CNL, JCST) onto a data abstraction form specially designed for the review. Differences between review authors were resolved by discussion or by appeal to a fifth review author if necessary.

The following patient data were extracted: age, gender, performance status, clinical pretreatment staging (American Joint Committee on Cancer (AJCC) TNM), location of primary tumor (upper, middle or lower third or GE junction), histopathological subtype (SCC vs. adenocarcinoma), and pathological staging (if available). Modalities used for pretreatment clinical staging such as barium studies, endoscopy, endoscopic ultrasound, computed tomography and positron emission tomography, if documented, were noted.

Similarly, the following data on types of intervention were extracted:

- 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 will be documented;
- chemotherapy: chemotherapeutic agents, biologics, schedule, route of administration, dose intensity and compliance to the recommended protocol will be documented.

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

For time to event (OS and PFS) data, we extracted the log of the hazard ratio \[\text{log}(HR)\] and its standard error from trial reports; if these are not reported, we attempted to estimate the log (HR) and its standard error using the methods of 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 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 error.

Both unadjusted and adjusted statistics were extracted.

Data extracted were utilized in an intention-to-treat analysis, in which participants were analyzed in the groups to which they were assigned.
The time points at which outcomes were reported were noted.

**Assessment of risk of bias in included studies**

Risk of bias in included randomized controlled trials were assessed using The Cochrane Collaboration’s tool and the following criteria.

**Was the allocation sequence adequately generated?**

Yes, for example, participants assigned to either arm by random sequence generation; such as computer-generated random numbers, coin/dice tossing, referring to a random-number table, shuffling cards or envelopes, drawing of lots.

No, for example, participants assigned to either arm non-randomly; such as based on date of birth, day (or date) of admission, case record number, surname, preference of the person (or clinician), availability of the intervention.

Unclear, for example, not reported, information not available.

**Was allocation adequately concealed?**

Yes, for example, allocation sequence could not be foretold; such as serially numbered opaque sealed envelopes, or independent central randomization office (including telephone, web-based randomization).

No, for example, allocation sequence could be foretold by participants or investigators; such as open allocation schedule, non-opaque (or unsealed) envelopes, date of birth, case record number, alternation (or rotation).

Unclear, for example, not reported.

**Were outcome assessors adequately prevented from knowing the allocated interventions during the study?**

Yes, for example, blinding of outcome assessment ensured, or no blinding of outcome assessment but review authors judge that the outcome measurement is unlikely to be influenced by lack of blinding.

No, for example, blinding of outcome assessment present but likely to have been broken, or no blinding of outcome assessment and the outcome measurement is likely to be influenced by the lack of blinding.

Unclear.

**Was incomplete data adequately addressed?**

Yes, for example, no missing data within each outcome, missing data balanced in numbers across treatment arms and similar reasons for missing data, reasons for missing outcome data unlikely to be related to true outcome, or proportion/effect size of missing outcomes not enough to have a clinically relevant impact on the observed effect estimate

No, for example, reason for missing outcome data likely related to true outcome (either imbalance in numbers or reasons for missing data across treatment arms), proportion/effect size of missing outcomes enough to have a clinically relevant impact on the observed effect estimate, potentially inappropriate application of simple imputation, or ‘as-treated’ analysis done with substantial departure of the intervention received from that assigned at randomization.

Unclear.

**Are the reports of the study free of suggestion of selective outcome reporting?**

Yes, for example, all prespecified outcomes in protocol, or methods section, were reported in the prespecified way.

No, for example, not all of prespecified outcomes were reported, outcomes reported using measurements or analysis methods or subsets of the data that were not prespecified, incomplete reporting of outcomes.

Unclear.

**Was the study apparently free of other problems that could put it at a high risk of bias?**

Yes.

No, for example, potential source of bias related to the specific study design used, claimed to have been fraudulent.

Unclear.

The ‘Risk of bias’ tool was applied independently by four review authors (BAV, YYS, CNL, JCST) and any disputes resolved by consensus, or if necessary by a fifth review author (LLJ). Results were summarized in a both ‘Risk of bias’ graph and a ‘Risk of bias’ summary table. Results of meta-analyses was interpreted with respect to the risk of overall bias.

**Measures of treatment effect**

We used the following measures of the effect of treatment:

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

**Dealing with missing data**

We did not impute missing outcome data.

**Assessment of heterogeneity**

Heterogeneity between studies was assessed by visual inspection of forest plots (L’Abbé 1987), by estimation of the
percentage heterogeneity between trials that cannot be attributed to sampling variation (Higgins 2003), by a formal statistical test of significance of the heterogeneity (Deeks 2001), and if possible, by subgroup analysis.

