# Epirubicin, Cisplatin, and Protracted Venous Infusion of 5-Fluorouracil for Esophagogastric Adenocarcinoma

## *Response, Toxicity, Quality of Life, and Survival*

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**BACKGROUND.** The results of chemotherapy for patients with esophagogastric carcinoma have generally been modest but regimens developed more recently have produced higher response rates, and rekindled interest in neoadjuvant chemotherapy. One such regimen is epirubicin, cisplatin, and 5-fluorouracil (ECF). This study evaluates its efficacy, toxicity, impact on quality of life (QL), and impact on survival in a large consecutive series of patients with metastatic and locally advanced disease (LAD).
**METHODS.** Patients with histologically confirmed esophagogastric carcinoma were treated with ECF (epirubicin 50 mg/m$^2$ and cisplatin 60 mg/m$^2$ every 3 weeks with continuous infusion of 5-fluorouracil (5-FU) 200 mg/m$^2$/d). Responses were evaluated with computed tomography (CT) scan and endoscopy. QL was assessed using the European Organization for Research and Treatment of Cancer QLQ-C30 questionnaire.
**RESULTS.** A total of 235 patients were treated, 173 with metastatic disease and 62 with LAD. The mean number of cycles delivered was 6 (range: 1–11) and patients were followed-up for a median of 8 months. Response was observed in 135 of 220 (61%) evaluable patients, with a complete response (CR), 11% of the patients and a partial response in 50% of the patients. Patients with moderately differentiated adenocarcinomas and LAD responded most favorably. Symptomatic improvement was achieved in the majority of cases (63–78% depending on the symptom). Toxicity was generally only mild to moderate, with severe non hematologic toxicity in less than 12% of the patients and only 6 (2.5%) treatment related deaths. QL assessment showed no significant negative impact on emotional functioning and good symptomatic control. Surgery following response to ECF was performed in 29 of the LAD patients, and in 19 cases (66%) a potentially curative resection was possible, with histologic CR in 32% of the patients.
**CONCLUSIONS.** ECF is a highly active regimen with acceptable toxicity in patients with esophagogastric adenocarcinoma. In a proportion of patients with LAD, chemotherapy enabled potentially curative surgery to be performed. The results justify further investigation of this regimen in a neoadjuvant setting. ***Cancer* 1996; 77:1978–85.** © *1996 American Cancer Society.*

**KEYWORDS: gastric carcinoma, esophageal carcinoma, chemotherapy, infusional treatment, neoadjuvant chemotherapy, quality of life.**

Despite a decrease in the overall incidence in developed countries, esophagogastric (EG) adenocarcinoma remains one of the most common causes of cancer death worldwide, and in Western European males the incidence of esophagogastric junction (EGJ) tumors is increasing.[1] Surgical resection is the only therapeutic modality capable of cure, and improvements in early diagnosis, preoperative assessment, and surgical technique have increased the number of potentially curative resections over the last 20 years.[2] Despite this, the prognosis of the disease

remains poor with 10 to 15% 5-year survival. The reasons for this grim outlook include the fact that both local and distant relapse, even after an apparently complete resection, are common and that many patients have inoperable disease at diagnosis (70–80% in the Western hemisphere).

Until recently, one of the most widely used chemotherapy regimens for gastric carcinoma was 5-fluorouracil (5-FU), adriamycin, and mitomycin (FAM). Its use has, however, declined following the results of randomized studies demonstrating its inferiority to 5-FU, adriamycin, and methotrexate (FAMTX) for advanced disease[3] and its lack of benefit over control in an adjuvant setting.[4] Like FAMTX, newer regimens, such as epirubicin, cisplatin, and protracted venous infusion 5-FU (ECP) and etoposide, adriamycin, and cisplatin (EAP) have higher response rates than FAM in Phase II studies. These results have rekindled enthusiasm for the neoadjuvant approach (giving chemotherapy to downstage locally advanced and operable tumors prior to surgery) with the aim of increasing the complete resection rate and reducing the rate of distant relapse, thus enhancing the chance of cure. The results of pilot studies using EAP and FAMTX in this setting are encouraging,[5,6] but concerns about the toxicity of these combinations[7,8] warrant continued investigation of alternatives such as ECF which appears to have a more acceptable side-effect profile. In advanced disease, the role of chemotherapy has been controversial but two recent randomized trials have shown a significant survival benefit of combination chemotherapy when compared with best supportive care.[9,10]

