Complete Summary

GUIDELINE TITLE

Combined modality radiotherapy and chemotherapy in the non-surgical management of localized carcinoma of the esophagus.

BIBLIOGRAPHIC SOURCE(S)

Gastrointestinal Cancer Disease Site Group. Wong RKS, Malthaner RA, Zuraw L, Rumble RB. Combined modality radiotherapy and chemotherapy in the non-surgical management of localized carcinoma of the esophagus. Toronto (ON): Cancer Care Ontario (CCO); 2005 Feb 10. 21 p. (Practice guideline report; no. 2-12). [49 references]

GUIDELINE STATUS

This is the current release of the guideline.

The FULL REPORT, initially the full original Guideline, over time will expand to contain new information emerging from their reviewing and updating activities.

Please visit the Cancer Care Ontario Web site for details on any new evidence that has emerged and implications to the guidelines.

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SCOPE

DISEASE/CONDITION(S)

Localized carcinoma of the esophagus

GUIDELINE CATEGORY

Assessment of Therapeutic Effectiveness
Management
Treatment

CLINICAL SPECIALTY

Gastroenterology
Oncology
Radiation Oncology

INTENDED USERS

Physicians

GUIDELINE OBJECTIVE(S)

To evaluate whether combined modality radiotherapy and chemotherapy improves survival compared with radiotherapy alone in patients with localized carcinoma of the esophagus for whom a non-surgical approach is used

TARGET POPULATION

Adult patients with localized (T1-3, small volume N1, M0) carcinoma of the esophagus and good performance status who are considering a non-surgical approach and for whom combined radiotherapy and chemotherapy can be tolerated in the judgment of the treating oncologist

INTERVENTIONS AND PRACTICES CONSIDERED

1. Concomitant radiotherapy and chemotherapy
2. Radiotherapy alone

MAJOR OUTCOMES CONSIDERED

- Overall survival
- Local recurrence
- Adverse effects

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

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

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

Literature Search Strategy

Original Guideline

MEDLINE (1966 to December 2001), CANCERLIT (1983 to October 2001), and the Cochrane Library (2001, Issue 4) were searched with no language restrictions. Medical subject heading (MeSH) terms employed included "esophageal neoplasms" with subheadings "drug therapy," "radiotherapy," or "therapy." The terms used to capture randomized trials included the use of "randomized controlled trials," "controlled clinical trials," "random allocation," "exp clinical trials," and the text word "random." The proceedings of the 1999, 2000, and 2001 annual meetings of the American Society of Clinical Oncology (ASCO) and the American Society for Therapeutic Radiology and Oncology (ASTRO) were also searched. Ongoing trials were identified through the Physician Data Query (PDQ) database (http://www.cancer.gov/search/clinical_trials/).

February 2005 Update

The literature search was updated on February 10, 2005 using the following databases: MEDLINE (through February week 1, 2005), EMBASE (through week 6, 2005), and the Cochrane Library's Database of Systematic Reviews (through Issue 4, 2004). Abstracts published in the proceedings of the annual meetings of the American Society of Clinical Oncology and the American Society for Therapeutic Radiology and Oncology through 2004 were also searched for relevant evidence. The National Cancer Institute's (NCI) clinical trials database was also searched on February 10, 2005 for listings of ongoing clinical 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 randomized trials of combination chemotherapy and radiotherapy compared with radiotherapy alone in adult patients with primary esophageal carcinoma.

Exclusion Criteria

- Esophagectomy as a planned intervention
- Use of pure radiosensitizer (e.g. misonidazole) with radiotherapy

NUMBER OF SOURCE DOCUMENTS

Ten randomized trials of concomitant chemoradiotherapy (RTCT) met the inclusion criteria. After a careful evaluation of the methodology, it was decided to include only eight of these trials in the analysis. In addition, five fully published, randomized trials of sequential chemoradiotherapy met the inclusion criteria and were included in this 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
Systematic Review with Evidence Tables

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Synthesizing the Evidence

Studies of combined modality radiotherapy and chemotherapy can generally be categorized as using a **concomitant** or **sequential** approach based on the relative timing of the radiotherapy and chemotherapy, with different biological bases behind their designs. In this report, the trials that used a concomitant approach were described and analyzed separately from trials using a sequential approach. When data from trials of sequential and concomitant approaches were examined together, the pooled data were heterogeneous, suggesting that the studies are different in nature. Thus, a combined analysis of both approaches was rejected.

