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**Evidence-based Series 2-11 Version 4 REQUIRES UPDATING**

## A Quality Initiative of the Program in Evidence-Based Care (PEBC), Cancer Care Ontario (CCO)

# Preoperative or Postoperative Therapy for Resectable Esophageal Cancer

*Members of the Gastrointestinal Cancer Disease Site Group*

**An assessment conducted in December 2021 indicated that Evidence-Based Series 2-11 Version 4 REQUIRES UPDATING. It is still appropriate for this document to be available while this updating process unfolds. The PEBC has a formal and standardized process to ensure the currency of each document (PEBC Assessment & Review Protocol).**

**EBS 2-11v4 is comprised of 4 sections. You can access the summary and full report here:**
**https://www.cancercareontario.ca/en/guidelines-advice/types-of-cancer/631**

**Section 1: Clinical Practice Guideline**
**Section 2: Systematic Review**
**Section 3: EBS Development Methods and External Review Process and Results**
**Section 4: Document Review Summary and Tool**

**June 1, 2016**



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or contact the PEBC office at:
Phone: 905-527-4322 ext. 42822 Fax: 905-526-6775 E-mail: ccopgi@mcmaster.ca

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Malthaner RA, Wong RKS, Rumble RB, Zuraw L; Members of the Gastrointestinal Cancer Disease Site Group of Cancer Care Ontario's Program in Evidence-based Care. Neoadjuvant or adjuvant therapy for resectable esophageal cancer: a clinical practice guideline. BMC Cancer. 2004 Sep;4:67.

Malthaner RA, Wong RKS, Rumble RB, Zuraw L; Members of the Gastrointestinal Cancer Disease Site Group of Cancer Care Ontario's Program in Evidence-based Care. Neoadjuvant or adjuvant therapy for resectable esophageal cancer: a systematic review and meta-analysis. BMC Med. 2004 Sep;2:35.

# Guideline Report History

| GUIDELINE VERSION | SYSTEMATIC REVIEW | | PUBLICATIONS | NOTES AND KEY CHANGES |
|---|---|---|---|---|
| | Search Dates | Data | | |
| Original version April 2002 | 1966 - December 2001 | Full Report | Web publication | NA |
| April 13, 2005 | 1966 - January 2005 | Full Report | Web publication | NA |
| May 21, 2008 | 1966 – April 2007 | Full Report | Web publication | NA |
| Reviewed December 2012 | 2007- December 2012 | New data found in Appendix I | Updated Web publication | 2008 recommendations are **ENDORSED** |
| Current Version 4 June 2016 | 2012 – March 2016 | New data found in section 4: Document Review Tool | Updated Web publication | 2008 recommendations are **ENDORSED** |

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**Evidence-based Series #2-11 Version 4: Section 1**

# Preoperative or Postoperative Therapy for Resectable Esophageal Cancer: Guideline Recommendations

*RA Malthaner, RKS Wong, K Spithoff, RB Rumble, L Zuraw, and the Gastrointestinal Cancer Disease Site Group*

A Quality Initiative of the
Program in Evidence-based Care (PEBC), Cancer Care Ontario (CCO)

These guideline recommendations have been ENDORSED, which means that the recommendations are current and relevant for decision making. Please see Section 4: Document Review Summary and Review Tool for a summary of the updated evidence published between 2012 and 2016, and for details on how the Clinical Practice Guideline was ENDORSED

**Report Date: May 21, 2008**

## QUESTION

Should patients with resectable esophageal cancer receive preoperative or postoperative therapy along with surgery?

## TARGET POPULATION

These recommendations apply to adult patients with resectable, operable, and potentially curable thoracic (lower two thirds of esophagus) esophageal cancer for whom surgery is considered appropriate.

## RECOMMENDATIONS

- Preoperative cisplatin-based chemotherapy plus radiotherapy is recommended as the preferred modality for the management of surgically resectable patients with esophageal cancer.
- Preoperative cisplatin-based chemotherapy alone is an alternative choice for the management of surgically resectable patients with esophageal cancer.

## QUALIFYING STATEMENTS

- Based upon results from the *"CROSS"* trial, the Gastrointestinal Cancer Disease Site Group (GI DSG) acknowledges that recommendations indicating use of "preoperative cisplatin

based" chemotherapy should be revised to include the use of "preoperative platinum based" chemotherapy.
- The GI DSG acknowledges there is evidence indicating survival benefits with either preoperative chemotherapy or chemoradiotherapy compared with surgery alone. Based on the majority of the evidence available at this time, the GI DSG believes that preoperative chemoradiotherapy for resectable carcinoma of the esophagus is the preferred approach.
- Clinicians should recognize that the survival advantage of preoperative therapy may be minimal and a discussion with patients regarding potential adverse effects is required. Decisions to administer preoperative therapy should be based on patient preferences, comorbidities, and suitability for trimodality therapy.

## KEY EVIDENCE

- A literature meta-analysis of 10 randomized trials comparing preoperative chemoradiotherapy followed by surgery to surgery alone showed a 13% absolute benefit in survival at two years for preoperative chemoradiotherapy (hazard ratio [HR], 0.81; 95% confidence interval [CI], 0.70-0.93; p=0.002) (1).
- A published abstract of an individual patient data (IPD)-based meta-analysis of nine randomized trials (2,102 patients) comparing preoperative chemotherapy followed by surgery (CT+S) to surgery alone demonstrated a 4% (from 16 to 20%) absolute overall survival advantage for chemotherapy at five years (HR, 0.87; 95% CI, 0.79-0.95; p=0.003). Based on seven trials (1,849 patients), the HR for disease-free survival (DFS) was 0.82 (95% CI, 0.74-0.91; p=0.001) in favour of chemotherapy plus surgery, representing a five-year absolute DFS benefit of 4% (from 6 to 10%). No difference was seen in postoperative death (6.7%) (2).
- Randomized trials demonstrated no survival benefit for radiotherapy given alone, either preoperatively or postoperatively, compared with surgery alone.
- Randomized trials demonstrated no survival benefit for postoperative chemotherapy given alone compared with surgery alone.

## RELATED GUIDELINES

- PEBC Practice Guideline Report #2-12: *Combined Modality Radiotherapy and Chemotherapy in the Non-surgical Management of Localized Carcinoma of the Esophagus*.

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*Contact Information*

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## REFERENCES

1. Gebski V, Burmeister B, Smithers BM, Foo K, Zalcberg J, Simes J, et al. Survival benefits from neoadjuvant chemoradiotherapy or chemotherapy in oesophageal carcinoma: a meta-analysis. Lancet Oncol. 2007;8:226-34.
2. Thirion PG, Michiels S, Le Maître A, Tierney J. Individual patient data-based meta-analysis assessing pre-operative chemotherapy in resectable oesophageal carcinoma. J Clin Oncol. 2007;25 Suppl 18:4512.

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**Evidence-based Series #2-11 Version 4: Section 2**

# Preoperative or Postoperative Therapy for Resectable Esophageal Cancer: Evidentiary Base

*RA Malthaner, RKS Wong, K Spithoff, RB Rumble, L Zuraw, and the Gastrointestinal Cancer Disease Site Group*

A Quality Initiative of the
Program in Evidence-based Care (PEBC), Cancer Care Ontario (CCO)

These guideline recommendations have been ENDORSED, which means that the recommendations are current and relevant to decision making. Please see Section 4: Document Review Summary and Review Tool for A summary of the updated evidence published between 2012 and 2016, and for Details on how the Clinical Practice Guideline was ENDORSED

**Report Date: May 21, 2008**



## QUESTION

Should patients with resectable esophageal cancer receive preoperative or postoperative therapy along with surgery?

## INTRODUCTION

Carcinoma of the esophagus is an aggressive malignancy that continues to kill more than 90% of people with the disease within five years (1) (See Appendix 1 for the International Union Against Cancer (UICC) staging). The incidence of adenocarcinoma of the esophagus is rising faster than any other malignancy (2). In 2007, the estimated annual number of deaths due to esophageal cancer in Canada was 1,700, and many more people suffer because of the disease (3). Its virulence, in terms of symptoms and mortality, justifies a continued search for optimal therapy.

Any treatment modality chosen for esophageal cancer appears to depend on local practices. Surgical esophagectomy remains the preferred treatment for clinically localized thoracic esophageal carcinoma (1,4-6). Two randomized trials comparing surgery alone to radiation alone found surgery to be the better treatment for resectable cancer (5,6). Fok et al randomly assigned 39 patients to surgery and 35 patients to 45 to 53 Gy radiation over four to five weeks (5). The median survival time and five-year survival rate for surgery were 21.6 months and 16%, respectively, compared with 8.2 months and 7% for radiation ($p<0.05$). Badwe et al compared 47 surgical patients to 52 patients undergoing 50 Gy radiation in 28 fractions plus 15

Gy boost in 8 fractions or 15 Gy brachytherapy (6). Overall survival was better with surgery (odds ratio [OR], 2.74; 95% confidence interval [CI], 1.51 to 4.98; log-rank p=0.002). The swallowing status was better in the surgery arm at six months after treatment (p=0.03). The Gastrointestinal Cancer Disease Site Group (GI DSG) pooled the data on survival from these two trials. The pooled results favoured surgery alone. There was no statistical heterogeneity ($X^2$=0.02, p=0.9) and a 52% relative increase in the risk of death at three years with radiotherapy compared with surgery alone (risk ratio [RR], 1.52; 95% CI, 1.23 to 1.86; p=0.0007).

The failure of surgery alone is attributed to the systemic nature of the disease at the time of presentation (7,8). Early and effective systemic chemotherapy and local radiotherapy, directed at micro-metastases and added to surgical resection, could lead to increased survival. Many clinical trials have evaluated the role of postoperative therapy, both preoperatively and postoperatively, with conflicting results. Patients with cervical esophageal cancer are generally treated with chemoradiation (CRT) in an attempt to avoid a laryngoesophagectomy and preserve the larynx. Although the majority of studies have been performed in squamous cell carcinomas, adenocarcinomas were included in some studies, but a distinction between the two histological subtypes was not made in this guideline report because previous studies have not consistently found that they respond differently to chemotherapy or radiation (9-17).

The large and growing number of patients affected, the high mortality rates, the geographic variation in practice, and the large body of good quality research evidence warrants the development of a practice guideline for patients with esophageal cancer. A previous version of this practice guideline was completed in 2002 and was last updated in 2005. In this guideline, the GI DSG recommended surgery alone without preoperative or postoperative therapy as standard practice for resectable thoracic esophageal cancer (18,19). Due to the availability of new evidence, particularly in the form of individual patient meta-analysis and meta-analysis of mortality hazard ratios, it was felt that a revision of the literature review and recommendations was required.

## METHODS

### Guideline Development

The evidence-based series (EBS) guidelines developed by Cancer Care Ontario's Program in Evidence-based Care (PEBC) use the methods of the Practice Guidelines Development Cycle (20). For this project, the core methodology used to develop the evidentiary base was the systematic review. Evidence was selected and reviewed by two members of the PEBC's GI DSG and methodologists.

The systematic review is a convenient and up-to-date source of the best available evidence on preoperative or postoperative therapy for resectable esophageal cancer. The body of evidence in this report is primarily comprised of mature randomized controlled trial and meta-analysis data. That evidence forms the basis of a clinical practice guideline developed by the GI DSG. The systematic review and companion recommendations are intended to promote evidence-based practice in Ontario, Canada. The PEBC is supported by the Ontario Ministry of Health and Long-Term Care through Cancer Care Ontario. All work produced by the PEBC is editorially independent from its funding source.

### Literature Search Strategy

MEDLINE (1966 to April week 3, 2007), EMBASE (to week 17, 2007), CANCERLIT (1983 to October 2001) and the Cochrane Library (2007, Issue 2) databases were searched with no language restrictions. "Esophageal neoplasms" (Medical subject heading (MeSH)) was combined with "chemotherapy, adjuvant" (MeSH), "radiotherapy, adjuvant" (MeSH), "immunotherapy, adjuvant" (MeSH), and each of the following phrases used as text words: "preoperative", "neoadjuvant", "chemotherapy", "radiotherapy", "radiation therapy", "irradiation",

"immunotherapy", "chemoradiotherapy", "chemoradiation", and "hyperthermia". These terms were then combined with the search terms for the following study designs or publication types: practice guidelines, meta-analyses, and randomized controlled trials (Appendix 2). In addition, the National Cancer Institute (NCI) (formerly the Physician Data Query [PDQ] database on the Internet [http://www.cancer.gov/search/clinical_trials/]) and the conference proceedings of the 1997 to 2007 annual meetings of the American Society of Clinical Oncology (ASCO) and the 1999 to 2006 annual meetings of the American Society for Therapeutic Radiology and Oncology (ASTRO) were searched for reports of new or ongoing trials. Relevant articles and abstracts were reviewed, and the reference lists from these sources were searched for additional trials. This formal search was supplemented with published abstracts from thoracic surgery and oncology conferences, conversations with colleagues and experts in the field, and a review of textbooks related to esophageal oncology.

**Inclusion Criteria**

Articles were selected for inclusion in this systematic review of the evidence if they were fully published reports, published abstracts, or meta-analyses of randomized trials of preoperative or postoperative treatments compared with surgery alone or surgery plus another preoperative or postoperative treatment in patients with resectable and operable thoracic esophageal cancer. Data on survival had to be reported. Other outcomes of interest were adverse effects and quality of life.

**Exclusion Criteria**

Carcinomas located in the cervical esophagus were excluded.

**Synthesizing the Evidence**

Because diverse treatment strategies were evaluated, the eligible studies were grouped into 13 basic treatment approaches (Table 1). An individual patient data (IPD)-based meta-analysis is believed to be the highest level of evidence available and was used if available in the published literature. If no IPD meta-analysis was available, a literature meta-analysis using estimated time-to-event hazard ratios was considered as the next-highest level of evidence (21). If neither of these methods were available in the literature, data were pooled by the GI DSG at a common time-point (e.g., mortality at one or three years). The time point selected for meta-analyses must be clinically credible and relevant but not so far along the survival curve that wide confidence intervals result from fewer patients contributing to the estimate. Since time points prior to the median will generally ensure that there is sufficient data to be credible, the median survival times, weighted by the size of the treatment arms (22), were calculated to determine an appropriate time point for each meta-analysis.

Pooling was conducted using one-year mortality data for all meta-analyses except for the comparison of postoperative chemotherapy versus surgery alone, for which three-year mortality data was considered most appropriate for pooling. Studies that did not provide values for survival at the time of pooling were not included in each meta-analysis, although they were included in calculating the weighted median survival time, if values were provided. A meta-analysis software package, Review Manager 4.2 (Metaview © Update Software), available through the Cochrane Collaboration, was used[1]. Pooled results were expressed as mortality risk ratio (RR) with 95% CI using the random effects model. An RR less than 1.0 favours the treatment arm and an RR greater than 1.0 favours the control arm. The denominator in the pooled analysis is the number of randomized patients unless results for only the evaluable or

[1] RevMan Analyses [Computer program]. Version 1.0.2 for Windows. In: Review manager (RevMan) 4.2.7. Oxford (England): The Cochrane Collaboration, 2003.

eligible patients were reported. Heterogeneity of study results was assessed using a visual plot of the outcomes and by calculating the Chi-square statistic using a planned cut-off for significance of $p<0.05$.

### Study Quality Evaluation

For comparisons for which new evidence was available since the publication of the original guideline in 2004 (18,19), each trial was assessed for important study quality characteristics, including reporting of funding, randomization method, blinding, statistical power, follow-up, and intention-to-treat (ITT) analysis.

## RESULTS

### Literature Search Results

Thirty-nine randomized trials (5,23-61), and ten meta-analyses (62-71), including two Cochrane Reviews (66,68), were identified (Table 1). If results were reported or updated in more than one publication, only the most recent publication with updated results has been listed unless data were only available in older publications. The four-arm trials by Fok et al (5) and Nygaard et al (32) contributed to multiple comparisons.

**Table 1. Studies included in this practice guideline report.**

| Treatment Approach | Number of Trials | Reference Numbers | Summary of Results (Appendix 3) |
|---|---|---|---|
| **Randomized Controlled Trials** | | | |
| Preoperative RT v. Surgery Alone | 6 | 5*,23,25,28,31,32† | Table 4 |
| Preoperative CT v. Surgery Alone | 9 | 32†,33,38,46‡,47,49,50,52,53 | Table 5 |
| Preoperative CRT v. Surgery Alone | 10 | 32†,36,37,43§,45,51,54§,58,59,60,61‡, | Table 6 |
| Postoperative CT v. Surgery Alone | 3 | 42,44,55 | Table 7 |
| Postoperative CT v. Postoperative CRT | 1 | 56 | Table 8 |
| Postoperative RT v. Surgery Alone | 5 | 5*,30,34,41,57 | Table 9 |
| Preoperative RT v. Postoperative RT | 1 | 5* | Table 10 |
| Preoperative RT + Postoperative RT v. Postoperative RT | 1 | 26 | Table 11 |
| Preoperative CT + Postoperative CT v. Surgery Alone | 2 | 27,48 | Table 12 |
| Postoperative CT v. Postoperative RT | 1 | 35 | Table 13 |
| Preoperative CT v. Preoperative RT | 2 | 29,32† | Table 14 |
| Preoperative CRT v. Preoperative RT | 1 | 24 | Table 15 |
| Postoperative Immunotherapy with RT or CRT v. RT or CRT | 1 | 40 | Table 16 |
| Preoperative Hyperthermia with CRT v. preoperative CRT | 1 | 39 | Table 17 |
| **Meta-analyses** | | | |
| Preoperative RT v. Surgery Alone | 1 | 66 | - |
| Preoperative CT v. Surgery Alone | 6 | 62,64,68-71 | Table 2 |
| Preoperative CRT v. Surgery Alone | 6 | 63-65,67,69,70 | Table 3 |

Note: CT indicates chemotherapy; CRT, chemoradiation/chemoradiation therapy; RT, radiotherapy; v., versus.
* The four-arm trial by Fok et al [5] contributed to three comparisons.
† The four-arm trial by Nygaard et al [32] contributed to four comparisons.
‡ Reports published in abstract form only [46,61].
§ One RCT reported data in two publications [43,54]

**Outcomes**

For the following comparisons, no new studies were identified since the publication of the original systematic review and practice guideline in 2004 (18,19):

- postoperative radiotherapy versus surgery alone
- preoperative radiotherapy versus postoperative radiotherapy
- preoperative plus postoperative radiotherapy versus surgery plus postoperative radiotherapy alone
- preoperative plus postoperative chemotherapy versus surgery alone
- postoperative chemotherapy versus postoperative radiotherapy
- preoperative chemotherapy versus postoperative radiotherapy
- postoperative immunotherapy with radiotherapy or chemoradiotherapy versus radiotherapy or chemoradiotherapy alone
- preoperative hyperthermia with chemoradiotherapy versus preoperative chemoradiotherapy alone.

No trials were able to detect a significant difference in survival for any of the comparisons above, with the exception of one randomized controlled trial (RCT) comparing preoperative radiotherapy with preoperative chemotherapy in which a significant survival benefit was reported for preoperative radiotherapy. However, neither preoperative radiotherapy nor preoperative chemotherapy demonstrated a significant survival benefit over the control arm of surgery alone in this trial (32). Details of the trials identified for these comparisons are found in Appendix 3. For comparisons where more than one trial was available (postoperative radiotherapy versus surgery alone and preoperative plus postoperative chemotherapy versus surgery alone), the GI DSG pooled mortality data at one year (Appendix 4). No significant survival benefit over surgery alone was detected for either comparison.

New data in the form of RCTs or published meta-analyses since the publication of the original guideline (18,19) were identified for the following comparisons:

- preoperative radiotherapy versus surgery alone
- preoperative chemotherapy versus surgery alone
- preoperative chemoradiotherapy versus surgery alone
- postoperative chemotherapy versus surgery alone
- postoperative chemotherapy versus postoperative chemoradiotherapy.

***Trial Quality Characteristics***

See Table 18 (Appendix 5) for a summary of key quality characteristics for the 27 trials included in comparisons for which new data were available. Two RCTs are only available in abstract form (46,61), and one is published in Chinese with only the abstract available in English (28). Funding source was reported in only seven of the 27 trials (25,38,44,4553,55,59), none of which reported funding from pharmaceutical companies. Randomization methods were described in 11 trial reports (23,31,49,53,42,44,45,55,58-60) and were not reported for 16 trials. Five studies reported an imbalance between treatment groups in at least one characteristic at baseline (28,32,42,45,58). None of the trials reported that patients or study investigators were blinded to treatment allocation after randomization. Calculations to determine statistical power and target sample size were not reported in 14 of 27 trials (5,23,35,28,31,32,35,36,38,46,49,52,60,61), and target sample size was not achieved for various reasons in eight (33,37,43,45,47,50,55,58) of 13 trials that did report calculations. Median follow-up ranged from 10 months (43,54) to 8.2 years (51). One trial excluded 15 patients from analysis due to inoperability or refusal to undergo operation (23), and one trial excluded two patients from analysis due to protocol violation or loss to follow-up (33).

***Preoperative Radiotherapy and Surgery versus Surgery Alone***

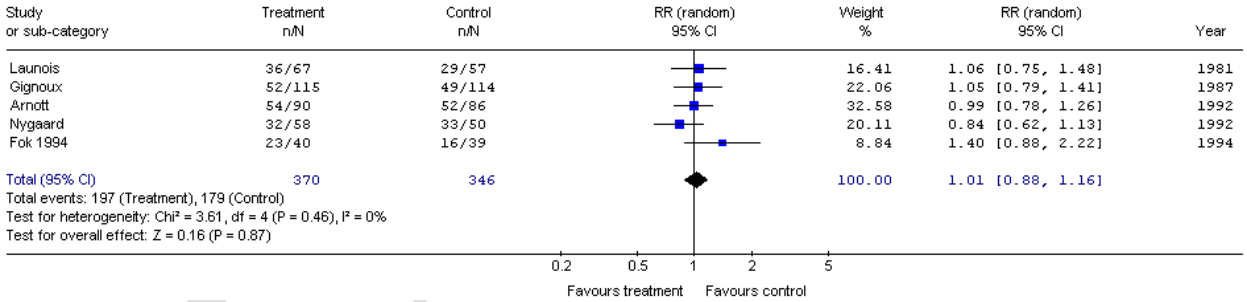
Six randomized trials of preoperative radiotherapy and surgery versus surgery alone are presented in Table 4 (5,23,25,28,31,32), all of which were included in the original publication of this guideline (18,19). The radiotherapy regimens varied, using low to moderate doses ranging from 20 Gy in 10 fractions to 53 Gy in 20 fractions. Treatment was delivered between one to four weeks prior to surgery. None of the six trials demonstrated a significant survival benefit for preoperative radiotherapy over surgery alone. Quality of life assessments were not conducted in any of the six trials.

*Meta-analyses*

A Cochrane review with meta-analysis published in 2005 using updated individual patient data on 1147 patients from five trials (23,25,28,31,32) reported a hazard ratio for death of 0.89 (95% CI, 0.78 to 1.01; p=0.062) for preoperative radiotherapy compared with surgery alone using a fixed effects model (66). The authors concluded that the meta-analysis could not conclusively demonstrate a survival benefit for preoperative radiotherapy compared with surgery alone. This meta-analysis included additional patients from the study by Wang et al (28) with no description of why these patients were excluded from the published report of the trial (a total of 418 patients from this study were included in the meta-analysis versus 206 included in the trial report). The trial by Fok et al (5) was not included in the published meta-analysis.

The GI DSG pooled one-year mortality rates available from five studies, including the study by Fok et al (5,23,35,31,32). Details of the meta-analysis are illustrated in Figure 1. There was no statistical heterogeneity ($Chi^2$=3.61, p=0.46) and no significant difference was detected in the risk of death with preoperative radiotherapy at one year compared with surgery alone (RR, 1.01; 95% CI, 0.88 to 1.16; p=0.87).

**Figure 1. Meta-analysis examining preoperative radiotherapy and surgery compared to surgery alone: mortality at one year.**




Overall risk ratio = 1.01 (95% CI, 0.88 to 1.16; p=0.87)

***Preoperative Chemotherapy and Surgery versus Surgery Alone***

Nine randomized trials, including eight published in full (24,31-33,35-38) and one in abstract form (46), of preoperative chemotherapy and surgery versus surgery alone are presented in Table 5. Two additional trials compared preoperative plus postoperative chemotherapy and surgery with surgery alone and were not included in this section (27,48) (Appendix 3, Table 12). Quality of life was not assessed in any of the trials. Two trials reported a significant survival benefit favouring preoperative chemotherapy (46,53). The MRC trial (53) reported a significant difference between survival curves with chemotherapy (HR, 0.79; 95% CI, 0.67 to 0.93; p=0.004), and Kok et al (46) reported a significant benefit for chemotherapy on median survival (18.5 months versus 11 months, p=0.002). One trial reported no overall survival benefit for chemotherapy except in patients who had a complete response (50). An RCT by Wang et al (52), reported in Chinese, found a significant survival advantage for preoperative chemotherapy

at five years but details of chemotherapy, type of surgeries, and other survival information were not provided.

*Meta-analyses*

Six meta-analyses of RCTs that compared preoperative chemotherapy plus surgery to surgery alone were identified in literature (62,64,68-71). One meta-analysis pooled one-, two-, and three-year mortality (62), one, pooled one-year mortality (70), one pooled absolute survival differences at two years (64), two pooled mortality HRs (68,69), and one was an IPD meta-analysis (71). The IPD meta-analysis is considered the highest level of evidence; however, it is only available in abstract form to date. For this reason, meta-analyses of published hazard ratios and point-in-time mortality data were also included and are reported in Table 2 below.

The IPD meta-analysis by Thirion et al reported in an abstract a 4% (from 16 to 20%) absolute overall survival advantage at five years (HR, 0.87; 95% CI, 0.79-0.95; p=0.003) (71). Based on seven trials (1,849 patients), the HR for DFS was 0.82 (95% CI, 0.74-0.91; p=0.001) in favour of CT plus surgery, representing a five-year absolute DFS benefit of 4% (from 6 to 10%). No difference was seen in postoperative death (6.7%). Two of the trials included in the analysis administered both preoperative and postoperative chemotherapy in the treatment arm and have been included under a separate category in this review (27,48).