The ECF regimen was developed in the GI unit of the Royal Marsden Hospital (RMH) and first reported in 1990.[11] The choice of the three drugs in the regimen was based on their single agent activity in upper GI cancer,[12–15] and the potential synergy between 5-FU and cisplatin shown in experimental models.[16] An anthracycline was included because of the anticipated enhanced cytotoxicity afforded by combing it with the other two drugs. Evidence for this potential increase in efficacy is provided by the results of a recently reported randomized trial of advanced gastric carcinoma in which the addition of epirubicin to a combination of bolus 5-FU and cisplatin resulted in a significant survival benefit compared with 5-FU and cisplatin alone.[17]

The regimen was also designed to minimize systemic toxicity, hence epirubicin was chosen instead of adriamycin because of its association with lower rates of mucositis and cardiac toxicity.[18] 5-FU was administered by protracted venous infusion, because this schedule has been shown to produce higher response rates and less myelotoxicity compared with bolus administration for patients with colorectal carcinoma.[19]

Preliminary results in 139 patients treated with ECF at two centers (RMH and St. George's Hospital) showed a response rate of 71% with moderate toxicity.[20] We report our extended experience with 235 patients treated at a single center (RMH) between July 1989 and January 1994.

## MATERIALS AND METHODS

Patients were required to have inoperable adenocarcinoma of the esophagus, EGJ, or stomach. The histology was reviewed for all of the cases. Tumors of the lower esophagus were classified as esophageal when at least 50% was extending in to esophagus, while tumors with at least 50% of their extent in the stomach were classified as EGJ carcinoma. Primary tumor was classified as inoperable on the basis of either the findings at laparotomy or computed tomography (CT) scan and endoscopic results. Criteria for inoperability were: (1) tumor greater than 7 cm in dimension on endoscopy; (2) locoregional lymph nodes greater than 2 cm in dimension on CT scan; and (3) invasion of adjacent structures. Peritoneal or distant lymph node involvement was classified as metastatic disease. A creatinine clearance of more than 40 mL per minute, a bilirubin of less than 30 mmol/L, and a life expectancy of at least 3 months were also required to enter the study. A multigated cardiac scan was performed when there was suspicion of left ventricular dysfunction. If the left ventricular ejection fraction was less than 50%, epirubicin was omitted. Pregnant women were excluded and female patients were advised to take adequate precautions to prevent pregnancy. All of the patients were treated at least 4 weeks after any surgical procedure performed prior to referral. Written informed consent, approved by the Royal Marsden Hospital Research Ethics Committee, was obtained from each patient before entering the study.

### Intravenous Access

Chemotherapy was administered through a double lumen indwelling catheter (Quintin) placed in the subclavian vein via a subcutaneous tunnel under local anaesthesia. Warfarin (1 mg/d orally) was administered throughout the treatment to prevent catheter thrombosis. The catheter was removed under local anaesthetic at the end of the treatment.

### Chemotherapy

5-FU was given as a continuous intravenous infusion at a dose of 200 mg/m$^2$/d using a portable battery powered pump (Medex, or Graseby Andersen, Atlanta, GA). The infusion was continued for up to 6 months allowing 6 to 8 courses of cisplatin and epirubicin.