Data on survival and local recurrence were pooled and the results were examined for statistical heterogeneity. For each meta-analysis, data were pooled at a common time-point (e.g., mortality at one-year). 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 because the weighted median survival time was less than one year for both the concomitant and sequential groups.

The study results were pooled using Review Manager 4.0.3 (Metaview© Update Software), which is available through the Cochrane Collaboration. The random effects model was used as the more conservative estimate of effect. Results were expressed as odds ratios (OR) with 95% confidence intervals (CI). An odds ratio less than 1.0 favours the experimental treatment (i.e., radiochemotherapy [RTCT]) and an odds ratio greater than 1.0 favours the control (i.e., radiotherapy [RT] alone). In addition, the absolute difference is presented as percent difference in outcome, calculated from the pooled event rates. The number of patients that need to be treated with RTCT for one additional patient to benefit (NNT) was also calculated.

Results for adverse effects were not pooled because the primary authors of eligible trials reported data on adverse effects using different scoring systems and symptom categories. The presentation of the incidence of adverse effects (as opposed to the numbers of patients affected within each toxicity grade) makes a quantitative summary statistic difficult. The results were summarized in a descriptive fashion for this review based on the incidence of grade of toxicity for acute and late adverse effects, where available across the studies, to allow for a qualitative comparison.

Data extraction was performed independently by two members of the Gastrointestinal Cancer Disease Site Group (DSG). Discrepancies were resolved through consensus.

Subgroup Analysis

It was hypothesized a priori that the use of cisplatin versus non-cisplatin chemotherapy would have an impact on the effectiveness of treatment, and a subgroup analysis was planned to examine this hypothesis. The two most commonly employed chemotherapy regimens in Canada are 5-fluorouracil (5FU)/mitomycin and 5FU/cisplatin, and one of the major decisions facing clinicians is what type of chemotherapy to use if the combined modality approach is adopted. Furthermore, cisplatin-based chemotherapy has been used in combination with radiotherapy in many other disease systems resulting in significant improvement in outcome. It is, therefore, important to explore the impact of cisplatin versus non-cisplatin chemotherapy within the context of combined modality.

Potential Sources of Heterogeneity and Sensitivity Analysis

The following factors were postulated *a priori* to be potential sources of heterogeneity: study quality using scores on the Jadad scale (>2 versus $\leq$2); dose of radiotherapy (biological effective [or equivalent] dose (BED)* >60 versus BED $\leq$60); and type of chemotherapy (cisplatin-containing versus others). These factors were used to explore any significant heterogeneity of results across the trials. Heterogeneity of study results was assessed using a visual plot and by calculating the Breslow-Day statistic using a planned cut-off for significance of $p<0.05$. The robustness of our conclusions was examined through subsequent sensitivity analyses using these factors.

*Note: 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

Disease Site Group Consensus Process

The Gastrointestinal Cancer Disease Site Group (DSG) readily agreed upon and approved the contents of the practice guideline report. The committee felt, however, that it was important to highlight the following issues.

The meta-analysis of survival benefit was based on one-year data only; therefore, caution must be used when interpreting the results, especially when long-term survival benefit is considered.

The Gastrointestinal Cancer DSG members debated how to address the issue of what type of chemotherapy to recommend in the context of a combined radiotherapy and chemotherapy approach. The current review was undertaken to address the general question of whether a combined approach is superior to radiotherapy alone and, therefore, was not designed to answer the question of what specific type of chemotherapy-radiotherapy regimen is superior to others. To address the latter question, the DSG would need to review randomized studies comparing a standard type of combined radiotherapy and chemotherapy versus an experimental one, but these studies are not available. In the current review, it was hypothesized that whether or not cisplatin-based chemotherapy was used would have an impact on the conclusion of the review, and the subgroup analysis in fact did support this. The current clinical practice in North America in this area has been heavily shaped by the results of the Radiation Therapy Oncology Group (RTOG) study. There has been a substantial increase in the use of combined radiotherapy and chemotherapy in recent years, and when it is used, 5-fluorouracil (5FU) and cisplatin are the chemotherapy agents most commonly employed. The DSG felt that given the results of the meta-analysis and the current practice pattern, the use of a cisplatin-containing regimen should be the treatment of choice when concomitant radiotherapy and chemotherapy is used. For patients with poor performance status, radiotherapy alone or optimal palliative therapy should be considered.

