Canadian Association of General Surgeons and American College of Surgeons Evidence-Based Reviews in Surgery. 25.

Perioperative chemotherapy and surgery versus surgery alone for resectable gastric cancer

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CAGS Evidence-Based Reviews in Surgery

The term "evidence-based medicine" was first coined by Sackett and colleagues as "the conscientious, explicit and judicious use of current best evidence in making decisions about the care of individual patients."[1] The key to practising evidence-based medicine is applying the best current knowledge to decisions in individual patients. Medical knowledge is continually and rapidly expanding, and it is impossible for an individual clinician to read all the medical literature. For clinicians to practise evidence-based medicine, they must have the skills to read and interpret the medical literature so that they can determine the validity, reliability, credibility and utility of individual articles. These skills are known as critical appraisal skills. Generally, critical appraisal requires that the clinician have some knowledge of biostatistics, clinical epidemiology, decision analysis and economics, as well as clinical knowledge.

The Canadian Association of General Surgeons and the American College of Surgeons jointly sponsor a program entitled "Evidence-Based Reviews in Surgery (EBRS)," which is supported by an educational grant from ETHICON and ETHICON ENDO SURGERY, both units of Johnson & Johnson Medical Products, a division of Johnson & Johnson, and ETHICON INC. and ETHICON ENDO-SURGERY, INC. divisions of Johnson & Johnson Inc. The primary objective of this initiative is to help practising surgeons improve their critical appraisal skills. During the academic year, 8 clinical articles are chosen for review and discussion. They are selected not only for their clinical relevance to general surgeons but also because they cover a spectrum of issues important to surgeons; for example, causation or risk factors for disease, natural history or prognosis of disease, how to quantify disease (measurement issues), diagnostic tests and the early diagnosis of disease, and the effectiveness of treatment. A methodological article is supplied that guides the reader in critical appraisal of the clinical article. Both methodological and clinical reviews of the article are performed by experts in the relevant areas and posted on the EBRS website. As well, a listserv discussion is held where participants can discuss the monthly article. Members of the Canadian Association of General Surgeons and the American College of Surgeons can access Evidence-Based Reviews in Surgery through the Canadian Association of General Surgeons website (www.cags-accg.ca) or the American College of Surgeons website (www.facs.org). All journal articles and reviews are available electronically through the EBRS website. We also have a library of past articles and reviews that can be accessed at any time. Surgeons who participate in the monthly packages can obtain Royal College of Physicians and Surgeons of Canada Maintenance of Certification credits and/or Continuing Medical Education credits for the current article by reading the monthly articles, participating in the listserv discussion, completing the monthly online evaluation and answering the online multiple choice questionnaire. For further information about EBRS, the reader is directed to the CAGS or ACS website or should email the administrator, Marg McKenzie, at mmckenzie@mtsinai.on.ca.

In addition to making the reviews available through the CAGS and ACS websites, 4 of the reviews are published in condensed versions in the *Canadian Journal of Surgery* and 4 in the *Journal of the American College of Surgeons* each year. We hope readers will find EBRS useful in improving their critical appraisal skills and also in keeping abreast of new developments in general surgery. Comments regarding EBRS may also be directed to mmckenzie@mtsinai.on.ca.

Reference

1. Evidence-Based Medicine Working Group. Evidence-based medicine. *JAMA* 1992;268:2420-5.

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Selected Article

Cunningham D, Allum WH, Stenning SP, et al. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. *N Engl J Med* 2006;355:11–20.

Abstract

Question: Does perioperative adjuvant therapy improve the outcome of operable gastric cancer? **Design:** Multicentre randomized controlled trial. **Setting:** Forty-five centres in the United Kingdom as well as centres in the Netherlands, Germany, Brazil, Singapore and New Zealand. **Patients:** Five hundred and three patients with histologically proven adenocarcinoma of the stomach, esophogastric junction or lower esophagus were randomized to perioperative chemotherapy plus surgery (n = 250 patients) or surgery alone (n = 253 patients). **Interventions:** Patients who were assigned to the perioperative chemotherapy and surgery group received 3 doses of chemotherapy (epirubicin, cisplatin and fluorouracil) preoperatively, followed by surgery 3–6 weeks after the third dose, and then 3 doses of postoperative chemotherapy beginning 6–12 weeks after surgery. Patients assigned to surgery alone were scheduled to have surgery within 6 weeks of randomization. The main outcome measure was overall survival. Secondary outcomes were progression-free survival, assessments of downstaging, the surgeon's assessment of whether the surgery was curative and quality of life. **Results:** Rates of postoperative complications were similar in both groups (46% v. 45%, respectively), as were the numbers of deaths within 30 days of surgery. The resected tumours were significantly smaller and less advanced in the group that received perioperative chemotherapy. With a mean follow-up of 4 years, 144 (60%) of the patients in the perioperative chemotherapy group and 170 (67%) of the patients in the surgery group died. The likelihood of overall survival was higher in the perioperative chemotherapy group (hazard ratio [HR] for death 0.75, 95% confidence interval [CI] 0.60–0.93; p = 0.009; 5-year survival rate 36% v. 23%), as was the likelihood of progression-free survival (HR for progression 0.66; 95% CI 0.53–0.81; $p < 0.001$). **Conclusion:** Compared with the group receiving surgery alone, overall survival improved in the group receiving perioperative chemotherapy, as did progression-free survival among patients with resectable adenocarcinoma of the stomach, esophogastric junction or lower esophagus.

