Complete Summary

GUIDELINE TITLE

Neoadjuvant or adjuvant therapy for resectable gastric cancer.

BIBLIOGRAPHIC SOURCE(S)

Gastrointestinal Cancer Disease Site Group. Earle CC, Maroun J, Zuraw L. Neoadjuvant or adjuvant therapy for resectable gastric cancer [full report]. Toronto (ON): Cancer Care Ontario (CCO); 2003 May 21 [online update]. 21 p. (Practice guideline; no. 2-14). [79 references]

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SCOPE

DISEASE/CONDITION(S)

Resectable gastric cancer

GUIDELINE CATEGORY

Assessment of Therapeutic Effectiveness
Evaluation
Treatment

CLINICAL SPECIALTY

Gastroenterology
Internal Medicine
Oncology
Radiation Oncology

INTENDED USERS

Physicians

GUIDELINE OBJECTIVE(S)

To evaluate whether patients with resectable gastric cancer should receive neoadjuvant or adjuvant therapy in addition to surgery

TARGET POPULATION

Adults patients with potentially curable surgically resected (T1-4, N0-2, M0) gastric cancer

INTERVENTIONS AND PRACTICES CONSIDERED

Surgical resection of gastric cancer alone compared with surgery + one of the following treatments:

1. Adjuvant combined chemoradiotherapy (5-fluorouracil + radiotherapy or 5-fluorouracil/leucovorin + radiotherapy)
2. Adjuvant systemic chemotherapy (thiotepa, 5-fluorouracil, cytarabine [Ara-C], bacillus Calmette-Guerin, carmustine, cyclophosphamide, etoposide, doxorubicin [Adriamycin], cisplatin, mitomycin C, fluorodeoxyuridine, methyl lomustine, methotrexate)
3. Adjuvant intraperitoneal chemotherapy (cisplatin, 5-fluorouracil, leucovorin, mitomycin C)
4. Adjuvant radiotherapy
5. Adjuvant chemoimmunotherapy (mitomycin C, 5-fluorouracil, cytarabine, bacillus Calmette-Guerin, cyclophosphamide, methyl lomustine, levamisole, OK-432 [picibanil], polysaccharide K, cimetidine)
6. Neoadjuvant chemotherapy
7. Neoadjuvant radiotherapy
8. Neoadjuvant immunotherapy (OK-432, propionibacterium avidum KP-40, polysaccharide K)

MAJOR OUTCOMES CONSIDERED

- Survival rates (overall and relapse-free)
- Toxicity

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

Original Guideline

MEDLINE (1966 to January 2002), CANCERLIT (1983 to October 2001), and the Cochrane Library (Issue 1, 2002) databases were searched with no language restrictions. "Stomach neoplasms" (Medical subject heading [MeSH]) and the text word "gastric cancer" were combined with "chemotherapy, adjuvant" (MeSH), "radiotherapy, adjuvant" (MeSH), "immunotherapy" (MeSH), and the following phrases used as text words: "preoperative or neoadjuvant," "chemotherapy," "radiotherapy," "radiation therapy," "irradiation," "immunotherapy," "chemoimmunotherapy," "immunochemotherapy," "immunoradiotherapy," and "radioimmunotherapy." These terms were then combined with the search terms for the following study designs and publication types: practice guidelines, meta-analyses, and randomized controlled trials. In addition, the Physician Data Query (PDQ) clinical trials database on the Internet, and the proceedings of the 1996 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 selected and reviewed by one reviewer and the reference lists from these sources were searched for additional trials.

2003 Update

The original literature search has been updated using the MEDLINE database (February 2002 through April 2003) and the Cochrane Library database of Systematic Reviews (Issue 1, 2003). Due to the U.S. National Library of Medicine's decision to no longer update the CANCERLIT database in April 2003, the Gastrointestinal Cancer DSG will not be searching this database for future updates. The 2002 proceedings of American Society of Clinical Oncology and American Society for Therapeutic Radiology and Oncology were also searched for relevant abstracts. In addition, the Physician Data Query (PDQ) clinical trials database was searched for relevant trials.