**Table 2. Meta-analyses of preoperative chemotherapy and surgery versus surgery alone.**

| Report, year (reference) | Meta-analysis data | # of included trials (# of patients) | References of included trials | Survival / mortality results |
|---|---|---|---|---|
| Urschel, 2002 (62) | 1-, 2-, and 3-year mortality rates | 11 (1,976) | 27,32,33,38,46-50,53ıı | 1-year: OR 1.00 (95% CI, 0.76 to 1.30; p=0.98)<br>2-year: OR 0.88 (95% CI, 0.62 to 1.24; p=0.45)<br>3-year: OR 0.77 (95% CI, 0.37 to 1.59; p=0.48) |
| Kaklamanos, 2003 (64) | Absolute survival differences at 2 years | 7 (1,683) | 27,32,38,47,48,50,53ıı | 4.4% absolute survival benefit at 2 years for preoperative CT (95% CI, 0.3 to 8.5) |
| Malthaner, 2006 (68) | Mortality hazard ratios‡ | 8* (1,729) | 32,33,38,47,48,50,52,53ıı | HR 0.88 (95% CI, 0.75 to 1.04; p=0.15) |
| Graham, 2007 (70) | 1-year mortality | 6 (1.460) | 32,38,47,48,50,53ıı | RR 0.94 (95% CI, 0.82 to 1.08; p>0.05) |
| Gebski, 2007 (69) | Mortality hazard ratios‡ | 8 (1,724) | 27,32,33,38,47,48,50,53ıı | HR 0.90 (95% CI, 0.81 to 1.00; p=0.05) |
| Thirion, 2007 (71) *abstract* | Individual patient data | 9† (2,102) | 27,32,38,46-48,50,53,one unpublishedıı | HR 0.87 (95% CI, 0.79 to 0.95; p=0.003) |

Notes: OR, odds ratio; HR, hazard ratio; CI, confidence interval; RR, relative risk;
* 11 RCTs identified in total, but only 8 provided sufficient data to estimate mortality hazard ratios.
† 12 RCTs were identified, but only 9 had individual patient data available.
‡ Parmar method (21).
ıı Two trials (27,48) administered preoperative plus postoperative chemotherapy.

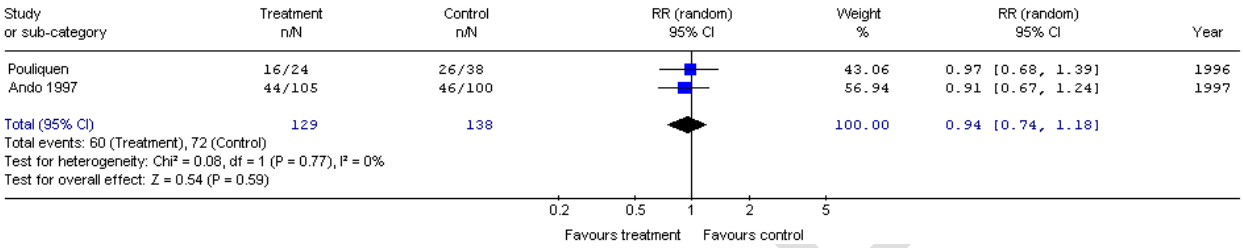
### *Postoperative Chemotherapy and Surgery versus Surgery Alone*

Three randomized trials of postoperative chemotherapy and surgery compared with surgery alone are presented in Table 7 (42,44,55). All three trials used cisplatin-based regimens. Pouliquen et al (42) found no improvement in the survival rate with postoperative chemotherapy. The patients were stratified into two groups: the first, complete resections with or without nodal involvement and the second, palliative resections for positive margins or metastatic disease. Only the completely resected group was included in our analysis. Ando et al (44) resected early (T1b) carcinomas and did not find any improvement in survival. A second study by Ando et al (55) also found no survival benefit for postoperative chemotherapy in localized squamous cell carcinoma of the thoracic esophagus. Pouliquen et al (42) assessed quality of life and found that the duration of improved dysphagia was similar for both groups.

*Meta-analysis*

The GI DSG pooled the survival results of two trials (42,44) at three years. Details of the meta-analysis are illustrated in Figure 2. There was no significant heterogeneity ($X^2$=0.06; p=0.77), and no significant difference in the risk of death was detected at three years (RR, 0.94; 95% CI, 0.74 to 1.18; p=0.59) for postoperative chemotherapy compared with surgery alone. The second trial by Ando et al (55) could not be included in the pooled analysis because the three-year survival rates were not reported.

**Figure 2. Meta-analysis examining postoperative chemotherapy and surgery compared to surgery alone: mortality at three years.**




Overall risk ratio = 0.94 (95% CI, 0.74 to 1.18; p=0.59)

***Preoperative Chemotherapy and Radiotherapy and Surgery versus Surgery Alone***

Ten randomized trials of combined modality preoperative chemotherapy and radiotherapy are presented in Table 6 (32,36,37,43,45,51,54,58-61). There were no reports on quality of life. Eight of the ten RCTs reported no significant difference in overall survival between treatment groups (32,36,37,45,51,58-60). Walsh et al (43,54) detected a significant overall increase in the survival rate at three and five years with combined preoperative CRT. An ITT analysis detected a median survival advantage for the trimodality treatment arm (p=0.002). The authors concluded that preoperative CRT therapy enhances survival for patients with minimal residual disease and recommended that future trials target this treatment for those patients. However, this trial has been criticized for the lack of preoperative staging using computerized tomography scans, premature closure after interim analysis, and an unusually poor survival rate in the surgery-alone arm.

A small Intergroup study by Tepper et al, published in abstract form (61), reported a significant benefit for trimodality therapy on median survival (p=0.02) and five-year overall survival. The trial by Bosset et al (45) reported a significant benefit for chemoradiotherapy in DFS (p=0.003) and time free of local disease (p=0.01) but no significant difference in time to distant metastasis (p=0.24). Four additional RCTs reported no significant difference in DFS (37,51), event-free survival (58), or progression-free survival (59).

*Meta-analyses*

Six meta-analyses of RCTs comparing preoperative CRT and surgery versus surgery alone were identified in the literature (63-65,67,69,70). One meta-analysis pooled three-year mortality (65), one pooled one-year mortality (70), one pooled one-, two-, and three-year mortality (63), one pooled number of deaths per patient month of follow-up (67), one pooled absolute survival differences at two years (64),, and one pooled mortality HRs (69). Pooling of mortality HRs was considered the highest level of evidence available; however, the meta-analyses using other methods are also reported in Table 3.

Gebski et al (69) published a meta-analysis comparing preoperative chemoradiotherapy plus surgery to surgery alone. This analysis included the trial by Lee et al (58), in which 60% of patients in the preoperative CRT arm also received postoperative CT. The mortality HR and 95% CI were obtained or estimated for each study and the pooled estimate was calculated. The pooled estimate favoured CRT (HR, 0.81; 95% CI, 0.7-0.93), corresponding to a 13% absolute

difference in survival at two years. A sensitivity analysis excluding the trial by Walsh et al (43) did not change the conclusions of the analysis and the benefit for CRT remained significant.

**Table 3. Meta-analyses of preoperative chemoradiotherapy and surgery versus surgery alone.**

| Report, year (reference) | Meta-analysis method | # of included trials (# of patients) | References of included trials | Survival / mortality results |
|---|---|---|---|---|
| Urschel, 2003 (63) | 1-, 2-, and 3-year survival | 9 (1.116) | 32,36,37,43,45,51, 59, two abstracts not included in PEBC review | 1-year survival: OR 0.79 (95% CI, 0.59 to 1.06; p=0.12) 2-year survival: OR 0.77 (95% CI, 0.56 to 1.05; p=0.10) 3-year survival: OR 0.66 (95% CI, 0.47 to 0.92; p=0.016)† |
| Kaklamanos, 2003 (64) | Absolute survival differences at 2 years | 5 (669) | 32,37,43,45,51 | 6.4% absolute survival benefit at 2 years for preoperative CRT (95% CI, -1.2 to 14.0) |
| Fiorica, 2004 (65) | 3-year survival | 6 (764) | 32,36,37,43,45,51 | 3-year survival: OR 0.53 (95% CI, 0.31 to 0.92; p=0.03; NNT 10)* |
| Greer, 2005 (67) | Deaths per patient month of follow-up | 6 (738) | 32,36,37,43,45,51 | RR 0.86 (95% CI, 0.74 to 1.01; p=0.07) |
| Graham, 2007 (70) | 1-year survival | 6 (733) | 32,36,37,43,45,51 | RR 0.87 (95% CI, 0.75 to 1.02; p>0.05) |
| Gebski, 2007 (69) | Mortality hazard ratios, Parmar method | 10 (1,209) | 32,36,37,43,45,51, 58,59,61, one unpublished | HR 0.81 (95% CI, 0.70 to 0.93; p=0.002) 13% absolute difference in survival at 2 years. |

Notes: NR, not reported; QALY, quality-adjusted life year; CRT, chemoradiotherapy; RR, relative risk; HR, hazard ratio;
* Postoperative mortality was significantly higher in the surgery plus CRT arm (OR 2.10; 95% CI, 1.18 to 3.73; p=0.01).
† 3-year survival benefit was most pronounced when CRT was given concurrently as opposed to sequentially.

### *Postoperative Chemotherapy and Surgery versus Postoperative Chemoradiotherapy and Surgery*

A single trial was obtained comparing postoperative cisplatin (50mg/m$^2$) plus 5-fluorouracil (300 mg/m$^2$) chemotherapy with the same postoperative chemotherapy pus 50 Gy radiotherapy (Table 8) (56). No statistically significant difference between the groups was detected after a median follow-up of 35 months.

### *Adverse Effects*

Adverse effects were inconsistently reported (Tables 2-15). Most patients experienced treatment-related adverse effects due to radiotherapy or chemotherapy.

## DISCUSSION

Most trials excluded patients with cancers located in the cervical esophagus, and, therefore, the interpretation of this review is limited to tumours in the more distal two thirds.

Overall, a number of RCTs included in this review were methodologically limited due to no reporting of target sample size to detect a clinically important difference between treatment groups, failure to meet the specified target sample size, imbalance in baseline characteristics, or no reporting of randomization methods or allocation concealment. In addition, length of follow-up varied greatly between studies (Appendix 4). The authors of this review have used meta-analysis as the highest level of evidence; however, the limitations of meta-analyses that pool data from individual studies with substantial methodological limitations need to be recognized. It may be that well-conducted large RCTs provide a stronger basis on which to reach conclusions than a meta-analysis including smaller, methodologically limited RCTs (72,73). Where such large high-quality RCTs were available, these results were considered in the development of recommendations.

The options for preoperative or postoperative therapy for resectable thoracic esophageal cancer are many. On reviewing the results of randomized trials and the meta-analyses, the GI DSG supports the use of preoperative CRT based on the evidence available at this time.

Preoperative CRT appears to improve survival compared to surgery alone. When examining the individual trial results, only the trials by Walsh et al (43) and Tepper et al (61) detected a statistically significant survival benefit; however, the Walsh trial has been criticized for its methodology, and the Tepper trial has only been published in abstract form. A meta-analysis of six RCTs by Fiorica et al (65) and another meta-analysis of nine RCTs by Urschel et al (63) both detected a statistically significant difference in survival favouring preoperative CRT at three years only. While the method employed in these published meta-analyses (using a time point prior to the median duration of follow up across the studies) provides the most robust estimate of relative benefit, it is more conservative and insensitive in terms of detecting longer term benefits reported in only a subset of trials. The use of more labour intensive and complex meta-analytic technique, as employed in more recent meta-analyses on this topic, provided a more sensitive method in detecting smaller but clinically relevant longer term benefits. Gebski et al (69) pooled HRs and demonstrated a significant benefit for preoperative CRT over surgery alone. The GI DSG support of preoperative CRT is based on these pooled results.

Preoperative cisplatin-based chemotherapy alone may also slightly improve survival. Only three of the nine trials that compared preoperative chemotherapy plus surgery to surgery alone (46,52,53) detected a significant survival advantage favouring preoperative cisplatin-based chemotherapy. Kok et al (46) reported a survival advantage for chemotherapy but only reported median survival results in abstract form. The two largest trials produced conflicting results (48,53). The Kelsen et al trial comparing preoperative and postoperative chemotherapy to surgery alone (48) detected no survival advantage, while the MRC OE02 trial comparing preoperative chemotherapy to surgery alone (53) did detect a significant survival advantage for preoperative chemotherapy (HR, 0.79; 95% CI, 0.67 to 0.93; p=0.004). Although all chemotherapy protocols were cisplatin-based, the varying dosages, the number of cycles completed, and the other agents used contributed to clinical heterogeneity. A Cochrane review (68) consisting of a meta-analysis of mortality HRs from eight RCTs did not detect a statistically significant difference in survival between preoperative CT and surgery alone (HR, 0.88; 95% CI, 0.75 to 1.04) and a review by Gebski et al (69) of the same trials found similar, although marginally significant results (HR, 0.90; 95% CI, 0.81 to 1.00). The slight difference appears to be related to estimates of HR in the trials that did not report them. The most recent analysis of nine available individual patient data from twelve trials presented in abstract found similar benefit but with a narrower confidence interval (HR, 0.87; 95% CI, 0.79 to 0.95; p=0.003) (71).

The available evidence from three randomized trials does not support the use of postoperative chemotherapy over surgery alone (42,44,55). Preoperative radiotherapy does not improve survival compared with surgery alone and postoperative radiotherapy may, in fact, be harmful (30,34).

Two randomized trials have examined whether surgery is needed in patients receiving high dose CRT. In both trials, patients almost exclusively had squamous cell carcinomas. The Essen trial by Stahl et al. (74) randomized patients to CRT plus surgery (CRTS) versus the same CRT with further CRT boost. In the FFCD 9102 trial by Bedenne et al (75), only patients who were considered responders to initial CRT were then randomized to CRTS versus further CRT. Both trials used a non-inferiority design, with a delta of 15% and 10% respectively. In other words, the two regimens were considered not statistically different if the difference in the primary outcome, overall survival, was less than 15% or 10%. Within these assumptions, neither of the two trials demonstrated a significant difference in overall survival between treatment arms. Stahl et al. observed an overall survival at two years of 40% (CRTS) versus 35% (CRT) (74), while in the FFCD trial this was 34% (CRTS) versus 40% (CRT) (75). Local control, however, was superior in both trials when surgery was included. The Essen trial described a two year local control rate of 64% (CRTS) versus 41% (CRT) (HR, 2.1; 95% CI, 1.3-3.5; p=0.003) (74), while the FFCD trial observed 66% (CRTS) versus 57% (CRT) (HR, 1.64; 95% CI, 1-2.6; p=0.03) (75). There was significantly greater treatment related mortality in patients receiving CRTS.

Perioperative mortality was 13% (CRTS) versus 4% (CRT) (p=0.03) for Stahl et al (74), and 12% (CRTS) within six months and 0% CRT in FFCD 9102 (75). The results of these trials need to be interpreted cautiously. For the majority of more fit patients, the assumption that an overall survival difference of less than 10% to 15% is not clinically significant (i.e., delta for the non inferiority design) may not be acceptable. In patients (with squamous cell carcinomas), where a greater operative risk is anticipated, the adoption of a non-surgical approach is favoured based on these results.

## CONCLUSIONS

Examination of the results of randomized trials, including the pooling of all the evidence, supports the use of preoperative therapy for patients with resectable carcinoma of the thoracic esophagus. While the GI DSG acknowledges that these reports were inconsistent for specific time points, published meta-analyses of HRs taking into account data from the entire survival curves did detect a benefit in survival favouring preoperative therapy. The majority of evidence favours CRT compared to surgery alone, although there is also support for preoperative chemotherapy. Preoperative cisplatin-based chemotherapy plus radiotherapy, or preoperative chemotherapy alone, is recommended as the preferred modality for the management of surgically resectable patients with esophageal cancer. Future trials should continue to assess multi-modality treatments for this patient population, and the GI DSG will continue to examine new evidence as it becomes available.

## ONGOING TRIALS

The National Cancer Institute (NCI)® database of ongoing clinical trials (http://www.cancer.gov/search/clinical_trials/) was searched on October 24, 2007. A listing of relevant trials appears in Appendix 6.

## CONFLICT OF INTEREST

Members of the GI DSG were polled for potential conflicts of interest. No conflicts were declared.

## JOURNAL REFERENCES

The following updated practice guideline has been published by Clinical Oncology (© 2010 The Royal College of Radiologists; http://www.clinicaloncologyonline.net/home):

- Malthaner R, Wong RKS, Spithoff K; on behalf of the Gastrointestinal Cancer Disease Site Group of Cancer Care Ontario's Program in Evidence-based Care. Preoperative or postoperative therapy for resectable oesophageal cancer: an updated practice guideline. Clin Oncol. 2010 May;22(4):250-6. doi:10.1016/j.clon.2010.02.005.

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- Malthaner RA, Wong RKS, Rumble RB, Zuraw L; Members of the Gastrointestinal Cancer Disease Site Group of Cancer Care Ontario's Program in Evidence-based Care. Neoadjuvant or adjuvant therapy for resectable esophageal cancer: a systematic review and meta-analysis. BMC Med. 2004 Sep;2:35.
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**Appendix 1. UICC staging for esophageal cancer*.**

| Stage | T (Primary Tumour) | N (Regional Lymph Nodes) | M (Distant Metastases) |
|---|---|---|---|
| 0 | Tis | N0 | M0 |
| I | T1 | N0 | M0 |
| IIA | T2<br>T3 | N0<br>N0 | M0<br>M0 |
| IIB | T1<br>T2 | N1<br>N1 | M0<br>M0 |
| III | T3<br>T4 | N1<br>Any N | M0<br>M0 |
| IV | Any T | Any N | M1 |

Note: UICC, International Union Against Cancer.
* Further details about this staging system in Hermanek P, Sobin LH, editors. TNM classification of malignant tumours. 4th ed. Berlin: Springer-Verlag; 1987. p. 42.

## Appendix 2. Literature search strategies.

MEDLINE

1. esophageal neoplasms/
2. chemotherapy, adjuvant/
3. radiotherapy, adjuvant/
4. (preoperative or neoadjuvant).mp.
5. 4 and chemotherapy.mp.
6. 4 and (radiotherapy or radiation therapy or irradiation).mp.
7. immunotherapy.mp.
8. (chemoradiotherapy or chemoradiation).mp.
9. hyperthermia.mp.
10. exp immunotherapy/
11. or/2-10
12. 1 and 11
13. practice guideline?.pt.
14. guideline?.pt,sh,tw.
15. 13 or 14
16. 12 and 15
17. meta-analysis.pt,sh,tw.
18. meta-analyses.tw.
19. metaanaly:.tw.
20. meta analy:.tw.
21. or/17-20
22. 12 and 21
23. random:.tw,sh,pt,mp.
24. 12 and 23
25. 16 or 22 or 24

EMBASE

1. exp esophagus cancer/
2. adjuvant chemotherapy/
3. adjuvant therapy/
4. (preoperative or neoadjuvant).mp.
5. (chemotherapy or radiotherapy or radiation or irradiation).mp.
6. immunotherapy.mp.
7. exp immunotherapy/
8. (chemoradiotherapy or chemoradiation).mp.
9. hyperthermia.mp.
10. or/2-9
11. 1 and 10
12. guideline:.mp.,pt.
13. 11 and 12
14. (meta-analy: or metaanaly: or meta analy:).mp.
15. 11 and 14
16. random:.mp.
17. 11 and 16
18. 13 or 15 or 17

## Appendix 3. Summary of RCT results.

### Table 4. Randomized trials of preoperative radiotherapy (RT) and surgery versus surgery alone.

| Study (Reference) | Study characteristics | Interventions | # of Pts | Median Survival (Months) | Survival Rate (%) | | | | | Statistical Significance | Adverse Effects |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | 1yr | 2yr | 3yr | 4yr | 5yr | | |
| Launois 1981 (23) | France, single centre, squamous cell, Mar 1973-June 1976 | 64 - 90 Gy preop RT + esophagectomy | 67 | 4.5 (mean) | 46 | 20 | 15 | 14 | 10 | No significant difference in survival, p=NR. † | 23% perioperative mortality in both groups. |
| | | esophagectomy (left thoracotomy) | 57 | 8.2 (mean) | 50 | 35 | 25 | 20 | 12 | | |
| Gignoux 1987 (25) | EORTC, 8 centres, squamous cell, no cervical lesions, no previous cancer, no previous treatment | 33 Gy preop RT + esophagectomy | 115 | 12.3 (mean) | 55 | 24 | 20 | 17 | 10 | No significant difference in survival, p=0.943. †<br>Significant benefit for preop RT in time to local recurrence for resected patients, p=0.045. | 2 tracheoesophageal fistula<br>1 bleeding<br>1 esophagitis<br>6 respiratory deaths |
| | | esophagectomy | 114 | 12 (mean) | 57 | 30 | 14 | 11 | 9 | | 8 respiratory deaths |
| Wang 1989 (28) | June 1977-May 1985 China, single centre<br>histology not reported<br>< 65 years age<br>< 8 cm length<br>no metastases | 40 Gy preop RT + esophagectomy | 104 | NR | NR | NR | NR | NR | 35 | No significant difference in survival, p>0.05. † | 1 leak<br>5 perioperative deaths |
| | | esophagectomy | 102 | NR | NR | NR | NR | NR | 30 | | 5 leaks<br>5 perioperative deaths |
| Nygaard* 1992 (32) | Jan 1983-Jan 1988 Scandinavia, multicentre, squamous cell, age < 75 years<br>KPS > 50<br>T1, T2, Nx, M0<br>> 21 cm from incisors | 35 Gy preop RT + esophagectomy | 58 | 10 | 44 | 25 | 21 | NR | NR | No significant difference in survival, p=0.08. † | 5 respiratory<br>2 leaks<br>4 postoperative deaths |
| | | esophagectomy | 50 | 7 | 34 | 13 | 9 | NR | NR | | 5 respiratory<br>2 leaks<br>5 postoperative deaths |

**Table 4 cont'd.**

| Study (Reference) | Study characteristics | Interventions | # of Pts | Median Survival (Months) | Survival Rate (%) | | | | | Statistical Significance | Adverse Effects |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | 1yr | 2yr | 3yr | 4yr | 5yr | | |
| Arnott 1992 (31) | 1979-1983, Scotland, single centre, age < 80 years squamous cell adenocarcinoma, distal 2/3 of esophagus | 20 Gy preop RT + esophagectomy | 90 | 8 | 40 | 22 | 13 | 9 | 9 | No significant difference in survival, p=0.40. † | 10 respiratory<br>10 postoperative deaths |
| | | esophagectomy (left thoracoabdominal) | 86 | 8 | 40 | 28 | 23 | 21 | 17 | | 5 respiratory<br>8 postoperative deaths<br>2 surgical |
| Fok* 1994 (5) | 1968-1981, Hong Kong, single centre, squamous cell, middle 1/3 esophagus | 24-53 Gy preop RT + esophagectomy | 40 | 11 | 42 | 34 | 24 | 10 | 10 | No significant difference in survival, p=NR. † | 20 respiratory<br>12 postoperative deaths<br>11 leaks |
| | | esophagectomy (right thoracotomy, left neck, and abdomen) | 39 | 22 | 58 | 36 | 24 | 16 | 16 | | 15 respiratory<br>3 postoperative deaths<br>7 leaks |

Notes: EORTC, European Organisation for Research and Treatment of Cancer; KPS, Karnofsky Performance Status; NR, not reported.
*Patients randomized to four groups; data shown are for radiotherapy + surgery versus surgery alone.
† Statistical power and target sample size not reported.

**Table 5. Randomized trials of preoperative chemotherapy (CT) and surgery versus surgery alone.**

| Study (Reference) | Study characteristics | Interventions | # of Pts | Median Survival (Months) | Survival Rate (%) | | | | | Statistical Significance | Adverse Effects |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | 1yr | 2yr | 3yr | 4yr | 5yr | | |
| Nygaard* 1992 (32) | Jan 1983-Jan 1988 Scandinavia, multicentre squamous cell. age < 75 years, KPS >50 T1, T2, Nx, M0 > 21 cm from incisors | cisplatin 20 mg/m$^2$ x 5 days x 2 cycles bleomycin 10 mg/m$^2$ x 5 days x 2 cycles + esophagectomy | 56 | 7 | 31 | 6 | 3 | NR | NR | No significant difference in survival, p=NR. † | 3 respiratory<br>3 leaks<br>6 postoperative deaths<br>1 hematologic<br>1 alopecia |
| | | esophagectomy (laparotomy and right thoracotomy) | 50 | 7 | 34 | 13 | 9 | NR | NR | | 5 respiratory<br>2 leaks<br>5 postoperative deaths |
| Schlag 1992 (33) | Germany, single centre, squamous cell, age < 68 years, KPS > 70, Stage I, II, III | cisplatin 20 mg/m$^2$ x 5 days x 3 cycles 5-fluorouracil 1 g/m$^2$ x 5 days x 3 cycles + esophagectomy | 22 | 7.5 | 20 | NR | NR | NR | NR | No significant difference in survival, p=0.91.ıı | 11 vomiting<br>10 alopecia<br>2 fever<br>5 bone marrow suppression<br>2 renal |
| | | esophagectomy (abdominothoracic or thoracoabdominocervical with gastric or colon interposition) | 24 | 5 | 32 | NR | NR | NR | NR | | NR |
| Maipang 1994 (38) | Aug 1988-Dec 1990 Thailand, single centre, squamous cell, age < 75 years ECOG 1, 1, 2, Stage I, II, III, distal 2/3 esophagus | cisplatin 100 mg/m$^2$ x 1 day x 2 cycles vinblastine 3 mg/m$^2$ x 4 days x 2 cycles bleomycin 10 mg/m$^2$ x 5 days x 2 cycles + esophagectomy | 24 | 17 | 58 | 31 | 31 | NR | NR | No significant difference in survival, p=0.186. Early survival better in surgery alone group. † | 15 hematologic<br>15 vomiting<br>14 alopecia<br>3 hepatic<br>1 lung<br>8 urologic<br>4 perioperative deaths |
| | | esophagectomy (laparotomy, right thoracotomy with gastric or colon interposition) | 22 | 17 | 85 | 40 | 36 | NR | NR | | None reported |

**Table 5 cont'd.**

| Study (Reference) | Study characteristics | Interventions | # of Pts | Median Survival (Months) | Survival Rate (%) | | | | | Statistical Significance | Adverse Effects |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | 1yr | 2yr | 3yr | 4yr | 5yr | | |
| Law<br>1997 (47) | Dec 1989-Jan 1995,<br>Hong Kong, single centre,<br>squamous cell, exclude non regional nodes, tracheal involvement, and metastases | cisplatin 100 mg/m$^2$ x 1 day x 2 cycles<br>5-fluorouracil 500 mg/m$^2$ x 5 days x 2 cycles<br>+ esophagectomy | 74 | 16.8 | 60 | 44 | 38 | 28 | 28 | No significant difference in median survival, p=0.17‡.<br><br>No significant difference in 2-yr survival, p=0.13. | 45 anemia<br>43 leukopenia<br>12 thrombocytopenia<br>24 renal<br>34 vomiting<br>21 electrolytes<br>3 leaks<br>10 pulmonary<br>14 respiratory failure<br>5 perioperative deaths |
| | | esophagectomy (transhiatal or Lewis-Tanner) | 73 | 13 | 50 | 31 | 14 | 14 | NR | | 11 pulmonary<br>22 respiratory failure<br>6 perioperative deaths |
| Kok<br>1997 (46)<br><br>abstract | 1990-1996<br>Netherlands, multi-centered<br>Squamous cell | cisplatin 80 mg/m$^2$ x 1 day X 2 cycles<br>etoposide 100 mg IV x 2 days + 200 mg/m$^2$ PO x 2 days x 2 cycles<br>+ esophagectomy § | 74 | 18.5 | NR | NR | NR | NR | NR | Significant benefit in median survival favouring CT, p=0.002. | 1 toxic death<br>67 alopecia<br>10 renal |
| | | esophagectomy (transhiatal) | 74 | 11 | NR | NR | NR | NR | NR | | NR |
| Baba<br>2000 (49) | 100% squamous cell,<br>< 75 years,<br>KPS > 90<br>upper, middle, and lower third esophageal tumours,<br>No metastases, no previous cancer, no TE fistulas,<br>Japan,<br>single centre | Cisplatin 70 mg/m2 x 1 day x 2 cycles<br>5-Fluorouracil 700 mg/m$^2$ x 5 days x 2 cycles<br>leucovorin 20 mg/m$^2$ x 5 days x 2 cycles +<br>esophagectomy | 21 | NR | NR | NR | NR | NR | NR | NR | 5 anastomotic leaks<br>9 pulmonary |
| | | esophagectomy (right thoracotomy, laparotomy, neck incision, gastric or colon interposition with 2 or 3 field node dissection) | 21 | NR | NR | NR | NR | NR | NR | | 6 anastomotic leaks<br>4 pulmonary |

**Table 5 cont'd.**

| Study (Reference) | Study characteristics | Interventions | # of Pts | Median Survival (Months) | Survival Rate (%) | | | | | Statistical Significance | Adverse Effects |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | 1yr | 2yr | 3yr | 4yr | 5yr | | |
| Ancona 2001(50) | Italy, Single centre | 5-FU 1000 mg/m$^2$ CI d1-5 + Cisplatin 100 mg/m$^2$ d1 | 47 | 25 | 75 | 55 | 44 | 42 | 34 | No significant difference in survival, p=0.55.ıı | 4.2% treatment related mortality<br>10 grade 3-4 neutropenia |
| | | Surgery alone | 47 | 24 | 75 | 55 | 41 | 38 | 22 | | 4.2% treatment related mortality |
| Wang 2001 (52) | China, single centre<br>97% squamous cell,<br>3% adenocarcinoma,<br>stage II, III,<br>English abstract only | Cisplatin 30 mg / day x 5 days x 1 cycle<br>? PCM for squamous cell<br>? Me-PMF for adenocarcinoma<br>+ esophagectomy | 50 | NR | NR | NR | NR | NR | 46 | Significant benefit in survival favouring CT, p<0.05. | 2 cardiac<br>41 gastrointestinal |
| | | esophagectomy | 50 | NR | NR | NR | NR | NR | 32 | | 1 cardiac<br>0 gastrointestinal |
| MRC OE02 2002 (53) | Mar 1992 to June 1998,<br>United Kingdom, multicentered,<br>Resectable esophageal cancer,<br>67% adenocarcinoma,<br>33% squamous or undifferentiated | cisplatin 80 mg/m$^2$ x 1 day x 2 cycles<br>5-fluorouracil 1 g/ m$^2$ x 4 days x 2 cycles<br>+ esophagectomy | 400 | 16.8 | 59 | 43 | 35 | 28 | 26 | Significant benefit in survival favouring CT, hazard ratio 0.79 (95% CI 0.67 to 0.93), p=0.004. | 41% postoperative complications<br><br>10% postoperative deaths |
| | | esophagectomy | 402 | 13.3 | 54 | 34 | 27 | 20 | 15 | | 42% postoperative complications<br><br>10% postoperative deaths |

Notes: CT, chemotherapy; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; KPS, Karnofsky Performance Score; NR, not reported; TE, tracheoesophageal; yr, year.

