Neoadjuvant or adjuvant therapy for resectable gastric cancer? A practice guideline

Craig C. Earle, MD;[*] Jean Maroun, MD;[†] Lisa Zuraw, MSc;[‡] and the Cancer Care Ontario Practice Guidelines Initiative Gastrointestinal Cancer Disease Site Group[§]

Objective: To make recommendations on the use of neoadjuvant or adjuvant therapy in addition to surgery in patients with resectable gastric cancer (T1–4, N1–2, M0). **Options:** Neoadjuvant or adjuvant treatments compared with "curative" surgery alone. **Outcomes:** Overall survival, disease-free survival, and adverse effects. **Evidence:** The MEDLINE, CANCERLIT and Cochrane Library databases and relevant conference proceedings were searched to identify randomized trials. **Values:** Evidence was selected and reviewed by one member of the Cancer Care Ontario Practice Guidelines Initiative (CCOPGI) Gastrointestinal Cancer Disease Site Group and methodologists. A systematic review of the published literature was combined with a consensus process around the interpretation of the evidence in the context of conventional practice, to develop an evidence-based practice guideline. This report has been reviewed and approved by the Gastrointestinal Cancer Disease Site Group, comprising medical oncologists, radiation oncologists, surgeons, a pathologist and 2 community representatives. **Benefits, harms and costs:** When compared with surgery alone, at 3 years adjuvant chemoradiotherapy has been shown to increase overall survival by 9% (50% v. 41%, $p = 0.005$) and to improve relapse-free survival from 31% to 48% ($p = 0.001$). At 5 years, it has been shown to increase overall survival by 11.6% (40% v. 28.4%) and to improve relapse-free survival from 25% to 38% ($p < 0.001$). Treatment has been associated with toxic deaths in 1% of patients. The most frequent adverse effects (> grade 3 [Southwest Oncology Group toxicity scale] are hematologic (54%), gastrointestinal (33%), influenza-like (9%), infectious (6%) and neurologic (4%). The radiation fields used can possibly damage the left kidney, resulting in hypertension and other renal problems. Furthermore, this therapy could increase the demand on radiation resources. Physicians and patients should understand the tradeoffs between survival benefit and toxicity and cost before making treatment decisions. **Recommendations:** After surgical resection, patients whose tumours have penetrated the muscularis propria or involve regional lymph nodes should be considered for adjuvant combined chemoradiotherapy. The current standard protocol consists of 1 cycle of 5-fluorouracil (5-FU) (425 mg/m^2 daily) and leucovorin (20 mg/m^2 daily) administered daily for 5 days, followed 1 month later by 45 Gy (1.8 Gy/d) of radiation given with 5-FU (400 mg/m^2 daily) and leucovorin (20 mg/m^2 daily) on days 1 through 4 and the last 3 days of radiation.One month after completion of radiation, 2 cycles of 5-FU (425 mg/m^2 daily) and leucovorin (20 mg/m^2 daily) in a daily regimen for 5 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 those 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 radiotherapy or immunotherapy, either alone or in combination, outside a clinical trial. **Validation:** A

**Dana-Farber Cancer Institute, Boston, Mass; †Ottawa Regional Cancer Centre, Ottawa, Ont.; ‡Cancer Care Ontario Practice Guidelines Initiative, McMaster University, Hamilton, Ont.*

*§Olusegun Agboola, MD, Ottawa; Murray Citron; Bernard Cummings, MD, Toronto; Franco G. Denardi, MD, Hamilton; Alvaro Figueredo, MD, Hamilton; Sheldon Fine, MD, Mississauga; Barbara Fisher, MD, London; Colin Germond, MD, Sudbury; Derek Jonker, MD, Ottawa; Kong Khoo, MD, Kelowna, BC; Walter Kocha, MD, London; Marion Lethbridge; Wycliffe Lofters, MD, Kingston; Richard Malthaner, MD, London; Robin McLeod, MD, Toronto; Malcolm Moore, MD, Toronto; Ved Tandan, MD, Hamilton; Rebecca Wong, MD, Toronto. [For a complete list of members see the Cancer Care Ontario Practice Guidelines Initiative Web site at **www.ccopebc.ca/gastro.html**]*

Accepted for publication July 25, 2002.