Inclusion Criteria

Articles were selected for inclusion in this overview of the evidence if they were fully published reports or published abstracts of randomized trials or systematic overviews of randomized trials of adjuvant or neoadjuvant treatments compared with "curative" surgery alone in patients with resectable gastric cancer. Data on overall survival had to be reported. Other outcomes of interest were disease-free survival and adverse effects.

NUMBER OF SOURCE DOCUMENTS

Original Guideline

The literature search identified 47 randomized trials of adjuvant therapy, including combined chemoradiotherapy, systemic and intraperitoneal chemotherapy, radiotherapy, and chemoimmunotherapy, as well as three literature-based meta-analyses of adjuvant chemotherapy compared with surgery alone. Nine randomized trials of surgery alone compared with neoadjuvant chemotherapy, radiotherapy, or immunotherapy were also found.

2003 Update

Updating procedures obtained five new reports relevant to this guideline. One report compared an adjuvant chemoradiotherapy regimen to surgery alone. Another compared a systemic chemotherapy regimen to surgery alone. Two others are literature-based meta-analyses of randomized trials comparing systemic chemotherapy to surgery alone. The fifth report compared neoadjuvant radiotherapy to surgery alone.

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

Review of Published Meta-Analyses
Systematic Review with Evidence Tables

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Not stated

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) agreed upon and approved the contents of the guideline, indicating that it was an important change to the longstanding standard practice of surgery alone for resectable gastric cancer. Gastrointestinal Cancer DSG members want to emphasize that multi-disciplinary assessment of each patient should be carried out before committing them to adjuvant chemoradiotherapy, to ensure that all participants agree on the appropriateness of the treatment plan.

The DSG discussed the issue of whether unpublished studies available in only abstract form should be admitted as evidence for guidelines. It was decided that this should be determined on a case by case basis. The Southwest Oncology Group chemoradiotherapy trial was a large, multi-centre trial that clearly demonstrated a survival benefit in favour of adjuvant chemoradiotherapy compared with surgery alone. Based on the results of this trial, the DSG members felt that there was sufficient evidence to recommend that patients with adenocarcinoma of the stomach or gastroesophageal junction whose tumours

penetrated the muscularis propria or involved regional lymph nodes should be considered for adjuvant combined chemoradiotherapy following surgical resection.

Adjuvant chemotherapy was not the standard of care prior to the Southwest Oncology Group (SWOG) chemoradiotherapy trial, as evidenced by the no treatment control arm in that trial. However, the results of the three literature-based meta-analyses suggest that adjuvant chemotherapy alone would be a reasonable alternative in patients unable to undergo radiation. The interventions in the component trials were heterogeneous, however, so no specific regimen could be recommended.

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 166 practitioners in Ontario (27 medical oncologists, 21 radiation oncologists, 155 surgeons, and three gastroenterologists). The survey consisted of 21 items evaluating the methods, results, and interpretive summary used to inform the draft recommendations outlined 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 results of the survey have been reviewed by the Gastrointestinal Cancer Disease Site Group.

The practice guideline reflects the integration of the draft recommendations with feedback obtained from the external review process. It has been approved by the Gastrointestinal Cancer Disease Site Group and the Practice Guidelines Coordinating Committee.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

- Following surgical resection, patients whose tumours penetrated the muscularis propria or involved regional lymph nodes should be considered for adjuvant combined chemoradiotherapy. The current standard protocol consists of one cycle of 5-fluorouracil (FU) (425 mg/m^2/day) and leucovorin

