# Complete Summary

## GUIDELINE TITLE

Neoadjuvant or adjuvant therapy for resectable esophageal cancer.

## BIBLIOGRAPHIC SOURCE(S)

Gastrointestinal Cancer Disease Site Group. Malthaner RA, Wong RKS, Rumble RB, Zuraw L. Neoadjuvant or adjuvant therapy for resectable esophageal cancer. Toronto (ON): Cancer Care Ontario (CCO); 2005 Apr 13. 35 p. (Practice guideline report; no. 2-11). [65 references]

## GUIDELINE STATUS

**Note**: This guideline has been updated. The National Guideline Clearinghouse (NGC) is working to update this summary.

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## SCOPE

### DISEASE/CONDITION(S)

Resectable esophageal cancer

### GUIDELINE CATEGORY

Assessment of Therapeutic Effectiveness
Treatment

### CLINICAL SPECIALTY

Gastroenterology
Oncology

Radiation Oncology
Surgery

## INTENDED USERS

Physicians

## GUIDELINE OBJECTIVE(S)

To evaluate if patients with resectable esophageal carcinoma should receive neoadjuvant or adjuvant therapy along with surgery

## TARGET POPULATION

Adult patients with resectable and potentially curable thoracic (lower two-thirds of esophagus) esophageal cancer for whom surgery is considered appropriate

## INTERVENTIONS AND PRACTICES CONSIDERED

**Neoadjuvant or adjuvant therapy, versus surgery alone or surgery plus another neoadjuvant or adjuvant therapy, including the following**:

1. Preoperative radiotherapy and surgery
2. Postoperative radiotherapy and surgery
3. Preoperative radiotherapy versus postoperative radiotherapy
4. Preoperative radiotherapy and postoperative radiotherapy versus postoperative radiotherapy alone
5. Preoperative chemotherapy and surgery
6. Preoperative and postoperative chemotherapy and surgery
7. Postoperative chemotherapy and surgery
8. Preoperative chemoradiation and surgery
9. Postoperative chemotherapy and surgery versus postoperative chemoradiation and surgery
10. Postoperative chemotherapy and radiotherapy
11. Postoperative chemotherapy versus postoperative radiotherapy
12. Preoperative chemotherapy versus preoperative radiotherapy
13. Preoperative chemoradiation versus preoperative radiotherapy
14. Postoperative immunotherapy in combination with radiotherapy or chemoradiation
15. Preoperative hyperthermia in combination with chemoradiation

**Note**: None of the above adjuvant or neoadjuvant therapies are recommended as standard practice for resectable thoracic esophageal cancer if surgery is considered appropriate.

## MAJOR OUTCOMES CONSIDERED

- Survival/mortality rates
- Adverse effects
- Quality of life

## METHODOLOGY

### METHODS USED TO COLLECT/SELECT EVIDENCE

Hand-searches of Published Literature (Primary Sources)
Hand-searches of Published Literature (Secondary Sources)
Searches of Electronic Databases

### DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

#### April 2002 Guideline

MEDLINE (1966 to December 2001), CANCERLIT (1983 to October 2001), and the Cochrane Library (2001, Issue 4) 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. In addition, the Physician Data Query (PDQ) clinical trials database on the Internet http://www.cancer.gov/search/clinical_trials/ and the conference proceedings of the 1997 to 2001 annual meetings of the American Society of Clinical Oncology (ASCO) and the 1999 to 2001 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.

#### February 2005 Update

The original literature search has been updated using the following databases: MEDLINE (1966 through January week 3, 2005), EMBASE (to week 5, 2005), and the Cochrane Library database of Systematic Reviews (2004, Issue 4). Additionally, abstracts published in the proceedings of the annual meetings of ASCO to 2004 and ASTRO to 2004 were also searched for relevant trial reports. The National Cancer Institute (NCI) (formerly the PDQ database) clinical trials database on the Internet (http://www.cancer.gov/search/clinical_trials/) was also searched for reports of ongoing trials.

#### Inclusion Criteria

Articles were selected for inclusion in this systematic review of the evidence if they were fully published reports or published abstracts of meta-analyses or randomized trials of neoadjuvant or adjuvant treatments compared with surgery alone or surgery plus another neoadjuvant or adjuvant 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.

## NUMBER OF SOURCE DOCUMENTS

### April 2002 Guideline

Twenty-six fully published randomized clinical trials, three randomized trials in abstract form, and two published meta-analyses were reviewed.

### February 2005 Update

Thirteen new reports were identified, including nine randomized controlled trials, three meta-analyses, and one Cochrane Review.

## METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Expert Consensus (Committee)

## RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Not applicable

## METHODS USED TO ANALYZE THE EVIDENCE

Meta-Analysis of Randomized Controlled Trials
Review of Published Meta-Analyses
Systematic Review with Evidence Tables

## DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Because diverse treatment strategies were evaluated, the eligible studies were grouped into 13 basic treatment approaches (Table 1 in the original guideline document), and each group was examined separately for statistical heterogeneity. For each meta-analysis, data were pooled 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, 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 4.1 (Metaview© Update Software), available through the Cochrane Collaboration, was used. Pooled results were expressed as mortality risk ratio (RR) with 95% confidence interval (CI) using the random effects model. A RR less than 1.0 favours neoadjuvant or adjuvant treatment and a RR greater than 1.0 favours surgery alone. The denominator in the pooled analysis is the number of randomized patients unless results for only the evaluable or eligible patients were reported.

### Potential Sources of Heterogeneity and Sensitivity Analysis

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 $p<0.05$. Potential sources of heterogeneity were postulated a priori and included study quality using the Jadad scale (>2 versus ≤2), full article publication versus abstract publication, squamous cell versus adenocarcinoma, type of chemotherapy (cisplatin-containing versus others), radiotherapy dose (BED*>48 versus BED< 48), and type of surgery (transthoracic versus transhiatal). These factors were used to explore any significant heterogeneity of results across the trials. The robustness of our conclusions was examined through subsequent sensitivity analyses using these factors. The sensitivity analysis results are not detailed, as they would not change the conclusions.

*BED = biological equivalent dose and, in this case, also equates with the biological effective dose. To facilitate comparison across trials, radiotherapy dose was converted to biological equivalent dose using the equation BED=nd (1+d/alpha/beta), where n=number of fractions, d=dose per fraction, and the assumption that alpha/beta =10 for tumour effect. Due to the limitations of this model, no allowance can be made for time gaps in split-course treatments.

## METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

## DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

### April 2002 Guideline

After discussion, the Gastrointestinal Cancer Disease Site Group (DSG) agreed that the evidence does not support a recommendation for neoadjuvant or adjuvant chemotherapy or radiotherapy for resectable thoracic esophageal cancer. The role of radiotherapy alone and chemoradiation alone without surgery is addressed in the National Guideline Clearinghouse guideline summary of the Practice Guideline Initiative guideline #2-12, Combined Modality Radiotherapy and Chemotherapy in the Non-surgical Management of Localized Carcinoma of the Esophagus.

### February 2005 Update

After approval of the original practice guideline, the companion document on combined modality radiotherapy and chemotherapy in the non-surgical management of localized carcinoma of the esophagus was published in the Int J Radiat Oncol Biol Phys.

### RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

### COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

### METHOD OF GUIDELINE VALIDATION

External Peer Review
Internal Peer Review

### DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

Practitioner feedback was obtained through a mailed survey of 163 practitioners in Ontario (27 medical oncologists, 21 radiation oncologists, 112 surgeons, and three gastroenterologists). The survey consisted of items evaluating the methods, results, and interpretative summary used to inform the draft recommendations and whether the draft recommendations should be approved as a practice guideline. Written comments were invited. Follow-up reminders were sent at two weeks (post card) and four weeks (complete package mailed again). The Gastrointestinal Cancer Disease Site Group (DSG) reviewed the results of the survey.

The practice guideline report was circulated to members of the Practice Guidelines Coordinating Committee (PGCC) for review and approval. All 11 members of the PGCC returned ballots. Eight PGCC members approved the practice guideline report as written and three members approved the guideline conditional on the Gastrointestinal DSG addressing specific concerns.

The final practice guideline reflects the integration of the draft recommendations with feedback obtained from the external review process. It has been approved by the Gastrointestinal DSG and the PGCC.

## RECOMMENDATIONS

### MAJOR RECOMMENDATIONS

**Note**: This guideline has been updated. The National Guideline Clearinghouse (NGC) is working to update this summary. The recommendations that follow are based on the previous version of the guideline.

If surgery is considered appropriate, then surgery alone (i.e., without neoadjuvant or adjuvant therapy) is recommended as the standard practice for resectable thoracic esophageal cancer.

### CLINICAL ALGORITHM(S)

None provided

## EVIDENCE SUPPORTING THE RECOMMENDATIONS

### TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The recommendations are supported by meta-analyses and randomized trials.

## BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

### POTENTIAL BENEFITS

Appropriate treatment of patients with resectable esophageal carcinoma

### POTENTIAL HARMS

Adverse effects were inconsistently reported (see Tables 2-7 in the original guideline document). Most patients experienced treatment-related adverse effects due to radiotherapy or chemotherapy.