Assessment of reporting biases
Funnel plots corresponding to the meta-analysis of the primary outcome were examined for publication bias (Lau 1997). If the funnel plots suggest that treatment effects may not be sampled from a symmetric distribution, as assumed by a random-effects model, further meta-analyses was performed using a fixed-effect model.

Data synthesis
If sufficient studies are available, their data was pooled in a meta-analysis.

For dichotomous outcomes, the RR was calculated for each study and pooled.

For continuous outcomes, the mean difference between the two arms at the end of follow-up was pooled, if all trials measured the outcome on the same scale. If different scales were used, standardized mean differences was pooled.

If any trials have multiple treatment groups, the ‘shared’ comparison group was divided into the number of treatment groups and comparisons between each treatment group and the split comparison group will be treated as independent comparisons.

Random-effects models with inverse variance weighting will be used for all meta-analyses (DerSimonian 1986).

If possible, studies making different comparisons were synthesized using the methods of Bucher (Bucher 1997).

Subgroup analysis and investigation of heterogeneity
We would have performed subgroup analysis, grouping the trials 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 vs. cisplatin-based vs. others);
4. histological subtype (SCC vs. adenocarcinoma);
5. type of surgery (transhiatal vs. transthoracic vs. two- or three-stage resections);
6. type of radiation delivery techniques (intensity modulated vs. conventional vs. brachytherapy);
7. sequencing of intervention in the experimental arm (chemoradiotherapy followed by surgery vs. surgery followed by chemoradiotherapy).

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

Sensitivity analysis
We would have performed 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
From the search results, we identified 6 references (Stahl 2005; Bedenne 2007; Bonnetain 2006; Crehange 2007; Burtin 2008; Vincent 2015) from two randomized controlled trials (Stahl 2005; Bedenne 2007) including 431 patients (Figure 1), using the search strategy summarized in Appendix 2.

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

Stahl 2005 included locally advanced (cT3-T4 and/or N+) squamous cell cancers of the upper or mid-thoracic esophagus. Patients 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 fluorouracil 500mg/m2, leucovorin 300mg/m2, etoposide 100mg/m2 and cisplatin 30mg/m2 on days 1-3 every 3 weeks.

The surgical arm received chemoradiotherapy consisting of cisplatin 50mg/m2 (D2-8) and etoposide 80mg/m2(D3-5) with 40Gy of radiation (2Gy per fraction, over 4 weeks). The volume of irradiation, included the gross tumour with 5cm superior-inferior margin and 2cm axial margin, as well as the supra/infra-clavicular 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 paraesophageal, paracardial, left gastric and celiac lymph nodes (two-field lymphadenectomy).

Patients in the non-surgical arm were treated with chemoradiotherapy involving the same chemotherapeutic agents and radiation volumes (to 40Gy). This was followed by a sequential radiation boost. For T4 or obstructing T3 tumours, the gross tumour with a 2cm superior-inferior margin and 1cm axial margin (CTVboost) was treated to 50Gy, followed by a
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Hyperfractionated boost to 65Gy (1.5Gy BID, 6 hours apart, over 1 week). Non-obstructing tumours were treated to 60Gy (CTV boost) followed by 2 fractions of high-dose rate brachytherapy boost (4Gy to 5mm depth).

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

**Bedenne 2007** trial included patients with operable T3N0 thoracic esophageal cancer. There was no restriction regarding histology or tumour location. All registered patients (n=444) received induction chemoradiation, however only patients who showed objective response were randomized (n=259).

Chemotherapy consisted of fluorouracil 800mg/m2 and cisplatin 15mg/m2 (D1-5) given every 3 weeks. All patients received 2 cycles prior to randomization, and the non-surgical arm received 3 more cycles together with radiation.

Radiotherapy was permitted to given by conventional fraction or split-course, until January 1999, when the split-course arm was discontinued to inferior results. Radiotherapy volumes included the gross tumour and lymph nodes, with a 3cm superior-inferior margin and 2cm axial margin. Split course radiotherapy was delivered in daily fraction of 3Gy, 2 sequences of 5 days (15Gy each, 2 weeks apart) prior to randomization and 1 sequence after (total 45Gy). Conventional radiotherapy was delivered to 46Gy (2Gy per fraction, 5 fractions per week) prior to randomization, and 20Gy after (total 66Gy).