* Patients randomized to four groups; data shown are for chemotherapy + surgery versus surgery alone; NR, not reported.

‡ Responders to CT lived longer but non-responders had lower median survival than controls (p=0.03). Lower local recurrence with CT.

§ CT responders received an additional 2 cycles of CT prior to surgery while non-responders received only 2 cycles.

† Statistical power and target sample size not reported.

ıı Target sample size not achieved.

**Table 6. Randomized trials of preoperative chemoradiation (CRT) and surgery versus surgery alone.**

| Study (Reference) | Study characteristics | Interventions | # of Pts | Median Survival (Months) | Survival Rate (%) | | | | | Statistical Significance | Adverse Effects |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | 1yr | 2yr | 3yr | 4yr | 5yr | | |
| Nygaard 1992 (32)* | Jan 1983-Jan 1988<br>Scandinavia, multicentre, squamous cell, age < 75 years, KPS > 50, T1, T2, Nx, M0 > 21 cm from incisors | cisplatin 20 mg/m$^2$ x 5 days x 2 cycles<br>bleomycin 5 mg/m$^2$ x 5 days x 2 cycles<br>+ 35 Gy sequential radiotherapy<br>+ esophagectomy | 53 | 7 | 39 | 23 | 17 | NR | NR | No significant difference between survival curves, p=0.3.** | 2 leaks<br>10 respiratory |
| | | esophagectomy (laparotomy and right thoracotomy) | 50 | 7 | 34 | 13 | 9 | NR | NR | | 5 respiratory<br>2 leaks<br>5 postoperative deaths |
| Le Prise 1994 (37) | Jan 1988-April 1991<br>France, single centre squamous cell age < 70 years < 15% weight loss excluded poor performance, metastases, tracheoesophageal fistula | cisplatin 100 mg/m$^2$ x 1 day x 2 cycles<br>5-fluorouracil 600 mg/m$^2$ x 4 days x 2 cycles<br>+ 20 Gy concurrent radiotherapy<br>+ esophagectomy | 41 | 11 | 47 | 27 | 19 | NR | NR | No significant difference in median survival, p=0.56. ††<br><br>No significant difference in 1yr, 2yr or 3yr overall survival, p=NR.<br><br>No significant difference in median disease-free survival, p=0.10. | 1 neuropathy<br>7 hematologic<br>2 renal<br>3 tracheo-esophageal fistulae<br>4 infections<br>2 effusions<br>3 deaths<br>1 pulmonary embolism<br>1 respiratory failure |
| | | esophagectomy | 45 | 11 | 47 | 33 | 14 | NR | NR | | 5 tracheoesophageal fistulae<br>7 infections<br>3 effusions<br>3 deaths |
| Apinop 1994 (36) | Thailand, single centre, Jan 1986-Dec 1992, squamous cell carcinoma, Mid to distal 1/3 esophagus, operable | cisplatin 100 mg/m$^2$ x 1 day x 2 cycles<br>5-fluorouracil 1000 mg/m$^2$ x 8 days x 2 cycles<br>+ 40 Gy concurrent radiotherapy<br>+ esophagectomy | 35 | 9.7 | 49 | 30 | 26 | 24 | 24 | No significant difference in median survival, p=0.4.<br><br>No significant difference between survival curves, p=NR ‡. ** | 1 leak<br>2 toxic deaths<br>2 respiratory<br>1 esophageal perforation<br>2 cardiovascular<br>2 electrolytes |
| | | esophagectomy (right thoracotomy) | 34 | 7.4 | 39 | 23 | 20 | 19 | 10 | | 2 leaks<br>2 respiratory<br>1 cardiovascular |

**Table 6 cont'd.**

| Study (Reference) | Study characteristics | Interventions | # of Pts | Median Survival (Months) | Survival Rate (%) | | | | | Statistical Significance | Adverse Effects |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | 1yr | 2yr | 3yr | 4yr | 5yr | | |
| Bosset 1997 (45) | Jan 1989-June 1995, France, multicentre, squamous cell, age < 70 years < 15% weight loss < WHO status 2 resectable, Exclude tracheal fistula, T3N1, T4N0, T4N1 | cisplatin 80 mg/m$^2$ x 3 days x 2 cycles + 37 Gy concurrent radiotherapy + esophagectomy | 143 | 18.6 | 69 | 48 | 39 | 35 | 33 | No difference in median survival.<br><br>No significant difference between survival curves, p=0.78. ††<br><br>Significant benefit for CRT in disease-free survival (p=0.003) and time free of local disease (p=0.01) but no significant difference in time to distant metastasis (p=0.24). | 37 vomiting<br>3 neutropenia<br>1 toxic death<br>17 postoperative deaths<br>6 respiratory failure<br>7 sepsis<br>Note: Trial stopped early 282/320 due to increased mortality in CRT group. |
| | | esophagectomy (right thoracotomy + cervical anastomosis) | 139 | 18.6 | 67 | 43 | 37 | 34 | 32 | | 2 sepsis<br>5 postoperative deaths |
| Urba 2001 (51) | 1989-1994 Michigan, single centre, 25% squamous cell 75% adenocarcinoma, age < 75 years | cisplatin 20 mg/m$^2$ x 5 days x 2 cycles vinblastine 1 mg/m$^2$ x 4 days x 2 cycles 5-fluorouracil 300 mg/m$^2$ x 21 days + 45 Gy concurrent radiotherapy +esophagectomy | 50 | 17.6 | 72 | 42 | 30 | 25 | 20 | No significant difference in median survival, 1yr or 3yr overall survival, p=NR.**<br><br>No significant difference between survival curves, p=0.15†<br><br>No significant difference in disease-free survival, p=0.16. | 38 grade 3/4 granulocytopenia<br>15 grade 3/4 thrombocytopenia<br>19 neutropenic fever<br>8 red blood cell transfusion<br>31 feeding tube<br>1 perioperative deaths<br>5 anastomotic leaks |
| | | esophagectomy (transhiatal with cervical anastomosis) | 50 | 16.9 | 58 | 38 | 16 | 14 | 10† | | 2 perioperative deaths<br>7 anastomotic leaks |

**Table 6 cont'd.**

| Study (Reference) | Study characteristics | Interventions | # of Pts | Median Survival (Months) | Survival Rate (%) | | | | | Statistical Significance | Adverse Effects |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | 1yr | 2yr | 3yr | 4yr | 5yr | | |
| Walsh 2002 (43,54) | May 1990-Sept 1995, Ireland, single centre, adenocarcinoma age < 76 years, excluded poor performance, metastases, other cancers, previous chemotherapy or radiotherapy | cisplatin 75 mg/m$^2$ x 1 day x 2 cycles 5-fluorouracil 15 mg/kg x 5 days x 2 cycles + 40 Gy concurrent radiotherapy + esophagectomy | 58 | 17 | 52 | 37 | 32 | NR | 29 | Significant benefit for CRT in median survival, p=0.002.<br><br>Significant benefit for CRT in 3yr and 5yr overall survival, p=NR. | 4 gastrointestinal<br>2 hematologic<br>15 cardiac<br>1 toxic deaths<br>28 respiratory<br>2 leaks<br>1 recurrent laryngeal nerve palsy<br>1 chylothorax |
| | | esophagectomy (transhiatal, or Lewis-Tanner, or abdominal and left thoracotomy) | 55 | 12 | 44 | 26 | 6 | NR | 5 | | 2 leaks<br>1 recurrent laryngeal nerve palsy<br>1 chylothorax<br>32 respiratory<br>13 cardiac |
| Lee 2004 (58) | March 1999 – May 2002, Stage II/III, resectable esophageal SCC | Cisplatin 60 mg/m$^2$ IV d1, 5FU 1,000mg/m2 IV d2-5, cisplatin 60 mg/m2 IV d22 + RT 45.6 Gy, 1.2 Gy bid d1-28 + surgery 3-4 weeks post RT. 3 additional cycles of postoperative CT given for disease that was stable or responsive to CRT. | 51 | 28.2 | 68 | 55 | NR | NR | NR | No significant difference in median survival or between survival curves, p=0.69. ††<br><br>No significant difference in event-free survival, p=0.93. | 8 deaths<br>(2 CRT-related<br>1 surgery-related<br>1 secondary primary cancer<br>3 other cause;<br>1 unknown cause)<br>6 neutropenia<br>3 mucositis<br>1 thrombocytopenia<br>1 acute MI<br>1 unstable angina |
| | | Surgery alone | 50 | 27.3 | 81 | 57 | NR | NR | NR | | 4 deaths<br>(1 surgery-related<br>2 other cause<br>1 unknown cause) |

**Table 6 cont'd.**

| Study (Reference) | Study characteristics | Interventions | # of Pts | Median Survival (Months) | Survival Rate (%) | | | | | Statistical Significance | Adverse Effects |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | 1yr | 2yr | 3yr | 4yr | 5yr | | |
| Burmeister 2005 (59) | Multicentre, T1-3,N0-1, ECOG PS 0-1 | Cisplatin 80 mg/m$^2$ d1 + 5-FU 800 mg/m$^2$ d2-5 + RT 35 Gy in 15 fractions + surgery | 128 | 22.2 | 72§ | 50§ | 37§ | 30§ | 27§ | No significant difference between survival curves, p=0.57.<br><br>No significant difference in progression-free survival, p=0.32. | 5 surgery-related deaths<br>63 surgical complications (25 pulmonary, 15 cardiac, 6 leaks, 24 anastomotic strictures)<br>20 esophagitis<br>6 nausea or vomiting |
| | | Surgery alone | 128 | 19.3 | 63§ | 42§ | 33§ | 29§ | 24§ | | 6 surgery-related deaths<br>70 surgical complications (36 pulmonary, 14 cardiac, 6 leaks, 31 anastomotic strictures) |
| Tepper 2006 (61)<br><br>abstract | Stage 1-3 disease, Oct 1997-Mar 2000 | Cisplatin 100 mg/m$^2$ + 5-FU 1000 mg/m$^2$/d x 4d, wk 1,5 + concurrent RT 50.4 Gy in 28 fractions over 5.6 wks + esophagectomy with lymph node resection | 30 | 54 | NR | NR | NR | NR | 39 | Significant benefit for CRT in median survival, p=0.02.<br><br>Significant benefit in 5yr overall survival, p<0.008.¶ | 14 surgical complications<br>54% ≥gr3 hematopoietic toxicity<br>40% ≥gr3 esophagitis/dysphagia |
| | | Surgery alone | 26 | 21.6 | NR | NR | NR | NR | 16 | | 17 surgical complications<br>2 post-surgical deaths |
| Natsugoe, 2006 (60) | Jan 1997-Dec 2001, squamous, no visceral organ metastasis or tracheobronchial fistula, operable, age<70,KPS>90% | Cisplatin 7 mg + 5-FU 350 mg + RT 40Gy in 2Gy fractions 5d/wk, 4 wks | 20ıı | Not reached | NR | NR | NR | NR | 57 | No significant difference in 5-year survival rate, p=0.58 ** | 3 gr 3 leukopenia<br>1 gr 3 anemia<br>1 gr 3 decreased platelets<br>4 anastomotic leaks<br>2 pneumonia |
| | | Surgery alone | 23 | NR | NR | NR | NR | NR | 41 | | 4 anastomotic leaks<br>3 pneumonia |

Notes: CRT, chemoradiotherapy; ECOG, Eastern Cooperative Oncology Group; FU, fluorouracil; Gy, gray; IV, intravenous; KPS, Karnofsky Performance Score; NR, not reported; Pts, patients; SCC, squamous cell carcinoma; WHO, World Health Organization; wk(s), week(s); yr, year.

*Patients randomized to four groups; data shown are for chemotherapy + radiotherapy + surgery versus surgery alone.

** Statistical power and target sample size not reported.

† Survival curves for patients in CRT arm with complete response had significantly increased survival compared to patients with residual disease (p=0.01).

‡ Patients with a complete or partial response had improved survival compared to patients with no response (p=0.001).

§ Estimated from survival curves.

ıı Two patients did not undergo surgery due to bone metastases and were not included in the analysis.

¶ Data from presentation slides, publically available online at www.ASCO.org †† Target sample size not achieved.

**Table 7. Randomized trials of surgery and postoperative chemotherapy (CT) versus surgery alone.**

| Study (Reference) | Study characteristics | Interventions | # of Pts | Median Survival (Months) | Survival Rate (%) | | | | | Statistical Significance | Adverse Effects |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | 1yr | 2yr | 3yr | 4yr | 5yr | | |
| Pouliquen 1996 (42) | 120 patients total. Palliative resections with positive nodes and or positive margins or metastases Stratified by completeness of resection. 62 had curative resections and are reported here (no residual disease), France, 15 centres, July 1987-Mar 1992 Excluded tracheal fistula, >30% liver metastases, brain metastases, node negative resections | esophagectomy + cisplatin 100 mg/m$^2$ x 1 day x 6-8 cycles 5-fluorouracil 1000 mg/m$^2$ x 5 days x 6-8 cycles | 24 | 20 | 83 | 34 | 32 | 18 | 17† | No significant difference in survival, p=NR. | (for 120 pts, including those without complete resection) 9 tracheoesophageal fistulae 5 sepsis 11 infections 13 pulmonary 26 gastrointestinal 9 neurologic 14 leukopenia 9 thromobcytopenia 15 renal 4 deaths |
| | | esophagectomy | 38 | 20 | 70 | 44 | 32 | 20 | 12† | | 8 tracheoesophageal fistulae 4 sepsis 9 infections 12 pulmonary 18 gastrointestinal; 1 neurologic 3 leukopenia 5 thromobcytopenia 1 renal 0 deaths |

**Table 7 cont'd.**

| Study (Reference) | Study characteristics | Interventions | # of Pts | Median Survival (Months) | Survival Rate (%) | | | | | Statistical Significance | Adverse Effects |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | 1yr | 2yr | 3yr | 4yr | 5yr | | |
| Ando 1997 (44) | Japan, Multicentre, Dec 1988-July 1991, Resectable T1b, Age < 75 years | esophagectomy + cisplatin 70 mg/m$^2$ x 1 day x 2 cycles vindesine 3 mg/m$^2$ x 2 days X 2 cycles | 105 | 57 | 90 | 67 | 58 | 58 | 48 | No significant difference in survival, p=0.60. | 2 anemia<br>13 neutropenia<br>13 vomiting<br>8 renal<br>2 diarrhea<br>1 infection<br>16% unable to complete chemotherapy due to complications. |
| | | esophagectomy (laparotomy and right thoracotomy with 3 field radical lymphadenectomy with gastric or colon interposition) | 100 | 47 | 90 | 67 | 54 | 48 | 45 | | None reported |
| Ando 2003 (55) | Japan, multicentre Jul 1992-Jan 1997 ECOG PS 0-2 age < 75 years | esophagectomy + cisplatin 80mg/m$^2$ x 2 cycles 5-fluorouracil (800 mg/m$^2$ x 5 days x 2 cycles | 120 | Not reached | 93 | 75 | 68 | 66 | 52 | No significant difference in survival, p=0.13.* | Grade 3 or 4 hematologic or non-hematologic toxicities were limited in the chemotherapy group. |
| | | esophagectomy | 122 | 84 | 90 | 75 | 66 | 58 | 61 | | NR |

Notes: KPS, Karnofsky Performance Score; NR, not reported; Pts, patients.
† This survival analysis is based only on complete resections.
* Target sample size not achieved.

**Table 8. Randomized trials of postoperative chemotherapy (CT) and surgery versus postoperative chemoradiotherapy (CRT) and surgery.**

| Study (Reference) | Study characteristics | Interventions | # of Pts | Median Survival (Months) | Survival Rate (%) | | | | | Statistical Significance | Adverse Effects |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | 1yr | 2yr | 3yr | 4yr | 5yr | | |
| Tachibana 2003 (56) | Nov 1991- Dec 2000, squamous, age < 80 years, KPS 0-3. | Post-op CT -cisplatin 50 mg/m$^2$ IV d1,15+5-FU 300 mg/m$^2$ daily for 5 weeks | 23 | 28 | 100 | 69 | 63 | 48 | 38 | No significant difference in survival, p=0.97.* | (Gr. 3 or 4)<br>1 decreased hemoglobin<br>2 thrombocytopenia<br>2 elevated BUN/Cr or decreased 24hrCCr<br>2 diarrhea |
| | | Postop CRT -cisplatin 50 mg/m$^2$ IV d1,15+5-FU 300 mg/m$^2$ daily for 5 weeks+RT 50 Gy to the mediastinum | 22 | 31 | 80 | 69 | 58 | 58 | 50 | | (Gr. 3 or 4)<br>2 leucocytopenia<br>1 stomatitis |

Notes: KPS, Karnofsky Performance Score; NR, not reported; Pts, patients.
* Statistical power and target sample size not reported.

**Table 9. Randomized trials of surgery and postoperative radiotherapy (RT) versus surgery alone.**

| Study (Reference) | Study characteristics | Interventions | # of Pts | Median Survival (Months) | Survival Rate (%) | | | | | Statistical Significance | Adverse Effects |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | 1yr | 2yr | 3yr | 4yr | 5yr | | |
| Teniere 1991 (30) | Dec 1979-Dec 1985 France, multicentre, squamous cell, distal 2/3 esophagus | esophagectomy + 45-55 Gy postop RT | 102 | 18 | 68 | 50 | 27 | 24 | 21‡ | No significant difference in survival, p=NR. | minor 18<br>major 4<br>death 1 |
| | | esophagectomy (transhiatal or right thoracotomy with stomach or colon interposition) | 119 | 18 | 73 | 51 | 29 | 22 | 19‡ | | None reported |
| Fok 1993 (34) | July 1986-Dec 1989 Hong Kong, single centre, squamous cell adenocarcinoma, excluded leaks, respiratory failure, poor performance, metastases | esophagectomy + 49-52.5 Gy postop RT | 65 | 8.7 | 34 | 18 | 16 | 16 | NR† | Significantly shorter survival with postop RT, p=0.02. | 6 gastritis<br>17 ulcer<br>1 tracheo-esophageal fistula<br>6 strictures |
| | | esophagectomy (Lewis-Tanner or transhiatal or sternal split) | 65 | 15.2 | 65 | 25 | 21 | 16 | NR† | | 3 gastritis<br>1 ulcer<br>6 strictures |
| Fok* 1994 (5) | 1968-1981 Hong Kong, single centre, squamous cell, middle 1/3 esophagus | esophagectomy (one or two stage) + 45-53 Gy postop RT | 42 | 11 | 48 | 17 | 17 | 12 | 10 | No significant difference in survival, p=NR. | 25 respiratory<br>3 postoperative deaths<br>11 leaks |
| | | esophagectomy (right thoracotomy, left neck, and abdomen) | 39 | 22 | 58 | 36 | 24 | 16 | 16 | | 15 respiratory<br>3 postoperative deaths<br>7 leaks |
| Zieren 1995 (41) | June 1988-Dec 1991 Germany, single centre, squamous cell, excluded cervical location, metastases, other cancers, previous treatment | esophagectomy + 55.8 Gy postop RT | 33 | 14 | 57 | 29 | 22 | NR | NR | No significant difference in survival, p=NR. | 1 tracheo-esophageal fistula<br>18 skin |
| | | esophagectomy (transhiatal or right thoracotomy with stomach interposition) | 35 | 13 | 53 | 31 | 20 | NR | NR | | NR |

**Table 9 cont'd.**

| Study (Reference) | Study characteristics | Interventions | # of Pts | Median Survival (Months) | Survival Rate (%) | | | | | Statistical Significance | Adverse Effects |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | 1yr | 2yr | 3yr | 4yr | 5yr | | |
| Xiao 2003 (57) | | esophagectomy + midplane dose of 50-60 Gy in 25-30 fractions over 5-6 weeks | 220 | 36 | 79 | 63 | 51 | 48 | 41 | No significant difference in survival, p=0.45. | NR |
| | | esophagectomy | 275 | 26 | 79 | 58 | 44 | 40 | 37 | | NR |

Notes: NR, not reported; Pts, patients.
*Patients randomized to four groups; data shown are for surgery + radiotherapy versus surgery alone.
† Better local control with RT (p=0.06) but with more complications.
‡ Local or regional recurrence was lower with RT (70% versus 85%, p-value not reported).

## Table 10. Randomized trials of preoperative radiotherapy (RT) versus postoperative RT.

| Study (Reference) | Study characteristics | Interventions | # of Pts | Median Survival (Months) | Survival Rate (%) | | | | | Statistical Significance | Adverse Effects |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | 1yr | 2yr | 3yr | 4yr | 5yr | | |
| Fok* 1994 (5) | 1968-1981, Hong Kong, single centre, squamous cell, middle 1/3 esophagus | 24-53 Gy preop RT + esophagectomy | 40 | 10.5 | NR | NR | NR | NR | 10 | No significant difference in survival, p=NR. | 20 respiratory<br>12 postoperative deaths<br>11 leaks |
| | | esophagectomy (one or two stage) + 45-53 Gy postop RT | 42 | 11.3 | NR | NR | NR | NR | 10 | | 25 respiratory<br>3 postoperative deaths<br>11 leaks |

Notes: KPS, Karnofsky Performance Score; NR, not reported; Pts, patients.
*Patients randomized to four groups; data shown are for surgery + radiotherapy versus surgery alone.

## Table 11. Randomized trial of preoperative and postoperative radiotherapy (RT) versus postoperative RT.

| Study (Reference) | Study characteristics | Interventions | # of Pts | Median Survival (Months) | Survival Rate (%) | | | | | Statistical Significance | Adverse Effects |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | 1yr | 2yr | 3yr | 4yr | 5yr | | |
| Iizuka, 1988 (26) | Japan, Aug 1982 – Nov 1983, multicentre, no recognizable metastases. | Preop RT 30Gy/15, surgery, postop RT 50Gy/25 (24Gy in areas that received preop RT) | 104* | 13 | NR | NR | NR | NR | NR | Significant benefit in survival for pts who did not receive preop RT, p=0.0069. | 14 pneumonia<br>12 leaks<br>1 chylothorax |
| | | Surgery, postop RT 50Gy/25. | 103* | 21.3 | NR | NR | NR | NR | NR | | 10 pneumonia<br>10 leaks |

Notes: KPS, Karnofsky Performance Score; NR, not reported; Pts, patients.
*Number of eligible patients.

**Table 12. Randomized trials of preoperative chemotherapy (CT) and postoperative chemotherapy (CT) versus surgery alone.**

| Study (Reference) | Study characteristics | Interventions | # of Pts | Median Survival (Months) | Survival Rate (%) | | | | | Statistical Significance | Adverse Effects |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | 1yr | 2yr | 3yr | 4yr | 5yr | | |
| Roth 1988 (27) | Nov 1982-May 1986<br>NCI, single centre<br>squamous cell<br>Stage I, II, III | cisplatin 120 mg/m$^2$ x 1 day x 1 cycle<br>vindesine 3 mg/m$^2$ x 4 days x 2 cycles<br>bleomycin 10 U/m$^2$ x 4 days x 2 cycles<br>+ esophagectomy<br>+ cisplatin 120 mg/m$^2$ q 6 wks x 6 months<br>+ vindesine 3 mg/m$^2$ q 12 wks x 6 months | 17 | 9 | 50 | 28 | 25 | NR | NR | No significant difference in survival, p=0.34†. | 17 alopecia<br>2 vomiting<br>1 pneumonia<br>1 sepsis<br>1 neurological<br>1 respiratory failure<br>1 renal<br>1 leak<br>3 chylothorax<br>1 pulmonary embolus<br>1 wound infection |
| | | esophagectomy (transthoracic with cervical or thoracic anastomosis) | 19 | 9 | 35 | 15 | 5 | NR | NR | | 3 leaks<br>1 chylothorax<br>1 pulmonary embolus<br>1 pneumonia<br>1 strictures<br>1 empyema<br>1 subphrenic abscess |
| Kelsen 1998 (48) | Aug 1990 to Dec 1995,<br>North America, multicentered,<br>Resectable esophageal cancer,<br>55% adenocarcinoma<br>45% squamous cell | cisplatin 100 mg/m$^2$ x 1 day x 3 cycles<br>5-fluorouracil 1 g/m$^2$ x 5 days x 3 cycles<br>+ esophagectomy<br>+ cisplatin 75 mg/m$^2$ x 1 day x 2 cycles if responded | 233 | 14.9 | 59 | 35 | 23 | 19 | 18 | No significant difference in survival, p=0.53. | 49 minor<br>53 major<br>9 toxic deaths<br>68 neutropenia<br>58 mucositis<br>10 postoperative deaths |
| | | esophagectomy | 234 | 16.1 | 60 | 37 | 26 | 21 | 20 | | 67 minor<br>57 major<br>13 postoperative deaths |

Notes: KPS, Karnofsky Performance Score; NCI, National Cancer Institute; NR, not reported; Pts, patients; wks, weeks.
† Survival advantage in responders and if less than 10% weight loss.