Correspondence to: *Dr. Jean Maroun, Chair, Gastrointestinal Cancer Disease Site Group, Ottawa Regional Cancer Centre, General Division, 501 Smyth Rd., Ottawa ON K1H 8L6; fax 613 247-3511; jean.maroun@cancercare.on.ca*

draft version of this document was circulated to 166 clinicians using a 21-item feedback questionnaire. Ninety-nine (63%) returned the questionnaire, and 74 of these indicated that the guideline was relevant to their clinical practice and completed the survey. Of the 74 clinicians, 52 (70%) agreed that the document should be approved as a practice guideline. Sponsors: The CCOPGI is supported by Cancer Care Ontario and the Ontario Ministry of Health and Long-Term Care.

Objectif : Formuler des recommandations sur l'utilisation d'une thérapie néoadjuvante ou adjuvante en plus de l'intervention chirurgicale chez des patients atteints d'un cancer de l'estomac résécable (T1–4, N1–2, M0). Options : Traitements néoadjuvants ou adjuvants comparativement à l'intervention chirurgicale «curative» seulement. Résultats : Survie globale, survie sans maladie et effets indésirables. Données probantes : On a effectué des recherches dans les bases de données MEDLINE, CANCERLIT et Cochrane Library, ainsi que dans des actes de conférences pertinentes pour trouver des essais randomisés. Valeurs : Un membre du Groupe de travail sur les sites du cancer gastro-intestinal de l'Initiative sur les lignes directrices en matière de pratique d'Action Cancer Ontario (ILDPACO) et des méthodologistes ont sélectionné les données probantes et les ont étudiées. On a combiné un examen systématique des documents publiés à un exercice de concertation portant sur l'interprétation des données probantes dans le contexte de la pratique conventionnelle afin d'élaborer un guide de pratique factuel. Le Groupe de travail sur les sites du cancer gastro-intestinal, constitué de médecins oncologues, de radio-oncologues, de chirurgiens, d'un pathologiste et de deux représentants communautaires, a étudié et approuvé ce rapport. Avantages, préjudices et coûts : Comparativement à la chirurgie seulement, on a démontré que la chimiothérapie d'appoint à trois ans augmentait la survie globale de 9 % (50 % c. 41 %, $p = 0{,}005$) et portait la survie sans rechute de 31 % à 48 % ($p = 0{,}001$). À cinq ans, on a démontré qu'elle accroît la survie globale de 11,6 % (40 % c. 28,4 %) et porte la survie sans rechute de 25 % à 38 % ($p < 0{,}001$). On a établi un lien entre le traitement et la mort causée par des agents toxiques chez 1 % des patients. Les effets indésirables les plus fréquents (> grade 3 [Échelle de toxicité du Southwest Oncology Group] sont hématologiques (54 %), gastro-intestinaux (33 %), quasi grippaux (9 %), infectieux (6 %) et neurologiques (4 %). Les champs de rayonnement utilisés peuvent endommager le rein gauche et provoquer une hypertension et d'autres problèmes rénaux. Cette thérapie pourrait en outre augmenter la demande de ressources en radiothérapie. Les médecins et les patients devraient comprendre les compromis entre l'avantage pour la survie, la toxicité et le coût avant de prendre des décisions sur le traitement. Recommandations : Après une résection chirurgicale, il faudrait envisager une chimioradiothérapie combinée d'appoint dans le cas des patients dont la tumeur a pénétré la couche longitudinale ou a atteint les ganglions lymphatiques régionaux. Le protocole normalisé courant prévoit un cycle de 5-fluorouracil (5-FU) (425 mg/m^2 par jour) et de leucovorine (20 mg/m^2 par jour) administré tous les jours pendant cinq jours, suivi un mois plus tard de 45 Gy (1,8 Gy/d) de radiothérapie administrée avec le 5-FU (400 mg/m^2 par jour) et la leucovorine (20 mg/m^2 par jour) les jours 1 à 4 et les trois derniers jours de la radiothérapie. Un mois après la fin de la radiothérapie, on administre à des intervalles d'un mois deux cycles de 5-FU (425 mg/m^2 par jour) et de leucovorine (20 mg/m^2 par jour) tous les jours pendant cinq jours. Il n'y a pas de données probantes sur lesquelles s'appuyer pour formuler une recommandation dans le cas des patients dont les tumeurs sans atteinte des ganglions n'ont pas pénétré la couche longitudinale. Dans le cas des patients qui ne peuvent subir une radiothérapie, la chimiothérapie d'appoint seule peut présenter un avantage, particulièrement chez les sujets qui présentent des métastases aux ganglions lymphatiques. Le régime optimal reste à définir. Les essais randomisés n'ont pas produit suffisamment de données probantes pour permettre de recommander une chimiothérapie néoadjuvante ou une radiothérapie néoadjuvante ou adjuvante, ou une immunothérapie, seules ou combinées, en dehors d'un essai clinique. Validation : On a distribué une version préliminaire de ce document à 166 cliniciens et utilisé un questionnaire de rétroaction de 21 questions. Quatre-vingt-dix-neuf (63 %) ont renvoyé le questionnaire et 74 d'entre eux ont indiqué que le guide était pertinent à leur pratique clinique et ont répondu au questionnaire. Sur les 74 cliniciens, 52 (70 %) ont reconnu qu'il fallait approuver le document comme guide de pratique. Commanditaires : L'ILDPACO a l'appui d'Action Cancer Ontario et du ministère de la Santé et des Soins de longue durée de l'Ontario.

