The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JULY 6, 2006 VOL. 355 NO. 1

Perioperative Chemotherapy versus Surgery Alone for Resectable Gastroesophageal Cancer

David Cunningham, M.D., William H. Allum, M.D., Sally P. Stenning, M.Sc., Jeremy N. Thompson, M.Chir., Cornelis J.H. Van de Velde, M.D., Ph.D., Marianne Nicolson, M.D., J. Howard Scarffe, M.D., Fiona J. Lofts, Ph.D., Stephen J. Falk, M.D., Timothy J. Iveson, M.D., David B. Smith, M.D., Ruth E. Langley, M.D., Ph.D., Monica Verma, M.Sc., Simon Weeden, M.Sc., and Yu Jo Chua, M.B., B.S., for the MAGIC Trial Participants*

ABSTRACT

BACKGROUND

A regimen of epirubicin, cisplatin, and infused fluorouracil (ECF) improves survival among patients with incurable locally advanced or metastatic gastric adenocarcinoma. We assessed whether the addition of a perioperative regimen of ECF to surgery improves outcomes among patients with potentially curable gastric cancer.

METHODS

We randomly assigned patients with resectable adenocarcinoma of the stomach, esophagogastric junction, or lower esophagus to either perioperative chemotherapy and surgery (250 patients) or surgery alone (253 patients). Chemotherapy consisted of three preoperative and three postoperative cycles of intravenous epirubicin (50 mg per square meter of body-surface area) and cisplatin (60 mg per square meter) on day 1, and a continuous intravenous infusion of fluorouracil (200 mg per square meter per day) for 21 days. The primary end point was overall survival.

RESULTS

ECF-related adverse effects were similar to those previously reported among patients with advanced gastric cancer. Rates of postoperative complications were similar in the perioperative-chemotherapy group and the surgery group (46 percent and 45 percent, respectively), as were the numbers of deaths within 30 days after surgery. The resected tumors were significantly smaller and less advanced in the perioperative-chemotherapy group. With a median follow-up of four years, 149 patients in the perioperative-chemotherapy group and 170 in the surgery group had died. As compared with the surgery group, the perioperative-chemotherapy group had a higher likelihood of overall survival (hazard ratio for death, 0.75; 95 percent confidence interval, 0.60 to 0.93; $P=0.009$; five-year survival rate, 36 percent vs. 23 percent) and of progression-free survival (hazard ratio for progression, 0.66; 95 percent confidence interval, 0.53 to 0.81; $P<0.001$).

CONCLUSIONS

In patients with operable gastric or lower esophageal adenocarcinomas, a perioperative regimen of ECF decreased tumor size and stage and significantly improved progression-free and overall survival. (Current Controlled Trials number, ISRCTN93793971.)

From the Departments of Medicine (D.C., Y.J.C.) and Surgery (W.H.A., J.N.T.), Royal Marsden Hospital, Surrey and London; the Medical Research Council Clinical Trials Unit, Cancer Group, London (S.P.S., R.E.L., M.V., S.W.); the Department of Oncology, Aberdeen Royal Infirmary, Aberdeen (M.N.); the Department of Medical Oncology, Christie Hospital, Manchester (J.H.S.); the Department of Medical Oncology, St. George's Hospital, London (F.J.L.); the Department of Oncology, Bristol Haematology and Oncology Centre, Bristol (S.J.F.); the Medical Oncology Unit, Southampton General Hospital, Southampton (T.J.I.); and the Clatterbridge Centre for Oncology, Liverpool (D.B.S.) — all in the United Kingdom; and the Department of Surgery, Leiden University Medical Center, Leiden, the Netherlands (C.J.H.V.V.). Address reprint requests to Prof. Cunningham at the Department of Medicine, Royal Marsden Hospital, Downs Rd., Sutton, Surrey SM2 5PT, United Kingdom, or at david.cunningham@rmh.nhs.uk.

*Participants in the Medical Research Council Adjuvant Gastric Infusional Chemotherapy (MAGIC) Trial are listed in the Appendix.

N Engl J Med 2006;355:11-20.

The outcome among patients with gastric or lower esophageal cancer is determined by the stage of the disease at presentation. Localized disease, limited to the mucosa and submucosa, is best treated surgically and has a five-year survival rate of 70 to 95 percent.[1,2] Once tumor cells have spread through the submucosa, the risk of lymph-node metastases increases and the likelihood of prolonged disease-free survival diminishes. Western surgical and population-based series show that most patients present with tumor that has penetrated the submucosa; they have a five-year survival rate of 20 to 30 percent.[3] In Japan, extended surgery prolongs survival in such cases, even in the presence of lymph-node metastases,[2] but this effect has not been reproduced in Western trials.[4-7]

The regimen of epirubicin, cisplatin, and infused fluorouracil (ECF), which was developed in the late 1980s,[8] achieves response rates between 49 percent and 56 percent in randomized trials of the treatment of locally advanced gastric cancer.[9,10] As compared with a regimen of fluorouracil, doxorubicin, and methotrexate (FAMTX), the ECF regimen improves survival and response rates among patients with advanced esophagogastric cancer,[9,11] and the side-effect profile is acceptable. These results have not been improved by substituting mitomycin for epirubicin.[10] A recent meta-analysis found that in advanced disease, epirubicin and cisplatin contribute independently to the efficacy of combination chemotherapy.[12]

The present trial was designed to determine whether a regimen of ECF given before and after radical surgery improves the outcomes of operable gastric cancer. The potential benefits of administering ECF preoperatively include increasing the likelihood of curative resection by downstaging the tumor, eliminating micrometastases, rapidly improving tumor-related symptoms, and determining whether the tumor is sensitive to the chemotherapy. The primary end point of the trial was overall survival; secondary end points were progression-free survival, surgical and pathological assessments of down-staging (i.e., tumor diameter, tumor stage, and nodal status), the assessments by the surgeons about whether the surgery was curative, and quality of life.