Toxicity was graded according to the National Cancer Institute (NCI) common toxicity criteria.[21] Patients developing Grade 1 diarrhea were treated with codeine phosphate while those with Grade 1 mucositis received sucralfate or nystatin if there was evidence of oral thrush. If symptoms failed to settle or presented as Grade 2, pa-

TABLE 1
Patient Characteristics

| | | |
|---|---|---|
| Age | Median | 59 (28–79) |
| Sex | Male | 175 |
| | Female | 60 |
| Extent of disease | Metastatic | 173 |
| | Locally advanced | 62 |
| Performance status | 0 | 25 |
| | 1 | 117 |
| | 2 | 61 |
| | 3 | 16 |
| | 4 | 10 |
| | Not recorded | 6 |
| Site | Gastric | 116 |
| | Esophagogastric | 86 |
| | Esophageal | 33 |
| Histology | Adeno | 221 |
| | Undifferentiated | 12 |
| | Others | 2 |
| Differentiation | Poor | 119 |
| | Moderate | 86 |
| | Well | 4 |
| | Undifferentiated | 12 |
| | Unclassified | 14 |

tients were given a 1-week treatment break and were restarted with a 50 mg/m$^2$/d dose reduction in the 5-FU. For patients with more severe nonhaematologic toxicity, the 5-FU was stopped until symptoms resolved and restarted with a dose reduction of 100 mg/m$^2$ for Grade 3 toxicity and 150 mg/m$^2$ for Grade 4. Patients developing plantar palmar syndrome were given pyridoxine 50 mg tds and if symptoms failed to improve, 5-FU was discontinued for 1 week and restarted at a reduced dose.

Cisplatin 60 mg/m$^2$ was administered every 3 weeks with standard hydration. Dose modification for cisplatin was based on glomerular filtration rate (GFR), which was estimated using $^{51}$Cr-EDTA clearance. If the GFR was greater than or equal to 60 mL per minute, a full cisplatin dose was given, if 40 to 60 mL per minute, the dose of cisplatin in mg equalled the GFR value in mL per minute and if the GFR was lower than 40 mL per minute the patient was either not entered into the study or had no further cisplatin. Epirubicin was given as a bolus intravenous (i.v.) injection every 3 weeks. If on the day treatment was due the white cell count was less than $2.0 \times 10^9$/L or platelets less than $100 \times 10^9$/L, epirubicin and cisplatin were delayed for 1 week or until myelosuppression had resolved. A second episode of treatment delay due to myelosuppression or an episode of neutropenic sepsis required a 25% dose reduction of epirubicin on subsequent treatments. If there were repeated episodes of Grade 3 or 4 toxicity, in spite of dose modification, treatment was stopped.

Superficial infection of the indwelling catheter was treated with oral flucloxacillin or according to bacteriology results. Indwelling catheters were removed in the following situations: septicemia due to catheter infection; catheter infection worsening in spite of appropriate antibiotic treatment; catheter thrombosis; intolerable shoulder pain; and incorrect placement of the catheter.

### Assessment of Response

Responses were classified according to World Health Organization (WHO) criteria.[22] CT scan and endoscopy were repeated after Cycles 4, 6, and 8. All CT scans were reviewed by a single radiologist. In addition to WHO criteria, histologic confirmation at endoscopy or surgery was required for the classification of a response at the primary site to be complete. When disease was not assessable by CT scan, response was evaluated by endoscopy alone. Symptomatic response was also recorded. Response of dysphagia was defined as the improvement of dysphagia to the level of normal swallowing of food and fluid. Response of body weight was defined as a maintenance or increase in the pretreatment weight.