**Table 13. Randomized trials of postoperative chemotherapy (CT) and surgery versus postoperative radiotherapy (RT) and surgery.**

| Study (Reference) | Study characteristics | Interventions | # of Pts | Median Survival (Months) | Survival Rate (%) | | | | | Statistical Significance | Adverse Effects |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | 1yr | 2yr | 3yr | 4yr | 5yr | | |
| Iizuka, 1993 (35) | Japan, multicentre, curative resection, age <75 years, Aug 1985 – Aug 1987. | Postop RT 50Gy, 2Gy/day, 5x per wk, 5wks | 127 | 38* | 80 | 61 | 51 | 46 | 44 | Significant benefit in 1yr survival for CT, p<0.05.<br><br>No significant difference between survival curves, p=0.8061.<br><br>No significant difference in time to recurrence, p=0.9265. | 3 grade 3/4 decreased WBC count<br>11 grade 1/2 elevated BUN<br>9 grade 1-3 elevated creatinine concentration |
| | | Cisplatin 50mg/m$^2$, vindesine 3mg/m$^2$, day 1. Repeated twice at interval of 3wks. | 126 | 38* | 90 | 60 | 52 | 47 | 42 | | 12 grade 3/4 decreased WBC count<br>26 grade 1/2 elevated BUN<br>27 grade 1-3 elevated creatinine concentration<br>1 CT-related death |

Notes: BUN, blood urea nitrogen; CT, chemotherapy; KPS, Karnofsky Performance Score; NR, not reported; Pts, patients; WBC, white blood cell.
* Estimated from survival curves.

**Table 14. Randomized trials of preoperative chemotherapy (CT) and surgery versus preoperative radiotherapy (RT) and surgery.**

| Study (Reference) | Study characteristics | Interventions | # of Pts | Median Survival (Months) | Survival Rate (%) | | | | | Statistical Significance | Adverse Effects |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | 1yr | 2yr | 3yr | 4yr | 5yr | | |
| Nygaard 1992 (32) | Jan 1983-Jan 1988 Scandinavia, multicentre, squamous cell, age < 75 years, KPS > 50, T1, T2, Nx, M0 > 21 cm from incisors | cisplatin 20 mg/m$^2$ x 5 days x 2 cycles bleomycin 10 mg/m$^2$ x 5 days x 2 cycles + esophagectomy | 56 | 7 | 31 | 6 | 3 | NR | NR | Significant benefit in survival for RT, p=0.01. | 3 respiratory<br>3 leaks<br>6 postoperative deaths<br>1 hematologic<br>1 alopecia |
| | | 35 Gy preop RT + esophagectomy | 58 | 10 | 44 | 25 | 21 | NR | NR | | 5 respiratory<br>2 leaks<br>4 postoperative deaths<br>1 lung lesion<br>1 septicemia |
| Kelsen, 1990 (29) | 1981-1987, epidermoid carcinoma of esophagus, no distant metastases | Cisplatin 120mg/m$^2$ or 3mg/kg, d 1,29, vindesine 3mg/m$^2$ d 1,8,15,22,29,36,43, bleomycin 10U/m$^2$ IV bolus followed by 4 days continuous infusion d 3-7, 31-36 + esophagectomy | 48 | 10.4 | NR | NR | NR | NR | NR | No significant difference in survival, p=0.61. | NR |
| | | RT 45 Gy followed by boost to 55 GY to the primary tumour + esophagectomy | 48 | 12.4 | NR | NR | NR | NR | NR | | NR |

Notes: KPS, Karnofsky Performance Score; NR, not reported; Pts, patients.

**Table 15. Randomized trial of postoperative chemoradiotherapy (CRT) and surgery versus preoperative radiotherapy (RT) and surgery.**

| Study (Reference) | Study characteristics | Interventions | # of Pts | Median Survival (Months) | Survival Rate (%) | | | | | Statistical Significance | Adverse Effects |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | 1yr | 2yr | 3yr | 4yr | 5yr | | |
| Andersen, 1984 (24) | Squamous cell carcinoma, Nov 1977 – May 1981, Scandinavia, multicentre | RT 35 Gy in 4 wks + esophagectomy | 59* | 6.0 | NR | 19 | NR | NR | NR | No significant difference in median survival or 2 yr survival, p=0.56. | NR |
| | | RT 30 Gy in 4 wks, bleomycin 5 mg x 20/ 4 wks + esophagectomy | 65* | 5.8 | NR | 25 | NR | NR | NR | | NR |

Notes: NR, not reported; Pts, patients.
* Number of evaluable patients.

**Table 16. Randomized trials of postoperative immunotherapy plus radiotherapy (RT) or chemoradiotherapy (CRT) and surgery.**

| Study (Reference) | Study characteristics | Interventions | # of Pts | Median Survival (Months) | Survival Rate (%) | | | | | Statistical Significance | Adverse Effects |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | 1yr | 2yr | 3yr | 4yr | 5yr | | |
| Ogoshi, 1995 (40) | Japan, multicentre, squamous cell carcinoma, Feb 1983 – Nov 1985, | RT >20Gy | 31 | 27 | 70 | 57 | 43 | 40 | 40 | No significant difference in survival between the RT and the RT + PSK groups.<br><br>No significant difference in survival between the RT + CT and the RT + CT + PSK groups, p=0.1930. | No toxicity |
| | | RT >20Gy + PSK 3.0g/d for 3 months | 38 | 29 | 76 | 51 | 46 | 42 | 42 | | 1 mild nausea |
| | | RT >20Gy + CT bleomycin hydrochloride or pepleomycin sulphate, followed by oral Futraful | 49 | 14 | 61 | 38 | 34 | 29 | 29 | | 1 mild nausea<br>2 mild diarrhea<br>1 alopecia<br>3 liver dysfunction<br>2 leukopenia |
| | | RT >20Gy + CT + PSK 3.0g/d for 3 months | 56 | 21 | 76 | 47 | 44 | 37 | 37 | | 1 mild nausea<br>1 erythema<br>2 liver dysfunction<br>2 leukopenia |

Notes: KPS, Karnofsky Performance Score; NR, not reported; Pts, patients; PSK, protein-bound polysaccharide K.

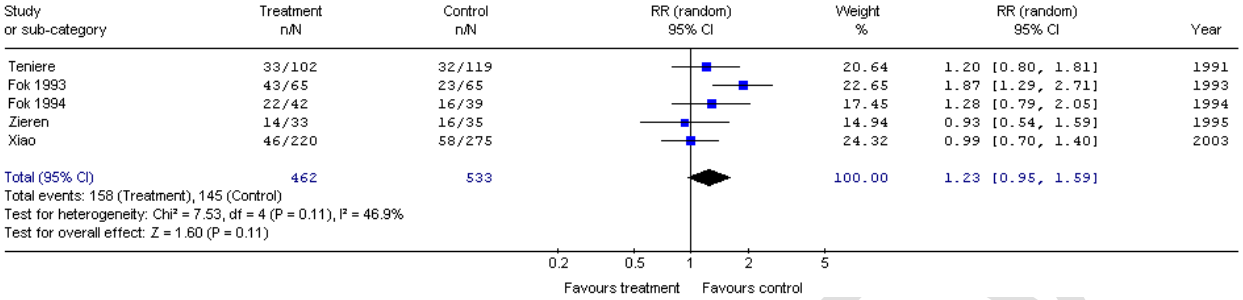
**Table 17. Randomized trials of preoperative hyperthermia and chemoradiotherapy.**

| Study (Reference) | Study characteristics | Interventions | # of Pts | Median Survival (Months) | Survival Rate (%) | | | | | Statistical Significance | Adverse Effects |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | 1yr | 2yr | 3yr | 4yr | 5yr | | |
| Kitamura, 1995 (39) | Jan 1988 – June 1992, | RT 30 Gy, IV 30 mg bleomycin or 180 mg of cisplatin + hyperthermia | 32 | 36* | 68 | 57 | 50 | NR | NR | NR | No postoperative complications. |
| | | RT 30 Gy, IV 30 mg bleomycin or 180 mg of cisplatin | 34 | 20* | 60 | 40 | 24 | NR | NR | | No postoperative complications. |

Notes: KPS, Karnofsky Performance Score; NR, not reported; Pts, patients.
* Estimated from survival curves.

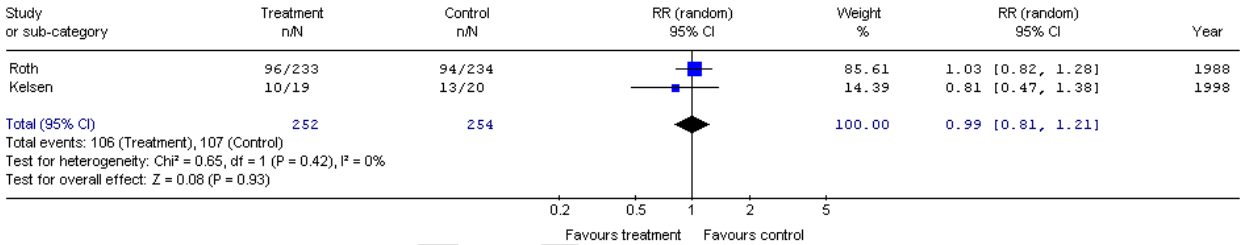
**Appendix 4. Pooled one-year mortality data for comparisons with no new data since publication of original guideline (18,19).**

**Figure 3. Meta-analysis examining postoperative radiotherapy and surgery compared to surgery alone: mortality at one year.**




Overall risk ratio = 1.23 (95% CI, 0.95 to 1.59; p=0.11)

**Figure 4. Meta-analysis examining preoperative and postoperative chemotherapy and surgery to surgery alone: mortality at one year.**




Overall risk ratio = 0.99 (95% CI, 0.81 to 1.21; p=0.93)

## Appendix 5. Study quality evaluation.

### Table 18. Study quality characteristics of included randomized controlled trials.

| Study | Publication status | Funding | Randomization method | Baseline characteristics | Blinding | Statistical Power | Achievement of Target Sample Size | Follow-up | Intention-to-Treat (ITT) analysis |
|---|---|---|---|---|---|---|---|---|---|
| **Preoperative radiotherapy and surgery versus surgery alone** | | | | | | | | | |
| Fok (5) | Full publication | NR | NR | Balanced | NR | NR | NR | Analysis adjusted for pts lost to follow-up | NR |
| Launois (23) | Full publication | NR | Consecutive patients allotted numbers from random number table. Patients with even numbers received preoperative RT. | Balanced | NR | NR | NR | NR | 15 pts excluded: 14 inoperable, 1 refused operation. |
| Gignoux (25) | Full publication | NCI | NR | Balanced | NR | NR | NR | Mean 3.6 years | All eligible pts analyzed.<br>15 ineligible pts not analyzed. |
| Wang (28) 1989 | Full publication | NR | NR | More stage IIp pts in RT+S group. | NR | NR | NR | Pts lost to follow-up counted as dead at last communication | NR |
| Nygaard (32) | Full publication | NR | NR | Moderate sex imbalance | NR | NR | NR | 13 pts lost to follow-up<br>F-u for 36 mos | Only correctly-treated patients are reported but ITT analysis results not different |
| Arnott (31) | Full publication | NR | Sealed sequentially numbered envelopes. | Balanced | NR | NR | NR | Minimum 5 years or death<br>1 pt lost to follow-up | Yes. Also, analysis of only patients who received allocated treatment. |
| **Preoperative chemotherapy and surgery versus surgery alone** | | | | | | | | | |
| Nygaard (32) | *See results under preoperative radiotherapy and surgery versus surgery alone* | | | | | | | | |
| Schlag (33) | Full publication | NR | NR | Balanced | NR | 80% power to detect increase in resectability rate from 60% to 85% and increase in 2-year survival from 25% to 50% with 57 pts per group | Target not achieved. 46 pts randomized. | 1 pt lost to follow-up | 2 pts not evaluated: 1 protocol violation and 1 loss to follow-up |

| Study | Publication status | Funding | Randomization method | Baseline characteristics | Blinding | Statistical Power | Achievement of Target Sample Size | Follow-up | Intention-to-Treat (ITT) analysis |
|---|---|---|---|---|---|---|---|---|---|
| Maipang (38) | Full publication | Government grant | NR | NR | NR | NR | NR | 5 pts lost to follow-up | Yes |
| Law (47) | Full publication | NR | NR | Balanced | NR | 90% power to detect increase in 2-year survival from 30% to 50% with 150 pts | Target not achieved. 147 pts. | Median 17 mos | ITT analysis showed no difference between chemotherapy group and control |
| Kok (46) | Abstract | NR | NR | NR | NR | NR | NR | Median 15 mos | NR |
| Baba (49) | Full publication | NR | Stratified blocked randomization. Stratified by age, tumour size, peri-tumour fat density, lymph node size. Treatment allocation controlled by university. | Balanced | NR | NR | NR | NR | 1 randomized patient not analyzed |
| Ancona (50) | Full publication | NR | Permuted blocks of six | Balanced | NR | 80% power to detect 20% difference in survival at 2 years with 240 pts over 6 years | Target not achieved. 96 patients. | Median NR Adequate f-u for all pts | Yes |
| Wang (52) 2001 | Only abstract available in English | - | - | NR | - | - | - | - | - |
| MRC OE02 (53) | Full publication | British Medical Research Council | By telephone Assigned by minimization using criteria of surgeon, tumour site, WHO-PS and histology | Balanced | None | 90% power to detect 2-year survival improvement from 20% to 30% with 800 pts | Target achieved | Median 36.9 mos in CS pts, 37.9 mos in surgery-alone pts | 69 pts from China excluded after randomization. All others analysed by ITT. |
| **Preoperative chemoradiation and surgery versus surgery alone** | | | | | | | | | |
| Nygaard (32) | *See results under preoperative radiotherapy and surgery versus surgery alone* | | | | | | | | |
| Le Prise (37) | Full publication | NR | Stratified by stage | Balanced | NR | 90% power to detect 2-year survival improvement from 10% to 30% with 150 pts | Target not achieved | Median 16 mos | Yes |

| Study | Publication status | Funding | Randomization method | Baseline characteristics | Blinding | Statistical Power | Achievement of Target Sample Size | Follow-up | Intention-to-Treat (ITT) analysis |
|---|---|---|---|---|---|---|---|---|---|
| Apinop (36) | Full publication | NR | NR | Balanced | NR | NR | NR | NR | Yes |
| Bosset (45) | Full publication | Ligue Départemen-tale de Lutte Contre le Cancer du Doubs, France | Patients randomly assigned by a central office.<br>Balanced by institution. | Higher proportion of ECOG PS 1 in treatment arm | NR | 80% power to detect increase in 5-year survival from 15% to 20% with 320 pts (256 deaths) | Recruitment stopped early due to higher than anticipated rate of postoperative mortality in combined treatment group | 4 pts lost to follow-up<br>Median 55.2 mos | Yes |
| Urba (51) | Full publication | NR | Stratified by histology, tumour size and tumour location | Balanced | NR | 80% power to detect increase in median survival from 1 year to 2.2 years | NR | Median 8.2 yrs | Yes |
| Walsh (43,54) | Full publication | NR | NR | Balanced | NR | 80% power with 190 pts | Target not achieved but statistically significant difference detected | Minimum 5 years | Yes |
| Lee (58) | Full publication | NR | Permuted block randomization<br>Stratified by age and PS | Slightly higher proportion without clinical lymph node involvement in surgery group | NR | 80% power to detect improvement from 30% to 50% (HR 0.625) with 190 pts | Target not achieved | Median 25 mos | Yes |
| Burmeister (59) | Full publication | NHMRC | Central phone randomization<br>Blocks of 4<br>Minimization<br>Stratified by histology, sex, institution<br>Allocation sequence concealed to all staff. | Balanced | Research staff and investigators blinded to treatment assignment before, but not after, randomization.<br>Patients not blinded to treatment assignment. | 80% power to detect a 15% difference in 3-year PFS with 230 pts (250 allowing for crossovers) | Target achieved | Median 65 mos | Yes |

| Study | Publication status | Funding | Randomization method | Baseline characteristics | Blinding | Statistical Power | Achievement of Target Sample Size | Follow-up | Intention-to-Treat (ITT) analysis |
|---|---|---|---|---|---|---|---|---|---|
| Tepper (61) | Abstract | NR | Stratified by nodal status, histology, staging | Balanced | NR | 500 pts targeted for enrolment. | Closed due to poor accrual after 56 pts entered. | Median 6 years | Yes |
| Natsugoe (60) | Full publication | NR | Blocked randomization Stratified by age, tumour diameter and presence of lymph node metastases | Balanced for TNM staging | NR | NR | NR | Median 24 mos F-u data for all pts | Yes |
| **Surgery and postoperative chemotherapy versus surgery alone** | | | | | | | | | |
| Pouliquen (42) | Full publication | NR | Unstapling right corner of booklet in which treatment was inscribed Inscriptions predetermined by random number tables balanced for every 4 pts per stratum per centre | Mean age of control group 5 years older than treated group | NR | 100 pts required to detect 17% increase in survival | Target achieved | Minimum 2.5 yrs Maximum 7.5 yrs | 4 randomized patients excluded from analysis for ineligibility or loss to follow-up |
| Ando 1997 (44) | Full publication | Grant-in-aid for research funding | Block randomization using # of patients as blocking factor. Stratified by presence of lymph node metastasis. | Balanced | NR | 80% power to detect increase in 5-year survival from 40% to 60% with 98 pts per group | Target achieved | Median 59.2 mos | Yes |
| Ando 2003 (55) | Full publication | Grant-in-aid for research funding | Minimization to balance institution and pathological lymph node status | Balanced | NR | 80% power to detect 13% improvement with 290 pts | Target not achieved | Median 62.8 mos | Yes |
| **Postoperative chemotherapy and surgery versus postoperative chemoradiotherapy and surgery** | | | | | | | | | |
| Tachibana (56) | Full publication | NR | NR | Balanced | NR | NR | NR | Median 35 mos No pts lost to follow-up | Yes |

Notes: f-u, follow-up; HR, hazard ratio; ITT, intention-to-treat; mos, months; NCI, National Cancer Institute; NHMRC, National Health and Medical Research Council; NR, not reported; PFS, progression-free survival; PS, performance score; pts, patients; RT, radiotherapy; yrs, years.

**Appendix 6. Ongoing trials.**

| **Phase III randomized study of neoadjuvant cisplatin and fluorouracil versus cisplatin, epirubicin, and fluorouracil in patients with resectable adenocarcinoma of the esophagus** | |
|---|---|
| **Protocol ID** | MRC-OE05, EU-20204, NCT00041262 |
| **Date last modified:** | May 18, 2007 |
| **Trial type:** | Randomized, multi-centre, active control |
| **Accrual:** | 1,300 patients (650 per treatment arm) will be accrued |
| **Sponsorship:** | Medical Research Council Clinical Trials Unit |
| **Status:** | Open to accrual |

| **Phase III randomized study of neoadjuvant radio-chemotherapy and surgery versus surgery alone in patients with resectable thoracic esophageal cancer** | |
|---|---|
| **Protocol ID** | FFCD-9901, EORTC-40001, EU-20215, NCT00047112, EORTC-22001, FRE-FNCLCC-FFCD-9901, FRE-GERCOR-FFCD-9901, SFRO-FFCD-9901 |
| **Date last modified:** | December 5, 2006 |
| **Trial type:** | Randomized, open-label, multi-centre, active control |
| **Accrual:** | 380 patients (190 per treatment arm) were to be accrued within 3 years |
| **Sponsorship:** | Fédération Francophone de Cancérologie Digestive, GERCOR, EORTC Radiotherapy Group, EORTC Gastrointestinal Tract Cancer Group, Fédération Nationale des Centres de Lutte Contre le Cancer, Société Française de Radiothérapie Oncologique |
| **Status:** | Closed |

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**Evidence-based Series #2-11 Version 4: Section 3**

# Preoperative or Postoperative Therapy for Resectable Esophageal Cancer: EBS Development Methods and External Review Process

*RA Malthaner, RKS Wong, K Spithoff, RB Rumble, L Zuraw,*
*and the Gastrointestinal Cancer Disease Site Group*

A Quality Initiative of the
Program in Evidence-based Care (PEBC), Cancer Care Ontario (CCO)

These guideline recommendations have been ENDORSED, which means that the recommendations are current and relevant to decision making.
Please see Section 4: Document Review Summary and Review Tool for
A summary of the updated evidence published between 2012 and 2016, and for
Details on how the Clinical Practice Guideline was ENDORSED

**Report Date: May 21, 2008**



## THE PROGRAM IN EVIDENCE-BASED CARE

The Program in Evidence-based Care (PEBC) is an initiative of the Ontario provincial cancer system, Cancer Care Ontario (CCO) (1). The PEBC mandate is to improve the lives of Ontarians affected by cancer, through the development, dissemination, implementation, and evaluation of evidence-based products designed to facilitate clinical, planning, and policy decisions about cancer care.

The PEBC supports a network of disease-specific panels, termed Disease Site Groups (DSGs) and Guideline Development Groups (GDGs), as well as other groups or panels called together for a specific topic, all mandated to develop the PEBC products. These panels are comprised of clinicians, other health care providers and decision makers, methodologists, and community representatives from across the province.

The PEBC is well known for producing evidence-based guidelines, known as Evidence-based Series (EBS) reports, using the methods of the Practice Guidelines Development Cycle (1,2). The EBS report consists of an evidentiary base (typically a systematic review), an interpretation of and consensus agreement on that evidence by our Groups or Panels, the resulting recommendations, and an external review by Ontario clinicians and other stakeholders in the province for whom the topic is relevant. The PEBC has a formal standardized process to ensure the currency of each document, through the periodic review and evaluation of the scientific literature and, where appropriate, the integration of that literature with the original guideline information.

**The Evidence-Based Series**

Each EBS is comprised of three sections:

- *Section 1: Guideline Recommendations*. Contains the clinical recommendations derived from a systematic review of the clinical and scientific literature and its interpretation by the Group or Panel involved and a formalized external review in Ontario by review participants.
- *Section 2: Evidentiary Base.* Presents the comprehensive evidentiary/systematic review of the clinical and scientific research on the topic and the conclusions reached by the Group or Panel.
- *Section 3: EBS Development Methods and External Review Process.* Summarizes the evidence-based series development process and the results of the formal external review of the draft version of Section 1: Recommendations and Section 2: Evidentiary Base.

## DEVELOPMENT OF THIS EVIDENCE-BASED SERIES

### Development and Internal Review

This EBS was developed by the GI DSG of the CCO PEBC. The series is a convenient and up-to-date source of the best available evidence on preoperative or postoperative therapy for resectable esophageal cancer, developed through review of the evidentiary base, evidence synthesis, and input from external review participants in Ontario. The GI DSG comprises medical oncologists, radiation oncologists, surgeons, a methodologist, and a community representative. For a complete list of the GI DSG members, please visit the CCO Web site at http://www.cancercare.on.ca/.

This evidence-based series replaces the original version of this report first completed in 2002 and published in 2004 (3,4). The original guideline recommended surgery alone as the standard practice for resectable esophageal cancer. Since the publication of the guideline, several meta-analyses of randomized controlled trials (RCTs) have become available and the DSG agreed that the results of the highest quality meta-analyses support a recommendation for preoperative therapy. After much discussion, the DSG reached a general consensus that preoperative chemoradiotherapy should be the preferred modality, with preoperative chemotherapy alone as an alternative approach.

### Report Approval Panel

Prior to the submission of this EBS draft report for external review, the report was reviewed and approved by the PEBC Report Approval Panel, which consists of two members, including an oncologist, with expertise in clinical and methodology issues. Key issues raised by the Report Approval Panel included:

- An assessment of study quality should be performed.
- Clarification is required regarding the overlap of studies included in published meta-analyses and variance in methods and outcomes.
- Where data are available, additional information on the absolute magnitude of benefit should be reported.
- The authors should consider focusing on the two categories that are associated with potentially important improvements in outcome (preoperative chemotherapy and preoperative chemoradiotherapy) and provide a brief summary of the remaining categories in an appendix to indicate that the currently available data do not support the therapy tested.
- For the comparison of preoperative chemotherapy versus surgery alone, the large MRC trial (5) yields positive results that likely drive the meta-analysis. The authors should consider whether the highest priority in evaluating this comparison is to critically

appraise the MRC trial. There is evidence to suggest that well-conducted RCTs provide higher levels of evidence than a meta-analysis.
- The authors should consider emphasizing the results of the individual patient-data meta-analysis for the preoperative chemotherapy versus surgery alone comparison and minimize review of published data meta-analyses.

***Modifications in Response to Report Approval Panel Feedback***
- The authors added a table of key study quality characteristics to Section 2: Appendix 5 and added a summary paragraph to the Results section of Section 2.
- Tables summarizing the methods and results of published meta-analyses, including reference numbers for included trials, were added.
- Where available, absolute survival benefits were reported.
- The authors focused on a more detailed analysis of categories for which new evidence was available since the original publication of the guideline (3,4). Categories for which no new information was available were removed from the Results section of Section 2. Summary tables of all RCTs were retained in Section 2: Appendix 3.
- For the comparison of preoperative chemotherapy versus surgery alone, discussion focused on the individual patient-data meta-analysis. Additional meta-analyses of published data were retained but summarized in a table rather than fully described in the text.

**External Review by Ontario Clinicians**

Following the review and discussion of Section 1: Recommendations and Section 2: Evidentiary Base of this EBS and the review and approval of the report by the PEBC Report Approval Panel, the GI DSG circulated Sections 1 and 2 to external review participants in Ontario for review and feedback. Box 1 summarizes the draft recommendations and supporting evidence developed by the GI DSG.

**BOX 1:**
DRAFT RECOMMENDATIONS (approved for external review February 26, 2008)
**Question**

Should patients with resectable esophageal cancer receive preoperative or postoperative therapy along with surgery?

**Target Population**

These recommendations apply to adult patients with resectable and potentially curable thoracic (lower two thirds of esophagus) esophageal cancer for whom surgery is considered appropriate.