The incidence of gastric cancer has been decreasing steadily since the 1930s.[1] Despite this, gastric cancer is the eighth leading cause of cancer death because the majority of patients present with advanced disease.[2] The 5-year survival rate is approximately 75% 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 treatment results for this group of patients.

Adjuvant treatments after 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 adjuvant gastric cancer treatment have tended to be better for studies carried out in Asian countries, possibly because of 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 start 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 are therefore warranted.

Methods

Literature search strategy

MEDLINE (from 1966 to January 2002), CANCERLIT (from 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 (www.cancer.gov/search/clinical_trials/), 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.

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, systematic overviews or meta-analyses 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 up-to-date, published meta-analyses were available 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.

Guideline development

This practice guideline report was developed by the Cancer Care Ontario Practice Guidelines Initiative (CCOPGI), using the methodology of the Practice Guidelines Development Cycle.[5] Evidence was selected and reviewed by one member of the CCOPGI's Gastrointestinal Cancer Disease Site Group (DSG) and methodologists. Members of the Gastrointestinal Cancer DSG disclosed potential conflict of interest information.

The 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 report is intended to enable evidence-based practice. The Practice Guidelines Initiative is editorially independent of Cancer Care Ontario and the Ontario Ministry of Health and Long-Term Care.

External review by clinicians 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.

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

Results

Literature search results

A classification of the nature of the published evidence is shown in Table 1.[6–64] The literature search identified 47 randomized trials of adjuvant therapy, including combined chemoradiotherapy, systemic and intraperitoneal chemotherapy, radiotherapy, and chemoimmunotherapy, as well as 3 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. In many studies, patients with very early stage tumours

were excluded or were not reported separately.

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 during their illness.[65] However, adjuvant radiotherapy alone has been disappointing. To improve the efficacy of radiation, 5-fluorouracil (5-FU) has been used as a radiosensitizer in 3 randomized trials (Table 2).[6–8] Dent and associates[6] detected only a nonsignificant trend toward improved survival in patients randomized to adjuvant chemoradiotherapy. Conversely, Moertel and colleagues[7] detected improved survival in treated patients, but their study has been criticized because randomization took place before consent was obtained, and 25% of patients refused treatment. The patients who refused treatment actually had the best survival of all groups (30% 5-year survival). Furthermore, there was a high rate of treatment discontinuation in both studies[6,7] due to local side effects of radiotherapy.

