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Neoadjuvant or Adjuvant Therapy for Resectable Gastric Cancer
Practice Guideline Report #2-14

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ORIGINAL GUIDELINE: December 2000
MOST RECENT LITERATURE SEARCH: May 12, 2003
NEW EVIDENCE ADDED TO THE GUIDELINE REPORT: May 21, 2003

New evidence found by update searches since completion of the original guideline is consistent with the original recommendations.

SUMMARY

Guideline Question

Should patients with resectable gastric cancer (T1-4,N0-2,M0) receive neoadjuvant or adjuvant therapy in addition to surgery?

Target Population

These recommendations apply to adult patients with potentially curable surgically resected (T1-4,N0-2,M0) gastric cancer.

Recommendation

- 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-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.

Qualifying Statements

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

Methods

Entries to the MEDLINE database (1966 through April 2003), CANCERLIT (1983 to October 2001), and the Cochrane Library database of Systematic Reviews (2003, Issue 1) and 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 were systematically searched for evidence relevant to this practice guideline report.

Evidence was selected and reviewed by two members of the Practice Guidelines Initiative Gastrointestinal Cancer Disease Site Group and methodologists. This practice guideline report has been reviewed and approved by the Gastrointestinal Cancer Disease Site Group, which comprises medical oncologists, radiation oncologists, surgeons, a pathologist, and two patient representatives.

External review by Ontario practitioners was obtained through a mailed survey. Final approval of the practice guideline report was obtained from the Practice Guidelines Coordinating Committee.

The Practice Guidelines Initiative has a formal standardized process to ensure the currency of each guideline report. This process consists of periodic review and evaluation of the scientific literature and, where appropriate, integration of this literature with the original guideline information.

Key Evidence

- 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 detected modest benefits, particularly in lymph node-positive patients.
- Randomized trials of neoadjuvant chemotherapy, or neoadjuvant or adjuvant radiotherapy or immunotherapy have thus far failed to detect a consistent benefit for these treatments compared with surgery alone.

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PREAMBLE: About Our Practice Guideline Reports

The Practice Guidelines Initiative (PGI) is a project supported by Cancer Care Ontario (CCO) and the Ontario Ministry of Health and Long-Term Care, as part of the Program in Evidence-based Care. The purpose of the Program is to improve outcomes for cancer patients, to assist practitioners to apply the best available research evidence to clinical decisions, and to promote responsible use of health care resources. The core activity of the Program is the development of practice guidelines by multidisciplinary Disease Site Groups of the PGI using the methodology of the Practice Guidelines Development Cycle.[1] The resulting practice guideline reports are convenient and up-to-date sources of the best available evidence on clinical topics, developed through systematic reviews, evidence synthesis, and input from a broad community of practitioners. They are intended to promote evidence-based practice.

This practice guideline report has been formally approved by the Practice Guidelines Coordinating Committee (PGCC), whose membership includes oncologists, other health providers, patient representatives, and Cancer Care Ontario executives. Formal approval of a practice guideline by the Coordinating Committee does not necessarily mean that the practice guideline has been adopted as a practice policy of CCO. The decision to adopt a practice guideline as a practice policy rests with each regional cancer network that is expected to consult with relevant stakeholders, including CCO.

Reference:
[1] 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.

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FULL REPORT

I. QUESTION

Should patients with resectable gastric cancer (T1-4,N0-2,M0) receive neoadjuvant or adjuvant therapy in addition to surgery?

II. CHOICE OF TOPIC AND RATIONALE

The incidence of gastric cancer has been decreasing steadily since the 1930s (1). Despite this, it is the eighth leading cause of cancer death because the majority of patients present with advanced disease (2). The survival rate is about 75% at five years for patients with localized disease without regional lymph node involvement in whom the cancer is managed with surgery alone (3). However, the prognosis worsens with progressive lymph node involvement, which predicts an increase in the probability of local and distant recurrences. As a result, there is great interest in finding ways to improve the treatment results for this group of patients.

Adjuvant treatments following surgery have been shown to improve survival in several other cancers with similar patterns of relapse. Although many clinical trials have explored the value of neoadjuvant or adjuvant chemotherapy, radiotherapy, and immunotherapy in gastric cancer, these trials have produced conflicting results, making the role of neoadjuvant and adjuvant therapy controversial. Results of gastric cancer treatment have tended to be better for studies carried out in Asian countries, possibly related to etiologic or biologic differences in the disease or different practices such as screening for early stage cancer, the use of extended lymph node dissection, and the commencement of chemotherapy immediately after surgery. Attempts to replicate these interventions outside the Asian setting have not been successful (4), raising questions as to whether these trials should be compared to studies conducted in Western countries. A systematic review and practice guideline is therefore warranted.

III. METHODS

Guideline Development

This practice guideline report was developed by the Practice Guidelines Initiative (PGI) of Cancer Care Ontario's Program in Evidence-based Care (PEBC), using methods of the Practice Guidelines Development Cycle (5). Evidence was selected and reviewed by one member of the PGI Gastrointestinal Cancer Disease Site Group (DSG) and methodologists. Members of the Gastrointestinal Cancer DSG disclosed potential conflict of interest information.

The practice guideline report is a convenient and up-to-date source of the best available evidence on neoadjuvant and adjuvant therapy for resectable gastric cancer, developed through systematic reviews, evidence synthesis and input from practitioners in Ontario. The body of evidence in this report is primarily comprised of mature randomized controlled trial data; therefore, recommendations by the Gastrointestinal Cancer DSG are offered. The report is intended to enable evidence-based practice. The PGI is editorially independent of Cancer Care Ontario and the Ontario Ministry of Health and Long-Term Care.

External review by Ontario practitioners was obtained through a mailed survey consisting of items that address the quality of the draft practice guideline report and recommendations and whether the recommendations should serve as a practice guideline. Final approval of the original guideline report was obtained from the Practice Guidelines Coordinating Committee (PGCC).

The PGI has a formal standardized process to ensure the currency of each guideline report. This consists of periodic review and evaluation of the scientific literature and, where appropriate, integration of this literature with the original guideline information.

Literature Search Strategy

MEDLINE (1966 through January 2002), CANCERLIT (1983 through 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 (http://cancer.gov/search/clinical_trials/), 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.

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 ASCO and ASTRO were also searched for relevant abstracts. In addition, the Physician Data Query (PDQ) clinical trials database on the Internet (http://cancer.gov/search/clinical_trials/) 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.

Synthesizing the Evidence

It was decided not to pool the results of trials of adjuvant chemotherapy for gastric cancer because of the availability of up-to-date, published meta-analyses that included the most recent randomized trials of adjuvant chemotherapy compared with surgery alone. The trials of other neoadjuvant and adjuvant therapies not included in these literature-based meta-analyses were felt to be too clinically heterogeneous to pool.

IV. RESULTS

Literature Search Results

A classification of the nature of the published evidence is shown in Table 1. 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. Where results have been reported or updated in more than one publication, only the most recent publication is listed. Patients with very early stage tumours were excluded from many studies or were not reported separately.

Update

Updating procedures obtained five new reports relevant to this guideline (1u-5u). Hundahl et al (1u) compared an adjuvant chemoradiotherapy regimen to surgery alone. Bajetta et al (2u) compared a systemic chemotherapy regimen to surgery alone. Hu et al (3u) and Panzini et al (4u) are literature-based meta-analyses of randomized trials comparing systemic chemotherapy to surgery alone. Skoropad et al (5u) compared neoadjuvant radiotherapy to surgery alone. Results of these trials and meta-analyses are detailed in the update sections of this guideline.

Table 1. Randomized trials and meta-analyses of neoadjuvant or adjuvant therapy with surgery versus surgery alone in resectable gastric cancer.