**Recommendations**
- Preoperative cisplatin-based chemotherapy plus radiotherapy is recommended as the preferred modality for the management of surgically resectable patients with esophageal cancer.
- Preoperative cisplatin-based chemotherapy alone is an alternative choice for the management of surgically resectable patients with esophageal cancer.

**Key Evidence**
- A literature meta-analysis of 10 randomized trials comparing preoperative chemoradiotherapy followed by surgery to surgery alone showed a 13% absolute benefit in survival at two years for preoperative chemoradiotherapy (hazard ratio [HR], 0.81; 95% confidence interval [CI], 0.70-0.93; p=0.002) (1).

- A published abstract of an individual patient data (IPD)-based meta-analysis of nine randomized trials (2,102 patients) comparing preoperative chemotherapy followed by surgery (CT+S) to surgery alone demonstrated a 4% (from 16 to 20%) absolute overall survival advantage for chemotherapy at five years (HR, -0.87; 95% CI, 0.79-0.95; p=0.003). Based on seven trials (1,849 patients), the HR for disease-free survival (DFS) was 0.82 (95% CI, 0.74-0.91; p=0.001) in favour of CT+S, representing a five-year absolute DFS benefit of 4% (from 6 to 10%). No difference was seen in postoperative death (6.7%) (2).
- Randomized trials demonstrated no survival benefit for radiotherapy given alone, either preoperatively or postoperatively, compared with surgery alone.
- Randomized trials demonstrated no survival benefit for postoperative chemotherapy given alone compared with surgery alone.

**Qualifying Statements**

- The Gastrointestinal Cancer Disease Site Group (GI DSG) acknowledges there is evidence indicating survival benefits with either preoperative chemotherapy or chemoradiotherapy compared with surgery alone. No direct comparison between preoperative chemoradiotherapy versus preoperative chemotherapy alone is available. Based on the majority of the evidence available at this time, the GI DSG believes that preoperative chemoradiotherapy for resectable carcinoma of the esophagus is the preferred approach.
- Based upon results from the *"CROSS"* trial the DSG acknowledges that recommendations indicating use of "preoperative cisplatin based" chemotherapy should be revised to include the use of "preoperative platinum based" chemotherapy.

***Methods***

Feedback was obtained through a mailed survey of 133 external review participants in Ontario (29 medical oncologists, 19 radiation oncologists, 37 general surgeons, 29 thoracic surgeons, and 19 gastroenterologists). The survey consisted of items evaluating the methods, results, and interpretive summary used to inform the draft recommendations and whether the draft recommendations should be approved as a guideline. Written comments were invited. The survey was mailed out on February 26, 2008. Follow-up reminders were sent at two weeks (post card) and four weeks (complete package mailed again). The Gastrointestinal Cancer DSG reviewed the results of the survey.

***Results***

Forty-six responses were received out of the 133 surveys sent (35% response rate). Responses include returned completed surveys as well as phone, fax, and email responses. Of the participants who responded, 31 indicated that the report was relevant to their practice or organizational position, and they completed the survey. Key results of the feedback survey are summarized in Table 19.

**Table 19. Responses to eight items on the feedback survey.**

| Item | Number (%) | | |
|---|---|---|---|
| | **Strongly agree or agree** | **Neither agree nor disagree** | **Strongly disagree or disagree** |
| The rationale for developing a guideline, as stated in the "Introduction" section of the report, is clear. | 30 (97) | | 1 (3) |

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| There is a need for a guideline on this topic. | 28 (90) | 1 (3) | 2 (6) |
| The literature search is relevant and complete. | 26 (87) | 2 (7) | 2 (7) |
| The results of the trials described in the report are interpreted according to my understanding of the data. | 24 (77) | 5 (16) | 2 (6) |
| The draft recommendations in the report are clear. | 29 (97) | | 1 (3) |
| I agree with the draft recommendations as stated. | 24 (80) | 3 (10) | 3 (10) |
| This report should be approved as a practice guideline. | 25 (83) | 1 (3) | 4 (13) |
| If this report were to become a practice guideline, how likely would you be to make use of it in your own practice? | **Very likely or likely** | **Unsure** | **Not at all likely or unlikely** |
| | 25 (86) | 2 (7) | 2 (7) |

***Summary of Written Comments***

Fifteen respondents (48%) provided written comments. The main points contained in the written comments were:

- Five respondents provided comments expressing support for the guideline. One respondent also pointed out that the topic is evolving, and the guideline should be updated in approximately three years. One respondent commented that they would be more likely to refer patients to a cancer clinic first rather than a thoracic surgeon as a result of reading the guideline.
- "Resectable" esophageal cancer should be defined.
- It should be emphasized that these guidelines are for operable patients, as they could be used in the community to try to downstage incurable disease with no benefit for the patient.
- The recommendation for preoperative CRT is partly based on unpublished data by Wong et al. Guidelines should not be based on unpublished data.
- The guideline is too supportive of preoperative CRT and CT and too much weight is given to the Gebski meta-analysis. There are a number of concerns with the Gebski meta-analysis: the absolute benefit is much greater than anything previously reported, it included the study by Lee et al (2004) in which 60% of patients also received postoperative CT, and it gives too much weight to the flawed Walsh trial.
- The MAGIC trial, in which 15% of patients had lower esophageal cancer, should be included.
- There is no mention of separating squamous cell carcinoma from adenocarcinoma.
- There is no mention of the impact of extended lymphadenectomy (en bloc surgical resection) on the need for a second form of local therapy (i.e., radiotherapy).
- Chemoradiotherapy without surgery is a valid treatment option and the evidence for or against that option should also be summarized and included in this guideline.
- An absolute benefit in disease-free survival of 4 to 6% means that the number needed to treat and achieve survivors is high. A large number of resources will be used and only a small number will benefit, although this is no reason not to use the treatment.
- No large RCT has shown a statistically significant survival advantage, no quality of life was reported in the trials, and any survival advantage is likely minimal. Preoperative CRT should be reserved for patients who put absolute importance on a small survival advantage, not as a routine guideline.
- Many of the trials included highly selected patients. Many patients with esophageal cancer are elderly and have many associated medical problems. If the draft recommendations were applied across the board to every patient who was a surgical candidate, you would see a lot of morbidity and mortality in patients who receive preoperative CRT. The guidelines need to have some qualifiers about age and co-morbidity.

***Modifications/Responses***

- Resectability of esophageal tumours is generally based on the opinion of the thoracic surgeon and is influenced by a number of factors. The authors did not feel that further details regarding a definition of "resectable" would clarify the guideline.
- The Target Population was modified to state that the Recommendations apply to "adult patients with resectable, operable, and potentially curable thoracic esophageal cancer for whom surgery is considered appropriate". The Recommendations are not intended to downstage incurable disease.
- Unpublished data from the Wong et al meta-analysis comparing preoperative CRT with surgery alone was removed from the Results in Section 2. These unpublished data are in agreement with the results of the meta-analysis by Gebski et al (6) and provide support for the recommendation to offer preoperative CRT. The Wong et al data will be added to the next guideline update once the results have been published.
- The results of the Gebski meta-analysis (6) showing a significant survival benefit for preoperative CRT compared with surgery alone are supported by a similar meta-analysis by Wong et al (unpublished), which has been submitted to the Cochrane Collaboration. A note was made in the Results section and in Table 6 that 60% of patients in the preoperative CRT arm of the Lee et al trial (7) also received postoperative CT. The inclusion of the Lee trial in the Gebski meta-analysis provided a more conservative estimate of effect, as the hazard ratio for that trial was 0.88 (95% CI, 0.48-1.62) compared with the overall pooled hazard ratio (HR, 0.81; 95% CI, 0.70 to 0.93). Gebski et al performed a sensitivity analysis excluding the flawed Walsh trial (8) and reported that the effect of CRT remained significant.
- The MAGIC trial (9) was not included because it was primarily a gastric cancer trial with only a small subset of patients having tumours of the lower esophagus. There were insufficient data reported for patients with esophageal cancer to be included in this review. Analysis of treatment effect in patients with esophageal cancer in the MAGIC trial was performed merely to test for heterogeneity of treatment effect according to primary disease site.
- No differentiation between squamous cell carcinoma and adenocarcinoma of the esophagus was made in this guideline because there are no high-quality data indicating that there is a difference in outcome between these two histologies. There is currently no difference clinically in chemotherapy treatment between squamous cell carcinoma and adenocarcinoma.
- The impact of extended lymphadenectomy (en bloc surgical resection) on the need for local therapy was not addressed in the included trials, and this topic was not the focus of the current review. Extended lymphadenectomy is not commonly practiced; therefore, the authors chose not to address it in the guideline at this time.
- Trials examining the efficacy of chemoradiotherapy without surgery did not meet the inclusion criteria for this review. A paragraph summarizing the evidence on chemoradiotherapy without surgery was added to the Discussion in Section 2.
- A Qualifying Statement was added to emphasize that the potential survival benefit may be small, therapy may be associated with adverse effects, and decisions to administer neoadjuvant therapy should be made after consideration of patient preferences, comorbidities, and suitability for therapy. The recommendations are intended to be guidelines and are not prescriptive. As esophageal cancer is associated with poor outcome, the authors believe that any therapy offering improvement in outcome is beneficial and should be offered.

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**Evidence-based Series 2-11 Version 4: Section 4**

# A Quality Initiative of the Program in Evidence-Based Care (PEBC), Cancer Care Ontario (CCO)

# Preoperative or Postoperative Therapy for Resectable Esophageal Cancer

## Guideline Summary Review

*RKS Wong, R. Poon, and Members of the Gastrointestinal Cancer Disease Site Group*

**Review Date: June 1, 2016**

The 2008 guideline recommendations are

**ENDORSED**

*This means that the recommendations are still current and relevant for decision making*



### OVERVIEW

The original version of this guidance document was released by the Program in Evidence-based Care (PEBC), Cancer Care Ontario, on May 21, 2008. In December 2012, this document was assessed in accordance with the PEBC Document Assessment and Review Protocol and was determined to require a review. As part of the review, a PEBC methodologist conducted an updated search of the literature from 2007 to 2012 and the data supported the 2008 recommendations. Please see Appendix I for version 3 of the document summary and review table.

In October 2015, a second round of assessment was conducted and version 3 of this document was placed in review. An updated search of the literature from 2012 to 2016 was performed and a clinical expert reviewed and interpreted the new eligible evidence and proposed the existing recommendations could be endorsed. The Gastrointestinal Cancer Disease Site Group (DSG) endorsed the recommendations found in Section 1 (Clinical Practice Guideline) on June 1, 2016.

### DOCUMENT ASSESSMENT AND REVIEW RESULTS

## Question Considered

Should patients with resectable esophageal cancer receive preoperative or postoperative therapy along with surgery?

## Literature Search and New Evidence

The new search (November 2012 to March 29, 2016) yielded 3 practice guidelines, 10 meta-analyses, 7 randomized control trials (1 RCT had an ancillary abstract, 1 RCT had 2 publications and an ancillary abstract), and 15 abstracts. An additional search for studies on clinicaltrials.gov generated 8 potentially relevant ongoing trials. Brief results of these publications are shown in the Document Summary and Review Tool.

### Impact on Guidelines and Its Recommendations

The new data supports existing recommendations. In the area of neoadjuvant chemoradiotherapy (CRT), two new trials comparing neoadjuvant CRT to surgery alone plus long term results from the CROSS trial have been published. The Marriette et al (20) trial is negative for neoadjuvant CRT, but Zhao et al (18) continues to support neoadjuvant CRT. Nonetheless, long term results from the CROSS trial confirms survival benefit of neoadjuvant CRT. An additional trial by Klevebro et al (15) comparing neoadjuvant CRT to CT concluded no significant difference in the incidence of postoperative morbidity between the two groups, however, complications were significantly more severe after CRT. Taken against the existing evidence, neoadjuvant CRT remains appropriate. Hence, the Gastrointestinal DSG endorsed the 2008 recommendations on the management of surgically resectable patients with esophageal cancer.

### Document Summary and Review Tool

| | |
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| **Number and title of document under review** | EBS 2-11 Version 3 Preoperative or Postoperative Therapy for Resectable Esophageal Cancer |
| **Current Report Date** | August 14, 2013 |
| **Clinical Expert** | Dr. Rebecca Wong |
| **Research Coordinator** | Raymond Poon |
| **Date Assessed** | October 2015 |
| **Approval Date and Review Outcome (once completed)** | June 1, 2016 |

Original Question(s):

Should patients with resectable esophageal cancer receive preoperative or postoperative therapy along with surgery?

Target Population:

These recommendations apply to adult patients with resectable, operable, and potentially curable thoracic (lower two thirds of esophagus) esophageal cancer for whom surgery is considered appropriate.

Study Section Criteria:

**Inclusion Criteria**

Articles were selected for inclusion in this systematic review of the evidence if they were fully published reports, published abstracts, or meta-analyses of randomized trials of preoperative or postoperative treatments compared with surgery alone or surgery plus another preoperative or postoperative treatment in patients with resectable and operable thoracic esophageal cancer.

Data on survival had to be reported. Other outcomes of interest were adverse effects and quality of life.

**Exclusion Criteria**

Carcinomas located in the cervical esophagus were excluded.

Search Details:

November 2012 to March 29, 2016 (Medline, Embase, American Society of Clinical Oncology [ASCO] annual meetings, National Cancer Institute [NCI], National Institute for Health and Care Excellence [NICE], clinicatrials.gov).

Brief Summary/Discussion of New Evidence:

Of 228 total hits from Medline and Embase + 126 hits from ASCO + 31 hits from NCI + 284 hits from NICE + 35 hits from clinicaltrials.gov, 36 references representing 3 practice guidelines, 10 meta-analyses, 7 randomized control trials (1 RCT had an ancillary abstract, 1 RCT had 2 publications and an ancillary abstract), and 15 abstracts were found. There were 8 ongoing trials identified.

| Guidelines | | |
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| **Working Group** | **Recommendations** | **References** |
| National Comprehensive Cancer Network (NCCN) | **Version 3.2015**<br><br>• Preoperative chemoradiation is the preferred approach for localized adenocarcinoma of the thoracic esophagus or EGJ. Perioperative chemotherapy is an alternative option. (Category 2A)<br><br>**Preoperative Chemoradiation**<br>Infusional fluorouracil can be replaced with capecitabine<br>• Preferred Regimens:<br>Paclitaxel and carboplatin (Category 1)<br>Cisplatin and fluorouracil (Category 1)<br>Oxaliplatin and fluorouracil (Category 1)<br>• Other Regimens:<br>Irinotecan and cisplatin (Category 2B)<br>Paclitaxel and fluoropyrimidine (Fluorouracil or capecitabine) (Category 2B)<br><br>**Postoperative Chemoradiation**<br>• Fluoropyrimidine (infusional fluorouracil or capecitabine) before and after fluoropyrimidine-based chemoradiation (Category 2A)<br><br>**Perioperative Chemotherapy** (Only for adenocarcinoma of the thoracic esophagus or EGJ; 3 cycles preoperative and 3 cycles postoperative):<br>• ECF (epirubicin, cisplatin, and fluorouracil) (Category 1)<br>• ECF modifications (Category 2A)<br>Epirubicin, oxaliplatin, and fluorouracil<br>Epirubicin, cisplatin, and capecitabine<br>Epirubicin, oxaliplatin, and capecitabine<br>• Fluorouracil and cisplatin (Category 1) | Ajani et al, 2015 (1) |
| The Society of Thoracic Surgeons Workforces on Evidence Based Surgery and General Thoracic Surgery | • Radiotherapy as monotherapy before resection is not recommended. (Level of Evidence A)<br><br>• Neoadjuvant platinum-based doublet chemotherapy alone is beneficial before resection for patients with locally advanced esophageal adenocarcinoma. (Level of Evidence A)<br><br>• Neoadjuvant chemoradiotherapy should be used for locally advanced squamous cell cancer and either neoadjuvant chemotherapy or chemoradiotherapy for locally advanced adenocarcinoma; multimodality therapy has advantages over operation alone. (Level of Evidence A)<br><br>• Patients with adenocarcinoma who have not received neoadjuvant therapy should be considered for adjuvant chemoradiotherapy if the pathologic specimen reveals regional | Little et al, 2014 (2) |

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| | lymph node disease. (Level of Evidence B) | |
| European Society for Medical Oncology (ESMO) Guidelines Working Group | • Preoperative or postoperative radiation alone is not recommended for curative intent in localized tumors. (Level of evidence: I; grade of recommendation: A)<br><br>• Patients with adenocarcinoma of the lower oesophagus/oesophago-gastric junction should be managed with pre- and post-operative chemotherapy (or chemoradiation). (Level of evidence: I; grade of recommendation: B)<br><br>• Adjuvant chemotherapy in oesophageal squamous cell carcinoma is not recommended.<br><br>• For localized disease with suspected lymph node involvement, preoperative therapy is recommended in patients with adenocarcinoma.<br><br>• Chemoradiotherapy with planned surgery may be considered as a definitive treatment of selected patients with locally advanced disease. (Level of evidence: I; grade of recommendation: B)<br><br>• Perioperative chemotherapy with cisplatin and 5-FU should be considered standard in locally advanced adenocarcinoma of the oesophago-gastric junction. (Level of evidence: I; grade of recommendation: A)<br><br>• Preoperative chemoradiotherapy is preferred in oesophageal adenocarcinoma for selected patients. | Stahl et al, 2013 (3) |

**Meta-Analyses/Systematic Reviews**

| Interventions | Study | Population (N) | Outcomes | Brief results | References |
|---|---|---|---|---|---|
| Preoperative chemotherapy + surgery (CF, CEt)<br><br>vs.<br><br>Surgery with or without postoperative chemotherapy | 6 RCTs (included trials that administered postoperative chemotherapy) | 1202 patients with resectable thoracic esophageal squamous cell carcinoma | ● OS | ● There was no significant benefit on 5-year survival for preoperative chemotherapy + surgery. HR=0.81 (95% CI: 0.65-1.00; p=0.053). | Zheng et al, 2015 (4) |
| Postoperative chemotherapy + surgery (CF, CV)<br><br>vs.<br><br>Surgery alone | 3 RCTs | 509 patients with resectable thoracic esophageal squamous cell carcinoma | ● OS | ● There was no significant benefit on 3-year survival for postoperative chemotherapy + surgery. RR=0.95 (95% CI: 0.78-1.15; p=0.59). | Zhang et al, 2014 (5) |
| Preoperative chemoradiotherapy + surgery (CB, CF, C, CFV, CP, CFM, CbP, CN)<br><br>vs.<br><br>Surgery alone | 21 RCTs | 2755 patients with resectable esophageal carcinoma | ● OS<br><br>● AE | ● The 1-year (RR=1.08, 95% CI: 1.03-1.12; p=0.001), 2-year (RR=1.38, 95% CI: 1.26-1.50; p<0.00001) and 5-year (RR=1.41, 95% CI: 1.25-1.60; p<0.00001) survival rates were significantly higher for preoperative chemoradiotherapy + surgery.<br><br>● Pooled data from 17-18 trials showed no significant difference between the two groups in terms of postoperative complications (RR=1.13, 95% CI: 0.98-1.30, p=0.66) and mortality (RR=1.10, 95% CI: 0.73-1.65; p=0.66). | Wang et al, 2013 (6) |
| **Comparison 1:** Preoperative chemotherapy + surgery (CVB, CF, CFFa, CEt, CB, CFM)<br><br>vs.<br><br>Surgery alone | 9 RCTs (included trials that administered postoperative chemotherapy) | 2452 patients with resectable oesophageal and gastro-oesophageal junctional cancers | ● AE | ● Pooled data from 4-8 trials showed no significant difference between the two groups in terms of any postoperative complication (RR=1.01, 95% CI: 0.91-1.12; p=0.88), cardiac complication (RR=1.10, 95% CI: 0.73-1.66; p=0.927), respiratory | Kumagai et al, 2014 (7) |

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| | | | | complication (RR=1.27, 95% CI: 0.90-1.81; p=0.248), anastomotic leak (RR=0.96, 95% CI: 0.65-1.43; p=0.795), 30-day mortality (RR=0.97, 95% CI: 0.66-1.42; p=0.51), total postoperative mortality (RR=0.99, 95% CI: 0.72-1.38; p=0.986), and treatment-related mortality (RR=1.20, 95% CI: 0.71-2.03; p=0.904). | |
| **Comparison 2:** Preoperative chemoradiotherapy + surgery (CP, CB, CFM, CF, C, CFV, PCb)<br><br>vs.<br><br>Surgery alone | 14 RCTs | 2459 patients with resectable oesophageal and gastro-oesophageal junctional cancers | ● AE | ● Pooled data from 4-12 trials showed no significant difference between the two groups in terms of any postoperative complication (RR=1.07, 95% CI: 0.84-1.36; p=0.767), cardiac complication (RR=1.23, 95% CI: 0.90-1.69; p=0.888), respiratory complication (RR=1.01, 95% CI: 0.85-1.19; p=0.573), anastomotic leak (RR=1.00, 95% CI: 0.74-1.35; p=0.878), 30-day mortality (RR=1.11, 95% CI: 0.51-2.40; p=0.902), total postoperative mortality (RR=1.37, 95% CI: 0.88-2.13; p=0.746), and treatment-related mortality (RR=1.41, 95% CI: 0.91-2.19; p=0.707). | |
| **Comparison 3:** Preoperative chemoradiotherapy + surgery (CB, CFM, CFFaEt, CF)<br><br>vs.<br><br>Preoperative chemotherapy + surgery (CB, CFM, CFFa, CF) | 4 RCTs | 891 patients with resectable oesophageal and gastro-oesophageal junctional cancers | ● AE | ● Pooled data from 1-4 trials showed no significant difference between the two groups in terms of any postoperative complication (RR=1.00, 95% CI: 0.56-1.78; p=0.992), cardiac complication (RR=1.17, 95% CI: 0.44-3.10; p=0.757), respiratory complication (RR=1.71, 95% CI: 0.71-4.13; p=0.252), anastomotic leak (RR=1.07, 95% CI: 0.32-3.53; p=0.360), 30-day mortality (RR=1.16, 95% CI: 0.44-3.07; p=0.761), total postoperative mortality (RR=1.45, 95% CI: 0.63-3.34; p=0.386), and treatment-related mortality (RR=1.48, 95% CI: 0.44-4.96; p=0.530). | |
| **Comparison 1:** Preoperative radiotherapy with or without chemotherapy + surgery (CF)<br><br>vs.<br><br>Surgery alone | 2 RCTs | 409 patients with resectable gastro-oesophageal junction cancer | ● OS | ● There was no significant benefit on OS for preoperative radiotherapy with or without chemotherapy + surgery. HR=0.57 (95% CI: 0.28-1.16; p=0.084). | Kumagai et al, 2015 (8) |
| **Comparison 2:** Preoperative chemotherapy + surgery (FPlc, ECF, CF) | 4 RCTs (included trials that administered postoperative chemotherapy) | 782 patients with resectable gastro-oesophageal junction cancer | ● OS | ● There was no significant benefit on OS for preoperative chemotherapy + surgery. HR=0.69 (95% CI: 0.52-0.93; p=0.194). | |

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| vs.<br><br>Surgery alone | | | | | |
| **Comparison 3:** Preoperative chemoradiotherapy + surgery (CFFaEt, CT)<br><br>vs.<br><br>Preoperative chemotherapy + surgery (CFFa, CT) | 2 RCTs | 133 patients with resectable gastro-oesophageal junction cancer | ● OS<br><br>● PFS | ● There was no significant benefit on OS for preoperative chemoradiotherapy + surgery. HR=0.71 (95% CI: 0.45-1.12; p=0.146).<br><br>● There was no significant benefit on PFS for preoperative chemoradiotherapy + surgery. HR=0.70 (95% CI: 0.45-1.07; p=0.101). | |
| Preoperative chemoradiotherapy + surgery (CFV, CF, CFM, CP, C, PCb)<br><br>vs.<br><br>Surgery alone | 11 RCTs | 1692 patients with resectable esophageal cancer. | ● AE | ● Pooled data from 7-10 trials showed a significant decrease in postoperative mortality for preoperative chemoradiotherapy + surgery (RR=0.64, 95% CI: 0.49-0.84; p=0.001) but no significant difference in postoperative complications between the two groups (RR=1.09, 95% CI: 0.96-1.24; p=0.18). | Deng et al, 2014 (9) |
| Preoperative chemoradiotherapy + surgery (CB, C, CF, CFM)<br><br>vs.<br><br>Surgery alone | 12 RCTs | 1529 patients with operable esophageal carcinoma | ● OS<br><br>● AE | ● Pooled data from 8-12 trials showed a significant improvement for preoperative chemoradiotherapy + surgery in 1-year (RR=0.86, 95% CI: 0.74-0.98; p=0.03), 3-year (RR=0.82, 95% CI: 0.73-0.92; p=0.0007), and 5-year (RR=0.83, 95% CI: 0.72-0.96; p=0.01) survival.<br><br>● Pooled data from 11-12 trials showed no significant difference between the two groups in terms of postoperative morbidity (RR=0.97, 95% CI: 0.86-1.09; p=0.56) and mortality (RR=1.56, 95% CI: 0.97-2.50; p=0.07). | Wang et al, 2012 (10) |
| Preoperative chemotherapy + surgery (CF, CFL, CEt, CVB, CB, CEtLF, C)<br><br>vs.<br><br>Surgery alone | 12 RCTs (included trials that administered postoperative chemotherapy) | 2229 Patients with localized potentially resectable thoracic esophageal carcinoma | ● OS<br><br>● AE | ● Pooled data from 10 trials showed a significant benefit on OS for preoperative chemotherapy + surgery. HR=0.88 (95% CI: 0.80-0.96; p=0.0026).<br><br>● Pooled data from 2-10 trials showed no significant difference between the two groups in terms of anastomotic leaks (RR=0.92, 95% CI: 0.62-1.37; p=0.69), pulmonary complications (RR=1.10, 95% CI: 0.76-1.61; p=0.61), cardiac complications (RR=1.03, 95% CI: 0.69-1.55; p=0.89), infectious complications (RR=0.65, 95% CI: 0.41-1.02; p=0.062), gastrointestinal complications (RR=7.77, 95% CI: 0.02-3360.76; p=0.51), any complications (RR=0.93, 95% CI: 0.81-1.08; p=0.36), and postoperative deaths (RR=0.93, 95% CI: 0.68-1.28; p=0.67). | Kidane et al, 2015 (11) |
| Preoperative | 7 RCTs | 1085 patients | ● OS | ● Patients receiving preoperative | Fu et al, |