Methods

Eligibility

Patients of any age who had a World Health Organization (WHO) performance status of 0 or 1 were eligible if they had histologically proven adenocarcinoma of the stomach or lower third of the esophagus that was considered to be stage II (through the submucosa) or higher, with no evidence of distant metastases, or locally advanced inoperable disease, as evaluated by computed tomography, chest radiography, ultrasonography, or laparoscopy.[13] The original trial design included patients with gastric carcinomas only, but on the basis of the increased incidence of tumors of the esophagogastric junction, eligibility criteria were extended in 1999 to include adenocarcinomas of the lower third of the esophagus. This change coincided with the end of the Medical Research Council (MRC) OEO2 trial of neoadjuvant chemotherapy in patients with esophageal cancer.[14]

Patients were excluded if they had previously received cytotoxic chemotherapy or radiotherapy, had uncontrolled cardiac disease, or had creatinine clearance of 60 ml per minute or less. The protocol was approved by the relevant ethics committees, and patients gave written informed consent for participation in the trial.

Treatment

Patients were randomly assigned to either perioperative chemotherapy and surgical resection (the perioperative-chemotherapy group) or to surgical resection alone (the surgery group) by means of a telephone call to the MRC Clinical Trials Unit. Treatment was allocated with the use of the minimization method according to the following stratification factors: age, tumor site (e.g., stomach, esophagogastric junction, or lower esophagus), WHO performance status, and surgeon. Chemotherapy was administered for three cycles preoperatively and three cycles postoperatively. Each 3-week cycle consisted of epirubicin (50 mg per square meter of body-surface area) by intravenous bolus on day 1, cisplatin (60 mg per square meter) intravenously with hydration on day 1, and fluorouracil (200 mg per square meter) daily for 21 days by continuous intravenous infusion with the

use of a double-lumen Hickman catheter and a portable infusion pump. One mg of warfarin daily was recommended as prophylaxis against thrombosis.

Before each cycle of chemotherapy, a complete blood count was obtained and blood urea nitrogen, electrolyte, and serum creatinine levels and liver function were determined. Dose modifications of the ECF regimen were recommended for patients with myelosuppression and thrombocytopenia, and of fluorouracil for those with stomatitis, hand–foot syndrome (palmar–plantar erythrodysesthesia), and diarrhea. The left ventricular ejection fraction was measured by multiple gated acquisition scanning or echocardiography in patients with a history of ischemic heart disease. If the left ventricular ejection fraction was less than 50 percent, epirubicin was omitted. If there was a rise in the serum creatinine level, the creatinine clearance was determined and the cisplatin dose was modified if appropriate. Cisplatin was discontinued in patients with clinically significant ototoxicity or sensory neural damage. The severity of adverse effects, defined according to the National Cancer Institute Common Toxicity Criteria, and performance status were assessed every three weeks.

SURGERY

Surgery was scheduled to take place within six weeks after randomization in the surgery group and three to six weeks after completion of the third cycle of chemotherapy in the perioperative-chemotherapy group. Postoperative chemotherapy was to be initiated 6 to 12 weeks after surgery.

After undergoing laparotomy, patients had a preaortic, infracolic node removed and submitted to frozen section examination for metastatic involvement. If the nodes were involved, further management of the disease was at the discretion of the clinician. In radical total gastrectomy, the whole stomach was removed, with the proximal line of division through the distal esophagus, and the distal line of division through the proximal duodenum. The resection also included the greater and lesser omenta and any other organs involved by extension of the primary growth (e.g., pancreas, spleen, mesocolon, colon, or left lobe of liver). The procedure for a radical subtotal distal gastrectomy was the same, but a small, viable gastric remnant was left intact. In both procedures, the resection lines had to be at least 3 cm from the edge of the macroscopic tumor.

The surgeon decided the extent of the lymph-node dissection. Lymph nodes along the lesser and greater curvatures and at the origin of the left gastric artery were to be included. Nodal sampling for histologic examination of other groups was recommended. In esophagectomy the thoracic approach was not stipulated. The object of nodal dissection was to remove periesophageal nodes. Separate sampling of the subcarinal and celiac-axis lymph nodes was recommended.

Surgeons were asked to document the extent of dissection and to state whether the procedure was likely to be curative. The resection was judged curative, either absolutely or relatively, if all macroscopic and microscopic disease seemed to have been removed. All resected specimens were examined at local pathology laboratories according to a standard protocol that used the tumor–node–metastasis (TNM) classification.[13]

STATISTICAL ANALYSIS

On the basis of the results of the second British Stomach Cancer Group trial,[15] we estimated that the five-year survival rate after surgery alone would be 23 percent. The trial was designed to detect an absolute increase in survival of 15 percent in the perioperative-chemotherapy group, with a two-sided alpha level of 5 percent and a statistical power of 90 percent, given the enrollment of 500 patients over a period of four years, and approximately 250 deaths. Because smaller differences would still be clinically relevant, we originally intended to carry out a further joint analysis with another European trial of a similar design, which would have collectively given 90 percent power to detect an absolute increase in survival of 10 percent through the addition of perioperative chemotherapy. Since the latter trial closed early (February 1996)[16] after only 59 patients had undergone randomization, this was not possible. The initial analysis was to occur after 250,[17] patients had died and the final analysis was to occur, regardless of the results, after approximately 320 patients had died, when approximately 90 percent of patients had died or had

Table 1. Pretreatment Characteristics of the Patients.*

Characteristic	Perioperative-Chemotherapy Group (N=250)	Surgery-Only Group (N=253)
Age		
<60 yr — no. (%)	108 (43.2)	104 (41.1)
60–69 yr — no. (%)	91 (36.4)	95 (37.5)
≥70 yr — no. (%)	51 (20.4)	54 (21.3)
Median — yr	62	62
Range — yr	29–85	23–81
Sex — no. (%)		
Male	205 (82.0)	191 (75.5)
Female	45 (18.0)	62 (24.5)
WHO performance status — no. (%)†		
0	169 (67.6)	173 (68.4)
1	81 (32.4)	80 (31.6)
Site of tumor — no. (%)		
Stomach	185 (74.0)	187 (73.9)
Lower esophagus	37 (14.8)	36 (14.2)
Esophagogastric junction	28 (11.2)	30 (11.9)
Maximum tumor diameter		
0.0–3.9 cm — no. (%)‡	50 (30.9)	61 (33.3)
4.0–7.9 cm — no. (%)‡	79 (48.8)	87 (47.5)
8.0–11.9 cm — no. (%)‡	29 (17.9)	24 (13.1)
12.0–15.9 cm — no. (%)‡	2 (1.2)	8 (4.4)
>16.0 cm — no. (%)‡	2 (1.2)	3 (1.6)
Unknown — no. (%)	88 (35.2)	70 (27.7)
Median — cm	5.0	5.0
Interquartile range — cm	3.0–7.0	3.0–7.0