Treatment Approach	Number	Reference(s)	Summary of Results
Adjuvant			
Chemoradiotherapy	4	7-9,1u	Table 2
Systemic Chemotherapy	31	10-39,2u	Table 3
Literature-based meta-analyses	5	43,46,47,3u,4u	-
Intraperitoneal Chemotherapy	7	40,49,50-54	Table 4
Radiotherapy	2	28,55	Table 5
Chemoimmunotherapy	9	19,23,24,41,42,56-59	Table 6
Neoadjuvant			
Chemotherapy	3	65-67	-
Radiotherapy	4	68-70,5u	-
Immunotherapy	3	71-73	-

Combined Chemoradiotherapy versus Surgery

Interest in adjuvant radiation as a treatment is based on the observation that over 80% of patients who die from gastric cancer experience a local recurrence some time in their illness (6). However, as described below, adjuvant radiotherapy alone has been disappointing. To improve the efficacy of radiation, 5-fluorouracil (5-FU) has been used as a radiosensitizer in three randomized trials (7-9) (Table 2). A study by Dent et al (7) detected only a non-significant trend towards improved survival in patients randomized to adjuvant chemoradiotherapy. Conversely, a study by Moertel et al (8) detected improved survival in treated patients, but this study has been criticized because randomization took place before consent, and 25% of patients refused treatment. The patients who refused treatment actually had the best survival of all groups (five-year survival rate was 30%). Furthermore, there was a high rate of treatment discontinuation in both studies (7,8) due to local side effects from radiotherapy.

Recently, an intergroup trial led by the Southwest Oncology Group (SWOG) randomized 556 patients following potentially curative resection of gastric cancer to either observation alone (n=275) or adjuvant combined chemoradiotherapy (n=281) (SWOG-9008) (9). Eligibility criteria for this study included histologically confirmed adenocarcinoma of the stomach or gastroesophageal junction followed by complete resection of the neoplasm (stage IB through IVM0 according to American Joint Commission on Cancer's staging criteria (1988)), a SWOG performance status of 2 or lower, and adequate function of major organs. The treatment consisted of one cycle of 5-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 were given at monthly intervals. Median follow-up was five years. 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. 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. Also, there has been some suggestion that the surgery performed in this trial was often not up to the desired standards. For example, extensive (D2) lymph-node dissection was recommended for all patients, but only 10% actually received this treatment. For this reason, radiotherapy may have been making up for incomplete surgery. Initial patient compliance with radiotherapy treatment was reported in abstract form, and 35% had major or minor protocol deviations, but final quality analysis reviews of radiotherapy compliance showed major protocol deviations in only 6.5% of all treatment plans.

Update

The report on combined chemoradiotherapy versus surgery alone by Hundahl et al (1u) is a follow-up analysis and update of an earlier report (9) on the SWOG 9008 (Intergroup 0116) trial. Using the Maruyama Index, an analysis of surgical treatment variables was performed on the SWOG 9008 trial data. The Maruyama Index is a measure of unresected regional lymph-node involvement in gastric cancer performed by computer software that reports the percentage likelihood of disease at each of the 16 lymph node stations around the stomach as defined by the Japanese Research Society for the Study of Gastric Cancer. The efficacy of the Maruyama index as a predictor of lymph node involvement has been evaluated in several studies, and has shown high accuracy (1u). No statistically significant interaction between surgical or pathological variables was detected, but this analysis was deemed underpowered. A statistically significant difference for survival was detected favouring adjuvant chemoradiotherapy treatment versus surgery alone. In this study, the Maruyama Index was found to be an independent predictor of survival. The study also found surgical undertreatment to negatively impact survival.

Table 2. Adjuvant combined chemoradiotherapy versus surgery alone.

Author, Year (Reference)	Median Follow-up, Months	Treatment Groups	Number of Patients	% Survival 3yr	% Survival 5yr	p-value
Dent, 1979 (7)	NR	Obs 5-FU + RT	17 18	NR		NS (estimated survival rate at 140 weeks was 40% versus 32%)
Moertel, 1984 (8)	NR	Obs 5-FU + RT	23 39	7* 35*	4* 20*	p=0.024
Macdonald, 2001 (9)	60	Obs 5-FU/LV + RT	275 281	41 50	28 40	p=0.005 [two—sided log-rank test]
Hundahl, 2002 (1u) [update of reference 9]	NR	Obs 5-FU/LV + RT	275 281	41 50	28 40	p=0.005 [two—sided log-rank test]

Note: 5-FU/LV, 5-fluorouracil and leucovorin; NR, not reported; NS, not significant; Obs, observation; RT, radiotherapy.
* Estimated from survival curve.

Adjuvant Systemic Chemotherapy

Table 3 presents 30 randomized trials of postoperative adjuvant systemic chemotherapy versus surgery alone in resectable gastric cancer. A literature-based meta-analysis of 11 randomized trials (17,18,22,24-26,28,29,40,41,42) by Hermans et al (43) initially detected only a non-significant trend towards improved survival for adjuvant chemotherapy. Hermans et al (43) tested for statistical heterogeneity, and they attributed the significant heterogeneity to one particular trial. An early report (44) of the trial by Grau (29) detected a strong positive effect with mitomycin C, and the upper limit of the confidence interval (CI) around the odds ratio for this trial was far below the lower limit of the confidence interval around the pooled odds ratio for the other trials. The interventions were also varied as trials of intraperitoneal chemotherapy and immunochemotherapy were included in this meta-analysis of published reports. The authors wrote an addendum in 1994 (45) in which they

recalculated the odds ratio (OR). This addendum included two trials missing from the original meta-analysis (16,21). The mortality OR was 0.82 (95% CI, 0.68 to 0.98) in favour of adjuvant chemotherapy. Testing for heterogeneity was not reported.

Several subsequently reported trials detected at least trends towards benefit with adjuvant chemotherapy. A second literature-based meta-analysis (46) of 13 Western randomized trials of adjuvant systemic chemotherapy versus surgery alone (15-18,22,24,26,27,29,30,32,34,35) detected a statistically significant survival benefit favouring adjuvant treatment (OR, 0.80; 95% CI, 0.66 to 0.97). There was no significant heterogeneity in the results across trials. Subgroup analyses showed a trend towards a larger magnitude of the effect for trials in which at least two thirds of the patients had node-positive disease (OR, 0.74; 95% CI, 0.59 to 0.95).

A third literature-based meta-analysis of 20 trials (21 comparisons) reached similar conclusions; pooling detected a relative 18% reduction in the risk of death with adjuvant chemotherapy compared with surgery alone (hazard ratio, 0.82; 95% CI, 0.75 to 0.89; $p<0.001$) (47). The test for heterogeneity was statistically significant, and Mari et al (47) conducted separate pooled analyses for the subgroup of mono-chemotherapy trials, poly-chemotherapy trials with anthracycline, and poly-chemotherapy trials without anthracycline. The results indicated a larger magnitude of effect with mono-chemotherapy (mitomycin C) compared with poly-chemotherapy. The upper limit of the confidence interval around the hazards ratio for the mono-chemotherapy subgroup did not overlap with the lower limit of the confidence interval around the hazards ratio for either of the poly-chemotherapy subgroups. Mari et al (47) examined possible explanations including a dose-response relationship and study quality, but they noted that the pooled results of the trials of poly-chemotherapy would be more reliable because 17 trials involved poly-chemotherapy compared with only three mono-chemotherapy trials. Of note, Mari et al (47) included in the mono-chemotherapy subgroup both the trial by Grau (29) and an earlier report of the same trial (44). It is likely that this error contributed to the significant heterogeneity since the positive results of this trial were counted twice in the literature-based meta-analysis.