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| chemoradiotherapy + surgery (CF, PCb, CEt)<br><br>vs.<br><br>Preoperative chemotherapy + surgery or surgery alone (FL, CF) | | with resectable esophago-gastric adenocarcinoma | <br><br><br><br>● AE | chemoradiotherapy + surgery had a significantly longer OS. HR=0.74 (95% CI: 0.63-0.88; p=0.0005).<br><br>● Pooled data from 5 trials showed no significant difference in perioperative mortality between the two groups. OR=1.10 (95% CI: 0.62-1.93; p=0.75). | 2015 (12) |
| Preoperative chemotherapy + surgery<br><br>vs.<br><br>Surgery alone | 16 RCTs (included trials that administered postoperative chemotherapy) | 2594 patients with resectable esophageal carcinoma | ● OS<br><br><br><br><br><br><br><br><br>● AE | ● Pooled data from 9-11 trials showed no significant difference in 1-year survival between the two groups (RR=1.02, 95% CI: 0.95-1.10; p=0.54), but a significantly higher 3-year survival (RR=1.29, 95% CI: 1.13-1.47; p=0.0001) and 5-year survival (RR=1.31, 95% CI: 1.13-1.51; p=0.0003) in favor of preoperative chemotherapy + surgery.<br><br>● Pooled data from 12 trials showed no significant difference in operative mortality between the two groups. RR=0.89 (95% CI: 0.64-1.23; p=0.48). | Xu et al, 2012 (13) |

**Randomized Control Trials**

| Interventions | Population | N | Median follow up | Outcomes | Brief results | References |
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| **CROSS trial:**<br>Preoperative chemoradiotherapy + surgery (PCb; n=178)<br><br>vs.<br><br>Surgery alone (n=188) | Patients (WHO PS of 0 or 1) who were aged 75 years or younger with locally advanced, histologically proven, and potentially curable squamous cell carcinoma or adenocarcinoma of the oesophagus or oesophagogastric junction. Median age=60 years | 366 | 84.1 months | ● OS<br><br><br><br><br><br><br><br><br><br><br><br>● PFS | ● The median OS was significantly longer with preoperative chemoradiotherapy + surgery (48.6 months) than with surgery alone (24.0 months). HR=0.68 (95% CI: 0.53-0.88; p=0.003). Preoperative chemoradiotherapy + surgery significantly increased OS from 70% to 81% (HR=0.57, 95% CI: 0.37-0.88) at 1 year, 50% to 67% (HR=0.59, 95% CI: 0.43-0.82) at 2 years, 44% to 58% (HR=0.65, 95% CI: 0.49-0.88) at 3 years, and 33% to 47% (HR=0.67, 95% CI: 0.51-0.87) at 5 years.<br><br>● The median PFS was significantly prolonged in patients treated with preoperative chemoradiotherapy + surgery (37.7 months) than those treated with surgery only (16.2 months). HR=0.64 (95% CI: 0.49-0.82; p=0.000217). Preoperative chemoradiotherapy + surgery significantly increased PFS from 54% to 71% (HR=0.55, 95% CI: 0.39-0.77) at 1 year, 41% to 60% (HR=0.57, 95% CI: 0.42-0.77) at 2 years, 35% to 51% (HR=0.62, 95% | Shapiro et al, 2015 (14) |

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| | | | | | CI: 0.47-0.82) at 3 years, and 27% to 44% (HR=0.61, 95% CI: 0.47-0.78) at 5 years. | |
| | | | | ● AE | ● In the preoperative chemoradiotherapy + surgery group, the most common grade 3 or worse toxicities were leucopenia (6%), anorexia (5%), and fatigue (3%). There were 9 deaths from treatment-related causes in the preoperative chemoradiotherapy + surgery group and 7 in the surgery alone group. | |
| **NeoRes trial:** Preoperative chemoradiotherapy + surgery (C/O/Cb with F; n=90)<br><br>vs.<br><br>Preoperative chemotherapy + surgery (C/O/Cb with F; n=91) | Patients (WHO PS of 0 or 1) with histologically confirmed, non-distant-metastatic squamous cell carcinoma or adenocarcinoma of the oesophagus or gastro-oesophageal junction. Median age=63 years | 181 | NR | ● OS<br><br>● PFS<br><br>● CRR<br><br>● AE | ● There was no significant difference in 3-year OS between the two groups (47% vs. 49%; p=0.77)<br><br>● There was no significant difference in 3-year PFS between the two groups (44% vs. 44%; p=0.95)<br><br>● Histological CRR was significantly higher in patients after preoperative chemoradiotherapy + surgery (28% vs. 9%; p=0.002).<br><br>● There was no postoperative 30-day mortality in either group. There was no significant difference between the two groups in terms of 90-day mortality (6% vs. 3%; p=0.24), surgical complications (38% vs. 35%; p=0.69), nonsurgical complications (31% vs. 21%; p=0.13), any complications (55% vs. 45%; p=0.23), anastomotic leakage (13% vs. 9%; p=0.45), respiratory complications (22% vs. 13%; p=0.14), and cardiovascular complications (9% vs. 5%; p=0.37). Lymph node metastases were observed in significantly less patients who received preoperative chemoradiotherapy + surgery (35% vs. 62%; p=0.001) | Klevebro et al, 2015 (36); Klevebro et al., 2015 (15); Lindblad et al, 2014 (abstract) (16) |
| Perioperative chemoradiotherapy + surgery (2 cycles of OX before surgery and 6 cycles after; n=36)<br><br>vs.<br><br>Surgery alone (n=40) | Patients (ECOG PS of 0-2 and Karnofsky PS of >60) with Siewert II or III adenocarcinoma of the gastroesophageal junction and a pre-surgery tumor long diameter of ≤8cm. Median age=61 vs. 57 years | 76 | NR | ● AE | ● In the perioperative chemoradiotherapy + surgery group, incidences of grade 3 hematologic toxic effects were leukopenia (5.6%) and thrombocytopenia (11.1%). Furthermore, one patient developed a lymphatic fistula and one developed moderate pleural effusion and ascites. In the surgery alone group, one patient developed an esophageal jejunal anastomotic fistula and one had a wound dehisce. | Zhao et al, 2015 (17) |

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| Perioperative chemotherapy + surgery (2 cycles of PCF before surgery and 2 cycles after; n=175)<br><br>vs.<br><br>Preoperative chemotherapy + surgery (PCF; n=171) | Patients 18 years and older (WHO PS of 0 or 1) with resectable squamous cell carcinoma confined to primary and regional nodes (celiac nodal involvement was permitted for primary tumor localized in the distal esophagus or gastroesophageal junction). Median age=59 years | 346 | 60 months vs. 61 months | ● OS<br><br>● RFS<br><br>● AE | ● The median OS was 29 months for perioperative chemotherapy + surgery and 22 months for preoperative chemotherapy + surgery. HR=0.79 (95% CI: 0.59-0.95; p<0.001). The 5-year survival rates were 38% and 22%, respectively.<br><br>● The median RFS was 23 months for perioperative chemotherapy + surgery and 15 months for preoperative chemotherapy + surgery. HR=0.62 (95% CI: 0.49-0.73; p<0.001). The 5-year RFS rates were 35% and 19.1%, respectively.<br><br>● The most common grade 3/4 toxicities during preoperative chemotherapy were granulocytopenia (13.2%), lymphocytopenia (20.1%), and leukopenia (11.7%). There was no significant increase in the incidence of grade 3/4 toxicities associated with the addition of postoperative chemotherapy. | Zhao et al, 2015 (18); Zhao and Sui, 2014 (abstract) (19) |
| **FFCD 9901 trial:** Preoperative chemoradiotherapy + surgery (CF; n=98)<br><br>vs.<br><br>Surgery alone (n=97) | Patients age <75 years (WHO PS of 0 or 1) with untreated stage I or II thoracic esophageal adenocarcinoma or squamous cell carcinoma. Median age=58.1 vs. 57.6 years | 195 | 93.6 months | ● OS<br><br>● DFS<br><br>● AE | ● There was no significant difference in OS between the two groups. HR=0.99 (95% CI: 0.69-1.40; p=0.94). The median, 3-year, and 5-year OS for preoperative chemoradiotherapy + surgery were 31.8 months, 47.5%, and 41.1%, respectively. The median, 3-year, and 5-year OS for surgery alone were 41.2 months, 53.0%, and 33.8%, respectively.<br><br>● There was no significant difference in DFS between the two groups. HR=0.92 (95% CI: 0.66-1.30; p=0.648). The median and 5-year DFS for preoperative chemoradiotherapy + surgery were 27.8 months and 35.6%, respectively. The median and 5-year DFS for surgery alone were 26.7 months and 27.7% respectively.<br><br>● The most common grade 3/4 toxicities during preoperative chemotherapy were leucopenia (7.2%), neutropenia (6.1%), mucositis (5.1%), nausea/vomiting (4.0%), and other (9.2%). There were no treatment-related deaths before surgery. There was no | Mariette et al, 2014 (20) |

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| | | | | | significant difference between the two groups in terms of 30-day postoperative mortality (7.4% vs. 1.1%; p=0.055) and in-hospital postoperative morbidity (55.6% vs. 52.8%; p=0.720), but in-hospital postoperative mortality was significantly higher in the preoperative chemoradiotherapy + surgery group (11.1% vs. 3.4%; p=0.049). | |
| Preoperative chemoradiotherapy + surgery (CF; n=50)<br><br>vs.<br><br>Surgery alone (n=50) | Patients with lower-third esophageal cancer. Mean age=55 years | 100 | NR | ● AE | ● There was no significant difference between the two groups in terms of anatomotic leakage (0% vs. 2%; p>0.05), pulmonary complications (8% vs. 8%; p>0.99), cardiovascular complications (10% vs. 12%; p>0.99), deep vein thrombosis and related complications (4% vs. 6%; p>0.99), chylothorax (4% vs. 2%; p>0.99), and 30-day postoperative mortality (8% vs. 6%; p>0.99). | Rajabi Mashhadi et al, 2015 (34) |
| Preoperative chemoradiotherapy + surgery + postoperative chemotherapy (IC; n=47)<br><br>vs.<br><br>Preoperative chemoradiotherapy + surgery + postoperative chemotherapy (PC; n=46) | Patients (ECOG PS of 0-1) with T2N0M0, T3N0M0, T1-3N1M0, or T1-3N0-1M1A adenocarcinoma of the esophagus. Median age=56.9 vs. 59.9 years | 93 | 78 months | ● OS<br><br>● PFS<br><br>● AE | ● The median OS, 5-year, 6-year, and 7-year survival rates were 35 months, 46%, 39%, and 35%, respectively for IC. The median OS, 5-year, 6-year, and 7-year survival rates were 21 months, 27%, 27%, and 23%, respectively for PC.<br><br>● The median, 2-year, and 5-year PFS were 39.7 months, 53%, and 42%, respectively for IC. The median, 2-year, and 5-year PFS were 12.4 months, 31%, and 16%, respectively for PC.<br><br>● The most common grade 3/4 toxicities during preoperative chemoradiotherapy were leucocytes (IC=36.2% vs. PC=34.8%), neutrophils (IC=31.9% vs. PC=28.3%), anorexia (IC=19.1% vs. PC=4.3%), dysphagia (IC=12.8% vs. PC=17.4%), and nausea (IC=23.4% vs. PC=13.0%). During postoperative chemotherapy, 68.8% of patients in the IC group and 63.0% of patients in the PC group experienced 3/4 toxicities. | Kleinberg et al, 2016 (35) |

**Abstracts**

| Interventions | Population | N | Outcomes | Brief results | References |
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| **OEO5 trial:** Preoperative chemotherapy (ECX) + surgery (n=446) | Patients with lower oesophageal and junctional (Types I and II) adenocarcinoma. Median age=62 years | 897 | ● OS | ● There was no significant difference in OS between the two groups. HR=0.92 (95% CI: 0.79-1.08; p=0.3017). The 3-year | Alderson et al, 2015 (21); Cunningham et al, 2014 (22); |

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| vs.<br><br>Preoperative chemotherapy (CF) + surgery (n=451) | | | | survival rates were 42% and 39% for ECX and CF, respectively.<br><br>● The PFS favored ECX. HR=0.86 (95% CI: 0.74-1.01).<br><br>● The DFS favored ECX. HR=0.88 (95% CI: 0.75-1.03).<br><br>● The incidence of grade 3/4 toxicity was significantly lower with CF (30% vs. 47%; p<0.001). Postoperative complications (ECX=62% vs. CF=57%), deaths at 30 (ECX=2% vs. CF=2%) and 90 days post surgery (ECX=5% vs. CF=4%) were similar between the two groups.<br><br>● There were no clinically important differences in the global QoL and oesophageal cancer specific domains from the EORTC QLQ-C30 and QLQ-OES18 questionnaires 3-month post-operatively. | Cunningham et al, 2015 (33) |
| Preoperative chemotherapy + surgery (CF; n=164)<br><br>vs.<br><br>Postoperative chemotherapy + surgery (CF; n=166) | Patients with clinical stage II or III, excluding T4 esophageal squamous cell carcinoma. | 330 | ● OS | ● The 5-year OS in the preoperative chemotherapy + surgery (55%) was significantly superior to that of the postoperative chemotherapy + surgery group (42.7%). HR=0.73 (95% CI: 0.54-0.99; p=0.04). | Ando et al, 2012 (23) |
| Preoperative chemoradiotherapy + surgery<br><br>vs.<br><br>Preoperative chemotherapy + surgery<br><br>vs.<br><br>Preoperative radiotherapy + surgery | 33 RCTs involving patients with locally advanced, resectable esophageal cancer. | 6710 | ● OS<br><br>● AE | ● The OS for preoperative chemoradiotherapy + surgery was found to be significantly superior to that of preoperative chemotherapy + surgery (HR=0.84, 95% CI: 0.71-0.97) and preoperative radiotherapy + surgery (HR=0.80, 95% CI: 0.67-0.97).<br><br>● There were no significant differences in the risk for postoperative mortality. | Chan et al, 2014 (24) |
| Preoperative chemoradiotherapy + surgery (CF; n=39)<br><br>vs.<br><br>Preoperative chemotherapy + surgery (CF; n=36) | Patients with esophageal or gastro-esophageal junctional adenocarcinoma. Median age=61 years | 75 | ● OS<br><br>● QoL | ● There was no significant difference in median OS between preoperative chemoradiotherapy + surgery (32 months) and preoperative chemotherapy + surgery (29 months; p=0.83).<br><br>● Self-reported HRQL assessments (including role, emotional, cognitive and social function, and symptoms of pain fatigue, nausea, dysphagia and eating problems) for two years postoperatively were not significantly different between the two groups. | Cormack et al, 2014 (25) |
| Preoperative chemoradiotherapy w/ induction chemotherapy + surgery (O+S-1) | Patients with stage II, III, or IVA esophageal cancer. | 97 | ● OS<br><br>● PFS | ● There was no significant difference in 2-year OS between the two groups (w/ induction=70.1% vs. w/o induction=62.6%; p=0.515).<br><br>● There was no significant | Yoon et al, 2012 (26); Yoon et al, 2012 (27) |

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| vs.<br><br>Preoperative chemoradiotherapy w/o induction chemotherapy + surgery (O+S-1) | | | ● AE | difference in 2-year PFS between the two groups (w/ induction=63.8% vs. w/o induction=55.2%; p=0.626).<br><br>● Grade 3/4 thrombocytopenia was significantly more common w/ induction chemotherapy (37.5% vs. 4.1%; p<0.001). Three patients failed to survive for 90 days after surgery in the induction chemotherapy group and none in the other group. | |
| Preoperative chemoradiotherapy + surgery (CF; n=15)<br><br>vs.<br><br>Surgery alone (n=13) | Patients with adenocarcinoma of the oesophagus. | 28 | ● OS<br><br>● AE | ● There was no significant difference in the mean survival between the preoperative chemoradiotherapy + surgery group (15.2 months) and the surgery alone group (13.1 months; p=0.708). The 1-year survival was 50% and 27.3%, respectively.<br><br>● The most common operative complication was anastomotic leak (36% in each group). The operative morbidity rate was comparable with only one death in the preoperative chemoradiotherapy + surgery group. There was no significant difference in the perioperative outcomes. | Dash et al, 2014 (28) |
| **E1201 trial:** Perioperative chemoradiotherapy + surgery (concurrent IC before surgery and 3 cycles after; n=39)<br><br>vs.<br><br>Perioperative chemoradiotherapy + surgery (concurrent PC before surgery and 3 cycles after; n=42) | Patients with operable stage II-IVa esophageal adenocarcinoma. | 81 | ● OS<br><br>● AE | ● The median survival was 35 months for IC and 21 months for PC. The respective 5-, 6-, and 7-year survival were 46%, 39%, and 35% for IC and 27%, 27%, and 23% for PC. Survival differences for the treatments were not significant.<br><br>● The rate of grade 3 or higher toxic effects was similar between the two groups (IC=68% vs. PC=65%). | Kleinberg et al, 2012 (29) |
| Preoperative chemoradiotherapy + surgery<br><br>vs.<br><br>Surgery alone | 15 RCTs involving patients with resectable esophageal cancer. | 1957 | ● OS<br><br>● AE | ● There was a significant benefit in 5-year survival in favor of preoperative chemoradiotherapy + surgery. RR=1.47 (95% CI: 1.24-1.76).<br><br>● There was an overall significant increase in grade 3/4 AE in the preoperative chemoradiotherapy + surgery. RR=1.73 (95% CI: 1.15-2.60). | Njei et al, 2012 (30) |
| Preoperative radiotherapy + surgery<br><br>vs.<br><br>Surgery alone | Patients with resectable squamous cell carcinoma in lower third of oesophagus having good performance status. | NR | ● OS<br><br>● AE | ● The mean survival was 18 months in the preoperative radiotherapy + surgery group and 16 months in the surgery alone group.<br><br>● Postoperative morbidity rates were comparable between the two groups. | Ramachandran and Moosabba, 2012 (31) |
| Preoperative chemoradiotherapy + surgery (PCb; n=23) | Patients with resectable locally advanced esophageal squamous cell carcinoma. | 42 | ● DFS | ● The DFS at 18 months was 78.7% in the preoperative chemoradiotherapy + surgery group and 63.6% in the postoperative chemoradiotherapy + Surgery | Chen et al, 2014 (32) |

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| vs.<br><br>Postoperative chemoradiotherapy + Surgery (PCb; n=19) | | | ● AE | group.<br><br>● Among all the patients, the most common major hematologic toxic effects were anemia (16.6%), thrombocytopenia (14.3%), neutropenia (11.9%), and leukopenia (9.5%). The most common major non-hematologic toxic effects were cervical anastomotic fistula (19.1%), anorexia (14.3%), and fatigue (11.9%). Postoperative complications and treatment-related mortality were similar in the two groups. | |

**Ongoing Randomized Control Trials**
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| Interventions | Official title | Status | Protocol ID | Estimated primary completion date | Last updated |
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| Postoperative radiotherapy + surgery<br><br>vs.<br><br>Surgery alone | Phase III Study of Prophylactic Postoperative Intensity Modulated Radiation Therapy in Stage T2-3N0M0 Disease of Thoracic Esophageal Squamous Cell Carcinoma. | Recruiting | NCT01745107 | November 2017 | December 9, 2015 |
| Preoperative chemoradiotherapy + surgery (PCb)<br><br>vs.<br><br>Preoperative chemoradiotherapy + surgery (FOFa) | Preoperative Chemoradiation With Paclitaxel-carboplatin or With Fluorouracil-oxaliplatine-acide Folinique (FOLFOX) for Resectable Esophageal and Junctional Cancer - A Randomized Phase II Trial. | Recruiting | NCT02359968 | April 2018 | February 9, 2015 |
| Postoperative chemoradiotherapy + surgery (PC)<br><br>vs.<br><br>Postoperative radiotherapy + surgery<br><br>vs.<br><br>Surgery alone | A Phase II/III Study of Adjuvant Chemoradiotherapy, Radiotherapy After Surgery Versus Surgery Alone in Patients With Stage IIB-III Esophageal Carcinoma. | Recruiting | NCT02279134 | September 2016 | October 11, 2015 |
| Preoperative chemoradiotherapy + surgery + postoperative chemotherapy (O+S-1)<br><br>vs.<br><br>Postoperative chemotherapy (O+S-1) | Phase II/III Study of Preoperative Concurrent Chemoradiotherapy for Locally Advanced Gastroesophageal Junction or Upper Gastric Adenocarcinoma. | Recruiting | NCT02193594 | September 2017 | June 4, 2015 |
| Preoperative chemoradiotherapy + surgery (OX and PCb)<br><br>vs.<br><br>Preoperative chemoradiotherapy + surgery (OX) | A Randomized Phase II Study of Two Pre-operative Chemoradiotherapy Regimens (Oxaliplatin and Capecitabine Followed by Radiotherapy With Either Oxaliplatin and Capecitabine or Paclitaxel and Carboplatin) for Resectable Oesophageal Cancer. | Unknown | NCT01843829 | May 2015 | March 21, 2014 |
| Preoperative and postoperative | Randomized Clinical Trial of Neoadjuvant and Adjuvant | Recruiting | NCT01726452 | January 2024 | February 26, 2016 |

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| chemotherapy + surgery (ECF)<br><br>vs.<br><br>Preoperative chemoradiotherapy + surgery (PCb) | Chemotherapy (MAGIC Regimen) vs. Neoadjuvant Chemoradiation (CROSS Protocol) in Adenocarcinoma of the Oesophagus and Oesophago-gastric Junction. | | | | |
| Perioperative chemotherapy + surgery (FLOD)<br><br>vs.<br><br>Preoperative chemoradiotherapy + surgery (PCb) | Perioperative Chemotherapy (FLOT Protocol) Compared To Neoadjuvant Chemoradiation (CROSS Protocol) in Patients With Adenocarcinoma of the Esophagus. | Recruiting | NCT02509286 | January 2022 | April 8, 2016 |
| Postoperative chemoradiotherapy + surgery (PC)<br><br>vs.<br><br>Postoperative radiotherapy + surgery | Adjuvant Chemotherapy With Paclitaxel and Cisplatin in Lymph Node-Positive Thoracic Esophageal Squamous Cell Carcinoma: A Randomized Phase 3 Trial. | Recruiting | NCT02461043 | December 2020 | August 29, 2015 |

**abbreviations:** C=cisplatin; Et=etoposide; F=5-fluorouracil, V=vindesine; P=paclitaxel; L=leucovorin; O=oxaliplatin; D=docetaxel; Fa=d-L-folinic acid; E=epirubicin; T=tegafur; U=uracil; Plc=polyphaser liposome composita pro orale; M=mitomycin C; RR=risk ratio; OS=overall survival; PFS=progression-free survival; AE=adverse effects; RCT=randomized controlled trials; CI=confidence interval; B=bleomycin; Cb=carboplatin; N=navelbine; X=capecitabine; RFS=relapse-free survival; QoL=quality of life; w/=with; w/o=without; I=irinotecan; PS=performance status; NR=not reported; DFS=disease-free survival; WHO=world health organization; CRR=complete response rate; HR=hazard ratio; OR=odds ratio; vs.=versus; ECOG=Eastern Cooperative Oncology Group; HRQL=health related quality of life

Clinical Expert Interest Declaration:
None

**Instructions.** For each document, please respond YES or NO to all the questions below. Provide an explanation of each answer as necessary.

| | |
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| 1. Does any of the newly identified evidence, on initial review, contradict the current recommendations, such that the current recommendations may cause harm or lead to unnecessary or improper treatment if followed? | No |
| 2. On initial review,<br>a. Does the newly identified evidence support the existing recommendations?<br>b. Do the current recommendations cover all relevant subjects addressed by the evidence, such that no new recommendations are necessary? | a. Yes<br><br>b. Yes |
| 3. Is there a good reason (e.g., new stronger | No |

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| evidence will be published soon, changes to current recommendations are trivial or address very limited situations) to postpone updating the guideline? Answer Yes or No, and explain if necessary: | |
| 4. Do the PEBC and the DSG/GDG responsible for this document have the resources available to write a full update of this document within the next year? | No |

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| **Review Outcome** | ENDORSE |
| **DSG/GDG Approval Date** | June 1, 2016 |
| **DSG/GDG Commentary** | None |



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Literature Search Strategy:

*Medline*

1. meta-Analysis as topic.mp.
2. meta analysis.pt.
3. (meta analy$ or metaanaly$).tw.
4. (systematic review$ or pooled analy$ or statistical pooling or mathematical pooling or statistical summar$ or mathematical summar$ or Quantitative synthes?s or quantitative overview?).tw.
5. (systematic adj (review$ or overview?)).tw.
6. (exp Review Literature as topic/ or review.pt. or exp review/) and systematic.tw.
7. or/1-6
8. (cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or cinhal or science citation index or scisearch or bids or sigle or cancerlit).ab.
9. (reference list$ or bibliograph$ or hand-search$ or relevant journals or manual search$).ab.
10. (selection criteria or data extraction or quality assessment or jadad scale or methodological quality).ab.
11. (study adj selection).ab.
12. 10 or 11
13. review.pt.
14. 12 and 13
15. exp randomized controlled trials as topic/ or exp clinical trials, phase III as topic/ or exp clinical trials, phase IV as topic/
16. (randomized controlled trial or clinical trial, phase III or clinical trial, phase IV).pt.
17. random allocation/ or double blind method/ or single blind method/
18. (randomi$ control$ trial? or rct or phase III or phase IV or phase 3 or phase 4).tw.
19. or/15-18
20. (phase II or phase 2).tw. or exp clinical trial/ or exp clinical trial as topic/
21. (clinical trial or clinical trial, phase II or controlled clinical trial).pt.
22. (20 or 21) and random$.tw.
23. (clinic$ adj trial$1).tw.
24. ((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3 or dummy)).tw.
25. placebos/
26. (placebo? or random allocation or randomly allocated or allocated randomly).tw.
27. (allocated adj2 random).tw.
28. or/23-27
29. practice guidelines/
30. practice guideline?.tw.
31. practice guideline.pt.
32. or/29-31
33. exp esophagus cancer/
34. ((esophag$ or oesophag$) and (cancer$ or neoplas$ or adenocarcin$ or carcin$ or malig$ or tumo$)).tw.
35. ("resectable" or "oper$").tw.
36. (33 or 34) and 35
37. adjuvant chemotherapy/
38. adjuvant therapy/
39. (preoperative or neoadjuvant).tw.
40. (chemotherapy or radiotherapy or radiation or irradiation).tw.