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

The primary outcomes was overall survival, and 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 as full journal article by **Bonnetain 2006**. The results of split-course versus conventionally-fractionation were reported as full journal article by **Crehange 2007**. Outcome of the registered, but non-randomized, patients was published as a full journal article by **Vincent 2015**.

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

**Excluded studies**

We excluded **Wang 2007** after review of full manuscripts as a process of randomization was not described. Patients were prospectively assigned to neoadjuvant chemoradiotherapy followed by surgery or definitive chemoradiotherapy followed by consolidation chemotherapy in a non-randomized fashion.

We excluded **Nicklin 2010** after review of the trial protocol, as the trial arms were not in line with our inclusion criteria. This is an ongoing randomized controlled trial, in esophageal squamous cell cancer, between induction chemotherapy followed by chemoradiotherapy versus surgery.

**Risk of bias in included studies**

The risk of bias of the included studies are summarized under "Characteristics of studies" and **Figure 2**.

**Allocation (selection bias)**

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

**Blinding (performance bias and detection bias)**

Blinding of participants and personnel was only reported by **Stahl 2005**. This was an unblinded trial, as such risk of bias from lack of blinding was high for subjective outcomes 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, as such the risk of bias is unclear. Similar to the other trial, it is expected that risk of bias remains 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 (attrition bias)**

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

**Selective reporting (reporting bias)**

Risk of bias from selective reporting is low in both trials. **Stahl 2005** reported on the pre-specified primary outcome (OS) and **Bedenne 2007** reported on the pre-specified primary (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 funnel plot was initially planned to examine possible publication bias, but due to the small number of included studies, funnel plot analysis was deemed not useful and hence not performed.

**Effects of interventions**

**OVERALL SURVIVAL**
Overall survival (primary outcome) was reported in both the included studies (n=431). HRs as published, or estimated indirectly from published data, were used for the calculation of summary statistics. The data appears homogenous ($\chi^2=0.18, P=0.67$). Pooled data showed no significant benefit with HR=0.99 (95% CI 0.79 to 1.24).

**LOCAL PROGRESSION-FREE SURVIVAL (LPFS)**

We had defined local progression-free survival as a secondary outcome in the initial protocol. However, neither of the studies reported this data. Bedenne 2007 reported higher locoregional relapse without esophagectomy (HR=1.63, 95% CI 1.04 to 2.55, P=0.03). The other study 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) to report a lower loco-regional recurrence favouring esophagectomy HR 0.55 (95% CI 0.39 to 0.76). The data appears homogenous ($\chi^2=0.5, P=0.48$).

**DISTANT PROGRESSION-FREE SURVIVAL**

This outcome was reported by neither study, to be included in a summary statistic calculation. Bedenne 2007 reported 2-year metastatic probability 39.1% (SE 5.3) versus 29% (SE 4.7) (P=0.24) for trimodality therapy and chemo-radiation alone respectively.

**QUALITY OF LIFE**

QoL was only reported by the FFCD 9102 trial (Bonnetain 2006). As such, a pooled estimate could not be estimated.

In this study (n=259), QoL was assessed using the Spitzer QoL index (scored 0-10). QoL scores were worse, at 3 month follow-up, with trimodality therapy (7.52 versus 8.45, P<0.01). However, subsequent follow-up did not show any difference between treatment groups. (P=0.26).

**TREATMENT-RELATED MORTALITY**

Both studies reported the above outcome to be included for a pooled estimate (n=431). The pooled estimate for treatment-related mortality favoured chemo-radiation alone (RR 5.1 95% CI 1.74 to 15.02, P=0.003). The data appear homogenous ($\chi^2=1.02, P=0.31$)

**TREATMENT-RELATED TOXICITY (ACUTE AND CHRONIC)**

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

**USE OF SALVAGE PROCEDURES FOR DYSPHAGIA**

The above outcome was only reported by Bedenne 2007. A higher proportion of patients undergoing chemo-radiotherapy alone required salvage procedures, either dilation or stent placement, for dysphagia (46.2 versus 24%, P<0.001).

**Discussion**

**Summary of main results**

This meta-analysis showed that the addition esophagectomy to chemo-radiotherapy improved loco-regional control (GRADE quality moderate). However, there was an increased treatment related mortality (GRADE quality low) and no improvement in overall survival (GRADE quality high). The impact of esophagectomy on QoL, treatment related morbidity and use of salvage procedures for dysphagia remain undetermined.