* There were no significant differences between groups.
† A WHO performance status of 0 denotes asymptomatic, and 1 symptomatic but fully ambulatory.
‡ Percentages are based on the number of patients with tumors of a known diameter (i.e., 162 in the perioperative-chemotherapy group and 183 in the surgery group).

been followed up for a minimum of two years. This approach would provide this trial alone with at least 70 percent power to detect an absolute difference between the two groups of approximately 10 percent at five years. These criteria were met in December 2004, and the database was frozen for analysis on December 2, 2004.

Progression-free survival was calculated from randomization to the first event (i.e., local recurrence or progression, distant recurrence, or death from any cause), and overall survival was calculated from randomization to death. Data on patients who were event-free were censored on the date the patient was last seen. Kaplan–Meier curves for progression-free and overall survival were compared with the use of the log-rank test on an intention-to-treat basis. Hazard ratios were calculated with the use of a Cox regression model including treatment alone (primary analysis) and after adjustment for baseline stratification factors. Categorical data were compared with the use of chi-square tests, with a test for trend over ordered categories (e.g., T stage). Tumor measurements were compared with the use of nonparametric Mann–Whitney tests. All tests were two-sided and unadjusted for multiple comparisons.

The trial was overseen by an independent data-monitoring committee that met five times (approximately annually) to review accrual, safety, and efficacy data. The committee recommended continuation at each review. A formal stopping rule was not prespecified.

RESULTS

CHARACTERISTICS OF THE PATIENTS

Between July 1994 and April 2002, 503 patients were randomly assigned to treatment — 250 to perioperative chemotherapy and surgery and 253 to surgery alone. Most patients were from 45 centers in the United Kingdom. Other trial centers were in the Netherlands, Germany, Brazil, Singapore, and New Zealand; 129 surgeons took part. Table 1 shows that the two groups were similar in terms of age, sex, and WHO performance status. Distribution according to the site and size of the tumor was also well balanced.

TREATMENT

Chemotherapy

Preoperative data were available for 246 of 250 patients in the perioperative-chemotherapy group. Nine patients did not start chemotherapy for the following reasons: patient request (five patients), reassessment as inoperable (one), deterioration before chemotherapy could start (one), the necessity for immediate surgery (one), and problems with the Hickman catheter (one). Of the 237 who started treatment, 215 completed three cycles. The reasons for not completing three preoperative cycles

are as follows: toxic effects (12 patients), patient request (3), problems with the Hickman catheter (3), early cancer-related death (2), and other (2).

A total of 215 patients (86.0 percent of patients who were assigned to receive perioperative chemotherapy, and 90.7 percent of those who started chemotherapy) completed preoperative chemotherapy, of whom 209 (including 1 patient who received only one preoperative cycle) proceeded to surgery. Of those 209 patients, 137 (65.6 percent [54.8 percent of the 250 patients assigned to receive perioperative chemotherapy]) subsequently began postoperative chemotherapy. Postoperative treatment details were missing for three patients. Reasons for not starting postoperative chemotherapy after completion of the first three cycles were disease progression or early death (37 patients), patient choice (11), postoperative complications (10), problems with the Hickman catheter (4), previous toxic effects (3), lack of response to preoperative treatment (2), and worsening coexisting disease (2). Of the 137 patients who started postoperative chemotherapy, 104 (75.9 percent) completed the three postoperative cycles.

Therefore, 104 of 250 patients (41.6 percent) randomly assigned to perioperative chemotherapy completed all six cycles of chemotherapy and 103 of 208 patients (49.5 percent) who completed preoperative chemotherapy and surgery also completed postoperative treatment (1 patient received six cycles but did not undergo surgery). Of the 237 patients in the perioperative-chemotherapy group who started treatment, 4 died within 60 days after commencing treatment, 2 because of their cancer and 2 because of cardiac problems. After surgery, there was no clinically significant increase in the incidence of grade 3 or grade 4 toxic effects associated with the chemotherapy (Table 2).

Table 2. Adverse Effects Associated with Preoperative and Postoperative Chemotherapy.

Adverse Effect	Preoperative	Postoperative
	number of patients (percent)	
Hematologic		
Granulocytopenia	223	133
Grade 0, 1, or 2	170 (76.2)	96 (72.2)
Grade 3 or 4	53 (23.8)	37 (27.8)
Lymphocytopenia	231	136
Grade 0, 1, or 2	185 (80.1)	113 (83.1)
Grade 3 or 4	46 (19.9)	23 (16.9)
Leukopenia	235	135
Grade 0, 1, or 2	208 (88.5)	120 (88.9)
Grade 3 or 4	27 (11.5)	15 (11.1)
Hemoglobinopathy	235	135
Grade 0, 1, or 2	224 (95.3)	134 (99.3)
Grade 3 or 4	11 (4.7)	1 (0.7)
Thrombocytopenia	235	135
Grade 0, 1, or 2	234 (99.6)	131 (97.0)
Grade 3 or 4	1 (0.4)	4 (3.0)
Other hematologic abnormality	217	126
Grade 0, 1, or 2	216 (99.5)	124 (98.4)
Grade 3 or 4	1 (0.5)	2 (1.6)
Nonhematologic		
Nausea	233	138
Grade 0, 1, or 2	218 (93.6)	121 (87.7)
Grade 3 or 4	15 (6.4)	17 (12.3)
Vomiting	234	138
Grade 0, 1, or 2	221 (94.4)	124 (89.9)
Grade 3 or 4	13 (5.6)	14 (10.1)
Neurologic effects	234	137
Grade 0, 1, or 2	225 (96.2)	132 (96.4)
Grade 3 or 4	9 (3.8)	5 (3.6)
Skin effects	235	137
Grade 0, 1, or 2	227 (96.6)	135 (98.5)
Grade 3 or 4	8 (3.4)	2 (1.5)
Stomatitis	234	138
Grade 0, 1, or 2	224 (95.7)	133 (96.4)
Grade 3 or 4	10 (4.3)	5 (3.6)
Diarrhea	234	137
Grade 0, 1, or 2	228 (97.4)	132 (96.4)
Grade 3 or 4	6 (2.6)	5 (3.6)