Recently, an intergroup trial led by the Southwest Oncology Group (SWOG) randomized 556 patients after potentially curative resection of gastric cancer to either observation alone (275) or adjuvant combined chemoradiotherapy (281) (SWOG-9008).[8] 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 1 cycle of 5-FU (425 mg/m^2 daily) and leucovorin (20 mg/m^2 daily) in a daily regimen for 5 days, followed 1 month later by 45 Gy (1.8 Gy/d) of radiation given with 5-FU (400 mg/m^2 daily) and leucovorin (20 mg/m^2 daily) on days 1 through 4 and the last 3 days of radiation. One month after completion of radiation, 2 cycles of 5-FU (425 mg/m^2 daily) and leucovorin (20 mg/m^2 daily) in a daily regimen for 5 days were given at monthly intervals. Median follow-up was 5 years. Compared with surgery alone, overall survival at 3 years was improved by 9% (50% v. 41%, p = 0.005), and relapse-free survival was increased from 31% to 48%, p = 0.001 (2-sided log-rank test) in the chemoradiotherapy group. At 5 years, adjuvant chemoradiotherapy increased overall survival by 11.6% (40% v. 28.4%) and improved relapse-free survival from 25% to 38%, $p < 0.001$ (2-sided log-rank test) compared with surgery alone. The treatment was described as tolerable, although there were 3 (1%) toxic deaths. The most frequent adverse effects (> grade 3 [SWOG toxicity scale) were hematologic (54%), gastrointestinal (33%), influenza-like (9%), infectious (6%) and neurologic (4%). Furthermore, it is now suspected that the radiation fields used possibly damaged the left kidney of some patients, resulting in hypertension and other renal problems. Also, there has been some suggestion that

Table 1

Summary of Randomized Trials and Meta-Analyses According to Type of Treatment for Resectable Gastric Cancer, Describing Neoadjuvant or Adjuvant Therapy With Surgery Versus Surgery Alone

Treatment	No. of series	Series reference
Adjuvant		
Chemoradiotherapy	3	6–8*
Systemic chemotherapy	30	9–38
Literature-based meta-analyses	3	39–41
Intraperitoneal chemotherapy	7	42–48
Radiotherapy	2	27, 49
Chemoimmunotherapy	9	18, 22, 23, 50–55
Neoadjuvant		
Chemotherapy	3	61–63
Radiotherapy	3	56,57,64
Immunotherapy	3	58–60

*A summary of the results of these 3 series is given in Table 2.

Table 2

Adjuvant Combined Chemoradiotherapy Versus Surgery Alone. Results iin 3 Series

Series	Median follow-up, mo	Treatment groups	No. of patients	Survival, % 3 yr	Survival, % 5 yr	p value
Dent et al, 1979[6]	NR	Obs	17	NR	NR	NS (estimated survival rate at 140 wk was 40% v. 32% for chemoradiotherapy v. surgery alone)
		5-FU + RT	18			
Moertel et al, 1984[7]	NR	Obs	23	7*	4*	0.024
		5-FU + RT	39	35*	20*	
Macdonald et al, 2001(SWOG-9008)[8]	60	Obs	275	41	28	0.005 [2-sided log-rank test]
		5-FU/LV + RT	281	50	40	

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

the surgery performed in this trial was often not up to the desired standards. For example, extended (D2) lymph-node dissection was recommended for all patients, but only 10% actually received this treatment.[8] For this reason, radiotherapy may have been making up for incomplete surgery. Initial patient compliance with radiotherapy treatment was reported in abstract form,[8] 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.[8]

Adjuvant systemic chemotherapy

Thirty randomized trials of postoperative adjuvant systemic chemotherapy versus surgery alone in resectable gastric cancer[9–38] were examined. A literature-based meta-analysis of 11 randomized trials[16,17,21,23-25,27,28,42,50,51] by Hermans and associates[39] initially detected a nonsignificant trend toward improved survival for adjuvant chemotherapy. They tested for statistical heterogeneity, which they attributed to one particular trial.[39] An early report[66] of the trial by Grau and associates[28] detected a strong positive effect with mitomycin C, and the upper limit of the confidence interval (CI) around the odds ratio (OR) for this trial was far below the lower limit of the CI around the pooled OR 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[67] in which they recalculated the OR. This addendum included 2 trials missing from the original meta-analysis.[15,20] The mortality OR was 0.82 (95% CI, 0.68–0.98) in favour of adjuvant chemotherapy over surgery alone. Testing for heterogeneity was not reported.