**Overall completeness and applicability of evidence**

Despite our systematic and extensive search, we only found two eligible trials to be included 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 provide sufficient evidence to draw reliable conclusions for overall survival, loco-regional control 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**

Multimodality treatment is generally considered necessary for advanced esophageal cancers. No restrictions were placed on stage during selection of studies. However, it is important to note that these trials included only locally advanced, resectable, cancers and therefore the applicability should be restricted to this group i.e. cT3- T4 and/or Node positive. Stahl 2005 utilized 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 patients were incorrectly staged, as CT alone has been shown to be a poor assessor for depth of tumour infiltration (Kim 2009) . It remains unclear if the inclusion of a minority of patients with potentially Stage I or II disease would have changed our findings. Stahl 2005 only included patients with upper and middle esophageal tumours, whereas Bedenne included all thoracic esophageal tumours. It is unclear how many patients with distal esophageal...
cancers were included in the latter study, although most squamous cell carcinomas occur in the proximal 2/3 of the esophagus. As such, these results may not be applicable to distal esophageal/gastroesophageal junction tumours.

**Effect of histology**

There were no restrictions imposed during the search for the studies. However, Stahl 2005 included only squamous cell carcinoma (SCC) patients and Bedenne 2007 included 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 as two separate disease entities with individual treatment strategies. Therefore, these results should not be applied to patients with adenocarcinomas.

**Responders versus non-responders**

Bedenne 2007, for ethical purposes, only randomized patients who responded to induction chemo-radiation. In a recent publication by Vincent 2015, the non-responding patients were reported to have much poorer outcomes; however, the addition of salvage surgery in these patients improved OS (HR 0.39 (0.25 to 0.61, P<0.0001). Stahl 2005 randomized all patients, regardless of response to induction multi-agent chemotherapy. However, subgroup analysis corroborates that patients with response to induction therapy fared better. These results should not be applied to patients who do not respond to induction chemoradiation, i.e. who had progressive or residual primary tumors. Salvage surgery remains a strong consideration for such patients.

**Chemotherapy and Radiotherapy dose and design**

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

Stahl 2005 utilized differing radiotherapy regimens in both arms. Patients undergoing surgery had 40Gy of external beam radiotherapy whereas patients who received chemo-radiation alone received a total dose of 65Gy or more. Notably, all patients in the chemo-radiotherapy 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, patients in the surgical arm received chemo-radiotherapy (46Gy) whereas patients treated with chemo-radiotherapy alone received an additional 20Gy (total 66Gy). Based on our findings, the addition of surgery did not confer a survival benefit compared to high-dose chemo-radiotherapy alone (>65Gy). However, it remains unclear if surgery may have conferred a survival advantage compared to standard dose chemo-radiotherapy alone (50Gy).

Considering all patients within 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 patients treated without induction therapy.

**Quality of the evidence**

The quality of the evidence was judged to be high for the outcome of overall survival. However, outcomes of loco-regional control was judged to be moderate and treatment-related mortality was judged be of low quality. We determined the quality of evidence using the guideline development tool developed by the GRADE working group, with the following criteria.

(Please refer to Summary of findings table 1)

Risk of bias: Not serious for overall survival, and serious for the other two outcomes (as they were unblinded studies and assessors may have been influenced by treatment allocation)

Inconsistency: Not serious for all outcomes

Indirectness: Not serious for all outcomes

Imprecision: Serious for treatment-related mortality (due to large confidence intervals), and not serious for the other two outcomes

For overall survival, all plausible residual confounding would reduce the demonstrated effect.

**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 quantitative review to date.

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

A funnel-plot analysis was not performed, as only 2 studies were identified. As such, although publication bias may exist, it is unlikely that a large unpublished randomized controlled trial exists that would alter our findings. For the same reasons of limited studies, sensitivity and subgroup analysis (stated in the protocol) were not performed, as they would not be meaningful.
We had not specified, a priori, a sub-group analysis of outcomes between responders and non-responders to induction treatment. Bedenne 2007 did not randomize patients who failed to respond to induction chemo-radiotherapy, and Stahl 2005 did not provide sufficient information on non-responders. As such, a quantitative sub-group analysis cannot be performed.

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

Another limitation of this study is 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 2-year freedom from local progression, whereas Bedenne 2007 reported 2-year recurrence probability and locoregional relapses. Deviating from the protocol, we combined the available data to formulate a hazard ratio for loco-regional control. Although not stated a priori, this is provides a close and reliable estimate of local-progression free survival.