Surgery

In the perioperative-chemotherapy group, 229 patients (91.6 percent) underwent surgery, including those who did not complete preoperative chemotherapy, with a median time from randomization to surgery of 99 days. In the surgery group, 244 patients (96.4 percent) underwent surgery, with a median time from randomization to surgery of 14 days. The type of surgery performed and the pathological tumor stage and nodal status are

shown in Table 3. Resection was curative in 169 of 244 patients (69.3 percent) in the perioperative-chemotherapy group and in 166 of 250 patients (66.4 percent) in the surgery group. Among patients treated by radical surgery, resection was considered curative by the operating surgeon in 169 of 213 patients (79.3 percent) in the perioperative-chemotherapy group as compared with 166 of 236 patients (70.3 percent) in the surgery group (P=0.03). The incidence of postoperative complications was similar in the two groups (45.7 percent in the perioperative-chemotherapy group and 45.3 percent in the surgery group), as were the number of deaths within 30 days (14 [5.6 percent] and 15 [5.9 percent], respectively) and the median hospital stay (13 days in both groups).

PATHOLOGICAL FINDINGS

The median maximum diameter of the resected tumor was smaller in the perioperative-chemotherapy group than in the surgery group (3 cm vs. 5 cm, P<0.001); this finding is consistent with tumor shrinkage in the chemotherapy group. Among all patients undergoing resection, there was a greater proportion of stage T1 and T2 tumors in the perioperative-chemotherapy group than in the surgery group (51.7 percent vs. 36.8 percent, P=0.002 by the chi-square test for trend).

Table 3. Surgical and Pathological Results.

Variable	Perioperative-Chemotherapy Group (N=250)	Surgery Group (N=253)
	number of patients/total number (percent)	
Extent of resection according to surgeon		
Curative	169/244 (69.3)	166/250 (66.4)
Palliative	44/244 (18.0)	70/250 (28.0)
Opinion not specified	16/244 (6.6)	8/250 (3.2)
No surgery	15/244 (6.1)	6/250 (2.4)
Surgical status unknown	6/250 (2.4)	3/253 (1.2)
Operation performed*		
Esophagogastrectomy	58/219 (26.5)	52/238 (21.8)
D1 distal resection	19/219 (8.7)	30/238 (12.6)
D1 total resection	20/219 (9.1)	20/238 (8.4)
D2 distal resection	32/219 (14.6)	24/238 (10.1)
D2 total resection	61/219 (27.9)	72/238 (30.3)
Nonresectional surgery	29/219 (13.2)	40/238 (16.8)
Unknown	10/229 (4.4)	6/244 (2.5)
Pathology reports		
Tumor stage (all patients)		
T1	27/172 (15.7)	16/193 (8.3)
T2	62/172 (36.0)	55/193 (28.5)
T3	75/172 (43.6)	106/193 (54.9)
T4	8/172 (4.7)	16/193 (8.3)
Nodal status (patients with gastric cancer)		
N0	42/135 (31.1)	42/156 (26.9)
N1 (<7 nodes involved)	72/135 (53.3)	68/156 (43.6)
N2 (7–14 nodes involved)	19/135 (14.1)	34/156 (21.8)
N3 (>14 nodes involved)	2/135 (1.5)	12/156 (7.7)

* D1 denotes limited lymph-node dissection, and D2 extended lymph-node dissection.

Also, among patients with gastric cancer, there was a significant trend to less advanced nodal disease (i.e., N0 or N1) in the perioperative-chemotherapy group than in the surgery group (84.4 percent vs. 70.5 percent, P=0.01 by the chi-square test for trend).

PROGRESSION-FREE AND OVERALL SURVIVAL

At the time of analysis, the median follow-up was 49 months in the perioperative-chemotherapy group and 47 months in the surgery group; 90 percent of the patients had died or were followed for more than two years. The numbers of surviving patients with less than two years of follow-up were 17 in the perioperative-chemotherapy group and 35 in the surgery group. Before death, local recurrence was confirmed in 36 patients (14.4 percent) in the perioperative-chemotherapy group and 52 patients (20.6 percent) in the surgery group, with distant metastases confirmed in 61 patients (24.4 percent) and 93 patients (36.8 percent), respectively. A total of 319 patients died (149 in the perioperative-chemotherapy group and 170 in the surgery group) and 353 patients had disease progression or died (163 and 190, respectively).

As compared with the surgery group, the perioperative-chemotherapy group had a significantly higher likelihood of progression-free survival (hazard ratio for progression, 0.66; 95 percent confidence interval, 0.53 to 0.81; P<0.001) (Fig. 1A), and of overall survival (hazard ratio for death, 0.75; 95 percent confidence interval, 0.60 to 0.93; P=0.009) (Fig. 1B). Adjustment for stratification factors (excluding the surgeon) gave a hazard ratio for death of 0.74 (95 percent confidence interval, 0.59 to 0.93; P=0.008) in the perioperative-chemotherapy group. Five-year survival rates were 36.3 percent (95 percent confidence interval, 29.5 to 43.0 percent) among patients in the perioperative-chemotherapy group and 23.0 percent (95 percent confidence interval, 16.6 to 29.4 percent) among those in the surgery group. Figure 2 shows that there was no clear evidence of heterogeneity of treatment effect according to the site of the primary tumor, age group, sex, or the WHO performance status.