Several subsequently reported trials detected at least trends toward patient benefit from adjuvant chemotherapy. A second literature-based meta-analysis[40] of 13 Western randomized trials of adjuvant systemic chemotherapy versus surgery alone[14-17,21,23,25,26,28,29,31,33,34] detected a statistically significant survival benefit favouring adjuvant treatment (OR, 0.80; 95% CI, 0.66–0.97). There was no significant heterogeneity in the results across trials. Subgroup analyses showed a trend toward 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, 0.59–0.95).

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, 0.75–0.89, $p < 0.001$).[41] The test for heterogeneity was statistically significant. Mari and colleagues[41] conducted separate pooled analyses for the subgroup of monochemotherapy trials, polychemotherapy trials with anthracyclin, and polychemotherapy trials without anthracyclin. The results indicated a larger magnitude of effect with monochemotherapy (mitomycin C) than polychemotherapy. The upper limit of the CI around the hazard ratio for the monochemotherapy subgroup did not overlap with the lower limit of the CI around the hazard ratios for either of the polychemotherapy subgroups. These authors[41] examined possible explanations for this finding, including a dose–response relationship and study quality, but they noted that the pooled results of the polychemotherapy trials would be more reliable because 17 trials involved polychemotherapy compared with only 3 monochemotherapy trials. Of note, Mari and colleagues[41] included in the monochemotherapy subgroup both the trial by Grau and associates[28] and an earlier report of the same trial.[66] 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 these are often balanced by symptomatic improvement.[68] However, in many trials toxicity has resulted in less than 80% of planned doses being administered.[14,15,17,25,29]

Adjuvant intraperitoneal chemotherapy

Intraperitoneal chemotherapy has been studied in several randomized trials because resected gastric cancer tends to recur in the peritoneum or liver.[42–48] Survival results have been conflicting, however, and have even indicated harm from intraperitoneal therapy. 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% v. 16%, $p < 0.02$) and postoperative deaths (11% v. 2%) than in the control group, without any benefit in overall or recurrence-free survival.[46]

Adjuvant radiotherapy

Two randomized trials of adjuvant radiotherapy versus surgery alone[27,49] were examined. Radiotherapy alone as adjuvant treatment was investigated as one arm in a randomized trial conducted by the British Stomach Cancer Group.[27] The group reported that radiotherapy had no effect on local recurrence or survival. Similarly, a German study detected no benefit for intraoperative radiotherapy.[43]

Adjuvant chemoimmunotherapy

Randomized studies comparing adjuvant chemoimmunotherapy with a surgery-alone control group have had mixed results.[18,22,23,50–55] Two Ko-

rean studies, a Japanese study and a Polish study detected significant survival benefits favouring adjuvant chemoimmunotherapy,[18,51,52,54] whereas several European and other Japanese studies have found no significant difference in survival for adjuvant chemoimmunotherapy compared with surgery alone.[22,23,50,53] No obvious pattern or type of immunotherapy tested, trial size or study quality explains these mixed results. Immunotherapeutic compounds studied included bacille Calmette-Guerin,[18] levamisole[23] and picibanil (OK-432).[22] Based on the ability of H_2 antagonists to block T-suppresser cells, Langman and associates[55] randomly assigned 442 patients with gastric cancer (stages I–IV) to placebo or cimetidine in doses of 400 mg or 800 mg. In the subgroup of 226 patients who underwent surgery with curative intent (stages I–III), there was no significant difference in survival between the cimetidine and placebo groups (median survival, 26 v. 20 mo; 5-year survival, 34% v. 30%; $p = 0.44$). Several other Asian studies have compared adjuvant chemoimmunotherapy with adjuvant chemotherapy, but without a surgery-alone control group.[69–73] These results have also been inconsistent.