A further limitation is the heterogeneity in reporting outcomes such as distant-progression free survival, treatment-related morbidity, use of salvage procedures and QoL. The above outcomes were thought to be clinically relevant and therefore were included in our protocol. However, only Bedenne 2007 reported the above outcomes and hence we were unable to perform quantitative analysis.

Agreements and disagreements with other studies or reviews
We have not come across another meta-analysis with the same clinical question. However, prospective non-randomized studies corroborate our findings. Wang 2007 conducted a prospective non-randomized study comparing 50 patients with esophageal cancer, of which 67% had adenocarcinoma histology, between carboplatin/paclitaxel and radiotherapy to 45Gy followed by esophagectomy versus carboplatin/paclitaxel and radiotherapy to 50.4Gy followed by consolidation chemotherapy alone. The survival outcomes between both arms were not different (3-year survival 60% in both arms). A single institution retrospective series (Rawat 2013) similarly found no difference in survival outcomes with the addition of surgery.

Both of the included studies were conducted in the 1990’s, therefore one has to re-examine the effect of increased treatment-related mortality (Finks 2011; Jafari 2013) with esophagectomy, which may have negated any potential survival advantage. 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 patients with SCC undergoing definitive chemoradiation, unless there is evidence of persistent local disease for which salvage esophagectomy should be undertaken. Similarly, ESMO guidelines (Stahl 2013) recommend either chemo-radiation with planned surgery, or close surveillance with salvage surgery for patients with locally advanced SCC.

Authors’ conclusions

Implications for practice
There is moderate quality evidence that adding surgery to chemo-radiation improves loco-regional control. However, based on the available evidence, this comes at the cost of increased treatment-related mortality and no improvement in overall survival. There is insufficient evidence to determine the impact of surgery on QoL and treatment-related morbidity. Patients who do not respond to chemoradiation, or who have persistent local disease warrant upfront surgery. In addition, patients where surgery is deferred 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 patients 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, patient selection using advanced functional imaging (e.g. PET/CT) or predictive biomarkers may help select patient groups who may benefit from upfront surgery after definitive chemo-radiation.

Acknowledgements
We would like to thank Cochrane Upper Gastrointestinal and Pancreatic Diseases Group for assisting us with the search strategy.
We would also like to thank our reviewers (Dr. Sarah Rhodes and Dr. Richard Malthaner).

Contributions of authors
Conception and design: Vellayappan BA, Soon YY, Ku GY and Tey JCS.
Protocol writing: Vellayappan BA and Soon YY.
Final approval of protocol: Vellayappan BA, Soon YY, Ku GY, Leong CN, Lu JJ and Tey JCS.

Declarations of interest
Differences between protocol and review
We had intended to perform sub-group and sensitivity analysis in our protocol. However this was not carried out, due to limited available information and the presence of only two RCTs.

Published notes
Characteristics of studies
Characteristics of included studies
Bedenne 2007
## Methods

Randomized controlled trial

## 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; February 1993 to December 2000; France (multi-center)

Patients 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 insufficiency were excluded.

444 patients eligible for the study, of whom 259 were randomized (242 male, 17 female)

Patients randomized/analyzed in this meta-analysis: 259/259

Median follow-up time was 47.4 months.

## Interventions

All patients received induction chemoradiation initially.

Patients who responded to induction chemoradiation (D38-D41), were randomized to surgery vs further chemoradiation.

Initially, split-course and conventional radiotherapy were allowed (investigator's choice). From January 1999, only conventional radiotherapy was permitted.

Radiotherapy treatment volumes include macroscopic tumour and lymph nodes, with a 3-cm proximal/distal margin and 2-cm radial margin. (3 or 4 fields, and treating all fields daily)

- **Split-course:** 3Gy per day (D1-5, then D22-26) to a total dose of 30Gy. After randomization to further chemoradiation, 3Gy per day (D43 - 47) to a total dose of 45Gy.

- **Conventional:** 2Gy per fraction, 5 fractions per week to a total dose of 46Gy. After randomization to further chemoradiation, 2G per fraction, 5 fractions per week to a total dose of 66Gy.

Chemotherapy: 2 cycles of chemotherapy were delivered before random assignment, on D1 and D22. Three cycles were administered in arm B, after random assignment, (D43, D64, D92)

Chemotherapy consists of cisplatin 15mg/m2 (days 1 to 5), and continuous infusion fluorouracil 800mg/m2 daily (days 1 to 5)

Surgery: No particular type of surgery was required. Surgery was to be performed between D50 and D60.