Since our analysis in December 2004, only seven deaths have been reported. Since most patients have now passed the period during which deaths from gastric cancer are most likely to be reported (i.e., the steepest part of the Kaplan–Meier curves), we would expect the death rate to continue to decline.

DISCUSSION

In this randomized trial of chemotherapy in patients with resectable gastric cancer, we demon-

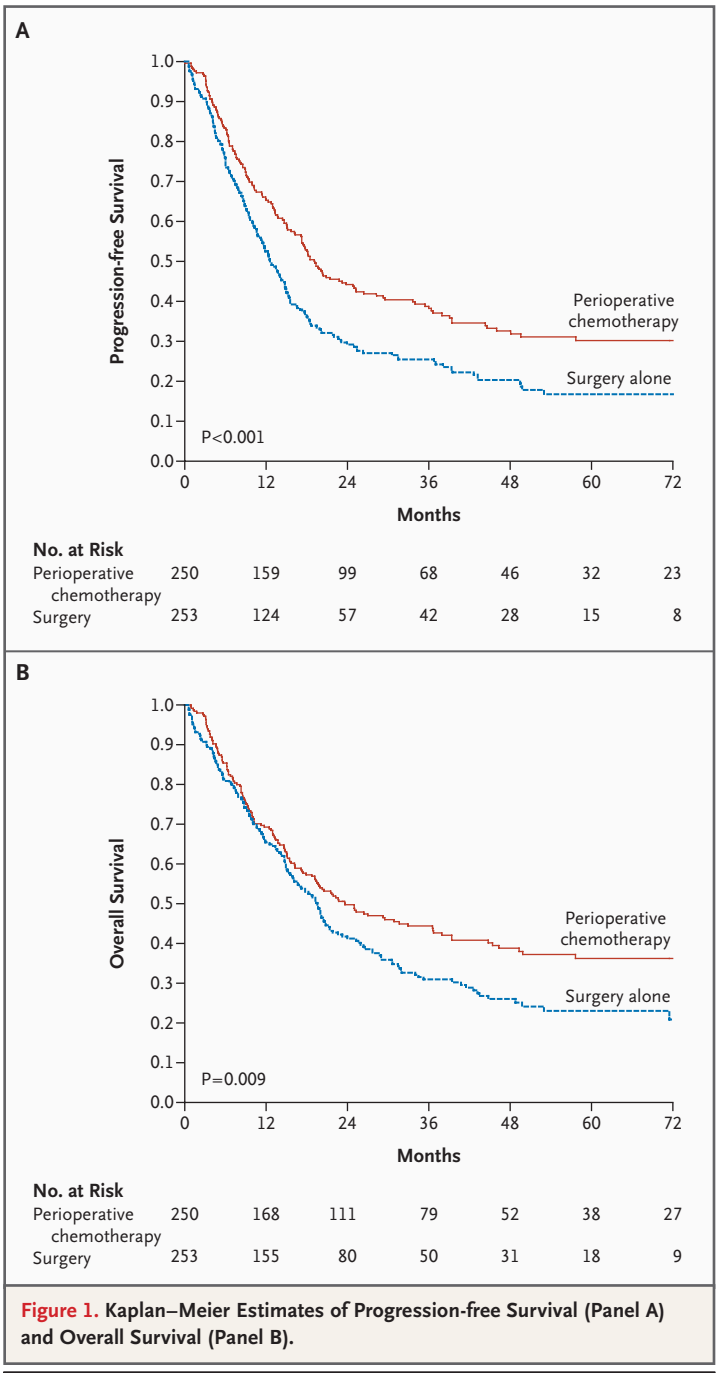

Figure 1. Kaplan–Meier Estimates of Progression-free Survival (Panel A) and Overall Survival (Panel B).

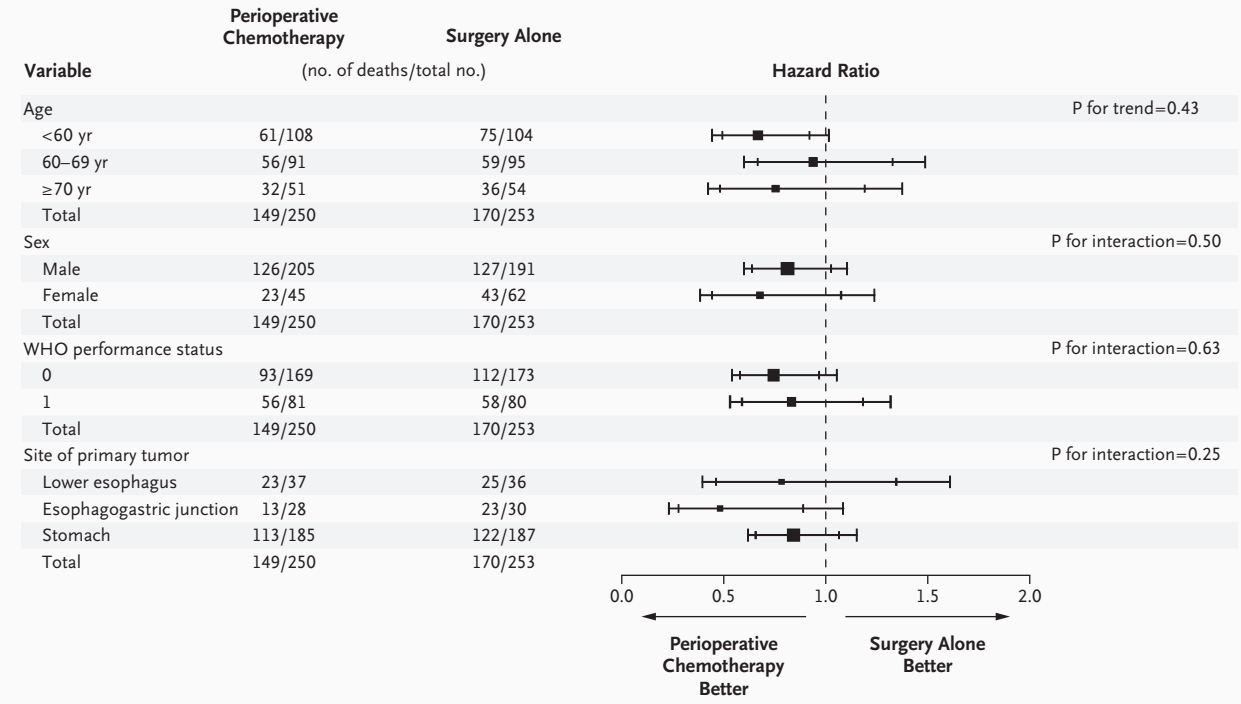

Figure 2. Tests for Heterogeneity of Treatment Effect According to the Baseline Characteristics of the Patients.
The hazard ratios show 95 percent (inner tick marks) and 99 percent (outer tick marks) confidence intervals.