### Quality of Life Assessment

Aspects of functional status, disease response, relapse rates, and toxicity, were evaluated using a multidimensional health functioning questionnaire [European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30[23]] at baseline (prior to commencing treatment), midtreatment (cycles 4–6), and at posttreatment follow-up. This 30-item questionnaire includes 5 functional scales (physical, role, cognitive, emotional, social), 3 symptom scales (fatigue, pain, nausea and vomiting), specific items assessing additional symptoms (dyspnea, appetite loss, sleep disturbance, constipation, diarrhea), a global health and QL scales, and perceived financial impact of disease or treatment. Ratings were made by the patient using standard instructions. Reliability and validity of this measure has been reported elsewhere.[24]

Scoring of the questionnaire was performed according to guidelines provided by the EORTC QL Group (Aaronson 1992, personal communication) with the conversion of all scores to a 0 to 100 scale, using the recommended standardization algorithm. Scores were interpreted so that increased functional status indicates a benefit to patients, whereas increased symptoms indicates a poorer QL.

### Statistics

Data for patients receiving ECF were collected and entered prospectively onto the GI Unit database. Categorical

TABLE 2
Toxicity[a]

| CTC Grade | 0 | 1 | 2 | 3 | 4 |
|---|---|---|---|---|---|
| Nausea + vomiting | 56 (25) | 55 (25) | 82 (37) | 27 (12) | 1 (1) |
| Diarrhea | 146 (66) | 32 (15) | 36 (16) | 7 (3) | 0 |
| Palmarplantar | 151 (68) | 45 (20) | 23 (10) | 2 (1) | 0 |
| Stomatitis | 152 (69) | 30 (13) | 28 (13) | 11 (5) | 0 |
| Infection | 153 (69) | 19 (9) | 33 (15) | 12 (5) | 4 (2) |
| Neuropathy | 187 (84) | 30 (15) | 4 (1) | 0 | 0 |
| Anemia | 43 (18) | 40 (17) | 101 (43) | 40 (17) | 11 (5) |
| Leukopenia | 75 (31) | 47 (20) | 61 (26) | 34 (14) | 18 (8) |
| Neutropenia | 81 (36) | 30 (13) | 39 (17) | 49 (21) | 30 (21) |
| Thrombocytopenia | 195 (83) | 8 (3) | 12 (5) | 8 (3) | 12 (5) |

[a] Data available from only 221 patients in nonhematological categories. Percentages in brackets (maximum experienced by each patient).

data was examined using the chi-square test and Fisher's exact test where the expected cell counts were less than 5. Survival data was examined using the product limit method of Kaplan and Meier and differences in survival were assessed using the log rank test. Multivariate analysis was performed using Cox's proportional hazards model to examine prognostic factors found to be significant with univariate survival analysis. QL data was assumed to be normally distributed. Mean values (95% confidence intervals) were plotted against baseline pre ECF, mid ECF, and post ECF time points. Differences between baseline and mid- and post ECF points were examined using two sample $t$ tests.

## RESULTS

Between July 1989 and January 1994, 235 patients with esophageal or gastric adenocarcinoma received ECF. Patient characteristics are shown in Table 1. In 41 cases, there was relapse of the disease after previous potentially curative operation (32 metastatic, 5 anastomotic, 2 adjacent tissues, 2 adjacent tissue and regional lymph node). Six of these patients had had adjuvant treatment in addition to surgery (4 radiotherapy, 1 chemotherapy 1 both). Ninety-nine of the remaining patients had surgery, palliative procedures were performed in 52 cases and laparotomy alone in 47. In the remaining 95 cases, endoscopy was the only procedure performed.

Locally advanced disease (LAD) was present in 62 patients at the beginning of chemotherapy. The majority (49) had been deemed inoperable as assessed by laparotomy (24), CT scan (18), endoscopy (1), and CT scan and endoscopy (6). Of the remainder, 9 had local relapse after potentially curative surgery, 2 had technically operable tumors but declined surgery, 2 were unfit for surgery, and 2 were referred for chemotherapy with the specific aim of reducing tumor bulk prior to surgery.

A total of 1425 cycles were administered. The mean number of cycles per patient was 6 (1–11). Epirubicin was omitted in 9 cases for the following reasons: 7 ischemic heart disease, 1 aortic valve disease, and 1 elevated bilirubin. The overall reductions compared with intended dose for each drug were 12% 5-FU, 5% cisplatin, 4% epirubicin.