Neoadjuvant chemotherapy

Three randomized trials have compared neoadjuvant chemotherapy given before surgery versus surgery alone. Only one of these trials 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.[61] The 2 other studies, one from Japan[62] and the other from Korea,[63] have been published only as abstracts. 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 (5-year survival rates, 30.1% v. 19.8%, $p = 0.009$).[64] More recently, 2 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.[56,57] 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.

Neoadjuvant immunotherapy

There have been 3 randomized trials of neoadjuvant immunotherapy versus surgery alone. These trials demonstrated no significant survival advantage for neoadjuvant intratumoral injection of OK-432,[58] infusional *Propionibacterium avidum* KP-40,[59] and PSK (*Coriolus versicolor*).[60]

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 hematologic toxicity, infections and gastrointestinal side effects, as described above with combined chemoradiotherapy.

Practitioner feedback results

A total of 166 clinicians were surveyed; 99 (63%) responded. Of these 99, 74 (75%) agreed that the guideline was relevant to their practice and completed the survey. Sixty-five (88%) of the respondents stated that they would use the draft recommendations in their practice, and 52 (70%) felt the draft guideline should be approved as a practice guideline. Thirty 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 the final publication of the SWOG-9008 trial results, and in seeing confirmatory randomized trials. Some practitioners commented that they are already using more modern chemotherapy regimens such as epirubicin, cisplatin, and 5-FU (ECF) combination therapy.

In response to the practitioner feedback survey, minor changes were made to the text of the document but not to the recommendations. A statement about the possibility of radiation damage to surrounding organs, such as the kidney, was added to the abstract and the 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 the 2000 annual meetings of the ASCO and the ASTRO. In the time since approval of this practice guideline by the CCOPGI, the 5-year results of the SWOG-9008 trial have been published in full.[8]

Discussion

The SWOG-9008 study[8] was a large, multicentre 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 3 literature-based meta-analyses indicating benefit from adjuvant chemotherapy in randomized trials involving over 2000 patients.[39–41,67] 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 who cannot 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 present. Future research should 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.

Disease Site Group consensus

The Gastrointestinal Cancer DSG agreed upon and approved the contents of the guideline, indicating that it was an important change to the long-standing standard practice of surgery alone for resectable gastric cancer. Gastrointestinal Cancer DSG members want to emphasize that multidisciplinary 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. Based on the results of the SWOG chemoradiotherapy trial,[8] 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 after surgical resection.

Adjuvant chemotherapy was not the standard of care prior to the SWOG chemoradiotherapy trial,[8] as evidenced by the no treatment control arm in that trial. However, the results of the 3 literature-based meta-analyses[39–41,67] 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.

Practice guideline

This practice guideline applies to patients with potentially curable surgically resected (T1–4,N0–2,M0) gastric cancer.

- 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 1 cycle of 5-FU (425 mg/m^2 daily) and leucovorin (20 mg/m^2 daily) in a daily regimen for 5 days, followed 1 month later by 45 Gy (1.8 Gy/d) of radiation given with 5-FU (400 mg/m^2 daily) and leucovorin (20 mg/m^2 daily) on days 1 through 4 and the last 3 days of radiation. One month after the completion of radiation, 2 cycles of 5-FU (425 mg/m^2 daily) and leucovorin (20 mg/m^2 daily) in a daily regimen for 5 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 those 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 a clinical trial.

Qualifying statement

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

Practice guideline date

Dec. 6, 2000.* Practice guidelines developed by the Cancer Care Ontario Practice Guidelines Initiative are reviewed and updated regularly. Please visit the Practice Guidelines Initiative Web site (www.cancercare.on.ca/ccopgi/) for updates to this guideline.