strated a survival benefit with the use of perioperative chemotherapy as compared with surgery alone, with an estimated improvement of 13 percentage points in the five-year survival rate, corresponding to a 25 percent reduction in the risk of death. In contrast, randomized trials of postoperative (adjuvant) chemotherapy[15,18,19] and a meta-analysis by Hermans et al.[20] concluded that postoperative chemotherapy did not add a survival benefit to surgery. A small but significant benefit of postoperative chemotherapy was found in two other meta-analyses, but these results have not generally influenced standard clinical practice.[21,22]

We initially planned to combine our results with those of a Dutch Gastric Cancer Group study,[16] which randomly assigned patients with operable gastric adenocarcinoma to four cycles of FAMTX before surgery or to surgery alone. This study was closed after 59 patients were enrolled and after an interim analysis showed inadequate rates of curative resection in the chemotherapy group. The median survival at the time of reporting was 18 months in the group receiving chemotherapy plus surgery and 30 months in the group undergoing surgery alone (P=0.17). This outcome may reflect the inferiority of the FAMTX regimen as compared with the ECF regimen in patients with advanced disease.[9,11]

An important trial involving patients with operable gastric cancer is the U.S. Southwest Oncology Group Intergroup study (SWOG 9008/INT-0116), in which 556 patients were randomly assigned to adjuvant chemoradiotherapy with fluorouracil or surgery alone. The trial showed that median survival was 36 months with postoperative chemoradiotherapy and 27 months with surgery alone (hazard ratio, 0.74; 95 percent confidence interval, 0.60 to 0.92; P=0.005).[23] Our results and those of the SWOG Intergroup study are not directly comparable because we enrolled patients at the time of diagnosis, whereas the other study enrolled patients only after they had undergone a complete resection.

A possible limitation of our trial is that only 42 percent of patients in the perioperative-chemotherapy group completed all protocol treatment;

34 percent of patients who completed preoperative chemotherapy and surgery did not begin postoperative chemotherapy, predominantly owing to early disease progression, patient request, or postoperative complications. Nevertheless, patients assigned to perioperative chemotherapy had a significant survival advantage over those who underwent surgery alone. Early disease progression reflects the aggressive biology of gastric cancer, and the acceptability of the ECF regimen to patients may have been adversely affected by the need for long-term intravenous access and an infusion pump. Because this trial evaluated perioperative treatment, it is not possible to attribute the favorable outcome to preoperative or postoperative chemotherapy. Comparisons of survival between patients completing preoperative chemotherapy only and patients who received all six cycles will be biased owing to the nonrandomized distribution of these groups. However, the efficacy of the ECF regimen in our trial provides support for the current U.S. Intergroup Trial of Adjuvant Chemoradiation after Resection of Gastric or Gastroesophageal Adenocarcinoma, which is testing a postoperative ECF regimen in addition to chemoradiation (Cancer and Leukemia Group B 80101).

New chemotherapy agents have become available since the inception of this trial. Both the oral fluoropyrimidine prodrug capecitabine and the non-nephrotoxic platinum compound oxaliplatin are being evaluated as substitutes for infused fluorouracil and cisplatin, respectively, in patients with previously untreated advanced esophagogastric cancer.[24]

In summary, our results show that perioperative chemotherapy with a regimen of ECF improves overall and progression-free survival among patients with resectable adenocarcinoma of the stomach, lower esophagus, or gastroesophageal junction, as compared with surgery alone. This treatment should therefore be considered as an option for patients with adenocarcinoma in these sites.

Supported by Pharmacia, for reimbursement of the costs of epirubicin, and by a core grant from the Medical Research Council for the design, conduct, and analysis of the trial.

No potential conflict of interest relevant to this article was reported.

We are indebted to all the surgeons, oncologists, pathologists, and research support staff in the participating centers listed in the Appendix.