## Outcomes

OS. Duration of hospital stay, quality of life, type of recurrence, procedures against dysphagia

## Notes

Risk of bias table
<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
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<tr>
<td>Random sequence generation</td>
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<td>Sequence was generated using a minimization program.</td>
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<td></td>
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<tr>
<td>Allocation concealment</td>
<td>Low risk</td>
<td>Allocation was done at a central site. (FFCD Data centre)</td>
</tr>
<tr>
<td>(selection bias)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blinding of participants and</td>
<td>Unclear risk</td>
<td>The risk of bias for the primary outcome (overall survival) is objective and therefore</td>
</tr>
<tr>
<td>personnel (performance bias)</td>
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<td>low. However, the risk of bias from lack of blinding was high for subjective outcomes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>such as quality of life, use of salvage procedures for dysphagia, duration of</td>
</tr>
<tr>
<td></td>
<td></td>
<td>hospital stay and type of recurrence.</td>
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<tr>
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</tr>
<tr>
<td>Blinding of outcome assessment</td>
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<td></td>
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<td>such as quality of life, use of salvage procedures for dysphagia, duration of hospital</td>
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<td>stay and type of recurrence.</td>
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</tr>
<tr>
<td>Selective reporting</td>
<td>Low risk</td>
<td>All pre-specified primary and secondary outcomes were reported</td>
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<tr>
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<tr>
<td>Other bias</td>
<td>Unclear risk</td>
<td>Quality assurance of radiotherapy planning and delivery were not reported.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Type and quality of surgeries performed were not audited and reported.</td>
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</tbody>
</table>

*Kahl 2005*
<table>
<thead>
<tr>
<th>Methods</th>
<th>Randomized controlled trial</th>
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<tbody>
<tr>
<td>Participants</td>
<td>Histologically proven squamous cell carcinoma of the upper and mid third esophagus (no exact definition given on tumour location from dental ridge). Age &lt;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)</td>
</tr>
<tr>
<td>Patients randomized/analysed in this meta-analysis : 172/172</td>
<td></td>
</tr>
<tr>
<td>Median observation time : 6 years</td>
<td></td>
</tr>
<tr>
<td>Interventions</td>
<td>Induction chemotherapy, followed by preoperative chemo-radiation vs induction chemotherapy, followed by chemo-radiation alone. Both groups received induction chemotherapy, consisting of three courses of bolus fluorouracil (500mg/m₂), leucovarin (300mg/m₂), etoposide (100mg/m₂), cisplatin (30mg/m₂) D1-D3 every 3 weeks. Intervention group: After induction chemotherapy, preoperative concomitant chemo-radiotherapy was given as detailed below. Chemotherapy: Cisplatin (50mg/m₂), etoposide (80mg/m₂) on D2-8 Radiotherapy: 2Gy per fraction, 5 fractions per week to a total dose of 40Gy. Radiotherapy clinical target volume included gross tumour with 5cm cranio-caudal margin and 2cm transverse margin. Supra-infraclavicular and lower cervical lymph nodes were included for upper thoracic tumours. AP and PA fields were used in conjunction with three-dimensional planning. Surgery: Trans-thoracic esophagectomy was performed 3 to 4 weeks after chemo-radiation. Resection included paraesophageal, paracardial, left gastric and celiac nodes (two-field lymphadenectomy) Control group: After induction chemotherapy, definitive chemo-radiotherapy was given. Chemotherapy: Cisplatin (50mg/m₂), etoposide (80mg/m₂) on D2-8 Radiotherapy: 2Gy per fraction, 5 fractions per week to a total dose of 50Gy initially. Following which, a boost was delivered. Radiotherapy boost to reduced volume: For T4 and obstructing T3 tumours, a total external beam dose of 65Gy was delivered. (i.e. 15Gy delivered using 1.5Gy twice a day, 6 hours intervals, over 5 days) For T3 and/or non-obstructing tumours, external beam dose to a total of 60Gy, followed by intra-cavitary brachytherapy. (two fractions of 4Gy high dose-rate administered with a 4 to 7 day interval; prescribed to 5mm depth from applicator to pre-radiotherapy tumour length and 5mm superior/inferior margin) Radiotherapy clinical target volume for the initial phase included gross tumour with 5cm cranio-caudal margin and 2cm transverse margin. Supra-infraclavicular and lower cervical lymph nodes were included for upper thoracic tumours. Radiotherapy clinical target volume (external beam) for the boost phase included gross tumour with 2cm cranio-caudal margin and 1cm transverse margin. AP, PA and oblique fields were used in conjunction with three-dimensional planning.</td>
</tr>
<tr>
<td>Outcomes</td>
<td>OS, local progression free survival, treatment-related mortality,</td>
</tr>
<tr>
<td>Notes</td>
<td>Risk of bias table</td>
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<tr>
<td>Bias</td>
<td>Authors’ judgement</td>
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</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
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<td>Low risk</td>
</tr>
<tr>
<td>Other bias</td>
<td>Unclear risk</td>
</tr>
</tbody>
</table>