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 (48). However, toxicity has resulted in less than 80% of planned doses being administered in many trials (15,16,18,26,30).

Update

Updating obtained three new reports on adjuvant systemic chemotherapy compared to surgery alone; one randomized trial (2u), and two meta-analyses (3u,4u). Bajetta et al (2u) reported the results of a trial by the Italian Trials in Medical Oncology (ITMO) Group that was included in the ongoing trials section of the original guideline report (74). In this trial, the efficacy of the EAP regimen (etoposide, adriamycin, and cisplatin) followed by the Machover regimen (5-FU plus leucovorin calcium) was compared to surgery alone. After a median follow-up of 66 months, no significant difference in overall survival at five years was detected. A systematic review and meta-analysis by Hu et al (3u) obtained 14 trials (4543 patients) comparing adjuvant systemic chemotherapy to surgery alone. In this meta-analysis a statistically significant difference favouring adjuvant chemotherapy was detected (OR, 0.56; 95% CI, 0.40 to 0.79; $p<0.05$). However, only three of the 14 trials obtained were deemed to be high quality according to assessment using the Jadad scale; therefore, the investigators were reluctant to make definitive conclusions regarding the efficacy of adjuvant chemotherapy over surgery alone in gastric cancer. The authors recommended that randomized, double-blind, placebo-controlled trials should be undertaken to test this hypothesis. The meta-analysis by Panzini et al (4u) obtained 17 RCT reports (3118 patients) comparing adjuvant chemotherapy to surgery alone. A statistically significant difference favouring treatment with adjuvant chemotherapy over surgery alone was detected (OR, 0.72; 95%CI, 0.62 to 0.84; $p<0.05$). No statistically heterogeneity was detected in the analysis. The investigators conclude that adjuvant chemotherapy has a survival benefit over surgery alone but recommend that this be confirmed in large randomized trials. It must be noted that these two meta-analyses only showed concordance

with each other for five trials (five trials of 14 (3u); and five of 18 (4u). The meta-analysis by Panzini et al only included two of the trials deemed by Hu et al to be of high quality (Lise et al, 1995; Cirera et al, 1999).

Table 3. Randomized trials of adjuvant systemic chemotherapy compared with surgery alone in resected gastric cancer.

Author, Year (Reference)	Median Follow-up, Months	Treatment Groups	Number of Patients	% Survival 3yr	% Survival 5yr	p-value
Longmuire/VASOG,* 1968 (10)	NR	Obs Thiotepa	272 259	26 31	19 21	NS (survival analysis excluded 30-day deaths)
Serlin,* 1969 (11)	NR	Obs FUDR	212 185	34 32	NR NR	NS (survival analysis excluded 30-day deaths)
Imanaga, 1977 (12)						
Study 1	NR	Obs MMC	283 242	60† 72†	54 68	p< 0.05 for study 1 (MMC twice weekly x 5 weeks) (survival analysis excluded 30-day deaths)
Study 2	NR	Obs MMC	265 255	64† 72†	60 60	
Study 3	NR	Obs MMC MMC+cyclo	152 135 146	NR		
Study 4	NR	Obs MMC MMC+5-FU+Ara-C	217 197 208	68 74 69	NR NR NR	
Nakajima,1978 (13)	NR	Obs MMC	223 207	NR NR	44 52	NS, best results in high risk patients
Nakajima, 1980 (14)	NR	Obs MMC MMC+Ara-C+5-FU	38 42 40	55† 67† 77†	50 64 67	p<0.05 for MMC+Ara-C+ 5-FU versus observation
Huguier, 1980 (15)	NR	Obs 5-FU+VLB+cyclo	26 27	30 38	18 16	NS
Schlag, 1982 (16)	NR	Obs 5-FU+BCNU	54 49	52 52	NR NR	NS
Douglass/GTSG, 1982 (17)	NR	Obs 5-FU+mCCNU	71 71	47† 62†	33† 46†	NS (p=0.06), after adjusting for covariates p=0.03
Higgins/VASOG, 1983 (18)	NR	Obs 5-FU+mCCNU	68 66	42† 45†	NR NR	NS (p=0.88)
Ochiai,* 1983 (19)	NR	Obs MMC+5-FU+Ara-C MMC+5-FU+Ara-C +BCG	40 49 49	32† 36† 52†	32† 18† 35†	NS for chemotherapy alone versus observation
Matsubara, 1984 (20)	NR	Obs Cyclo, short-term Cyclo, long-term	152 158 151	NR		NS
Nakajima, 1984 (21)	NR	Obs MMC+5-FU+Ara-C MMC+ftorafur+Ara-C	74 73 76	73† 73† 73†	51 68 62	NS (p=0.09)
Engstrom, 1985 (22)	64	Obs 5-FU+mCCNU	89 91	50† 52†	36† 27†	NS (p=0.73)
Yamamura, 1986 (23)	NR	Obs MMC+5-FU MMC+5-FU+OK-432	34 32 33	NR		NS
Bonfanti/GTSG, 1988 (24)	81	Obs MCCNU+5-FU MCCNU+5-FU+levamisole	69 75 69	66† 65† 55†	50 50 50	NS

Table 3. continued

Author, Year (Reference)	Median Follow-up, Months	Treatment Groups	Number of Patients	% Survival 3yr	% Survival 5yr	p-value
Allum, 1989 (25)	100	Obs 5-FU + MMC 5-FU + MMC+induction (FU, VCR, cyclo, MTX)	130 141 140	25† 27† 25†	18† 12† 18†	NS
Coombes/ICCG, 1990 (26)	68	Obs FAM	148 133	52 55	35 46	NS (p=0.21), high-risk subgroup reached significance
Krook, 1991 (27)	84	Obs 5-FU+ doxorubicin	64 61	38† 50†	33 32	NS
Hallissey, 1994 (28)	NR	Obs 5-FU+doxorubicin+MMC Radiotherapy	145 138 153	27† 25† 23†	20 19 12	NS (p=0.14)
Grau, 1993 (29)	105	Obs MMC	66 68	36† 50†	26 41	p<0.025
Lise/EORTC, 1995 (30)	78	Obs FAM	159 155	52† 50†	44† 41†	NS (p=0.295)
Chou, 1994 (31)	NR	Obs Ftorafur	56 59	Stage II 31 69 Stage III 22 41	 31 34 11 29	p<0.05 for stage III subgroup
Macdonald/SWOG, 1995 (32)	114	Obs FAM	100 93	43† 48†	32 37	NS (p=0.57)
Carrato, 1995 (33)	37	Obs MMC+tegafur	75 69	NR		NS
Neri, 1996 (34)	NR	Obs Epirubicin+levamisole +5-FU	55 48	15† 26†	NR NR	p<0.05
Tsavaris, 1996 (35)	60	Obs 5-FU+epirubicin+MMC	42 42	28† 40†	15† 21†	NS (p=0.248)
Nakajima, 1999 (36)	72	Obs MMC+5FU	291 288	85† 90†	82.9 85.8	NS (p=0.17)
Cirera, 1999 (37)	37	Obs MMC+tegafur	72 76	46† 58†	36 56	p=0.04
Ducreux, 2000 (38)	NR	Obs 5-FU+cisplatin	133 127	54.5 55.6	NR NR	NS
Di Bartolomeo, 2000 (39)	66	Obs EAP + 5FU+leucovorin	137 137	NR NR	48 52	NR
Bajetta, 2002 (2u) [update of reference 39]	66	Obs EAP + 5FU+leucovorin	137 137	NR NR	48 52	p=NS [hazard ratio=0.93; 95%CI 0.65-1.34]

Note: 5-FU, 5-fluorouracil; Ara-C, cytarabine; BCG, bacillus Calmette-Guerin; BCNU, carmustine; cyclo, cyclophosphamide; EAP, etoposide, doxorubicin, cisplatin; FAM, fluorouracil, adriamycin, mitomycin; FUDR, fluorodeoxyuridine; mCCNU, methyl lomustine; MMC, mitomycin C; MTX, methotrexate; NR, not reported; NS, not significant; Obs, observation; OK-432, picibanil; VCR, vincristine; VLB, vinblastine.
* Includes some patients resected for palliation.
† Estimated from survival curve.