## QUALIFYING STATEMENTS

### QUALIFYING STATEMENTS

- A meta-analysis of 11 randomized controlled trials did detect a statistically significant difference in survival favouring preoperative chemotherapy, but at five years only.
- A single randomized controlled trial comparing preoperative cisplatin chemotherapy with surgery alone detected a significant survival advantage for neoadjuvant chemotherapy at five years.
- Two meta-analyses comprised of the results from 15 randomized controlled trials, as well as pooling performed by the Gastrointestinal Cancer Disease Site Group, all detected a statistically significant difference in survival favouring preoperative chemoradiotherapy, but at three years only.
- Therefore, the Gastrointestinal Cancer Disease Site Group acknowledges there is evidence indicating survival benefits with either neoadjuvant chemotherapy or chemoradiotherapy compared with surgery alone; however, individual trial results are inconsistent. Based on the majority of the evidence available at this time, the Gastrointestinal Cancer Disease Site Group continues to support the stated recommendations and will continue to examine new evidence as it becomes available.
- Care has been taken in the preparation of the information contained in this document. Nonetheless, any person seeking to apply or consult these guidelines is expected to use independent medical judgment in the context of

individual clinical circumstances or seek out the supervision of a qualified clinician. Cancer Care Ontario makes no representation or warranties of any kind whatsoever regarding their content or use or application and disclaims any responsibility for their application or use in any way.

## IMPLEMENTATION OF THE GUIDELINE

### DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

## INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

### IOM CARE NEED

Living with Illness

### IOM DOMAIN

Effectiveness

## IDENTIFYING INFORMATION AND AVAILABILITY

### BIBLIOGRAPHIC SOURCE(S)

Gastrointestinal Cancer Disease Site Group. Malthaner RA, Wong RKS, Rumble RB, Zuraw L. Neoadjuvant or adjuvant therapy for resectable esophageal cancer. Toronto (ON): Cancer Care Ontario (CCO); 2005 Apr 13. 35 p. (Practice guideline report; no. 2-11). [65 references]

### ADAPTATION

Not applicable: The guideline was not adapted from another source.

### DATE RELEASED

2002 Apr (revised 2005 Apr 13)

### GUIDELINE DEVELOPER(S)

Program in Evidence-based Care - State/Local Government Agency [Non-U.S.]

### GUIDELINE DEVELOPER COMMENT

The Program in Evidence-based Care (PEBC) is a project supported by Cancer Care Ontario and the Ontario Ministry of Health and Long-Term Care.

### SOURCE(S) OF FUNDING

Cancer Care Ontario
Ontario Ministry of Health and Long-Term Care

## GUIDELINE COMMITTEE

Provincial Gastrointestinal Cancer Disease Site Group

## COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

*Primary Authors*: Malthaner RA, Wong RKS, Rumble RB, Zuraw L

For a current list of past and present members of the Gastrointestinal Cancer Disease Site Group, please see the Cancer Care Ontario Web site.

## FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Members of the Gastrointestinal Cancer Disease Site Group disclosed potential conflicts of interest.

## GUIDELINE STATUS

**Note**: This guideline has been updated. The National Guideline Clearinghouse (NGC) is working to update this summary.

## GUIDELINE AVAILABILITY

Electronic copies of the updated guideline: Available in Portable Document Format (PDF) from the Cancer Care Ontario Web site.

## AVAILABILITY OF COMPANION DOCUMENTS

The following are available:

- Neoadjuvant or adjuvant therapy for resectable esophageal cancer. Summary. Toronto (ON): Cancer Care Ontario, 2005 Apr 13. Electronic copies: Available from the Cancer Care Ontario Web site.
- Malthaner R, Wong R, Rumble RB, Zuraw L, and the Gastrointestinal Cancer Disease Site Group. Neoadjuvant or adjuvant therapy for resectable esophageal cancer: a systematic review and meta-analysis. BMC Medicine 2004;2:35.
- Malthaner R, Wong R, Rumble RB, Zuraw L, and the Gastrointestinal Cancer Disease Site Group. Neoadjuvant or adjuvant therapy for resectable esophageal cancer: a clinical practice guideline. BMC Medicine 2004;4:67.
- Browman GP, Levine MN, Mohide EA, Hayward RSA, Pritchard KI, Gafni A, et al. The practice guidelines development cycle: a conceptual tool for practice guidelines development and implementation. J Clin Oncol 1995;13(2):502-12.

## PATIENT RESOURCES

None available

## NGC STATUS

This NGC summary was completed by ECRI on May 14, 2004. The information was verified by the guideline developer on June 2, 2004. This summary was updated by ECRI on September 9, 2005. The updated information was verified by the guideline developer on October 3, 2005.

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