**Footnotes**

**Characteristics of excluded studies**

**Nicklin 2010**

**Reason for exclusion**

Trial arms not in line with our inclusion criteria. This is an ongoing randomized controlled trial investigating induction chemotherapy followed by chemoradiotherapy VS induction chemotherapy followed by surgery.

**Wang 2007**

**Reason for exclusion**

Process of randomization was not described, therefore presumed to be a prospective non-randomized study.

**Footnotes**

**Characteristics of studies awaiting classification**

**Footnotes**

**Characteristics of ongoing studies**

**Footnotes**

**Summary of findings tables**

1 Chemoradiotherapy versus chemoradiotherapy plus surgery for esophageal cancer
## Chemoradiotherapy versus chemoradiotherapy plus surgery for esophageal cancer

**Patient or population:** non-metastatic esophageal cancer  
**Setting:** curative intent  
**Intervention:** chemoradiotherapy plus surgery  
**Comparison:** chemoradiotherapy alone

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Anticipated absolute effects* (95% CI)</th>
<th>Relative effect (95% CI)</th>
<th>№ of participants (studies)</th>
<th>Quality of the evidence (GRADE)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall survival (OS) assessed with Hazard Ratio follow up: median 6 years</td>
<td>The mean overall survival was 0</td>
<td>The mean overall survival in the intervention group was 0.99 undefined more (0.74 more to 1.24 more)</td>
<td>-</td>
<td>431 (2 RCTs)</td>
<td>⊕⊕⊕⊕ HIGH</td>
</tr>
<tr>
<td>Treatment-related mortality assessed with risk ratio</td>
<td>Study population</td>
<td>RR 5.11 (1.74 to 15.02)</td>
<td>431 (2 RCTs)</td>
<td>⊕⊕⊕⊝ LOW</td>
<td>1 2</td>
</tr>
<tr>
<td></td>
<td>19 per 1000</td>
<td>95 per 1000 (32 to 278)</td>
<td>Moderate</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>21 per 1000</td>
<td>109 per 1000 (37 to 320)</td>
<td></td>
<td></td>
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<tr>
<td>Loco-regional control assessed with Hazard Ratio</td>
<td>The mean loco-regional control was 0</td>
<td>The mean loco-regional control in the intervention group was 0.55 undefined more (0.39 more to 0.76 more)</td>
<td>-</td>
<td>431 (2 RCTs)</td>
<td>⊕⊕⊕⊝ MODERATE 2</td>
</tr>
</tbody>
</table>

*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; OR: Odds 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 the effect

**Footnotes**  
1 Very large confidence interval  
2 Detection bias as investigators were not blinded

### Additional tables

### References to studies

#### Included studies

**Bedenne 2007**  

**Stahl 2005**  

#### Excluded studies

**Nicklin 2010**  
Published and unpublished data [DOI: 10.1186/ISRCTN89052791; ISRCTN: 89052791; Other: EudraCT number 2009-013877-16]

**Wang 2007**


**Studies awaiting classification**

**Ongoing studies**

**Other references**

**Additional references**

**Adverse Event Criteria**


**Altorki 2002**


**Bonnetain 2006**


**Bosset 1997**


**Bucher 1997**


**Burtin 2008**


**Cook 2009**


**Cooper 1999**


**Crehange 2007**


**Deeks 2001**


**DerSimonian 1986**


**El-Serag 2007**


**Finks 2011**

Higgins 2003

Hulscher 2002

Jafari 2013

Jemal 2011

Kelsen 1998

Kim 2009

Ku 2009

L'Abbé 1987

Lau 1997

Lu 2010

Macdonald 2001

Mariette 2007

Minsky 2002

Muller 1990

O'Reilly 1995

Orringer 1999
154 Chemoradiotherapy versus chemoradiotherapy plus surgery for esophageal cancer