### Toxicity

The most common side-effects are listed in Table 2. In addition, alopecia and loss of taste were observed in 206 (93%) and 93 (39%) patients, respectively. Only 69 of the 488 (14%) documented nonhematologic toxicities were Grade 3 or 4. Grade 3 or 4 leukopenia and neutropenia occurred in 22% and 38% of the patients, respectively, but Grade 3 or 4 infection was observed in only 7%. In 14 cases (6%) treatment was discontinued prematurely due to toxicity: diarrhea or stomatitis was the cause in 5 cases, recurrent infections in 2, and lethargy in 4, with haematologic toxicity, persistent vomiting, and palmar plantar syndrome the causes in the remaining 3.

Complications associated with indwelling catheters were: infections (28, 12%), thrombosis (10, 4%), pneumothorax (1, 0.5%), slippage (21, 9%), and damage (2, 1%). Lines had to be removed and reinserted in 37 patients (16%). In 3 cases, lines had to be removed twice. The reasons for the removal of Hickman lines were: 4 infection, 10 thrombosis, 21 slippage, 2 damage, and 3 shoulder pain. There were 6 (2.5%) treatment related deaths with the cause of death recorded as follows: pneumonia, septicemia with acute renal failure, pulmonary embolism, gastrointestinal hemorrhage, infection with pulmonary embolism, and sudden death outside the hospital (no postmortem).

### Tumor Response

Objective tumor response was observed in 135 (61%) of 220 evaluable patients with 24 (11%) complete responses

TABLE 3
Tumor Response Overall and by Stage, Location of Primary Site, and Degree of Histologic Differentiation in Diagnostic Specimen

| | CR | PR | CR + PR | NR | NE |
|---|---|---|---|---|---|
| Overall | 24 (11) | 111 (50) | 135 (61) | 85 (38) | 15 |
| *95% CI* | 7–15% | 44–57% | 55–67% | 31–43% | — |
| Stage | | | | | |
| LAD | 14 (24) | 30 (51) | 44 (75) | 15 (24) | 3 |
| Mets | 10 (6) | 81 (50) | 91 (57) | 70 (43) | 12 |
| Primary site | | | | | |
| Esophagus | 1 (3) | 13 (39) | 14 (42) | 17 (51) | 2 |
| EGJ | 11 (13) | 48 (57) | 59 (70) | 25 (31) | 2 |
| Gastric | 12 (11) | 50 (48) | 62 (59) | 43 (41) | 11 |
| Differentiation | | | | | |
| Moderate | 9 (11) | 48 (59) | 57 (70) | 24 (30) | 5 |
| Poor | 10 (9) | 52 (47) | 62 (56) | 49 (44) | 8 |

CR: complete response; PR: partial response; SD: standard deviation; NR: no response; CI: confidence interval; LAD: locally advanced disease; MTS: metastatic; OGJ: esophago-gastric junction.
[a] Percentages in brackets.

TABLE 4
Response at Primary and Metastatic Sites[a]

| Site | CR | PR | NR |
|---|---|---|---|
| Primary site | | | |
| (Metastatic patients) | 16 (15) | 37 (35) | 54 (50) |
| (LAD patients) | 11 (24) | 20 (43) | 15 (33) |
| Lymph nodes | | | |
| (Metastatic patients) | 17 (19) | 32 (36) | 40 (45) |
| (LAD patients) | 14 (52) | 10 (37) | 3 (11) |
| Liver | 12 (14) | 41 (47) | 34 (39) |
| Peritoneum | 3 (10) | 1 (4) | 25 (86) |
| Lung | 5 (20) | 6 (24) | 14 (56) |
| Bone | 1 (7) | 1 (7) | 12 (86) |

CR: complete response; PR: partial response; NR: no response; LAD: locally advanced disease.
[a] Percentages in brackets.