Adjuvant Intraperitoneal Chemotherapy

Intraperitoneal (i.p.) chemotherapy has been studied in several randomized trials because of the observation that resected gastric cancer tends to recur in the peritoneum or liver (40,49-54). Survival results have been conflicting, however, and have even indicated harm from i.p. therapy (Table 4). For example, 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 (52).

Table 4. Randomized trials of adjuvant intraperitoneal chemotherapy compared with surgery alone in resected gastric cancer.

Author, Year (Reference)	Median Follow-up, Months	Treatment Groups	Number of Patients	% Survival 3yr	% Survival 5yr	p-value
Schiessel, 1989 (40)	NR	Obs i.p. cisplatin	33 31	NR		NS (estimated 2-year survival was 35% versus 37%)
Hagiwara, 1992 (49)	NR	Obs i.p. MMC	25 25	27 69	NR NR	P<0.01
Sautner,* 1994 (50)	72	Obs i.p. cisplatin	34 33	30 33	24 21	NS (p=0.6)
Hamazoe, 1994 (51)	NR	Obs i.p. MMC	40 42	56† 67†	52.5 64.2	NS (p=0.24)
Rosen, 1998 (52)	20	Obs i.p. MMC	45 46	NR		NS (median survival 739 days versus 515 days, p=0.44)
Yu, 1998 (53)	~26 (mean)	Obs i.p. MMC+5-FU	92 92	NR NR	41 56	NS (p=0.194)
Lygidakis, 1999 (54)	~26 (mean)	Obs neoadjuvant + adjuvant i.p. MMC+5-FU+LV+ farmorubicin neoadjuvant + adjuvant i.p. MMC+5-FU+LV+ farmorubicin + systemic CT using the same drugs	19 19 20	29.8 37.2 48.6 (4-year survival)		NR

Note: 5-FU, 5-fluorouracil; CT, chemotherapy; i.p., intraperitoneal; LV, leucovorin; MMC, mitomycin C; NR, not reported; NS, not significant; and Obs, observation.
* Includes some patients resected for palliation.
† Estimated from survival curve.

Adjuvant Radiotherapy

Two randomized trials (28,55) of adjuvant radiotherapy versus surgery alone are presented in Table 5. Radiotherapy alone as adjuvant treatment was investigated as one arm in a randomized trial conducted by the British Stomach Cancer Group (28). They reported that radiotherapy had no effect on local recurrence or survival. Similarly, a German study detected no benefit for intra-operative radiotherapy (49).

Table 5. Randomized trials of adjuvant radiotherapy compared with surgery alone in resected gastric cancer.

Author, Year (Reference)	Median Follow-up, Months	Treatment Groups	Number of Patients	% Survival 3yr	% Survival 5yr	p-value
Hallissey, 1994 (28)	NR	Obs RT	145 153	27* 23*	20 12	NS (p=0.14)
Kramling, 1996 (55)	29.2 (mean)	Obs Intra-op RT	64 51	NR		NS (mean survival 26.9 months for RT versus 30.8 months for Obs)

Note: NR, not reported; NS, not significant; Obs, observation; and RT, radiotherapy.
* Estimated from survival curve.

Adjuvant Chemoimmunotherapy

Randomized studies comparing adjuvant chemoimmunotherapy with a surgery-alone control group have had mixed results (Table 6). Two Korean studies, a Japanese study, and a Polish study detected significant survival benefits favouring adjuvant chemoimmunotherapy (19,42,56,58), whereas several European and other Japanese studies found no significant difference in survival for adjuvant chemoimmunotherapy compared with surgery alone (23,24,41,57). No obvious pattern or type of immunotherapy tested, trial size, or study quality explains these mixed results. Immunotherapeutic compounds studied included levamisole (24), BCG (19) and OK-432 (picibanil) (23). Based on the ability of H2 antagonists to block T-suppresser cells, Langman et al (59) randomly assigned 442 patients with stage I-IV gastric cancer to placebo or cimetidine in doses of 400 mg or 800 mg. In the subgroup of 226 patients who underwent surgery with curative intent (stage I-III), there was no significant difference in survival between the cimetidine and placebo groups (median survival, 26 versus 20 months; five-year survival rate, 34% versus 30%; p=0.44). Several other Asian studies have compared adjuvant chemoimmunotherapy with adjuvant chemotherapy but without a surgery-alone control group (60-64). These results have also been inconsistent.

Table 6. Randomized trials of adjuvant chemoimmunotherapy compared with surgery alone in resected gastric cancer.

Author, Year (Reference)	Median Follow-up, Months	Treatment Groups	Number of Patients	% Survival 3yr	% Survival 5yr	p-value
Ochiai,* 1983 (19)	NR	Obs MMC+5-FU+Ara-C MMC+5-FU+Ara-C+BCG	40 49 49	32† 36† 52†	32† 18† 35†	p<0.01 for immunotherapy versus control, p<0.05 for immunotherapy versus CT)
Yamamura, 1986 (23)	NR	Obs MMC+5-FU MMC+5-FU+OK-432	34 32 33	NR		NS, trend in favor of treatment
Bonfanti/GTSG, 1988 (24)	81	Obs mCCNU+5-FU mCCNU+5-FU+levamisole	69 75 69	66† 65† 55†	50 50 50	NS
Jakesz, 1988 (41)	60	Obs MMC+5-FU+Ara-C±OK-432	34 53	37† 55†	29 45	NS
Kim, 1992 (42)	NR	Obs OK-432+ MMC+ 5-FU+Ara-C	64 74	44† 54†	23 45	p<0.05
Popeila, 1982 (56)	NR	Obs 5-FU 5-FU+BCG	44 16 39	NR		p<0.005 at 2 years for immunotherapy versus control (estimated 2-year survival rates, 71% versus 45%)
Imaizumi, 1990 (57)	NR	Obs MMC+5-FU MMC+5-FU+PSK or OK-432	284 253 282	NR	73 76 74	NS
Kim, 1997 (58)	NR	Obs 5-FU+MMC OK-432+5-FU+MMC	100 100 170	35† 50† 61†	24 30 45	p<0.05 for chemo-immunotherapy versus Obs and chemo-immunotherapy versus CT
Langman, 1999 (59)	NR	Obs cimetidine	220 215	25† 28†	18 21	NS

Note: 5-FU, 5-fluorouracil; Ara-C, cytarabine; BCG, bacillus Calmette-Guerin; CT, chemotherapy; MMC, mitomycin C; mCCNU, methyl lomustine; NR, not reported; NS, not significant; Obs, observation; OK-432, picibanil; PSK, polysaccharide K.
* Includes some resected patients for palliation.
† Estimated from survival curve.

Neoadjuvant Chemotherapy

Three randomized trials have compared neoadjuvant chemotherapy prior to surgery versus surgery alone. Only one of these has been fully published, and it detected no significant improvement in either the rate of "curative" resection or downstaging in 59 patients with operable gastric cancer (65). The other two studies, one from Japan (66) and the other from Korea (67), have been published only as abstracts. However, neither was able to demonstrate a survival benefit from neoadjuvant treatment.