**Parmar 1998**


**Post 2007**


**Rawat 2013**


**RevMan 2011**


**RTOG Criteria**


**Salazar 1998**


**Sjoquist 2011**


**Stahl 2013**


**Urba 2001**


**Van Hagen 2012**


**Vincent 2015**


**Walsh 1996**


**Wolf 2011**


**Other published versions of this review**

**Classification pending references**

**Data and analyses**

### 1 Chemo-radiotherapy plus surgery versus chemo-radiotherapy alone

<table>
<thead>
<tr>
<th>Outcome or Subgroup</th>
<th>Studies</th>
<th>Participants</th>
<th>Statistical Method</th>
<th>Effect Estimate</th>
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</thead>
<tbody>
<tr>
<td>1.1 Overall survival</td>
<td>2</td>
<td>431</td>
<td>Hazard Ratio(IV, Random, 95% CI)</td>
<td>0.99 [0.79, 1.24]</td>
</tr>
</tbody>
</table>
1.2 Treatment-related mortality

Risk Ratio (M-H, Random, 95% CI) 5.11 [1.74, 15.02]

1.3 Loco-regional control

Hazard Ratio (IV, Random, 95% CI) 0.55 [0.39, 0.76]

Figures

Figure 1

PRISMA flow diagram.

Caption

PRISMA flow diagram.

Figure 2
Caption
Risk of bias summary: review authors’ judgements about each risk of bias item for each included study.

Sources of support

Internal sources
• No sources of support provided

External sources
• No sources of support provided

Feedback

Appendices

1 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

2 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/
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9. radiochemotherap*.tw.
10. radio-chemotherap*.tw.
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12. 3 and 11
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1. controlled clinical trial.pt.
2. randomized.ab.
3. placebo.ab.
4. drug therapy.fs.
5. randomly.ab.
6. trial.ab.
7. groups.ab.
8. or/13-20
9. exp animals/ not humans.sh.
10. 21 not 22.
11. 12 and 23
12. case report*.tw.
14. (systematic adj (review* or overview*)).tw.
15. Review.pt.
16. or/25-28
17. 24 not 29

3 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

Graphs
1. Chemo-radiotherapy plus surgery versus chemo-radiotherapy alone
1.1 Overall survival

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>CRT plus surgery</th>
<th>CRT alone</th>
<th>Hazard Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total</td>
<td>Weight</td>
<td>IV, Random, 95% CI</td>
</tr>
<tr>
<td>Bodenne 2007</td>
<td>129</td>
<td>129</td>
<td>1.03 [0.77, 1.38]</td>
</tr>
<tr>
<td>Shahi 2005</td>
<td>86</td>
<td>86</td>
<td>0.99 [0.79, 1.24]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>219</td>
<td>216</td>
<td>1.00 [1.00, 1.00]</td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 0.00; Chi² = 1.01, df = 1 (P = 0.31); P = 97%
Test for overall effect Z = 1.00 (P = 0.31)

1.2 Treatment-related mortality

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>CRT plus surgery</th>
<th>CRT alone</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total</td>
<td>Weight</td>
<td>M.H. Random, 95% CI</td>
</tr>
<tr>
<td>Bodenne 2007</td>
<td>12</td>
<td>129</td>
<td>12.09 [9.86, 15.81]</td>
</tr>
<tr>
<td>Shahi 2005</td>
<td>11</td>
<td>88</td>
<td>3.67 [1.05, 12.68]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>219</td>
<td>216</td>
<td>5.11 [1.74, 15.02]</td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 0.02; Chi² = 1.02, df = 4 (P = 0.34); P = 2%
Test for overall effect Z = 2.97 (P = 0.003)

Confidential
### 1.3 Loco-regional control

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>log[Hazard Ratio]</th>
<th>SE</th>
<th>CRT plus surgery Total</th>
<th>CRT alone Total</th>
<th>Weight</th>
<th>Hazard Ratio IV, Random, 95% CI</th>
<th>Hazard Ratio IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bodenna 2007</td>
<td>-0.46</td>
<td>0.23</td>
<td>86</td>
<td>88</td>
<td>54.2%</td>
<td>0.61 [0.39, 0.96]</td>
<td></td>
</tr>
<tr>
<td>Stahl 2005</td>
<td>-0.73</td>
<td>0.25</td>
<td>129</td>
<td>130</td>
<td>45.8%</td>
<td>0.48 [0.30, 0.78]</td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>215</strong></td>
<td></td>
<td><strong>216</strong></td>
<td></td>
<td>100.0%</td>
<td><strong>0.55 [0.39, 0.76]</strong></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 0.00, Chi² = 0.50, df = 1 (P = 0.48); I² = 0%
Test for overall effect Z = 3.54 (P = 0.0004)

![Forest plot](image.png)