The DSG also felt that it is important to point out the significant risk of toxicity associated with concomitant radiotherapy and chemotherapy. This fact may indeed outweigh the potential benefits in survival and local control, depending on the patient's general condition. The decision to adopt a combined radiotherapy and chemotherapy approach over radiotherapy alone for the curative management of carcinoma of the esophagus should be undertaken only after due consideration of these factors and in consultation with the patient.

The group also felt it should be made clear that there are no randomized trials of chemoradiation alone versus surgery alone as the primary modality for patients with curable esophageal cancer who are suitable for both (surgical and non-surgical) approaches.

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

Practitioner feedback was obtained through a mailed survey of 163 practitioners in Ontario (28 medical oncologists, 21 radiation oncologists, 111 surgeons, and three 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 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.

Practice Guidelines Coordinating Committee Approval Process

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. Ten PGCC members approved the practice guideline report as written and one member approved the guideline conditional on the Gastrointestinal DSG addressing specific concerns.

Approved Practice Guideline Recommendations

These practice guideline recommendations reflect the integration of the draft recommendations with feedback obtained from the external review process. They have been approved by the Gastrointestinal Cancer DSG and the Practice Guidelines Coordinating Committee.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

- Concomitant radiotherapy and chemotherapy is recommended over radiotherapy alone. Based on considerations of the current clinical practice pattern and the currently available research evidence, a cisplatin-based chemotherapy regimen is a reasonable chemotherapy regimen to use when concomitant radiotherapy and chemotherapy is used.
- Patients should be made aware of the increased acute toxicity associated with this approach. The decision to use concomitant radiotherapy and chemotherapy should only be made after careful consideration of the potential risks, benefits, and the patient's general condition.
- Sequential radiotherapy and chemotherapy is not recommended as standard practice.
- Future clinical trials to better define the optimal chemoradiotherapy combination that would improve outcomes while limiting toxicities are strongly encouraged.

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

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

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

- A pooled analysis of seven randomized trials involving a total of 687 patients detected a statistically significant survival benefit at one year for concomitant radiotherapy and chemotherapy compared with radiotherapy alone (one-year mortality odds ratio, 0.61; 95% confidence interval, 0.44 to 0.84; $p<0.00001$).
- Local control is also significantly improved with concomitant radiotherapy and chemotherapy compared with radiotherapy alone where data are available (odds ratio, 0.52; 95% confidence interval, 0.31 to 0.89; $p=0.004$).

POTENTIAL HARMS

Concomitant radiotherapy and chemotherapy is associated with a significant increase in adverse effects, including life-threatening toxicities, compared with radiotherapy alone.

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

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 judgement 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
Patient-centeredness

IDENTIFYING INFORMATION AND AVAILABILITY

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ADAPTATION

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

DATE RELEASED

2002 Apr 17 (revised 2005 Feb 10)

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 Province of Ontario initiative sponsored 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

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

FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Members of the Gastrointestinal Cancer Disease Site Group (DSG) disclosed potential conflict of interest information.

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GUIDELINE AVAILABILITY

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

AVAILABILITY OF COMPANION DOCUMENTS

The following are available:

- Combined modality radiotherapy and chemotherapy in the non-surgical management of localized carcinoma of the esophagus. Summary. Toronto (ON): Cancer Care Ontario. Electronic copies: Available in Portable Document Format (PDF) from the Cancer Care Ontario Web site.
- 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 January 23, 2004. The information was verified by the guideline developer as of February 23, 2004. This NGC summary was updated by ECRI on November 23, 2005. The updated information was verified by the guideline developer on December 13, 2005.

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