Neoadjuvant Radiotherapy

A Chinese study of 370 patients indicated a significant survival benefit favouring neoadjuvant radiation compared with surgery alone (five-year survival rates, 30.1% versus 19.8%, p=0.0094) (68). More recently, two Russian studies published in abstract form suggest improved survival with preoperative radiation compared with surgery alone, especially in the subgroup of patients with lymph node metastases (69,70). Neoadjuvant radiotherapy was described as well tolerated. Consequently, it is being considered an important area of research for future refinement of adjuvant treatment in North American settings.

Update

A recent report by Skoropad et al (5u) is an update of a trial included in the original guideline (69). In this trial, preoperative radiation (20 Gy every 5 days) was compared to surgery alone. No significant difference in survival was detected between the two treatment groups (X^2=0.349, df=1, p=0.56). Investigators conclude that neoadjuvant radiotherapy at 20 Gy over 5 days is safe and tolerable but does not result in a survival advantage. In this trial, a positive trend was demonstrated for patients with locally advanced gastric cancer, and the authors recommend that further trials designed to explore this trend be performed.

Neoadjuvant Immunotherapy

There have been three randomized trials of neoadjuvant immunotherapy versus surgery alone. These trials demonstrated no significant survival advantage for neoadjuvant intratumoural injection of OK-432 (71), infusional propionibacterium avidum KP-40 (72), and PSK (73).

Adverse Effects

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, as described above with combined chemoradiotherapy.

V. INTERPRETIVE SUMMARY

The SWOG-9008 study (9) was a large, multi-centre trial that clearly demonstrated a benefit for adjuvant chemoradiotherapy, thus changing the standard of care for patients with resected gastric cancer. With respect to chemotherapy alone, there have now been three literature-based meta-analyses indicating benefit from adjuvant chemotherapy in randomized trials involving over 2000 patients (43,45,46,47). Subgroup analyses suggest that the benefit of chemotherapy may be greatest in patients with lymph node metastases. Thus, adjuvant chemotherapy is an acceptable alternative for patients unable to undergo radiation. However, the adverse effects of chemotherapy can be a significant factor when weighing the risks and benefits of treatment. Neoadjuvant radiation also shows promise but cannot be recommended at the present time. Future directions will focus on optimizing the chemotherapy regimen and exploring the potential role of neoadjuvant treatment for these patients. The results of randomized trials of adjuvant or neoadjuvant immunotherapy have not yielded consistent results.

VI. ONGOING TRIALS (as of May 2003)

Protocol ID	Description	Status
	Adjuvant Medical Treatment in Radically Resected Gastric Cancer with Poor Prognostic Factors. A phase III study by the Italian Trials in Medical Oncology (I.T.M.O.) group (74) • This is a randomized trial. • A total of 234 patients will be accrued.	• closed
CLB-80101, CTSU	**Phase III Randomized Study of Adjuvant Chemoradiation after Resection in Patients With Gastric or Gastroesophageal Adenocarcinoma** (summary last modified December 20, 2002) • This is a randomized, multi-centre study. Patients are randomized to 1 of 2 treatment arms. • A total of 824 patients (412 per treatment arm) will be accrued for this study within 4.5 years. • Patients are followed every 3 months for 2 years, every 4 months for 2 years, and then annually for 3 years.	• recruiting
MRC-ST02, EU-94035	**Phase III Randomized Study of Epirubicin, Cisplatin, and Fluorouracil (ECF) Before and After Resection Versus Resection Alone in Patients With Resectable Stage II or III Adenocarcinoma of the Stomach** (summary last modified June 1, 2001) • This is a randomized, multi-centre study. Patients are stratified by center and performance status (0 vs 1). • A total of 500 patients will be accrued for this study within 4 years. • Quality of life is assessed at baseline, at completion of study therapy, and then every 6 months for 2 years. Patients are followed every 6 months for 2 years and then annually thereafter.	• recruiting
SWS-SAKK-43/99, EU-99042	**Phase III Randomized Study of Preoperative Versus Postoperative Chemotherapy With Docetaxel, Cisplatin, and Fluorouracil in Patients With Locally Advanced Operable Gastric Carcinoma** (summary last modified September 9, 2001) • This is a randomized, open label, multi-centre study. • Approximately 240 patients (120 per arm) will be accrued for this study. • Quality of life is assessed before the first and third courses of chemotherapy, before and after surgery, and then at 1, 3, and 6 months. Patients are followed every 3 months for 3 years, every 6 months for 2 years, and then annually thereafter.	• recruiting
EORTC-40954	**Phase III Randomized Study of Surgery With or Without Neoadjuvant Cisplatin, Leucovorin Calcium, and Fluorouracil in Patients With Locally Advanced Gastric Cancer** (summary last modified November 1, 1999) • This is a randomized, open label, multi-centre study. • A total of 360 patients (180 per arm) will be accrued for this study over 4 years. • Quality of life is assessed before randomization, every 3 months for 1 year and at 2 years after randomization. Patients are followed every 3 months for 1 year, every 6 months for 2 years, then every 3 months thereafter until death.	• recruiting

FRE-FNCLCC-94012, **EU-96018**	**Phase III Randomized Study of Surgical Resection with vs. without Neoadjuvant Fluorouracil/Cisplatin for Adenocarcinoma of the Lower Third of the Esophagus or the Cardia** (summary last modified January 1, 1997) • This study is randomized for neoadjuvant chemotherapy. • A total of 250 patients will be entered. • Patients are followed every 3-4 months for at least 5 years.	• recruiting

VII. DISEASE SITE GROUP CONSENSUS PROCESS

The Gastrointestinal Cancer 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 SWOG chemoradiotherapy trial (9) was a large, multicentre 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 SWOG chemoradiotherapy trial (9), as evidenced by the no treatment control arm in that trial. However, the results of the three literature-based meta-analyses (43,45,46,47) 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, and so no specific regimen could be recommended.

VIII. EXTERNAL REVIEW OF THE PRACTICE GUIDELINE REPORT

Draft Recommendations

Based on the evidence above, the Gastrointestinal Cancer DSG drafted the following recommendations:

Target Population

These recommendations apply to adult patients with potentially curable gastric cancer.

Recommendations

- Following surgical resection, patients should be considered for adjuvant combined chemoradiotherapy. The current standard protocol consists of one cycle of 5-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 daily x 5 5-FU (425 mg/m^2/day) and leucovorin (20 mg/m^2/day) are given at monthly intervals.
- 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.
- Patients should understand the tradeoffs between survival benefit and toxicity before making treatment decisions.

- 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.

Practitioner Feedback

Methods

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 above 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 DSG.

Results

Key results of the practitioner feedback survey are summarized in Table 7. Ninety-nine (63%) surveys were returned. Seventy-four (75%) respondents (13 medical oncologists, 10 radiation oncologists, 50 surgeons, and one gastroenterologist) indicated that the practice-guideline-in-progress report was relevant to their clinical practice and completed the survey. Of the 74 clinicians who completed the survey, 70% agreed that the document should be approved as a practice guideline and 88% agreed that they would use it in their own clinical practice. The approval rate of 70% was felt to be borderline but acceptable, and mostly due to concerns about the toxicity of adjuvant treatment in this population.

Table 7. Practitioner responses to eight items on the practitioner feedback survey.

Item	Number (%)*		
	Strongly agree or agree	**Neither agree nor disagree**	**Strongly disagree or disagree**
The rationale for developing a clinical practice guideline, as stated in the "*Choice of Topic*" section of the report, is clear.	74 (100%)	0	0
There is a need for a clinical practice guideline on this topic.	70 (95%)	4 (5%)	0
The literature search is relevant and complete.	57 (77%)	12 (16%)	1 (1%)
The results of the trials described in the report are interpreted according to my understanding of the data.	68 (92%)	5 (7%)	0
The draft recommendations in this report are clear.	69 (93%)	1 (1%)	4 (5%)
I agree with the draft recommendations as stated.	67 (91%)	3 (4%)	4 (5%)
This report should be approved as a practice guideline.	52 (70%)	13 (18%)	6 (8%)
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**
	65 (88%)	6 (8%)	3 (4%)

* Percentages may not total 100% due to missing data.