(20 mg/m^2/day) in a daily regimen for five days, followed one month later by 4,500 cGy (180 cGy/day) of radiation given with 5-FU (400 mg/m^2/day) and leucovorin (20 mg/m^2/day) on days 1 through 4 and the last three days of radiation. One month after completion of radiation, two cycles of 5-FU (425 mg/m^2/day) and leucovorin (20 mg/m^2/day) in a daily regimen for five days are given at monthly intervals.
- There is no evidence on which to make a recommendation for patients with node-negative tumours that have not penetrated the muscularis propria.
- For patients unable to undergo radiation, adjuvant chemotherapy alone may be of benefit, particularly for patients with lymph node metastases. The optimal regimen remains to be defined.
- There is insufficient evidence from randomized trials to recommend neoadjuvant chemotherapy, or neoadjuvant or adjuvant radiation therapy or immunotherapy, either alone or in combination, outside of a clinical trial.

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

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

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

- A large intergroup trial has confirmed statistically significant improvement in overall and relapse-free survival with adjuvant combined chemoradiotherapy. Compared to surgery alone, overall survival at three years was improved by 9% (50% versus 41%, p=0.005), and relapse-free survival was increased from 31 to 48%, p=0.001 [two-sided log-rank test], in the chemo-radiotherapy group. At five years, adjuvant chemo-radiotherapy increased overall survival by 11.6% (40% versus 28.4%), and improved relapse-free survival from 25 to 38%, p<0.001 [two-sided log-rank test], compared to surgery alone.
- With respect to adjuvant chemotherapy alone, three literature-based meta-analyses of randomized trials also detected modest benefits, particularly in lymph node-positive patients.

POTENTIAL HARMS

In General

- Many of the adjuvant regimens reported in the literature have caused significant treatment-related morbidity and even death. Chemotherapy in

particular can cause hematological toxicity, infections, and gastrointestinal side effects.

Combined chemoradiotherapy

- The treatment was described as tolerable, although there were three (1%) toxic deaths, 41% grade 3 toxicity, and 32% grade 4 toxicity. The most frequent adverse effects (≥grade 3) were hematologic (54%), gastrointestinal (33%), influenza-like (9%), infectious (6%), and neurologic (4%). Furthermore, it is now suspected that the radiation fields used are known to possibly damage the left kidney, resulting in hypertension and other renal problems.

Adjuvant systemic chemotherapy

- Adverse effects, such as hematologic toxicity, infection, nausea and vomiting, stomatitis, and alopecia, can be significant with adjuvant chemotherapy, although often balanced by symptomatic improvement. However, toxicity has resulted in less than 80% of planned doses being administered in many trials.

Adjuvant intraperitoneal chemotherapy

- A trial by the Austrian Working Group for Surgical Oncology was terminated early because the intervention group had higher rates of postoperative complications (35% versus 16% in the control group, $p<0.02$) and postoperative deaths (11% versus 2%), without any benefit in overall or recurrence-free survival.

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

- Patients should understand the tradeoffs between survival benefit and toxicity before making treatment decisions.
- 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
Patient-centeredness

IDENTIFYING INFORMATION AND AVAILABILITY

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ADAPTATION

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

DATE RELEASED

2000 Dec 6 (updated online 2003 May)

GUIDELINE DEVELOPER(S)

Practice Guidelines Initiative - State/Local Government Agency [Non-U.S.]

GUIDELINE DEVELOPER COMMENT

The Practice Guidelines Initiative (PGI) is the main project of the Program in Evidence-based Care (PEBC), 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 disclosed potential conflict of interest information.

GUIDELINE STATUS

This is the current release of the guideline.

The FULL REPORT, initially the full original Guideline or Evidence Summary, 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.

GUIDELINE AVAILABILITY

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

AVAILABILITY OF COMPANION DOCUMENTS

The following is available:

- Neoadjuvant or adjuvant therapy for resectable gastric cancer. 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 June 23, 2003. The information was verified by the guideline developer as of July 16, 2003. This summary was updated by ECRI on January 23, 2004. The information was verified by the guideline developer as of February 23, 2004.

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