TABLE 5
Symptomatic Response Overall and According to Primary Site

| Percentage with resolution of | Overall | Esophageal | OGJ | Gastric |
|---|---|---|---|---|
| Weight loss (n = 142) | 75 | 69 | 75 | 77 |
| Pain (n = 111) | 78 | 69 | 85 | 77 |
| Anorexia (n = 110) | 75 | 76 | 72 | 76 |
| Dysphagia (n = 100) | 63 | 54 | 58 | 74 |
| Nausea (n = 61) | 67 | 50 | 58 | 80 |
| Vomiting (n = 62) | 65 | 55 | 62 | 70 |
| Heartburn (n = 80) | 75 | 86 | 65 | 77 |

EGJ: esophago-gastric junction.

and 111 (50%) partial responses (Table 3). Fifteen patients were excluded from response analysis, 9 because chemotherapy was stopped too early for a response to be evaluated and 6 because they did not have assessable disease. Patients with LAD showed a significantly greater response rate than those with metastases ($P = 0.015$). Patients with esophageal and poorly differentiated adenocarcinoma achieved significantly lower response rates than those with other primary sites and histologies ($P = 0.04$ and $P = 0.03$, respectively). The most frequent sites of metastases were: lymph nodes 59%, liver 55%, peritoneum 24%, lung 17%, and bone 11%. Response by site is shown in Table 4. Liver and lymph node metastases responded to chemotherapy in more than 50% of the cases while other sites responded less well, particularly peritoneal and bony metastases.

Symptomatic response rates are shown in Table 5. The majority of patients (50–86%) experienced an improvement in symptoms regardless of the site of the disease. Mean time of response from initiation of treatment was 3 weeks.

### Surgery Following ECF

Among the patients with locally advanced disease, 44 out of 59 (75%) responded with 3 nonevaluable. Six of the responding patients had their primary tumor removed during a palliative procedure prior to chemotherapy and were not considered for further surgery. The remaining 38 patients were considered for surgery: in 1 case, the tumor was still thought to be inoperable on the basis of CT scan and endoscopic findings and the patient received radiotherapy to the primary site; 2 patients were unfit for surgery, one of whom received radiotherapy, the other refused further treatment; 1 patient was treated with high dose chemotherapy in the context of another study; 2 patients refused surgery, and 3 patients showed progres-