41. exp immunotherapy/
42. (chemoradotherapy or chemoradiation).tw.
43. hyperthermia.mp.
44. or/37-43
45. 36 and 44
46. (7 or 8 or 9 or 14 or 19 or 22 or 28 or 32) and 45
47. (comment or letter or editorial or note or erratum or short survey or news or newspaper article or patient education handout or case report or historical article).pt.
48. 46 not 47
49. Animal/
50. Human/
51. 49 not 50
52. 48 not 51
53. (201211$ or 201212$ or 2013$ or 2014$ or 2015$ or 2016$).ed.
54. 52 and 53
55. limit 54 to english language

*Embase*
1. exp meta analysis/ or exp systematic review/
2. (meta analy$ or metaanaly$).tw.
3. (systematic review$ or pooled analy$ or statistical pooling or mathematical pooling or statistical summar$ or mathematical summar$ or Quantitative synthes?s or quantitative overview?).tw.
4. (systematic adj (review$1 or overview$1)).tw.
5. exp review/ or review.pt.
6. (systematic or selection criteria or data extraction or quality assessment or jadad scale or methodological quality).ab.
7. (study adj selection).ab.
8. 5 and (6 or 7)
9. or/1-4,8
10. (cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or cinhal or science citation index or scisearch or bids or sigle or cancerlit).ab.
11. (reference list$ or bibliograph$ or hand-search$ or relevant journals or manual search$).ab.
12. exp randomized controlled trial/ or exp phase 3 clinical trial/ or exp phase 4 clinical trial/
13. randomization/ or single blind procedure/ or double blind procedure/
14. (randomi$ control$ trial? or rct or phase III or phase IV or phase 3 or phase 4).tw.
15. or/12-14
16. (phase II or phase 2).tw. or exp clinical trial/ or exp prospective study/ or exp controlled clinical trial/
17. 16 and random$.tw.
18. (clinic$ adj trial$1).tw.
19. ((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3 or dummy)).tw.
20. placebo/
21. (placebo? or random allocation or randomly allocated or allocated randomly).tw.
22. (allocated adj2 random).tw.
23. or/18-22
24. practice guidelines/
25. practice guideline?.tw.
26. practice guideline.pt.
27. or/24-26
28. exp esophagus cancer/

29. ((esophag$ or oesophag$) and (cancer$ or neoplas$ or adenocarcin$ or carcin$ or malig$ or tumo$)).tw.
30. ("resectable" or "oper$").tw.
31. (28 or 29) and 30
32. adjuvant chemotherapy/
33. adjuvant therapy/
34. (preoperative or neoadjuvant).tw.
35. (chemotherapy or radiotherapy or radiation or irradiation).tw.
36. exp immunotherapy/
37. (chemoradotherapy or chemoradiation).tw.
38. hyperthermia.mp.
39. or/32-38
40. 31 and 39
41. (9 or 10 or 11 or 15 or 17 or 23 or 27) and 40
42. (editorial or note or letter or erratum or short survey).pt. or letter/ or case study/
43. 41 not 42
44. Animal/
45. Human/
46. 44 not 45
47. 43 not 46
48. (201211$ or 201212$ or 2013$ or 2014$ or 2015$ or 2016$).dd.
49. 47 and 48
50. limit 49 to English language

Searched http://www.cancer.gov/about-cancer/treatment/clinical-trials/search (NIC) by type/condition=esophageal.

Searched http://meeting.ascopubs.org/search (ASCO annal meetings) and http://www.evidence.nhs.uk/ (NICE) with keywords: “resectable” or “operable” and “esophageal” or “oesophageal” or “esophagus”.

Searched https://clinicaltrials.gov/ct2/search/advanced with keywords: “esophageal” and “preoperative” or “postoperative”. Filter was used to limit results to phase II-IV trials.

## OUTCOMES DEFINITION

1. **EDUCATION AND INFORMATION** – An archived document is a document that will no longer be tracked or updated but may still be useful for academic or other informational purposes. The document is moved to a separate section of our website, each page is watermarked with the word “ARCHIVED”.

2. **ENDORSED** – An endorsed document is a document that the DSG/GDG has reviewed for currency and relevance and determined to be still useful as guidance for clinical decision making. A document may be endorsed because the DSG/GDG feels the current recommendations and evidence are sufficient, or it may be endorsed after a literature search uncovers no evidence that would alter the recommendations in any important way.

3. **DELAY –** A delay means that there is reason to believe new, important evidence will be released within the next year that should be considered before taking further action.

4. **UPDATE** – An Update means that the DSG/GDG recognizes that there is new evidence that makes changes to the existing recommendations in the guideline necessary but these changes are more

involved and significant than can be accomplished through the Document Assessment and Review process. The DSG/GDG will rewrite the guideline at the earliest opportunity to reflect this new evidence. Until that time, the document will still be available as its existing recommendations are still of some use in clinical decision making.

## Appendix I: Version 3 of the Document Summary and Review Table

| | |
|---|---|
| **Number and title of document under review** | 2-11 Preoperative or Postoperative Therapy for Resectable Esophageal Cancer |
| **Current Report Date** | October 30, 2012 |
| **Clinical Expert** | Dr. Richard Malthaner |
| **Research Coordinator** | Robert Mackenzie |
| **Date Assessed** | Nov. 2012 |
| **Approval Date and Review Outcome (once completed)** | April 2nd 2013 "ENDORSE" |

Original Question(s):

1. Should patients with resectable esophageal cancer receive preoperative or postoperative therapy along with surgery?

Target Population:

These recommendations apply to adult patients with resectable, operable, and potentially curable thoracic (lower two thirds of esophagus) esophageal cancer for whom surgery is considered appropriate.

Study Selection Criteria:

***Inclusion Criteria***

Articles were selected for inclusion in this systematic review of the evidence if they were:

1. Fully published reports, published abstracts, or meta-analyses of randomized trials of preoperative or postoperative treatments compared with surgery alone or surgery plus another preoperative or postoperative treatment in patients with resectable and operable thoracic esophageal cancer.
2. Data on survival had to be reported. Other outcomes of interest were adverse effects and quality of life.

***Exclusion Criteria***

1. Carcinomas located in the cervical esophagus were excluded.

Search Details:

- April 2007 to November 2012 (Medline and Embase, ASCO Annual Meeting, ASH Meeting abstract, and Clinicaltrials.gov)

Brief Summary/Discussion of New Evidence:

Of 658 total hits from Medline, Embase, ASCO, Cochrane Library: 17 RCT's, 3 systematic reviews, 4 existing guidelines, and 12 on-going clinical trials were identified as relevant sources of information for updating of this guideline.

**Chemoradiotherapy + Surgery (CRTS) vs Surgery alone (S)**

| Interventions | Name of Trial | Population (n) | Outcomes | Brief results | Ref. |
|---|---|---|---|---|---|
| Chemoradiotherapy followed by surgery vs. surgery alone<br>• ***carboplatin (doses titrated to achieve an area under the curve of 2 mg per milliliter per minute) and paclitaxel (50 mg per square meter of body-surface area) for 5 weeks and concurrent radiotherapy (41.4 Gy in 23 fractions, 5 days per week), followed by surgery*** | CROSS | n=366<br>(75%) had adenocarcinoma, 84 (23%) had squamous-cell carcinoma, and 7 (2%) had large-cell undifferentiated carcinoma | Pathological complete response (PCR), MOS, OS | • PCR was achieved in 47 of 161 patients (29%) who underwent resection after chemoradiotherapy<br>• Median overall survival was 49.4 months in the chemoradiotherapy –surgery group versus 24.0 months in the surgery group<br>• Overall survival was significantly better in the chemoradiotherapy –surgery group (hazard ratio, 0.657; 95% confidence interval, 0.495 to 0.871; P = 0.003) | Van Hagen P., et al. |
| Neoadjuvant Chemoradiotherapy and selective surgery(CRTS) vs. Surgery Alone (S)<br>• ***CRT course consisted of two cycles of cisplatin and fluorouracil with split-*** | Prospective Comparison of Surgery Alone and Chemoradiotherapy With Selective Surgery in | n=99<br>Eligible patients had resectable T1–3N0–1M0 thoracic squamous cell esophageal cancer. | Survival (3yr, 5 yr.) | 3- and 5-year survival rates were 78.3% and 75.7%, respectively, in the CRTS group compared with | Ariga et al. |

| | | | | | |
|---|---|---|---|---|---|
| ***course concurrent radiotherapy of 60Gy in 30 fractions*** | Resectable Squamous Cell Carcinoma of the Esophagus | | | 56.9% and 50.9%, respectively, in the S group (p = 0.0169) | |
| Neoadjuvant Chemoradiotherapy followed by surgery vs. surgery alone<br>• ***Patients in combined therapy group were given two cycles of neoadjuvant chemotherapy (5-fluorouracil 500 mg/m2 + cisplatin 75 mg/m2) and the concurrent radiotherapy. Linear accelerator machine produced radiation at the dosage of 40 Gy. The tumor was resected at 3-5 weeks after concurrent chemotherapy and radiotherapy. Patients in the control group received surgery alone*** | Chemoradiotherapy versus surgery alone for esophageal squamous cell carcinoma | n=80<br>Patients had II B and III clinical stages squamous cell cancer and without contraindications for surgery and radiochemotherapy | Survival | The postoperative survival rate of the combined therapy group was significantly higher than that of the control group.<br>Specific survival rates were not reported in this abstract. | Peng L., et al. |
| Neoadjuvant Chemoradiotherapy followed by surgery vs. surgery alone<br>• ***Could not retrieve specific chemoradiotherapy regimen*** | Neoadjuvant chemoradiotherapy for clinical stage II-III esophageal squamous cell carcinoma | n=168<br>Patients with clinical stage II-III esophageal squamous cell cancer | Survival $_{(5\ yr.)}$, incidence complications | • 5-year survival rate was 47.7%( surgery alone) and 56.5% in the CRTS group (p=0.4831)<br>• 5-year survival rates of patients in whom CRTS was markedly effective was clearly better than that of the other patients (ineffective/slightly effective: 36.9%, moderately effective: 53.8%, markedly effective: 100%).<br>• Incidence of postoperative complications was 31.5% in the surgery alone group and 40.8% in the CRTS group (p=0.2121). | Saeki H., et al. |

**Chemotheradiation plus Surgery (CRTS) vs. Chemoradiation (CRT)**

| | | | | | |
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| Neoadjuvant chemoradiotherapy followed by surgery vs. surgery alone<br>• ***CRT consisting of weekly administrations of paclitaxel 50 mg/m2 and carboplatin AUC = 2 for 5 weeks and concurrent radiotherapy (41.4 Gy in 23 fractions, 5 days per week) followed by surgery versus surgery alone. Stratification parameters included performance status, histology, and lymph node status.*** | Effect of preoperative concurrent chemoradiotherapy on survival of patients with resectable esophageal or esophagogastric junction cancer: Results from a multicenter randomized phase III study (abstract) | n=363<br>Patients with resectable (T2-3N0-1M0) tumors (adeno/squamous/other carcinoma 273/86/4) | Survival(OS,MOS,1,2,3 yr.) , toxicities and complications | • In-hospital mortality was 3.7% in the surgery alone arm versus 3.8% in the CRTS arm<br>• The overall survival was significantly better (p = 0.011) in the group of patients treated with CRTS (HR 0.67 [95% CI 0.50-0.92]).<br>• Median survival was 49 months in the CRTS arm versus 26 months in the surgery alone arm.<br>• One, 2 and 3 years survival rates are 82%, 67% and 59% in the CRT arm and 70%, 52% and 48% in the surgery alone arm. | Gaast A.V., et al. |
| Cisplatin, fluorouracil, radiotherapy, and surgery vs. *surgery alone*<br>• ***Patients were randomly assigned to either esophagectomy with node dissection alone or cisplatin 100 mg/m(2) and fluorouracil 1,000 mg/m(2)/d for 4 days on weeks 1 and 5 concurrent with radiation therapy (50.4 Gy total: 1.8 Gy/fraction over 5.6 weeks) followed by esophagectomy with node dissection*** | Phase III trial of trimodality therapy with cisplatin, fluorouracil, radiotherapy, and surgery compared with surgery alone for esophageal cancer: CALGB 9781 | n=475<br>Patients with nonmetastatic esophageal cancer (squamous cell carcinoma or adenocarcinoma) | MOS, 5yr OS | • An intent-to-treat analysis showed a median survival of 4.48 v 1.79 years in favor of trimodality therapy (exact stratified log-rank, P = .002).<br>• Five-year survival was 39% (95% CI, 21% to 57%) v 16% (95% CI, 5% to 33%) in favor of trimodality therapy. | Tepper J., et al. |

| **Chemotherapy plus Surgery (CS) vs. Chemoradiotherapy plus Surgery (CRTS)** | | | | | |
|---|---|---|---|---|---|
| Treatment in arm A consisted of induction chemotherapy with 2.5 courses of cisplatin, fluorouracil, leucovorin (PLF). One course comprised a 6-week schedule of weekly fluorouracil (2 g/m 2, 24-hour infusion) and leucovorin (500 mg/m2,2-hour infusion) as well as biweekly cisplatin (50 mg/m 2, 1-hour infusion). Treatment of arm B consisted of 2.0 courses of the same induction chemotherapy. This was followed by 3 weeks of | Phase III comparison of preoperative chemotherapy compared with chemoradiotherapy in patients with locally advanced adenocarcinoma of the esophagogastric junction | N=126<br>histologically proven adenocarcinoma of the esophagogastric junction (type I to III according to Siewert's classification) | 3 yr. OS | • Preoperative radiation therapy improved 3-year survival rate from 27.7% to 47.4%<br>• log-rank P=.07<br>• hazard ratio adjusted for randomization strata variables 0.67, 95% CI, 0.41 to 1.07) | Stahl, M., et al. |

| | | | | | |
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| combined chemoradiotherapy. Surgery was performed 3 to 4 weeks after the end of chemotherapy (arm A) or chemoradiotherapy (arm B) | | | | | |
| Preoperative CT with cisplatin (80 mg/m(2)) and infusional 5 fluorouracil (1000 mg/m(2)/d) on days 1 and 21, vs. preoperative CRT with the same drugs accompanied by concurrent radiation therapy commencing on day 21 of chemotherapy and the 5 fluorouracil reduced to 800 mg/m(2)/d. The radiation dose was 35 Gy in 15 fractions over 3 weeks | Is concurrent radiation therapy required in patients receiving preoperative chemotherapy for adenocarcinoma of the oesophagus? A randomised phase II trial | N=75<br>resectable adenocarcinoma of the oesophagus and gastro-oesophageal junction | progression-free survival (PFS), overall survival (OS) | • Median PFS was 14 and 26 months for CT and CRT respectively (p = 0.37).<br>• median OS was 29 months for CT compared with 32 months for CRT (p = 0.83) | Burmeister B.H., et al. |

**Chemoradiotherapy plus Surgery (CRTS) vs. Chemoradiotherapy(CRT)**

| **Interventions** | **Name of Review** | **Population (n)** | **Outcomes** | **Brief results** | **Ref.** |
|---|---|---|---|---|---|
| Two cycles of fluorouracil (FU) and cisplatin (days 1 to 5 and 22 to 26) and either conventional (46 Gy in 4.5 weeks) or split-course (15 Gy, days 1 to 5 and 22 to 26) concomitant radiotherapy. Patients with response and no contraindication to either treatment were randomly assigned to surgery (arm A) or continuation of chemoradiation (arm B; three cycles of FU/cisplatin and either conventional [20 Gy] or split-course [15 Gy] radiotherapy) | Chemoradiation followed by surgery compared with chemoradiation alone in squamous cancer of the esophagus: FFCD 9102 | N=259<br>Operable T3N0-1M0 thoracic esophageal cancer (International Union Against Cancer criteria, 1987) epidermoid or adenocarcinoma of the thoracic esophagus and clinical and biologic eligibility for surgery or chemoradiation | OS | • Two-year survival rate was 34% in arm A versus 40% in arm B (hazard ratio for arm B v arm A = 0.90; adjusted P = .44).<br>• Median survival time was 17.7 months in arm A compared with 19.3 months in arm B | Bedenne L., et al. |

**Chemoradiotherapy plus Surgery (CTRS) vs. Surgery plus Chemoradiotherapy (CTRS) vs. Surgery Alone (S)**

| **Interventions** | **Name of Review** | **Population (n)** | **Outcomes** | • **Brief results** | **Ref.** |
|---|---|---|---|---|---|
| Preoperative vs. postoperative CRT vs. surgery alone (S) | Long-term efficacy of perioperative chemoradiotherapy on esophageal squamous cell carcinoma | N=238<br>locally advanced thoracic esophageal squamous cell carcinoma (ESCC) | PFS, OS | • Median follow-up of 45 mo.<br>• all the enrolled patients, significant differences in the 1-, 3-, 5-, 10-year ***OS*** (91.3%, 63.5%, 43.5%, 24.5% vs. 91%, 62.8%, | Lv. J., et al. (2010) |

| | | | | | |
|---|---|---|---|---|---|
| | | | | 42.3%, 24.4% vs. 87.5%, 51.3%, 33.8%, 12.5%, P = 0.0176)<br>&<br>***PFS*** (89.3%, 61.3%, 37.5%, 18.1% vs. 89.1%, 61.1%, 37.2%, 17.8% vs. 84.5%, 49.3%, 25.9%, 6.2%, P = 0.0151) were detected among the 3 arms.<br>• No significant differences in OS and PFS between the preoperative CRT and postoperative CRT arm (P > 0.05).<br>• For the patients who had radical resection, a significant difference was found for median PFS (48 mo. vs. 61 mo. vs. 39.5 mo., P = 0.0331) and median OS (56.5 mo. vs. 72 mo. vs. 41.5 mo., P = 0.0153) among the 3 arms,<br>• No significant differences found for OS and PFS between the preoperative CRT and postoperative CRT arm (P > 0.05). The local recurrence rates in the preoperative CRT, postoperative CRT group and S group were 11.3%, 14.1% and 35%, respectively (P < 0.05) | |

**Chemotherapy (CT) + Surgery (CS) vs. Surgery alone (S)**

| Interventions | Name of Trial | Population (n) | Outcomes | Brief results | Ref. |
|---|---|---|---|---|---|

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| Neoadjuvant chemotherapy followed by surgery vs. surgery alone<br>• ***chemotherapy group received preoperative cisplatin plus fluorouracil*** | Long-term results of RTOG trial 8911 (USA Intergroup 113): a random assignment trial comparison of chemotherapy followed by surgery compared with surgery alone for esophageal cancer | n=443<br>Histologically confirmed epidermoid or adenocarcinoma of the esophagus, including the gastroesophageal junction, with or without regional lymph node metastasis (tumor stages I, II, or III, any nodal stage, and no metastasis [M0]) using the TNM classification schema. All patients were at least 18 years of age, had adequate hepatic, renal, and bone marrow function, and could tolerate the planned surgical procedure. Patients with tumors in the cervical esophagus (upper border fewer than 18 cm from the incisor teeth), those with supraclavicular or distant metastasis, or those with T4 tumors were ineligible. Patients could not have received prior therapy for their esophageal cancer. | OS,DFS | • 32% of patients with R0 resections were alive and free of disease at 5 years, only 5% of patients undergoing an R1 resection survived for longer than 5 years<br>• No difference in overall survival for patients receiving perioperative chemotherapy compared with the surgery only group, patients with objective tumor regression after preoperative chemotherapy had improved survival. | Kelsen D.P., et al. |
| Neoadjuvant two cycles of combination cisplatin and fluorouracil followed by surgery (CS) vs. surgery alone (S)<br>• ***Preoperative chemotherapy comprised 2 cycles of cisplatin 80mg/m2 by intravenous infusion over 4 hours on day 1 and fluorouracil 1,000mg/m2 daily as a continuous infusion over 96 hours repeated every 3 weeks. Patients underwent surgery within 3 to 5 weeks of completing chemotherapy or as soon as possible in the surgical resection alone group.*** | Long-term results of a randomized trial of surgery with or without preoperative chemotherapy in esophageal cancer | n=802<br>Patients eligible for the trial had histologically confirmed, previously untreated, esophageal cancer and were considered suitable for radical surgery with curative intent. Squamous cell carcinoma (SCC), adenocarcinoma (ACA), and undifferentiated carcinoma were included. Tumor location in cluded the upper, middle, and lower thirds of the esophagus as well as the gastric cardia but excluded post cricoid cancers. Those with comorbid contra-indications to surgery or chemotherapy were excluded | DFS & OS | • (HR) of 0.84 (95% CI, 0.72 to 0.98; P = .03) which in absolute terms is a 5-year survival of 23.0% for CS compared with 17.1% for S<br>• Three-year survival by type of resection was R0 42.4%, R1 was 18.0%, and R2 was 8.6%. | Allum et al. |
| Neoadjuvant chemotherapy followed by surgery vs. surgery alone<br>• ***Patients were allocated either to two 3-day cycles of FLEP consisting of cisplatin 80-100 mg/m<sup>2</sup>, day 1; etoposide 100 mg/m<sup>2</sup>, leucovorine 20 mg/m<sup>2</sup> and*** | Neoadjuvant chemotherapy followed by transthoracic resection for locally advanced carcinoma of the esophagus: A randomized study | n=90<br>Patients with stage T<sub>3-4</sub>N<sub>0-1</sub>M<sub>0</sub>, T<sub>1-2</sub>N<sub>1</sub>M<sub>0</sub> resectable esophageal cancer (89 squamous cell cancer, one had adenocarcinoma) | DFS & OS | • 3-year and 5-year survival rates were 39.8% and 28.5% in the S group; 62.9% and 40.4% in the CS group (p = 0.08).<br>• 5-year disease-free survival benefit achieved statistical significance: 17.6% versus 32.7% (p = 0.04). | Bokhyan V et al. |

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| ***5-fluorouracil 500 mg/m<sup>2</sup>, days 1-3; 21 days apart, followed by surgical resection (C-S group, n = 45), or resection alone (S group, n = 45).*** | | | | | |
| Neoadjuvant Chemotherapy followed by Surgery vs. Surgery alone<br>• ***Previously untreated patients were randomized into CT (two cycles of FLEP: cisplatin 80 mg/m<sup>2</sup>, day 1; etoposide 80 mg/ <sup>2</sup> d 1-3, leucovorine 20 mg/m<sup>2</sup> and 5-fiuorouracil 425 mg/m<sup>2</sup>, bolus, days 1-3; every 21 days) followed by surgical resection (C-S group), or resection alone (S group). Four weeks after completion of CT patients underwent transthoracic subtotal esophageal resection with complete two-field (I. Lewis procedure).*** | Preoperative chemotherapy followed by surgery versus surgery alone in resectable esophageal cancer: A Single institute phase III TRIAL | n=115<br>Previously untreated patients with stage T<sub>3-4</sub>N<sub>0-1</sub>M0, T<sub>1-2</sub>N<sub>1</sub>M<sub>0</sub> resectable esophageal cancer were eligible (Predominant histological type was squamous cell carcinoma (94%)) | 3yr Median OS | • Median OS (3-year OS) were 22 months (45%) in CS group and 20 months (31%) in S group (p=0.24).<br>• Patients with objective response to chemotherapy had better OS compared with S group (3-year OS 75% and 31%, p=0,008, respectively). | Pokataev I, et al. |
| Chemotherapy followed by surgery (CS) versus surgery alone (S)<br>• ***Cisplatin, at a dose of 80 mg/m2, was given intravenously over 4 hours on day one of each cycle. Etoposide, at a dose of 100 mg/m2, was administered intravenously over 2 hours on day 1 (before cisplatin) and day 2, followed by etoposide 200 mg/m2 orally on days 3 and 5. This course was repeated in week 4. In case of clinical response, two subsequent courses of chemotherapy were administered in week 8 and 11. All patients received prophylactic anti-nausea treatment with 5-HT 3 receptor antagonists during chemotherapy. Re-treatment with the next*** | Chemotherapy followed by surgery versus surgery alone in patients with resectable oesophageal squamous cell carcinoma: long-term results of a randomized controlled trial | n=169<br>Patients had histologically confirmed squamous cell carcinoma of the intra-thoracic oesophagus. Patients were deemed resectable if the disease was clinically limited to the locoregional area (tumour stage 1, 2 or 3; any nodal stage and no metastases). Patients with carcinoma of the distal oesophagus and suspected celiac lymph nodes involvement (M1a) were also considered eligible for surgery. Patients had to be below 80 years of age, in adequate physical condition (Karnofsky score >70) to undergo surgery and had to have adequate hepatic, renal and bone marrow function. | OS,DFS | • 2-year survival rates were 42%(CS) and 30%(S); and 5-year survival rates were 26%(CS) and 17%,(S) respectively<br>• OS - significant overall survival benefit for patients in the CS group (P = 0.03, by the log-rank test; hazard ratio [HR] 0.71; 95%CI 0.51-0.98).<br>• DFS (from landmark time of 6 months after date of randomisation) was better in the CS-group than in the S group (P = 0.02, by the log-rank test; HR 0.72; 95%CI 0.52-1.0). | Boonstra J.J., et al. |

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| ***cycle was permitted only if the absolute neutrophil count was at least 3,500/mm3, and the platelet count was at least 100,000/mm3. A delay of treatment of up to 2 weeks was permitted. In patients with severe toxic renal or neurological effects (≥ WHO grade 3) chemotherapy was stopped and patients were referred for surgery.*** | | | | | |
| Neoadjuvant chemotherapy followed by surgery and adjuvant chemotherapy vs. with surgery alone<br>• ***Chemotherapy consisted of two or three preoperative cycles of intravenous cisplatin (100 mg/m(2)) on day 1, and a continuous intravenous infusion of fluorouracil (800 mg/m(2)/d) for 5 consecutive days (days 1 to 5) every 28 days and three or four postoperative cycles of the same regimen.*** | Perioperative chemotherapy compared with surgery alone for resectable gastroesophageal adenocarcinoma: an FNCLCC and FFCD multicenter phase III trial | N=224<br>patients with resectable adenocarcinoma of the lower esophagus, gastroesophageal junction (GEJ), or stomach | OS | • CS group vs. S group:<br>• OS (5-year rate 38% v 24%; hazard ratio [HR] for death: 0.69; 95% CI, 0.50 to 0.95; P = .02); and a better disease-free survival (5-year rate: 34% v 19%; HR, 0.65; 95% CI, 0.48 to 0.89; P = .003). | Ychou M., et al. |

**Chemoradiotherapy (CRT) vs. Surgery alone (S) vs. Chemotherapy + Surgery (CS)**

| Interventions | Name of RCT | Population (n) | Outcomes | Brief results | Ref. |
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| Chemoradiotherapy alone (CRT), surgery alone (S), neoadjuvant chemotherapy plus surgery (CS)<br>• Patients received four cycles ***of cisplatin (60 mg/m2) and 5-fluorouracil (5-FU; 300 mg/m2 decreased to 225 mg/m2 with radiotherapy), with cycles 3 and 4 given concurrently with 50 Gy conformal radiotherapy in 25 fractions. Carboplatin was given instead of cisplatin if the glomerular filtration rate was less than 40 ml/min or if significant neurotoxicity and/or nephrotoxicity occurred. Radiotherapy was administered using a 2-phase technique, starting with parallel*** | Stage-for-stage comparison of definitive chemoradiotherapy, surgery alone and neoadjuvant chemotherapy for oesophageal carcinoma | n=417<br>potentially curable oesophageal carcinoma of any cell type | 30 day morality rate, 2 yr OS | • Thirty-day mortality rates were zero, 7.9 and 0.8 per cent after CRT, surgery alone and CS respectively.<br>• Overall 2-year survival rates were 44.3, 56.2 and 42.4 per cent (P = 0.422) | Morgan MA, et al. |