Summary of Written Comments

Thirty (40%) respondents provided written comments. Most practitioners agreed with the recommendations, although several expressed reservations about the toxicity of chemoradiotherapy, its impact on radiation resources, and the risk/benefit tradeoff for very early stage patients with a relatively good prognosis. There was interest in seeing the final complete publication of the SWOG-9008 trial results, as well as in seeing confirmatory randomized trials. Some practitioners commented that they are already using more modern chemotherapy regimens such as epirubicin, cisplatin, 5-fluorouracil (ECF) combination therapy.

Modifications/Actions

Minor changes were made to the text of the document but not to the final recommendation. A statement about the possibility of radiation damage to surrounding organs, such as the kidney, was added to the abstract and full report. The Gastrointestinal Cancer DSG members noted that the SWOG-9008 trial detected a clear benefit for chemoradiotherapy. Interim results for this trial had been presented at both the 2000 annual meetings of ASCO and the ASTRO. Also, as an intergroup trial, there has been the added benefit of peer review from a large group of investigators. In the period of time since approval of this practice guideline by the PGI, the five-year results of the SWOG-9008 trial have been published in full (9).

IX. PRACTICE GUIDELINE

This 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 DSG and the PGCC

Target Population

These recommendations apply to adult patients with potentially curable surgically resected (T1-4,N0-2,M0) gastric cancer.

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-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.

Qualifying Statements

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

X. JOURNAL REFERENCE

Earle CC, Maroun J, Zuraw L, and the Cancer Care Ontario Gastrointestinal Cancer Disease Site Group. Neoadjuvant or adjuvant therapy for resectable gastric cancer? *Can J Surg* 2002;45(6):438-46.

XI. ACKNOWLEDGEMENTS

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For a complete list of the Gastrointestinal Cancer Disease Site Group members and the Practice Guidelines Coordinating Committee members, please visit our web site at http://www.ccopebc.ca/.

REFERENCES

1. Physician Data Query. Gastric Cancer. CancerNet. Available at: www.cancer.gov/cancer_information/cancer_type/stomach (accessed April 1996).
2. Agboola O. Adjuvant treatment in gastric cancer. *Cancer Treat Rev* 1994;20:217-40.
3. Middleton G, Cunningham D. Current options in the management of gastrointestinal cancer. *Ann Oncol* 1995; 6 Suppl 1:S17-S26.
4. Cuschieri A, Fayers P, Fielding J, Craven J, Bancewicz J, Joypaul V, et al. Postoperative morbidity and mortality after D1 and D2 resections for gastric cancer: preliminary results of the MRC randomised controlled surgical trial. *Lancet* 1996;347:995-9.
5. 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;13:502-12.
6. Gunderson LL, Sosin H. Adenocarcinoma of the stomach: areas of failure in re-operation series (second or symptomatic look) clinicopathologic correlation and implications for adjuvant therapy. *Int J Radiat Oncol Biol Phys* 1981;8:1-11.
7. Dent DM, Werner ID, Novis B, Cheverton P, Brice P. Prospective randomized trial of combined oncological therapy for gastric carcinoma. *Cancer* 1979;44:385-91.
8. Moertel CG, Childs DS, O'Fallon JR, Holbrook MA, Schutt AJ, Reitemeier RJ. Combined 5-fluorouracil and radiation therapy as a surgical adjuvant for poor prognosis gastric carcinoma. *J Clin Oncol* 1984;2:1249-54.
9. Smalley S, Benedetti J, Gunderson L, Martenson J, Tepper J, Kiel K, et al. Intergroup 0116 (SWOG 9008) phase III trial of postoperative adjuvant radiochemotherapy for high risk gastric and gastroesophageal junction adenocarcinoma: evaluation of efficacy and radiotherapy treatment planning [abstract]. *Int J Radiat Oncol Biol Phys* 2000;3:111-2. Abstract 3. UPDATED BY: Macdonald JS, Smalley SR, Benedetti J, Hundahl SA, Estes, NC, Stemmermann GN, et al. Chemoradiotherapy after surgery compared with surgery alone for adenocarcinoma of the stomach or gastroesophageal junction. *New Engl J Med* 2001;345(10):725-30.
10. Longmire WP, Kuzma JW, Dixon WJ. The use of triethylenethiophosphoramide as an adjuvant to the surgical treatment of gastric carcinoma. *Ann Surg* 1968;167:293-312.
11. Serlin O, Wolkoff HS, Amadeo HM, Keehn RJ. Use of 5-fluorodeoxuridine (FUDR) as an adjuvant to the surgical management of carcinoma of the stomach. *Cancer* 1969;24:223-8.
12. Imanaga H, Nakazato H. Results of surgery for gastric cancer and effect of adjuvant mitomycin C on cancer recurrence. *World J Surg* 1977;2:213-21.
13. Nakajima T, Fukami A, Ohashi I, Kajitani T. Long-term follow-up study of gastric cancer patients treated with surgery and adjuvant chemotherapy with mitomycin C. *Int J Clin Pharmacol Biopharm* 1978;16:209-16.
14. Nakajima T, Fukami A, Ohashi I, Kajitani T. Adjuvant chemotherapy with mitomycin C, and with a multi-drug combination of mitomycin C, 5 fluorouracil and cytosine arabinoside after curative resection of gastric cancer. *Jpn J Clin Oncol* 1980;10:187-94.
15. Huguier M, Destroyes H, Baschet C, Le Henand F, Bernard PF. Gastric carcinoma treated by chemotherapy after resection: a controlled study. *Am J Surg* 1980;139:197-9.
16. Schlag P, Schreml W, Gaus W, Herfarth C, Linder MM, Queisser W, et al. Adjuvant 5 fluorouracil and BCNU chemotherapy in gastric cancer: 3 year results. *Recent Results Cancer Res* 1982;80:277-83.
17. The Gastrointestinal Tumor Study Group. Controlled trial of adjuvant chemotherapy following curative resection for gastric cancer. *Cancer* 1982;49:1116-22.
18. Higgins GA, Amadeo JH, Smith DE, Humphrey EW, Keehn RJ. Efficacy of prolonged intermittent therapy with combined 5FU and methyl CCNU following resection for gastric