References

1. Physician Data Query. Gastric cancer. CancerNet. Available: 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 [review]. *Ann Oncol* 1995; 6 Suppl 1:S17-26.
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 RS, 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. 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.
7. 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.
8. Macdonald JS, Smalley SR, Benedetti J, Hundahl SA, Estes, NC, Stemmermann GN, et al. Chemoradiotherapy after surgery compared with surgery alone for

*New information integrated into the original document May 2002.

adenocarcinoma of the stomach or gastroesophageal junction. *N Engl J Med* 2001;345:725-30.
9. 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.
10. 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.
11. 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.
12. 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.
13. 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.
14. 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.
15. 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.
16. The Gastrointestinal Tumor Study Group. Controlled trial of adjuvant chemotherapy following curative resection for gastric cancer. *Cancer* 1982;49:1116-22.
17. 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.
18. 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.
19. 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.
20. 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.
21. 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.
22. 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.
23. The Italian Gastrointestinal Tumour Study Group. Adjuvant treatments following curative resection for gastric cancer. *Br J Surg* 1988;75:1100-4.
24. 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.
25. Coombes RC, Schein PS, Chilvers CE, 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.
26. Krook JE, O'Connell MJ, Wieand HS, Beart RW Jr, Leigh JE, Kugler JW, et al. A prospective, randomized evaluation of intensive-course 5-fluorouracil plus doxorubicin as surgical adjuvant chemotherapy for resected gastric cancer. *Cancer* 1991;67:2454-8.
27. 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.
28. Grau JJ, Estape J, Alcobendas F, Pera C, Daniels M, Teres J. Positive results of adjuvant mitomycin C in resected gastric cancer: a randomised trial on 134 patients. *Eur J Cancer* 1993;29A:340-2.
29. 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 regimen in resectable gastric cancer. *J Clin Oncol* 1995;13:2757-63.
30. 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.
31. 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.
32. 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).
33. 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.
34. 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.
35. Nakajima T, Nashimoto A, Kitamura M, Kito Y, Iwanaga T, Okabayashi K, et al, for the Gastric Cancer Surgical Study Group. Adjuvant mitocycin and fluorouracil followed by oral uracil plus tegafur in serosa-negative gastric cancer: a randomised trial. *Lancet* 1999;354:273-7.
36. 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.
37. 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).
38. 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).
39. Hermans J, Bonenkamp JJ, Boon MC, Bunt AM, 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.
40. 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.
41. Mari E, Floriani I, Tinazzi A, Buda A, Belfiglio M, Valentini M, et al. Efficacy of adjuvant chemotherapy after curative resection for gastric cancer: a meta-analysis of published randomised trials. A study of

the GISCAD (Gruppo Italiano per lo Studio dei Carcinomi dell'Apparato Digerente). *Ann Oncol* 2000;11:837-43.
42. 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.
43. 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.
44. 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.
45. 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.
46. 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.
47. Yu W, Whang I, Suh I, 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.
48. 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.
49. Kramling HJ, Wilkowski R, Duhmke E, Cramer C, Willich N, Schildberg RW. Adjuvant intraoperative radiotherapy of stomach carcinoma. *Langenbecks Arch Chir Suppl Kongressbd* 1996;113:211-3.
50. 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.
51. 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.
52. 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.
53. Imaizumi M, Kondo T, Kamei H, Ichihashi H. [Cooperative study on surgical adjuvant immunochemotherapy for prevention of postoperative recurrence of gastric cancer (II). Cooperative study group on surgical adjuvant immunochemotherapy for prevention of postoperative recurrence of gastric cancer supported by the Ministry of Health and Welfare (Kondo's group)]. *Gan To Kagaku Ryoho* 1990;17:2397-403.
54. Kim J-P. Recent advances in gastric cancer therapy with immunochemosurgery. *Asian J Surg* 1997;20:115-8.
55. 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.
56. 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).
57. 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).
58. 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; 16:263a (abstract 931).
59. 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.
60. 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).
61. 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.
62. 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).
63. 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).
64. 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.
65. 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.
66. 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.
67. Hermans J, Bonenkamp H. Meta-analyses need time, collaboration, and funding [letter, reply]. *J Clin Oncol* 1994;12:879-80.
68. 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.
69. Sakamoto J, Nakazato H. [Evaluation of adjuvant immunochemotherapy in advanced gastric cancer.] *Gan To Kagaku Ryoho* 1993;20:2525-30.
70. 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.
71. Ochiai T, Sato H. [Evaluation of postoperative immunotherapy of gastric cancer.] *Gan To Kagaku Ryoho* 1983;10:373-9.
72. 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 Res* 1983; 43:3001-7.
73. 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.