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| ***opposed fields followed by a three field, three-dimensional plan. Modifications made during the study. In 2005, capecitabine replaced infusional 5-FU and patients were treated with a single phase radiotherapy plan, with the same dose given to the same target volume using a four- or five-field beam arrangement and the following normal tissue constraints: lung V20 less than 25 per cent, heart V40 less than 30 per cent and spinal cord Dmax below 38 Gy, where Vx is the volume of organ receiving x Gy and Dmax is the maximum dose received by that organ.*** | | | | | |

| **SYSTEMATIC REVIEW / META-ANALYSIS** | | | | | |
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| **Interventions** | **Name of Review** | **Population (n)** | **Outcomes** | **Brief results** | **Ref.** |
| Neoadjuvant chemoradiotherapy followed by surgery vs. surgery alone<br>***Multiple chemotherapy schedules considered*** | Neoadjuvant chemoradiotherapy for resectable esophageal carcinoma: A meta-analysis | (RCTs) including 1308 patients Esophageal cancers not limited by histology | 1 yr., 3, 5yr survival, | • 1 yr. survival: Odds ratio (OR) [95% confidence interval (CI), P value], expressed as neoadjuvant chemoradiotherapy and surgery vs. surgery alone, was 1.28 (1.01-1.64, P = 0.05)<br>• 3 yr. survival: 1.78 (1.20-2.66, P = 0.004) for 3-year survival<br>• 5 yr. survival: 1.46 (1.07-1.99, P = 0.02) Histological subgroup analysis indicated that esophageal squamous cell carcinoma did not benefit from neoadjuvant chemoradiotherapy, OR (95% CI, P value) was 1.16 (0.85-1.57, P = 0.34) for 1-year survival, 1.34 (0.98-1.82, P = 0.07) for 3-year survival and 1.41 | Jin HL, et al. |

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| | | | | (0.98-2.02, P = 0.06) for 5-year survival | |
| Neoadjuvant chemoradiotherapy followed by surgery vs. surgery alone<br>***Multiple chemotherapy schedules considered*** | Effect of neoadjuvant chemoradiotherapy on prognosis and surgery for esophageal carcinoma | 14 RCTs that included 1737 patients<br>Esophageal cancers not limited by histology | 1yr, 2yr, 3yr, 4yr, 5yr Survival | CRTS vs. S (values > 1 favor CRTS arm)<br>• 1-year survival 1.19 (0.94-1.48, P = 0.28)<br>• 2-year survival 1.33 (1.07-1.65, P = 0.69)<br>• 3-year survival1.76 (1.42-2.19, P = 0.11)<br>• 4-year survival 1.41 (1.06-1.87, P = 0.11)<br>• 5-year survival 1.64 (1.28-2.12, P = 0.40)<br>• The 5-year survival benefit was most pronounced when chemotherapy and radiotherapy were given concurrently (OR: 1.45, 95% CI: 1.26-1.79, P = 0.015) instead of sequentially (OR: 0.85, 95% CI: 0.64-1.35, P = 0.26) | LV J, et al. (2009) |
| Neoadjuvant chemoradiotherapy followed by surgery vs. surgery alone<br>***Multiple chemotherapy schedules considered*** | Survival after neoadjuvant chemotherapy or chemoradiotherapy for resectable oesophageal carcinoma: an updated meta-analysis | 24 RCTs that included 4188 patients<br>Esophageal cancers not limited by histology | OS | HR for all-cause mortality for neoadjuvant chemoradiotherapy was 0.78 (95% CI 0.70-0.88; p<0.0001); the HR for squamous-cell carcinoma only was 0.80 (0.68-0.93; p=0.004) and for adenocarcinoma only was 0.75 (0.59-0.95; p=0.02). The HR for all-cause mortality for neoadjuvant chemotherapy was 0.87 (0.79-0.96; p=0.005); the HR for squamous-cell carcinoma only was 0.92 (0.81-1.04; p=0.18) and for adenocarcinoma only was 0.83 (0.71-0.95; | Sjokuist K.M. et al. (2011) |

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| | | | | p=0.01). The HR for the overall indirect comparison of all-cause mortality for neoadjuvant chemoradiotherapy versus neoadjuvant chemotherapy was 0.88 (0.76-1.01; p=0.07) | |

**Existing Guidelines**

| Title | Recommendations | Source | Date of Pub. |
|---|---|---|---|
| Preoperative or postoperative therapy for resectable oesophageal cancer: an updated practice guideline | Operative cisplatin-based chemotherapy plus radiotherapy is recommended as the preferred modality for the management of surgically resectable patients with oesophageal cancer. Preoperative cisplatin-based chemotherapy alone is an alternative choice for the management of these patients | Malthaner R., et al. (See references below) | 2010 |
| Esophageal Cancer | Diagnosis,, Staging, Pathology and Treatments. Treatment guidelines for with curative intent and non-curative intent.<br><br>**Curable Situations**<br>• TisN0 or T1N0 and T2N0 Disease: Esophagectomy with curative intent<br>• T3, T4a, or N+ Disease: Pre-Operative Chemoradiotherapy followed by Esophagectomy (if possible):<br>• These are preferred treatments, alternatives are also presented. | Alberta Health Services (See references below) | June 2011 |

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| | **Incurable Situations**<br>• Relieve pain, bleeding, and/or dysphagia with radiotherapy.<br>• Consider placement of an endoluminal stent24, 25 or photodynamic therapy26 to relieve dysphagia.<br>• Consider palliative chemotherapy to control disease and prolong survival in patients with a satisfactory performance status (ECOG ≤ 2 | | |
| Esophageal And Esophagogastric Junction Cancers(Excluding the proximal 5cm of the stomach) | Diagnosis, Staging, Pathology and Treatments.<br>Treatment guidelines for with curative intent and non-curative intent<br>• Goal of EMR and or ablation is complete removal of all Barrett's metaplasia in addition to eradication of early malignancy.<br>• Early stage disease, also known as high grade dysplasia needs to be fully characterized including evaluating the presence of nodularity lateral spread and ruling out multifocal disease. All focal nodes should be resected rather than ablated.<br>• T1a disease, carcinoma limited to the lamina propria or muscularis mucosae, in the absence of evidence of lymph node metastases, lymphovascular invasion or poor differentiation grade can be treated with full EMR. EUS staging prior to proceeding with mucosal resection in the setting of carcinoma is recommended. Ablative therapy of residual flat Barrett's esophagus associated with Tis or T1a disease should be performed following mucosal resection.<br>• Esophageal dilation can be performed with the use of dilating balloons or bougies to temporarily relieve obstruction from tumors or treatment related strictures. Caution should be exercised to avoid over dilation, to minimize the risk of perforation.<br>• Long term palliation of dysphagia can be achieved with endoscopic tumor ablation by ND:YAG Laser, PDT and cryotherapy, or endoscopic and radiographic assisted insertion of expandable metal or plastic stents.<br>• Long term palliation of anorexia, dysphagia or malnutrition may be achieved with endoscopic or radiographic assisted placement of feeding gastrostomy or jejunostomy. The placement of a gastronomy in the preoperative setting may compromise the gastric vasculature, thereby interfering with the creation of the gastric conduit in the reconstruction during esophagectomy and should be avoided. | NCCN (See references below) | 2012 |
| Provincial Esophageal Cancer and Gastro-esophageal junction Cancer Treatment Guidelines | Assessment & Investigations, Treatment, Follow-up<br>**T1/2, N0, M0 (GOOD PERFORMANCE STATUS):**<br>• Surgery alone is the treatment of choice. Definite chemoradiation therapy can be considered in medically unfit patients for surgery or if patient decline surgery<br>**(Selected T2)/ T3/T4, N0/N+, M0 (GOOD PERFORMANCE STATUS)**<br>• Multimodality therapy is preferred in patients with | Sask. Cancer Agency (See references below) | March 2012 |

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| | ≥ stage 2 esophageal cancers.<br>• Preoperative chemoradiation can be considered in eligible patients (cisplatin/5FUand external RT doses of 45-50.4 Gy in 25– 28 fractions followed by surgery in 4-6weeks or weekly carboplatin/paclitaxel and RT (doses of 41.4 Gy in 23 fractions or 45 -50.4 Gy in 25 -28 fractions followed by surgery in 4-6 weeks).<br>• Definitive chemoradiation therapy can be considered in medically unfit patients for surgery or if patient decline surgery<br>• Radical radiation alone to a dose of 54-60Gy in 1.8 to 2Gy/# may be considered in selected patients refusing or medically unfit for surgery and chemotherapy.<br>**T1-T4, N0/N+, M0 (POOR PERFORMANCE STATUS)**<br>• Palliative radiotherapy (40Gy/ 16#, 36Gy/12 #, 30Gy/10#, 20Gy/5#, 8Gy/1#).<br>• Palliative chemotherapy.<br>• Best supportive care.<br>• Palliative stenting for relief of dysphagia.<br>• Intra-luminal brachytherapy may be considered in selected patients. | | |

**On-Going Clinical Trials**

| Interventions | Official title | Status | Protocol ID | Last Updated |
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| Preoperative chemotherapy and radiation followed by surgery vs. surgery followed by postoperative chemotherapy and radiation for esophageal cancer | Quality of Life in Neoadjuvant Versus Adjuvant Therapy of Esophageal Cancer Treatment Trial (QUINTETT) | Recruiting | NCT00907543 | June 29, 2011 |
| Preoperative Chemoradiotherapy (Paclitaxel and carboplatin) Followed by Surgery **vs.** Surgery Followed by Postoperative Chemoradiotherapy (Paclitaxel and carboplatin) for Esophageal Cancer. | Prospective Randomized Phase Ⅱ Trial Comparing Preoperative Chemoradiotherapy (Paclitaxel and Carboplatin) Followed by Surgery to Surgery Followed by Postoperative Chemoradiotherapy (Paclitaxel and Carboplatin) for Esophageal Cancer | Not yet open for participant recruitment | NCT01463501 | October 29, 2011 |
| Radiation and Chemotherapy pre/post-surgery | Randomized Phase II Study of Preoperative Combined Modality Paclitaxel / Cisplatin / RT or Irinotecan / Cisplatin / RT Followed by Postoperative Chemotherapy With the Same Agents in Operable Adenocarcinoma of the Esophagus | Completed | NCT00033657 | August 1, 2011 |
| Behavioral: Questionnaires | Quality Of Life Outcomes Following Treatment for Esophageal Cancer | ongoing | NCT00598117 | November 22, 2011 |

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| Two preoperative cycles with Paclitaxel 200 mg/m² d1, Cisplatin 60 mg/m² d1, 5-Fluorouracil 700 mg/m² d1-5 repeated every 3 weeks followed by resection vs. two postoperative cycles with Paclitaxel 200 mg/m²/day d1, Cisplatin 60 mg/m²/day d1, 5-Fluorouracil 700 mg/m²/day d1-5 repeated every 3 weeks Among patients with no responses to preoperative chemotherapy, Capecitabine 625 mg/m² twice-daily dose as alternatives to infused 5-Fluorouracil in the postoperative chemotherapy regimen | Perioperative Versus Preoperative Chemotherapy With Surgery in Patients With Locoregional Squamous Carcinoma of Esophagus | completed | NCT01225523 | October 20, 2010 |
| 2 cycles carboplatin and paclitaxel days 1, 8, 15 given every 4 weeks: paclitaxel: 75 mg / m2 IV in 250 ml normal saline (NS) over 1 hour; carboplatin: dosed to an area under the curve of 3, by Calvert formula, as a 1 hour IV infusion vs. Other: Carboplatin paclitaxel plus concurrent radiotherapy 5 cycles carboplatin and paclitaxel given on days 1, 8, 15, 22 and 29 paclitaxel: 50 mg / m2 IV over 1 hour; carboplatin: dosed to an area under the curve of 2, by Calvert formula, as a 1 hour IV infusion, diluted in 500 ml Dextrose 5% Radiation Therapy Concurrent radiation therapy will begin within 24 hours of initiation of chemotherapy for patients randomized to chemoradiation treatment. Dose specifications: Total radiation prescription dose 45- 50.4 Gy given in 25-28 fractions of 1.8 Gy per fractions, 5 fractions / week, one treatment / day, starting on the first day of first cycle of chemotherapy. | Neoadjuvant Chemotherapy vs. Neoadjuvant Chemoradiation in Patients With Surgically Resectable Esophageal Cancer: a Pilot Randomized Study | Recruiting | NCT01404156 | January 5, 2012 |
| cetuximab - Loading dose 400 mg/m2 2h infusion Weekly: 250 mg/m2 1h infusion; Cisplatin 75 mg/m2 1h infusion d1, 22 25 mg/m2 1h infusion weekly x5; Docetaxel 75 mg/m2 1h infusion d1, 22; 20 mg/m2 1/2h infusion weekly x5 | Multimodal Therapy With and Without Cetuximab in Patients With Locally Advanced Esophageal Carcinoma - An Open-Label Phase III Trial | Recruiting | NCT01107639 | November 1, 2012 |

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| vs.<br>Weekly: 250 mg/m2 1h infusion; Cisplatin 75 mg/m2 1h infusion d1, 22 25 mg/m2 1h infusion weekly x5; Docetaxel 75 mg/m2 1h infusion d1, 22; 20 mg/m2 1/2h infusion weekly x5 | | | | |
| Arm A consists of 3 cycles of chemotherapy pre-surgery and a further 3 cycles of chemotherapy post-surgery. Each cycle of chemotherapy lasts 21 days/3 weeks. The drugs used in the MAGIC regimen include Epirubicin, Cisplatin and 5-Flourouracil/ Capecitabine<br>vs.<br>Arm B consists of the CROSS protocol, which includes a combination of chemotherapy and radiotherapy prior to surgery. The patient will receive 5 weeks of radiation therapy and 5 weekly cycles of chemotherapy. The radiation will generally commence on the 1st day of treatment and will run for 5 weeks as follows: days 1-5, days 8-12, days 15-19, days 22-26 and days 29-31 inclusive. The chemotherapy and radiotherapy will run concurrently over a 5-week period. Chemotherapy is given by intravenous infusion on days 1, 8, 15, 22 and 29. | Randomised Clinical Trial of Neoadjuvant and Adjuvant Chemotherapy (MAGIC Regimen) vs. Neoadjuvant Chemoradiation (CROSS Protocol) in Adenocarcinoma of the Oesophagus and Oesophago-gastric Junction | Recruiting | NCT01726452 | November 9, 2012 |
| Bevacizumab 7.5mg/kg IV Day 1 of each 21 cycle of chemotherapy (6 cycles) plus day 1 of each maintenance dose every 21 days for 6 doses; capecitabine dose banded as based on patient BSA. Oral dose given twice a day during each 21 day cycle of chemotherapy (6 cycles in total); cisplatin60mg/m2 IV day one of each 21 day cycle of chemotherapy (6 cycles in total); epirubicin hydrochloride 50mg/m2 IV day one of each 21 day cycle of chemotherapy (6 cycles in total); adjuvant therapy 3 cycles of ECX chemotherapy post operatively Procedure: conventional surgery Surgery undertaken after 3 cycles of pre- | A Randomized Controlled Phase II/III Trial of Peri-Operative Chemotherapy With or Without Bevacizumab in Operable Oesophagogastric Adenocarcinoma | Recruiting | NCT00450203 | January 27, 2012 |

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| operative chemotherapy. Followed by 3 cycles of chemotherapy. Procedure: neoadjuvant therapy 3 cycles of pre-operative ECX chemotherapy.<br><br>vs.<br><br>capecitabine dose banded as based on patient BSA. Oral dose given twice a day during each 21 day cycle of chemotherapy (6 cycles in total); cisplatin60mg/m2 IV day one of each 21 day cycle of chemotherapy (6 cycles in total); epirubicin hydrochloride 50mg/m2 IV day one of each 21 day cycle of chemotherapy (6 cycles in total); adjuvant therapy 3 cycles of ECX chemotherapy post operatively Procedure: conventional surgery Surgery undertaken after 3 cycles of pre-operative chemotherapy. Followed by 3 cycles of chemotherapy. Procedure: neoadjuvant therapy 3 cycles of pre-operative ECX chemotherapy. | | | | |
| Arm I (radiotherapy, chemotherapy, monoclonal antibody) Patients undergo radiotherapy once daily 5 days a week for 5.5 weeks. Patients also receive paclitaxel IV over 60 minutes and carboplatin IV over 60 minutes on days 1, 8, 15, 22, 29, and 36 and trastuzumab IV over 30-90 minutes on days 1, 8, 15, 22, 29, 36, and 57.<br><br>vs.<br><br>Beginning 21-56 days after surgery, all patients receive trastuzumab IV over 30-90 minutes on day 1. Treatment repeats every 21 days for 13 courses in the absence of disease progression or unacceptable toxicity.<br><br>Within 5-6 weeks after completion of radiotherapy, all patients undergo surgery. | A Phase III Trial Evaluating the Addition of Trastuzumab to Trimodality Treatment of HER2-Overexpressing Esophageal Adenocarcinoma | Recruiting | NCT01196390 | September 20, 2012 |

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| Arm I (radiotherapy, chemotherapy, monoclonal antibody) Patients undergo radiotherapy once daily 5 days a week for 5.5 weeks. Patients also receive paclitaxel IV over 60 minutes and carboplatin IV over 60 minutes on days 1, 8, 15, 22, 29, and 36 and trastuzumab IV over 30-90 minutes on days 1, 8, 15, 22, 29, 36, and 57.<br><br>vs.<br><br>Beginning 21-56 days after surgery, all patients receive trastuzumab IV over 30-90 minutes on day 1. Treatment repeats every 21 days for 13 courses in the absence of disease progression or unacceptable toxicity. Within 5-6 weeks after completion of radiotherapy, all patients undergo surgery. | A Phase III Trial Evaluating the Addition of Trastuzumab to Trimodality Treatment of HER2-Overexpressing Esophageal Adenocarcinoma | Recruiting | NCT01196390 | September 20, 2012 |
| Arm A: will receive combination of irinotecan and docetaxel regimen for 2 cycles, recycling every 21 days Irinotecan 100 mg/m2 by intra venous infusion over 2 hours in day1 and docetaxel 40 mg/m2 over one hour will be given on day 1 Assessment by PET scan and CT chest and abdomen will be done 2-3 weeks after end of 2nd cycle of irinotecan and docetaxel<br><br>vs.<br><br>Arm B will receive combination of cisplatin, fluorouracil and concurrent radiation therapy 50 Gy in 25 fractions over 5 weeks with cisplatin 75 mg/m2 on first day of week 1 and week 5 and fluorouracil 750 mg/m2 daily by continuous intra venous infusion at Day 1 and Day 29 of Radiation therapy for 4 days.<br><br>PET scan will be repeated 3-4 weeks after end of concurrent | A Trial Comparing Pre-operative Chemo-radiotherapy With Cisplatin and Fluorouracil Versus Chemotherapy with Docetaxel and Irinotecan in PET Non Responders Resectable Cancer Esophagus: a Multicenter Study | Recruiting | NCT01608464 | May 30,<br><br>2012 |

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| chemo-radiation therapy Patients in Arm A and B will go for esophagectomy 4-6 weeks after end of concurrent chemo-radiation therapy or chemotherap | | | | |

DFS= disease free survival; EFS= event free survival; HR= hazard ratio; m=months; n= number enrolled; N/A= not available; ORR= overall response rate; OS= overall survival; RR= risk ratio;

| **Instructions.** These questions are answered by the Clinical Expert assigned by the DSG/GDG. Beginning at question 1 answer the questions in order, following the instructions in the black boxes as you go. | |
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| 5. Does any of the newly identified evidence, on initial review, contradict the current recommendations, such that the current recommendations may cause harm or lead to unnecessary or improper treatment if followed? Answer Yes or No, and explain if necessary, citing newly identified references: | 1.No |
| 6. On initial review,<br>a. Does the newly identified evidence support the existing recommendations?<br>b. Do the current recommendations cover all relevant subjects addressed by the evidence, such that no new recommendations are necessary?<br>Answer Yes or No to each, and explain if necessary: | 2.A. Yes<br>b. Yes |
| 7. Is there a good reason (e.g., new stronger evidence will be published soon, changes to current recommendations are trivial or address very limited situations) to postpone updating the guideline? Answer Yes or No, and explain if necessary: | 3.No |
| 8. Do the PEBC and the DSG/GDG responsible for this document have the resources available to write a full update of this document within the next year? | 4.Yes. |

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| **Review Outcome** | ENDORSE |
| **DSG/GDG Approval Date** | April 2013 |

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| **DSG/GDG Commentary** | There are fundamental differences between squamous carcinoma of the esophagus and adenocarcinoma of the lower third of the esophagus and gastroesophageal junction. Etiology, epidemiology, tumor biology, pattern of recurrence, prognosis and susceptibility to induction therapy are different. Most studies have combined both cell types in their populations with similar outcomes.<br><br>The classification of tumours of the gastroesophageal junction remains a challenge. Some authors classify these tumours as esophageal carcinomas, others define them as gastric carcinomas and yet others consider them as an entity separate from esophageal and gastric cancer. The most agreed upon classification is that of Siewert et al. (1,2). They we have proposed dividing tumors that have their centres within 5 cm proximal or distal to the anatomical cardia into three types based on purely topographic anatomical criteria:<br><br>**Type I:** adenocarcinoma of the distal esophagus, which usually arises from an area with specialized intestinal metaplasia of the esophagus (i.e., Barrett esophagus) and may infiltrate the esophagogastric junction from above;<br>**Type II:** true carcinoma of the cardia arising immediately at the esophagogastric junction;<br>**Type III:** subcardial gastric carcinoma that infiltrates the esophagogastric junction and distal esophagus from below.<br>This classification postdates most trials on induction therapy and has led to confusion about the inclusion criteria and results of both esophageal and gastric cancer trials. For a discussion of the evidence around esophagogastric junction and gastric cancers, please see guideline 2-14<br><br>Once some ongoing trials using this new classification are complete, this guideline will be updated<br><br>**References**<br>1) JR Siewert, HJ Stein. Classification of the adenocarcinoma of the oesophagogastric junction. British Journal Surgery. 1998, 85: 1457-1459.<br><br>2) JR Siewert, M Feith, M Werner and HJ Stein. Adenocarcinoma of the esophagogastric junction. Annals of Surgery. 2000, 232(3): 353-361. |

New References Identified:


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25. Alberta Health Services. Accessed on December 4th, 2012. http://www.albertahealthservices.ca/hp/if-hp-cancer-guide-gi009-esophageal.pdf

## Literature Search Strategy:

**MEDLINE**

1. meta-Analysis as topic.mp.
2. meta analysis.pt.
3. (meta analy$ or metaanaly$).tw.
4. (systematic review$ or pooled analy$ or statistical pooling or mathematical pooling or statistical summar$ or mathematical summar$ or Quantitative synthes?s or quantitative overview?).tw.
5. (systematic adj (review$ or overview?)).tw.
6. (exp Review Literature as topic/ or review.pt. or exp review/) and systematic.tw.
7. or/1-6
8. (cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or cinhal or science citation index or scisearch or bids or sigle or cancerlit).ab.
9. (reference list$ or bibliograph$ or hand-search$ or relevant journals or manual search$).ab.
10. (selection criteria or data extraction or quality assessment or jadad scale or methodological quality).ab.
11. (study adj selection).ab.
12. 10 or 11
13. review.pt.
14. 12 and 13
15. exp randomized controlled trials as topic/ or exp clinical trials, phase III as topic/ or exp clinical trials, phase IV as topic/
16. (randomized controlled trial or clinical trial, phase III or clinical trial, phase IV).pt.
17. random allocation/ or double blind method/ or single blind method/
18. (randomi$ control$ trial? or rct or phase III or phase IV or phase 3 or phase 4).tw.
19. or/15-18
20. (phase II or phase 2).tw. or exp clinical trial/ or exp clinical trial as topic/
21. (clinical trial or clinical trial, phase II or controlled clinical trial).pt.
22. (20 or 21) and random$.tw.
23. (clinic$ adj trial$1).tw.
24. ((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3 or dummy)).tw.
25. placebos/
26. (placebo? or random allocation or randomly allocated or allocated randomly).tw.
27. (allocated adj2 random).tw.
28. or/23-27

29. practice guidelines/
30. practice guideline?.tw.
31. practice guideline.pt.
32. or/29-31
33. 7 or 8 or 9 or 14 or 19 or 22 or 28 or 32
34. (comment or letter or editorial or note or erratum or short survey or news or newspaper article or patient education handout or case report or historical article).pt.
35. 33 not 34
36. limit 35 to english
37. Animal/
38. Human/
39. 37 not 38
40. 36 not 39
41. exp esophagus cancer/
42. ("resectable" or "oper*").tw.
43. 41 and 42
44. adjuvant chemotherapy/
45. adjuvant therapy/
46. (preoperative or neoadjuvant).tw.
47. (chemotherapy or radiotherapy or radiation or irradiation).tw.
48. exp immunotherapy/
49. (chemoradotherapy or chemoradiation).tw.
50. hyperthermia.mp.
51. or/44-50
52. 43 and 51
53. (200704: or 2008: or 2009: or 2010: or 2011: or "2012").ed.
54. 52 and 53
55. limit 54 to english language
56. remove duplicates from 55

**EMBASE**

1. exp meta analysis/ or exp systematic review/
2. (meta analy$ or metaanaly$).tw.
3. (systematic review$ or pooled analy$ or statistical pooling or mathematical pooling or statistical summar$ or mathematical summar$ or Quantitative synthes?s or quantitative overview?).tw.
4. (systematic adj (review$1 or overview$1)).tw.
5. exp review/ or review.pt.
6. (systematic or selection criteria or data extraction or quality assessment or jadad scale or methodological quality).ab.
7. (study adj selection).ab.
8. 5 and (6 or 7)
9. or/1-4,8
10. (cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or cinhal or science citation index or scisearch or bids or sigle or cancerlit).ab.
11. (reference list$ or bibliograph$ or hand-search$ or relevant journals or manual search$).ab.
12. exp randomized controlled trial/ or exp phase 3 clinical trial/ or exp phase 4 clinical trial/
13. randomization/ or single blind procedure/ or double blind procedure/
14. (randomi$ control$ trial? or rct or phase III or phase IV or phase 3 or phase 4).tw.
15. or/12-14
16. (phase II or phase 2).tw. or exp clinical trial/ or exp prospective study/ or exp controlled clinical trial/
17. 16 and random$.tw.
18. (clinic$ adj trial$1).tw.
19. ((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3 or dummy)).tw.
20. placebo/
21. (placebo? or random allocation or randomly allocated or allocated randomly).tw.
22. (allocated adj2 random).tw.
23. or/18-22
24. practice guidelines/
25. practice guideline?.tw.
26. practice guideline.pt.
27. or/24-26
28. 9 or 10 or 11 or 15 or 17 or 23 or 27
29. (editorial or note or letter or erratum or short survey).pt. or letter/ or case study/

30. 28 not 29
31. limit 30 to english
32. Animal/
33. Human/
34. 32 not 33
35. 31 not 34
36. exp esophagus cancer/
37. ("resectable" or "oper*").tw.
38. 36 and 37
39. adjuvant chemotherapy/
40. adjuvant therapy/
41. (preoperative or neoadjuvant).tw.
42. (chemotherapy or radiotherapy or radiation or irradiation).tw.
43. exp immunotherapy/
44. (chemoradiotherapy or chemoradiation).tw.
45. hyperthermia.mp.
46. or/39-45
47. 38 and 46
48. (200704: or 2008: or 2009: or 2010: or 2011: or "2012").ew.
49. 47 and 48
50. limit 49 to english
51. remove duplicates from 50

**CLINICALTRIALS (clinicaltrials.guv)**

"esophageal" AND ("preoperative" OR "postoperative")

**ASCO**

esophageal and resectable and (preoperative or postoperative)

**SAGE GUIDELINES**

Search term: “esophageal”