carcinoma. A Veterans Administration Surgical Oncology Group Report. *Cancer* 1983;52:1105-12.
19. Ochiai T, Sato H, Hayashi R, Asano T, Sato H, Yamamura Y. Postoperative adjuvant immunotherapy of gastric cancer with BCG-cell wall skeleton. 3- to 6-year follow up of a randomized clinical trial. *Cancer Immunol Immunother* 1983;14:167-71.
20. Matsubara Y, Uragari Y, Yamamoto M, Goto M, Nakazato H, Imanaga H. A randomized clinical trial of adjuvant chemotherapy after resection in patients with stomach cancer. *Clin Ther* 1984;6:689-92.
21. Nakajima T, Takahashi T, Takagi K. Comparison of 5-fluorouracil with ftorafur in adjuvant chemotherapies with combined inductive and maintenance therapies for gastric cancer. *J Clin Oncol* 1984;2:1366-71.
22. Engstrom PF, Lavin PT, Douglas HO, Brunner KW. Postoperative adjuvant 5 fluorouracil plus methyl CCNU therapy for gastric cancer patients. Eastern Cooperative Oncology Group Study (EST 3275). *Cancer* 1985;55:1868-73.
23. Yamamura Y, Nishimura M, Sakamoto J, Yasui K, Morimoto T, Kato T, et al. A randomized controlled trial of surgical adjuvant therapy with mitomycin C, 5-fluorouracil and OK-432 in patients with gastric cancer. *Gan to Kagaku Ryoho* 1986;13:2134-40.
24. The Italian Gastrointestinal Tumor Study Group. Adjuvant treatments following curative resection for gastric cancer. *Br J Surg* 1988;75:1100-4.
25. Allum WH, Hallissey MT, Kelly KA. Adjuvant chemotherapy in operable gastric cancer. 5 year follow-up of first British Stomach Cancer Group trial. *Lancet* 1989;1:571-4.
26. Coombes RC, Schein PS, Chilvers CED, Wils G, Beretta JM, Bliss A, et al. A randomized trial comparing adjuvant fluorouracil, doxorubicin and mitomycin with no treatment in operable gastric cancer. *J Clin Oncol* 1990;8:1362-9.
27. Krook JE, O'Connell MJ, Wieand HS, Beart RW, Leigh JE, Kugler JW, et al. A prospective, randomised evaluation of intensive course 5-fluorouracil plus doxorubicin as surgical adjuvant chemotherapy for resected gastric cancer. *Cancer* 1991;67:2454-8.
28. Hallissey MT, Dunn HA, Ward LC, Allum WH. The second British Stomach Cancer Group trial of adjuvant radiotherapy or chemotherapy in resectable gastric cancer: five-year follow-up. *Lancet* 1994;343:1309-12.
29. Grau JJ, Estape J, Alcobendas F. Positive results of adjuvant mitomycin C in resected gastric cancer: a randomized trial on 134 patients. *Eur J Cancer* 1993;29A:340-2.
30. Lise M, Nitti D, Marchet A, Sahmoud T, Buyse M, Duez N, et al. Final results of a phase III clinical trial of adjuvant chemotherapy with the modified fluorouracil, doxorubicin, and mitomycin regiment in resectable gastric cancer. *J Clin Oncol* 1995;13:2757-63.
31. Chou FF, Sheen-Chen SM, Liu PP, Chen FC. Adjuvant chemotherapy for resectable gastric cancer: a preliminary report. *J Surg Oncol* 1994;57:239-42.
32. MacDonald JS, Fleming TR, Peterson RF, Berenberg JL, McClure S, Chapman RA, et al. Adjuvant chemotherapy with 5-FU, adriamycin, and mitomycin-C (FAM) versus surgery alone for patients with locally advanced gastric adenocarcinoma: A Southwest Oncology Group study. *Ann Surg Oncol* 1995;2:488-94.
33. Carrato A, Diaz-Rubio E, Medrano J, Calpena R, Marcuello E, Sanz J, et al. Phase III trial of surgery versus adjuvant chemotherapy with mitomycin and tegafur plus uracil (UFT), starting within the first week after surgery, for gastric adenocarcinoma [abstract]. *Proc Annu Meet Am Soc Clin Oncol* 1995;14:198. Abstract 468.
34. Neri B, de Leonardis B, Romano S, Andreoli F, Pernice LM, Bruno L, et al. Adjuvant chemotherapy after gastric resection in node-positive cancer patients: a multicentre randomised study. *Br J Cancer* 1996;73:549-52.
35. Tsavaris N, Tentas K, Kosmidis P, Mylonakis N, Sakelaropoulos N, Kosmas CH, et al. A randomized trial comparing adjuvant fluorouracil, epirubicin, and mitomycin with no treatment in operable gastric cancer. *Chemotherapy* 1996;42:220-6.

36. Nakajima T, Nashimoto A, Kitamura M, Kito Y, Iwanaga T, Okabayashi K, et al for the Gastric Cancer Surgical Study Group. Adjuvant mitomycin and fluorouracil followed by oral uracil plus tegafur in serosa-negative gastric cancer: a randomised trial. *Lancet* 1999;354:273-7.
37. Cirera L, Balil A, Batiste-Alentorn E, Tusquets I, Cardona T, Arcusa A, et al. Randomized clinical trial of adjuvant mitomycin plus tegafur in patients with resected stage III gastric cancer. *J Clin Oncol* 1999;17:3810-5.
38. Ducreux M, Nordlinger B, Ychou M, Milan C, Bouche O, Ducerf C, et al. Resected gastric adenocarcinoma: randomized trial of adjuvant chemotherapy with 5 FU-cisplatin (FUP). Final results of the FFCD 8801 trial [abstract]. *Proc Annu Meet Am Soc Clin Oncol* 2000;19:241a. Abstract 932.
39. Di Bartolomeo M, Bajetta E, Bordogna G, Aitini E, Fava S, Schieppati G, et al. Improved adjuvant therapy outcome in resected gastric cancer patients according to node involvement. 5-year results of a randomized study by the Italian Trials in Medical Oncology (ITMO) group [abstract]. *Proc Annu Meet Am Soc Clin Oncol* 2000;19:241a. Abstract 934.
40. Schiessel R, Funovics J, Schick B, Bohmig HJ, Depisch D, Hofbauer F, et al. Adjuvant intraperitoneal cisplatin therapy in patients with operated gastric carcinoma. Results of a randomized trial. *Acta Med Austriaca* 1989;16:68-9.
41. Jakesz R, Dittrich C, Funovics J, Hofbauer F, Rainer H, Reiner G, et al. The effect of adjuvant chemotherapy in gastric carcinoma is dependent on tumor histology: 5-year results of a prospective randomized trial. *Recent Results Cancer Res* 1988;110:44-51.
42. Kim J-P. Results of surgery on 6589 gastric cancer patients and immunochemosurgery as the best treatment of advanced gastric cancer. *Ann Surg* 1992;216:269-78.
43. Hermans J, Bonenkamp JJ, Boon MC, Bunt AMG, Ohyama S, Sasako M, et al. Adjuvant therapy after curative resection for gastric cancer: meta-analysis of randomized trials. *J Clin Oncol* 1993;11:1441-7.
44. Alcobendas F, Mula A, Estape J, Curto J, Pera C. Mitomycin-C as an adjuvant in resected gastric cancer. *Ann Surg* 1983;198:13-7.
45. Hermans J, Bonenkamp H. In reply [letter]. *J Clin Oncol* 1994;12:879-80.
46. Earle CC, Maroun JA. Adjuvant chemotherapy after curative resection for gastric cancer in non-Asian patients: revisiting a meta-analysis of randomised trials. *Eur J Cancer* 1999;35:1059-64.
47. Mari E, Floriani I, Tinazzi A, Buda A, Belfiglio M, Valentini M, Cascinu S, et al. Efficacy of adjuvant chemotherapy after curative resection for gastric cancer: a meta-analysis of published randomised trials. A study of the GISCAD. *Ann Oncol* 2000;11:837-43.
48. Glimelius B, Ekstrom K, Hoffman K, Graf W, Sjoden PO, Haglund U, et al. Randomized comparison between chemotherapy plus best supportive care with best supportive care in advanced gastric cancer. *Ann Oncol* 1997;8:163-8.
49. Hagiwara A, Takahashi T, Kojima O, Sawai K, Yamaguichi T, Yamane T, et al. Prophylaxis with carbon absorbed mitomycin against peritoneal recurrence of gastric cancer. *Lancet* 1992;339:629-31.
50. Sautner T, Hofbauer F, Depisch D, Schiessel R, Jakesz R. Adjuvant intraperitoneal cisplatin chemotherapy does not improve long-term survival after surgery for advanced gastric cancer. *J Clin Oncol* 1994;12:970-4.
51. Hamazoe R, Maeta M, Kaibara N. Intraperitoneal thermochemotherapy for prevention of peritoneal recurrence of gastric cancer. Final results of a randomized controlled study. *Cancer* 1994;73:2048-52.
52. Rosen HR, Jatzko G, Repse S, Potrc S, Neudorfer H, Sandbichler P, et al. Adjuvant intraperitoneal chemotherapy with carbon-adsorbed mitomycin in patients with gastric cancer: results of a randomized multicenter trial of the Austrian Working Group for Surgical Oncology. *J Clin Oncol* 1998;16:2733-8.