Commentary

Gastric cancer is a rare but deadly disease in the Western hemisphere. Patients often present with advanced disease and have a poor prognosis despite aggressive surgical management. Much has been written on the extent of resection, especially lymph node dissection, and its effect on outcome.

Cunningham and colleagues[1] assessed the effect of perioperative chemotherapy on survival of patients with resectable gastric cancer. Their trial (the MAGIC trial) initially included only patients with gastric cancer, but the trial was expanded to include patients with distal esophageal adenocarcinoma because of the known increase in incidence of esophageal adenocarcinoma.

Resectability was determined by the surgeon on the basis of imaging that could include plain film radiography, computed tomography (CT) and ultrasound and possible laparoscopy. Randomization was performed centrally at the Medical Council Research Group with a minimization algorithm to ensure that surgeons or centres had a mix of patients. The trial ran over 6 years and ultimately included 503 patients, of whom 26% had tumours of the distal esophagus and gastroesophageal junction. The trial involved 129 surgeons and was conducted in 45 centres in the United Kingdom as well as in centres in Europe, Brazil, New Zealand and Singapore.

Chemotherapy involved 3 preoperative and 3 postoperative cycles of epirubicin, cisplatin and fluorouracil. In total, 250 patients were randomized to the chemotherapy arm: 237 started chemotherapy, 215 had 3 cycles preoperatively, 209 went to surgery, 137 started postoperative chemotherapy, and 104 (42%) completed all 6 cycles. Surgery was performed a median of 99 days after randomization into the chemotherapy group and 14 days after randomization into the surgery-alone group.

The primary outcome measure was survival. Secondary measures were progression-free survival, assessments of downstaging, the surgeon's assessment of whether the surgery was curative and quality of life.

The 2 groups were similar in terms of age, sex, World Health Organization performance status and tumour site and clinical stage. Perioperative mortality was 6% overall; morbidity was around 45% and did not differ significantly between the groups. With regard to the primary outcome, the HR for death was 0.75 (95% CI 0.66–0.93). This corresponded to an absolute improvement in survival in the chemotherapy group of 13%. Estimated median survival in this group was 19 months, compared with 13 months in the group receiving surgery alone.

Results of secondary outcome measures showed a significant HR of 0.66 (95% CI 0.53–0.81) for progression in the chemotherapy group, an increased likelihood of curative resection as determined by the surgeon (p = 0.03) and significantly smaller ($p < 0.001$) and earlier-stage tumours (p = 0.002). Quality of life measures were not reported. The authors conclude that they have demonstrated a survival benefit in adding perioperative chemotherapy to surgery for

the management of gastroesophageal adenocarcinoma.

The trial has several strengths. Its pragmatic design asks whether perioperative chemotherapy should be added to resection in patients deemed resectable by the surgeon. The issue of resectability is one routinely encountered by surgeons. The design accepts the concept that some form of local therapy (i.e., resection) is necessary to relieve or prevent the bleeding and dysphagia common with tumours at this location. It is a large trial and uses chemotherapeutic agents that have known activity against adenocarcinoma. The large number of centres and surgeons involved suggests that results are generalizable.

The trial unfortunately has some significant weaknesses as well. The surgery was not standardized, and there is no quality assessment other than a simple comment on complication rates and operative mortality. It should be said that a 6% mortality seems reasonable in this population. Nonstandardized surgery means that pathologic staging may be less accurate, making the secondary outcome measure of stage less meaningful. Because the surgeon wasn't blinded to the patient's status, the assessment of curability might have been biased. Finally, although quality of life was said to be an outcome measure, it was not reported.

Perhaps the major weakness of this trial lies in its applicability. Patients with 2 different cancers with very different symptoms and very different operative approaches were included. While the preferred surgical technique for gastric cancer is discussed, there is no discussion of how esophagectomy should be performed. Most patients in this study were also asymptomatic, which is unusual in esophageal cancer and limits the applicability of the results. Although the results likely apply to gastric cancers, patients with esophageal cancer might prefer to avoid a 99-day delay in obtaining symptom relief. The last threat to applicability is the chemotherapy regimen, which has low tolerability, as indicated by the fact that only 42% of the patients completed the 6 cycles.

Adenocarcinoma of the esophagus and stomach is a disease with a poor prognosis. This trial has demonstrated a survival benefit overall and especially in gastric cancer patients, but it should not be considered the final answer. Future trials need to separate esophageal from gastric cancer, use more tolerable chemotherapy regimens and standardize the operations used to control for the effect of lymph node sampling and resection technique. In asymptomatic patients, the preferred study would perhaps be to compare preoperative to postoperative chemoradiation, which has also been demonstrated to improve survival.[2] In symptomatic patients, surgery should perhaps be the first step in all cases, followed by randomization to some form of adjuvant treatment. Cunningham and colleagues' paper is important because it shows us the direction for future research.

Competing interests: None declared.

References

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