APPENDIX

The following persons participated in the MAGIC Trial, which was developed by D. Cunningham and W.H. Allum on behalf of the MRC Gastric Cancer Working Party (now the National Cancer Research Institute Upper Gastrointestinal Cancer Clinical Studies Group) in collaboration with the British Stomach Cancer Group and the Dutch Gastric Cancer Group, and was coordinated by the MRC Cinical Trials Unit: **Statisticians** — P. Fayers, S. Weeden, S. Stenning; **Clinical Trial Managers** — J. Whaley, J. Lyddiard, M. Verma; **Reference Pathologists** — I. Filipe, D. Levison, F. Carey, A. Wotherspoon; **Independent Data Monitoring Committee** — A. Johnson, T. Priestman, J. Dunn; **Steering Committee** — M. Mason, P. Johnson, R. Rudd; **Investigators — United Kingdom:** *Aberdeen Royal Infirmary* — D. Gough, P. King, M. Nicolson, K. Park, S. Prasad, A. Qadir; *Addenbrooke's Hospital* — P. Corrie, P.J. Friend, D. Gilligan, R. Praseedon, C. Wilson; *Aintree Hospital* — D. Kerrigan, P. McCulloch; *Airedale General Hospital* — S.M. Crawford, E.P. Dewar; *Basildon Hospital* — D.G.S. Collier, F. Khan; *Bedford Hospital* — R. Foley; *Belfast City Hospital* — D. Carey, M. Eatoch, J. McAleer; *Belvoir Park Hospital* — R. Harte, R.F. Houston; *Bishop Auckland General Hospital* — S. Stock; *Blackburn Royal Infirmary* — D. Chang; *Bristol Oncology Centre* — S. Falk; *Bristol Royal Infirmary* — D. Alderson; *Broomfield Hospital* — M. Harvey, S. Tahir; *Charing Cross Hospital* — R.H. Phillips; *Chase Farm Hospital* — J. Bolton; *Chelsea & Westminster Hospital* — C. Wastell; *Cheltenham General Hospital* — R. Counsell, S. Elyan; *Christie Hospital National Health Service Trust* — H. Anderson, R. Hawkins, J.H. Scarffe; *Clatterbridge Centre for Oncology* — E. Marshall, A. Masters, S. O'Reilly, S. Sagar, D. Smith; *Colchester General Hospital* — D. Menzies; *Cookridge Hospital* — D.A. Anthoney, M. Seymour; *Crawley Hospital* — E.R.T. Owen; *Derby City Hospital* — R. Hall; *Derbyshire Royal Infirmary* — P. Chakraborti, S.Y. Iftikhar, G. Thomas; *Derriford Hospital* — J. Campbell, F. Daniel, J. Rahamin; *East Surrey Hospital* — R.G. Lightwood; *Epsom General Hospital* — W.H. Allum; *Essex County Hospital* — P. Murray, B. Sizer; *Glan Clwyd Hospital* — J. Clark, S. Gollins; *Glasgow Royal Infirmary* — R. Carter, D.J. Dunlop, M. Soukop, R. Stuart; *Gloucestershire Royal Hospital* — M. Vipond; *Hinchingbrooke Hospital* — B. Greenway, J. Read; *Homerton Hospital* — D. Shanahan; *Hope Hospital* — L. Formela; *James Cook University Hospital* — Y.K.S. Viswanath, S. Attwood, N. Wadd; *Joyce Green Hospital* — M.C. Parker; *King Edward VII Hospital, Midhurst* — S. Whitaker, R.E. Sayer; *King George Hospital* — S.J. Snooks; *Lagan Valley Hospital* — J.A. Kennedy; *Leeds General Infirmary* — I.G. Martin, H. Sue-Ling; *Lister Hospital* — T. Holme, J.H. Scarffe, S. Watkins; *Maidstone Hospital* — M. Hill, G. Trotter; *Manchester Royal Infirmary* — A.K. Siriwanda; *Mayday Hospital* — S.R. Ebbs; *Morriston Hospital* — J.N. Baxter, T.H. Brown; *Northern Centre for Cancer Treatment, Newcastle General Hospital* — F. Coxon, P. Mulvenna, J.M. Bozzino; *Ninewells Hospital & Medical School* — A. Cuschieri, J.A. Dewar, M.J. Lavelle-Jones; *Norfolk and Norwich University Hospital* — H. Baillie-Johnson, M. Lewis, M. Rhodes, D. Watson; *North Middlesex Hospital* — N. Davidson, S. Karp, D.L. Stoker; *Oldchurch Hospital* — D. Khoo, A. Gershuny; *Papworth Hospital* — A.J. Ritchie, F.C. Wells; *Pontefract General Infirmary* — M. Basheer; *Poole General Hospital* — S. Hosking, R. Osborne; *Princess of Wales Hospital, Brigend* — G.A. Pritchard; *Queen Elizabeth Hospital, Birmingham* — J. Fielding, D.J. Kerr; *Royal Bolton Hospital* — M.J.S. Wilkinson; *Royal Devon & Exeter Hospital* — R. Berrisford, M. Napier, C. Rowland; *Royal Glamorgan Hospital* — T. Havard; *Royal Liverpool Hospital* — G.J. Poston; *Royal London Hospital* — S.F. Purkiss, J. Rogers; *Royal Marsden Hospital (Fulham)* — W.H. Allum, J. Thompson; *Royal Marsden Hospital (Surrey)* — D. Cunningham, M. Hill; *Royal South Hants Hospital* — A. Bailey, T.J. Iveson; *Royal Surrey County Hospital* — N.D. Karanjia, C. Topham; *Royal Victoria Hospital, Belfast* — W.D.B. Clements, K. McManus, J.A. McGuigan, M.C. Regan; *Royal Victoria Infirmary, Newcastle* — M. Griffin, N. Hayes, D. Karat; *Russells Hall Hospital* — R.P. Grimley, A.N. Hamlyn, H.C. Norcott; *Salisbury District Hospital* — D. Finnis; *Singleton Hospital* — C. Askill; *South Tyneside District Hospital* — K.S. Wynne; *Southampton General Hospital* — I. Bailey; *Southend Hospital* — A. Brown, F. Hughes, A. Robinson, N.D. Rothnie, M.C.P.

Salter; *Southmead Hospital* — M.H. Thompson; *Southport & Formby District General Hospital* — M. Zeiderman; *St. Bartholomews Hospital* — M. Slevin, C. Gallagher; *St. Georges Hospital* — F. Lofts, M.J. Knight, J.L. Mansi, N. Sacks, R. Sayar, S. Mudan; *St. Helier Hospital* — J.N. Bett, A. Nash, D. Nehra, P.R. Thomas; *St. Lukes Cancer Center, Surrey County Hospital* — G. Middleton; *Stobhill General Hospital* — J.S. Smith; *Taunton & Somerset National Health Service Trust* — I.A. Eyre-Brooke, R. Welbourn; *Trafford General Hospital* — L.C. Barr; *University Hospital of North Staffordshire* — F. Adab, M. Deakin, J.B. Elder; *University Hospital of Wales* — P.D. Carey; *Velindre Hospital, Cardiff* — T. Crosby, T. Maughan, D. Mort, D.J. Webster; *Victoria Infirmary, Glasgow* — G. Gray; *Walton Hospital* — D. Smith; Western *Infirmary, Glasgow* — H. Yosef; *Whipps Cross Hospital* — A. Botha; *Whiston Hospital* — L.S. Chagla; *Worcester Royal Infirmary* — C. Robertson; *York District Hospital* — D.J. Alexander, D.M. Bottomley, J.L. Craven, G. Miller; *Ysbyty Gwynedd* — L.R. Jenkinson, N. Stuart, G.S.W. Whiteley; **the Netherlands:** *Canisius Wilhelmina Ziekenhuis* — E.D.M. Bruggink, H.R. Oosten; *Sophia Ziekenhuis* — J. Coenen, A. Honkoop, W. Van Rooyen, V.E. De Vries; *Reiner de Graaf Gasthuis* — M.E.M. Bos, E. Maartense, L.P.S. Stassen; *Leiden University Medical Centre* — H. Hardgrink, H.J. Keizer (deceased), J.W.R. Nortier, C. van de Velde, K.W.E. Welvaart; *Leijenburg Ziekenhuis,* — H.P. Sleeboom, W. Steup; *Rynland Hospital* — S. Adhin, F. Cluidman, A. Da Costa, W.J. Molendyk; **New Zealand:** *Wellington Hospital* — M. Findlay, D. Naik; **Germany:** *University of Tubingen* — R. Porschen, M. Starlinger; **Singapore:** *The National Cancer Centre* — E. Au; *Singapore General Hospital* — H. Chan, W. Wong; **Brazil:** *Hospital De Cancer De Pernambuco* — F. Menezes Da Silva, T. De Castro.