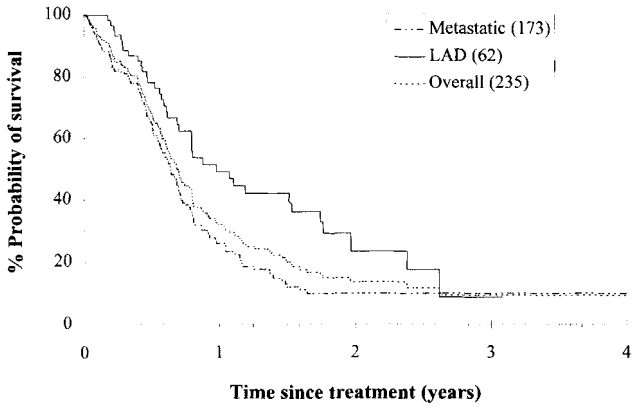


**FIGURE 1.** Overall survival is shown.

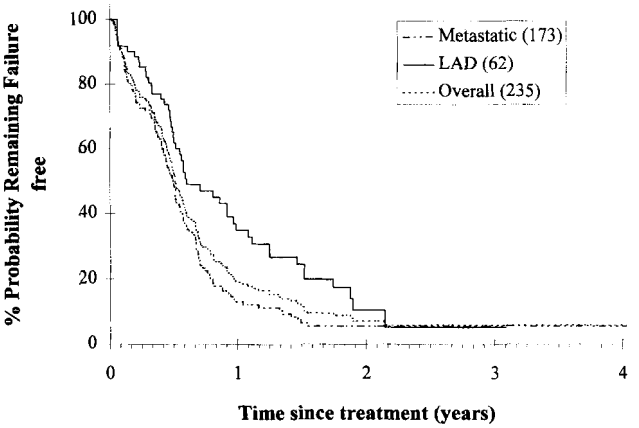


**FIGURE 2.** Failure free survival is shown.

sion of their disease prior to a planned operation. The remaining 29 patients went on to have surgery and in 19 (66%), a potentially curative resection was performed. On histologic examination of the resected specimen, no tumor was detected in 6 (32%) patients. Four (14%) patients died within 30 days of surgery, and 2 died after this period but with complications thought to be related to surgery. Postoperative chemotherapy (2–4 cycles) was given to only 4 patients who had a potentially curative resection, the remainder were unable to receive further treatment for reasons of cumulative renal or cardiac toxicity, early death, or patient choice.

## Quality of Life

In total, 74 patients receiving ECF were entered into the QL evaluation and completed baseline questionnaires. This subgroup showed no significant differences in pretreatment characteristics or response to chemotherapy compared with the group as a whole. Of these 74, 19 did not complete the second midpoint assessment having either died (6) or missed follow-up for other reasons (13) (e.g., questionnaires returned with missing data or failure to administer midpoint assessments). Median time between administration points was 12 weeks (baseline to midtreatment), 14 weeks (midtreatment to follow-up),and 26 weeks overall (baseline to follow-up). Physical and role functioning declined from baseline to midtreatment ($P < 0.05$), while constipation and sleep disturbance were reduced over the same period ($P < 0.05$). During follow-up there was no decline in physical and role functioning, while sleep disturbance continued to reduce from the baseline level ($P < 0.05$). Pain was significantly decreased at midtreatment compared with baseline ($P = 0.005$) and remained at a low level during follow-up. Global QL was improved at follow-up compared with baseline ($P = 0.01$), but there was no significant difference detected between responders and nonresponders. Symptom levels were low throughout for nausea and emesis, diarrhea and dyspnea. Emotional and cognitive functioning were unaffected by chemotherapy.

TABLE 6
**Survival and Failure Free Survival**

| | Survival | | | |
|---|---|---|---|---|
| | n | Median (mos) | 1-year (95% CI) | 2-year (95% CI) |
| All | 235 | 8.4 | 32% (26–39) | 14% (8–20) |
| LAD | 62 | 12.0 | 49% (35–62) | 23% (10–40) |
| Metastatic | 173 | 7.8 | 26% (19–34) | 10% (5–16) |
| | **Failure free survival** | | | |
| | n | Median (mos) | 1-year (95% CI) | 2-year (95% CI) |
| All | 235 | 6.2 | 19% (14–25) | 7% (4–12) |
| LAD | 62 | 7.3 | 35% (23–48) | 11% (3–23) |
| Metastatic | 173 | 6.0 | 13% (8–19) | 6% (2–11) |

n: number; CI: confidence interval; LAD: locally advanced disease.

## Survival

Median follow-up was 8 months (1–50 months) during which 165 (70%) patients died: 128 of 173 (74%) with metastatic disease and 37 out of 62 (60%) with LAD. The majority (144) of patients died of disease progression, 6 suffered treatment-related deaths, 6 patients died postoperatively, and 8 died of other causes. Figures 1 and 2 show the overall survival (OS) and failure free survival (FFS) for all of the patients. Median, 1-year and 2-year OS and FFS and confidence intervals are shown in Table 6. Using the log rank test, OS and FFS were found to be significantly worse for patients with metastatic disease ($P = 0.0016$ and 0.003, respectively), and OS was significantly worse

for patients with poor PS ($P = 0.0005$). Univariate analysis showed that PS, response to treatment, tumor differentiation, disease status, serum albumin, alkaline phosphatase (AP), and aminotransferase were significant prognostic factors for survival, whereas age, sex, site of disease, and histologic type were not. On multivariate analysis, PS, response to treatment, status of disease (LAD. vs metastatic), albumin, and AP were identified as independent prognostic factors ($P < 0.05$).

