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/ m² daily) and leucovorin (20 mg/ m² 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/ m² daily) and leucovorin (20 mg/ m² 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/ m² daily) and leucovorin (20 mg/ m² 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
The incidence of gastric cancer has been decreasing steadily since the 1930s. Despite this, gastric cancer is the eighth leading cause of cancer death because the majority of patients present with advanced disease. 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. 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, 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,” “imunochemotherapy,” “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. 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. 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. 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). Dent and associates detected only a non-significant trend toward improved survival in patients randomized to adjuvant chemoradiotherapy. Conversely, Moertel and colleagues 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 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). 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/m² daily) and leucovorin (20 mg/m² 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/m² daily) and leucovorin (20 mg/m² 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/m² daily) and leucovorin (20 mg/m² 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% vs. 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% vs. 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
the surgery performed in this trial was 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 cancer9–38 were examined. A literature-based meta-analysis of 11 randomized trials4,6,17,21,23,25,27,28,42,50,51 by Hermans and associates28 detected a strong positive effect with mitomycin C, and the upper limit of the confidence interval (CI) around the hazard 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 immunotherapy were included in this meta-analysis of published reports. The authors wrote an addendum in 199457 in which they recalculated the OR. This addendum included 2 trials missing from the original meta-analysis.35,40 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-analysis6 of 13 Western randomized trials of adjuvant systemic chemotherapy versus surgery alone4,14,17,21,23,25,26,28,29,31,33,34,42 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 colleagues41 conducted separate pooled analyses for the subgroup of monochemo therapy trials, polychemotherapy trials with anthracyclin, and polychemotherapy trials without anthracyclin. The results indicated a larger magnitude of effect with monoc chemotherapy (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 authors41 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 colleagues41 included in the monochemotherapy subgroup both the trial by Grau and associates48 and an earlier report of the same trial.46 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.

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 alone67,49 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, whereas several European and other Japanese studies have found no significant difference in survival for adjuvant chemoimmunotherapy compared with surgery alone. No obvious pattern or type of immunotherapy tested, trial size or study quality explains these mixed results. Immunotherapeutic compounds studied included bacille Calmette-Guerin, levamisole and picibanil (OK-432). Based on the ability of H2 antagonists to block T-suppressor cells, Langman and associates 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. 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. The 2 other studies, one from Japan and the other from Korea, 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 in-dicated a significant survival benefit favouring neoadjuvant radiation compared with surgery alone (5-year survival rates, 30.1% v. 19.8%; p = 0.009). 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. 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, infusional Propionibacterium avidum KP-40, and PSK (Coriolus versicolor). 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.

Adverse effects

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.

Discussion

The SWOG-9008 study 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. 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, 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, as evidenced by the no treatment control arm in that trial. However, the results of the 3 literature-based meta-analyses suggest that adjuvant chemotherapy alone would be a reasonable alternative in patients unable to undergo radiation. The interventions in the component trials were heterogeneous, however, so no specific regimen could be recommended.

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