53. Yu W, Whang I, Suh, Averbach A, Chang D, Sugerbaker PH. Prospective randomized trial of early postoperative intraperitoneal chemotherapy as an adjuvant to resectable gastric cancer. *Ann Surg* 1998;228:347-54.
54. Lygidakis NJ, Sgourakis G, Aphinives P. Upper abdominal stop-flow perfusion as a neo and adjuvant hypoxic regional chemotherapy for resectable gastric carcinoma. A prospective randomized clinical trial. *Hepatogastroenterology* 1999;46:2035-8.
55. Kramling HJ, Wilkowski R, Duhmke E, Cramer C, Willich N, Schildberg RW. Adjuvant intraoperative radiotherapy of stomach carcinoma. *Langenbecks Archiv fur Chirurgie - Supplement - Kongressband* 1996;113:211-3.
56. Popiela T, Zembala M, Oszacki J, Jedrychowski W. A follow-up study on chemoimmunotherapy (5-fluorouracil and BCG) in advanced gastric cancer. *Cancer Immunol Immunother* 1982;13:182-4.
57. Imaizumi M, Kondo T, Kamei H, Ichihashi H. Cooperative studies on surgical adjuvant immunochemotherapy for prevention of postoperative recurrence of gastric cancer (II). *Gan to Kagaku Ryoho* 1990;17:2397-403.
58. Kim J-P. Recent advances in gastric cancer therapy with immunochemosurgery. *Asian J Surg* 1997;20:115-8.
59. Langman MJ, Dunn JA, Witing JL, Burton A, Hallissey MT, Fielding JW, et al. prospective, double-blind, placebo-controlled randomized trial of cimetidine in gastric cancer. *Br J Cancer* 1999;81:1356-62.
60. Sakamoto J, Nakazato H. Evaluation of adjuvant immunochemotherapy in advanced gastric cancer. *Gan to Kagaku Ryoho* 1993;20:2525-30.
61. Niimoto M, Hattori T, Ito I, Tamada R, Inokuchi K, Orita K, et al. Levamisole in postoperative adjuvant immunochemotherapy for gastric cancer. A randomized controlled study of the MMC + Tegafur regimen with or without levamisole. Report I. *Cancer Immunol Immunother* 1984;18:13-8.
62. Ochiai T, Sato H. Evaluation of postoperative immunotherapy of gastric cancer. *Gan to Kagaku Ryoho* 1983;10:373-9.
63. Ochiai T, Sato H, Sato H, Hayashi R, Asano T, Isono K, et al. Randomly controlled study of chemotherapy versus chemoimmunotherapy in postoperative gastric cancer patients. *Cancer Research* 1983;43:3001-7.
64. Fujimoto S, Furue H, Kimura T, Kondo T, Orita K, Taguchi T, et al. Clinical evaluation of schizophyllan adjuvant immunochemotherapy for patients with resectable gastric cancer – a randomized controlled trial. *Jpn J Surg* 1984;14:286-92.
65. Songun I, Keizer HJ, Hermans J, Klementschitsch P, De Vries JE, Wils JA, Et Al For The Dutch Gastric Cancer Group (DGCG). Chemotherapy for operable gastric cancer: results of the Dutch randomised FAMTX trial. *Eur J Cancer* 1999;35:558-62.
66. Fujii M, Kosaki G, Tsuchiya S, Kimura K, Suzuki H, Nakajima T, et al for the Gastric Cancer Chemotherapy Group of Japan. Randomized trial of preoperative adjuvant chemotherapy using oral 5-FU in operable gastric cancer [abstract]. *Proc Annu Meet Am Soc Clin Oncol* 1999; 18:272a. Abstract 1045.
67. Kang YK, Choi DW, Im YH, Kim CM, Lee JI, Moon NM, et al. A phase III randomized comparison of neoadjuvant chemotherapy followed by surgery versus surgery for locally advanced stomach cancer [abstract]. *Proc Annu Meet Am Soc Clin Oncol* 1996;15:215. Abstract 503.
68. Zhang ZX, Gu XZ, Yin WB, Huang GJ, Zhang DW, Zhang RG. Randomized clinical trial on the combination of preoperative irradiation and surgery in the treatment of adenocarcinoma of gastric cardia (AGC) – report on 370 patients. *Int J Radiat Oncol Biol* Phys 1998;42:929-34.
69. Skoropad V, Berdov B. Preoperative short-term radiotherapy of resectable gastric cancer: complete 20-years follow up of a randomized trial [abstract]. *Eur J Cancer* 1999;35 Suppl 4:S147. Abstract 542.

70. Skoropad V, Berdov B. Randomized trial of preoperative and intraoperative radiotherapy versus surgery alone in resectable gastric cancer [abstract]. *Eur J Cancer* 1999;35 Suppl 4:S139. Abstract 508.
71. Gouchi A, Orita K, Fuchimoto S, Konaga E, Satoh K, Mannami T, et al. Randomized control study of preoperative intratumoral injection of OK-432 in gastric cancer patient. Ten years survival [abstract]. *Proc Annu Meet Am Soc Clin Oncol* 1997;263a. Abstract 931.
72. Peters KM, Beuth J, Ko HL, Pulverer G, Kluger J, Grundmann R. Preoperative immunostimulation with propionibacterium avidum KP-40 in patients with gastric carcinoma: a prospective randomized study. *Onkologie* 1990;13:124-7.
73. Terashima M, Takagane A, Sasaki T, Kusaka S, Kanno Y, Yashima T, et al. A prospective randomized trial of preoperative immunotherapy using PSK for the treatment of gastric cancer [abstract]. *Proc Annu Meet Am Soc Clin Oncol* 1998;17:304a. Abstract 1170.
74. Bajetta E. Adjuvant medical treatment in radically resected gastric cancer with poor prognostic factors. A phase III study by the Italian Trials in Medical Oncology (I.T.M.O.) group [abstract]. *Proc Annu Meet Am Soc Clin Oncol* 1997;16:282a. Abstract 1000.

Update

1u. Hundahl S, Macdonald J, Bendetti J, and Fitzsimmons T, for the Southwest Oncology Group and the Gastric Intergroup. Surgical treatment variation in a prospective, randomized trial of chemoradiotherapy in gastric cancer: The effect of undertreatment. *Ann Surg Oncol* 2002;9(3):278-86.
2u. Bajetta E, Buzzoni R, Mariana L, Beretta E, Bozzetti F, Bordogna G, et al. Adjuvant chemotherapy in gastric cancer: 5-year results of a randomised study by the Italian Trials in Medical Oncology. *Ann Oncol* 2002;13(2):299-307.
3u. Hu JK, Chen ZX, Zhou ZG, Zhang B, Tian J, Chen JP, et al. Intravenous chemotherapy for resected gastric cancer: meta-analysis of randomized controlled trials. *World J Gastroenterol* 2002; (6):1023-8.
4u. Panzini I, Gianni L, Fattori PP, Tassinari D, Imola M, Fabbri P, et al. Adjuvant chemotherapy in gastric cancer: a meta-analysis of randomized trials and a comparison with previous meta-analyses. *Tumori* 2002;88(1):21-7.
5u. Skoropad V, Berdov B, and Zagrebin V. Concentrated preoperative radiotherapy for resectable gastric cancer: 20-years follow-up of a randomized trial. *J Clin Oncol* 2002;80(2):72-8.