## DISCUSSION

The aim of this study was to assess the efficacy, toxicity, and effect on QL of the ECF regimen in a large series of consecutive patients with EG carcinoma treated at a single centre. The results confirm those reported by our group in a smaller number of such patients[20] and those from three other centres using ECF in upper GI tumors.[25-27] All of these studies demonstrate the high activity (response rate 60–70%) and low toxicity (treatment related deaths 0–3%) of ECF. The results are comparable to those of the most active regimens reported to date (FAMTX, EAP).[3,7,28]

ECF produces high response rates in the most frequent sites of metastases (lymph nodes and liver), while peritoneal disease is the most resistant site of disease, a point highlighted in previous studies.[29] Efficacy in locally advanced disease is significantly higher than in metastatic disease, with objective responses in 75% of the patients and complete responses in 24%. These results indicate a possible role for ECF in the neoadjuvant setting for downstaging inoperable tumors, which is supported by the small number of patients who underwent surgery following response to chemotherapy. Preoperative chemotherapy, with or without radiotherapy, can produce tumor regression and subsequent curative surgery in previously inoperable upper GI tumors.[30,31] Despite the fact our study was not originally designed to examine preoperative chemotherapy, and thus suitability for or acceptance of surgery were not entry criteria, 66% of the patients undergoing surgery following ECF had a potentially curative resection, with 32% histologic complete resection. Strict selection criteria for surgery following chemotherapy might reduce both the rate of inoperability and postoperative mortality. The latter may also be improved by reducing the duration of preoperative chemotherapy. These points will be addressed in the recently opened Medical Research Council randomized study of pre- and postsurgery ECF versus surgery alone (the "MAGIC" trial).

ECF resulted in good palliation, with 63 to 78% of the symptoms controlled, and dysphagia usually resolving after the first cycle of chemotherapy. QL data shows that chemotherapy was impacting on physical and role functioning, which is consistent with the known rigors of this treatment, but this did not have a significant negative impact on emotional functioning. Most of the patients returned to their pretreatment functional levels by follow-up. Conversely, pain, sleep disturbance, constipation, and anorexia were well controlled throughout treatment, while no significant nausea and vomiting, diarrhea or dyspnea were experienced as a result of the treatment. Global QL also improved from baseline to follow-up. Overall, the benefits of treatment appear to outweigh any toll in terms of QL.

In terms of chemotherapy related toxicity ECF was generally well tolerated. As expected, nausea and vomiting, diarrhea, stomatitis, and palmar plantar syndrome were the most frequent side-effects but Grade 3 or 4 toxicity was unusual. Hematologic toxicity was also relatively mild, rarely requiring hospitalization, and the treatment-related death rate was 2.5%. The incidence and severity of these toxicities is lower than that reported with EAP and FAMTX.[3,7,28-30] In particular, the rates of stomatitis with ECF are very much lower than with regimens incorporating bolus schedules of 5-FU.

Possible explanations for the high activity and low toxicity of this regimen have been discussed previously.[20] The important contribution of the 5-FU schedule has been emphasized by the results of a recently reported study in which a regimen consisting of the same drugs as ECF, but with 5-FU given as a bolus and the addition of folinic acid, produced inferior results.[33]

In conclusion, ECF appears to be an effective, well tolerated regimen for advanced EG cancer. It produces symptomatic response in the majority of patients, with no negative impact in QL. It has now entered ongoing Phase III studies, one in advanced disease comparing it with FAMTX and one in operable tumors comparing ECF before and after surgery with surgery alone. Definitive conclusions regarding the future role of ECF in this disease await the results of these trials.

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