REFERENCES

1. Sue-Ling HM, Johnston D, Martin IG, et al. Gastric cancer: a curable disease in Britain. BMJ 1993;307:591-6.
2. Sasako M, Sano T, Katai H, Maruyama K. Radical surgery. In: Sugimura T, Sasako M, eds. Gastric cancer. Oxford, England: Oxford University Press, 1997:223-48.
3. Siewert JR, Bottcher K, Roder JD, Busch R, Hermanek P, Meyer HJ. Prognostic relevance of systematic lymph node dissection in gastric carcinoma. Br J Surg 1993;80:1015-8.
4. Hartgrink HH, van de Velde CJ, Putter H, et al. Extended lymph node dissection for gastric cancer: who may benefit? Final results of the randomized Dutch gastric cancer group trial. J Clin Oncol 2004;22:2069-77.
5. Cuschieri A, Weeden S, Fielding J, et al. Patient survival after D1 and D2 resections for gastric cancer: long-term results of the MRC randomized surgical trial. Br J Cancer 1999;79:1522-30.
6. Bonenkamp JJ, Hermans J, Sasako M, et al. Extended lymph-node dissection for gastric cancer. N Engl J Med 1999;340:908-14.
7. McCulloch P, Nita ME, Kazi H, Gama-Rodrigues J. Extended versus limited lymph nodes dissection technique for adenocarcinoma of the stomach. Cochrane Database Syst Rev 2004;4:CD001964.
8. Findlay M, Cunningham D, Norman A, et al. A phase II study in advanced gastro-esophageal cancer using epirubicin and cisplatin in combination with continuous infusion 5-fluorouracil (ECF). Ann Oncol 1994;5:609-16.
9. Webb A, Cunningham D, Scarffe JH, et al. Randomized trial comparing epirubicin, cisplatin, and fluorouracil versus fluorouracil, doxorubicin, and methotrexate in advanced esophagogastric cancer. J Clin Oncol 1997;15:261-7.
10. Ross P, Nicolson M, Cunningham D, et al. Prospective randomized trial comparing mitomycin, cisplatin, and protracted venous-infusion fluorouracil (PVI 5-FU) with epirubicin, cisplatin, and PVI 5-FU in advanced esophagogastric cancer. J Clin Oncol 2002;20:1996-2004.
11. Waters JS, Norman A, Cunningham D, et al. Long-term survival after epirubicin, cisplatin and fluorouracil for gastric cancer: results of a randomized trial. Br J Cancer 1999;80:269-72.
12. Wagner AD, Grothe W, Behl S, et al. Chemotherapy for advanced gastric cancer. Cochrane Database Syst Rev 2005;2:CD004064.
13. Hermanek P, Sobin L, eds. International Union against Cancer: TNM classification of malignant tumours. Berlin: Springer-Verlag, 1987.
14. Medical Research Council Esophageal Cancer Working Group. Surgical resection with or without preoperative chemotherapy in esophageal cancer: a randomized controlled trial. Lancet 2002;359:1727-33.
15. Allum WH, Hallissey MT, Ward LC, Hockey MS. A controlled, prospective, randomized trial of adjuvant chemotherapy or radiotherapy in resectable gastric cancer: interim report. Br J Cancer 1989;60:739-44.
16. Hartgrink HH, van de Velde CJ, Putter H, et al. Neo-adjuvant chemotherapy for operable gastric cancer: long term results of the Dutch randomized FAMTX trial. Eur J Surg Oncol 2004;30:643-9.
17. Allum W, Cunningham D, Weeden S. Perioperative chemotherapy in operable gastric and lower esophageal cancer: a randomized, controlled trial (the MAGIC trial, ISRCTN 93793971). Proc Am Soc Clin Oncol 2003;22:249. abstract.
18. 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.
19. Macdonald JS, Fleming TR, Peterson RF, 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.
20. Hermans J, Bonenkamp JJ, Boon MC, et al. Adjuvant therapy after curative resection for gastric cancer: meta-analysis of randomized trials. J Clin Oncol 1993;11:1441-7.
21. Earle CC, Maroun JA. Adjuvant chemotherapy after curative resection for gastric cancer in non-Asian patients: revisiting a meta-analysis of randomized trials. Eur J Cancer 1999;35:1059-64.
22. Mari E, Floriani I, Tinazzi A, 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.
23. Macdonald JS, Smalley SR, Benedetti J, et al. Chemoradiotherapy after surgery compared with surgery alone for adenocarcinoma of the stomach or gastroesophageal junction. N Engl J Med 2001;345:725-30.
24. Sumpter K, Harper-Wynne C, Cunningham D, et al. Report of two protocol planned interim analyses in a randomized multicentre phase III study comparing capecitabine with fluorouracil and oxaliplatin with cisplatin in patients with advanced esophagogastric cancer receiving ECF. Br J Cancer 2005;92:1976-83.