ARTICLE

Adjuvant Chemotherapy in Completely Resected Gastric Cancer: A Randomized Phase III Trial Conducted by GOIRC

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On behalf of Italian Oncology Group for Cancer Research

Background Complete surgical resection of gastric cancer is potentially curative, but long-term survival is poor.

Methods Patients with histologically proven adenocarcinoma of the stomach of stages IB, II, IIIA and B, or IV (T4N2M0) and treated with potentially curative surgery were randomly assigned to follow-up alone or to intravenous treatment with four cycles (repeated every 21 days) of PELF (cisplatin [40 mg/m^2, on days 1 and 5], epirubicin [30 mg/m^2, days 1 and 5], L-leucovorin [100 mg/m^2, days 1–4], and 5-fluorouracil [300 mg/m^2, days 1–4] in a hospital setting. Frequencies and severity of adverse events were determined. Overall survival (OS) and disease-free survival (DFS) were compared between the treatment arms using Kaplan–Meier analysis and a Cox proportional hazards regression model. All statistical tests were two-sided.

Results From January 1995 through September 2000, 258 patients were randomly assigned to chemotherapy (n = 130) or surgery alone (n = 128). Patient characteristics were well balanced between the two arms. Among those who received chemotherapy, grade 3 or 4 toxic effects including vomiting, mucositis, and diarrhea were experienced by 21.1%, 8.4%, and 11.8% of patients, respectively. Leucopenia, anemia, and thrombocytopenia of grade 3 or 4 were experienced by 20.3%, 3.3%, and 4.2% of patients, respectively. After a median follow-up of 72.8 months, 128 patients (49.6%) experienced recurrence and 139 (53.9%) deaths were observed, one toxicity-related. Relative to treatment with surgery alone, adjuvant chemotherapy did not increase disease-free survival (hazard ratio [HR] of recurrence = 0.92; 95% confidence interval [CI] = 0.66 to 1.27) or overall survival (HR of death = 0.90; 95% CI = 0.64 to 1.26).

Conclusions Our results failed to provide proof of an effect of adjuvant chemotherapy with PELF on overall survival or disease-free survival. The estimated effect of chemotherapy (10% reduction in the hazard of death or relapse) is modest and consistent with the results of meta-analyses of adjuvant chemotherapy without platinum agents.

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Despite its declining incidence, gastric cancer remains a worldwide health problem that accounts for 10% of all new cancer diagnoses and 12% of all cancer-related deaths (1). Diagnosis of gastric cancer is often made when the disease is advanced and unresectable, which contributes to the high rate of morbidity and mortality. Complete gastric surgical resection with dissection of lymph nodes adjacent to the tumor or more extensive dissection (D_1–D_4) is the only potentially curative treatment for patients with gastric cancer in stages I–III (2). For the two-thirds of patients diagnosed as having stage II or III gastric cancer, the 5-year survival rate is only 16% (3).

Several randomized clinical trials have investigated whether adjuvant and neoadjuvant chemotherapy with or without radiotherapy can reduce the rate of recurrence and increase the rate of survival (4). Meta-analyses of some of these trials found that

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postoperative chemotherapy led to statistically significant reductions in mortality compared with surgery alone in the range of 15%–25%, corresponding to an absolute risk reduction of not more than 4% (5–8).

Various drug combinations that include platinum compounds, anthracyclines, 5-fluorouracil, taxanes, and/or irinotecan have demonstrated promising activity in advanced gastric cancer, with overall response rates (ORR) in the range of 37%–56% and a median overall survival (OS) of 9–11 months (9–12). In a trial in which patients with advanced gastric cancer were randomly assigned to a combination of cisplatin, epirubicin, 5-fluorouracil, and leucovorin (PELF regimen) or 5-fluorouracil, adriamycin, and mitomicin-C (FAM), the Italian Oncology Group for Cancer Research (GOIRC) observed a statistically significant difference in the overall response rate with PELF (ORR = 43% vs 15% in those receiving FAM), but patients assigned to PELF did not experience a statistically significant improvement in survival compared with those assigned to FAM (OS = 8.1 vs 5.6 months, respectively, P = 0.24) (11). Furthermore, in a subsequent trial, GOIRC evaluated PELF vs 5-fluorouracil, adriamycin, and methotrexate (FAMTX) in advanced gastric cancer patients and found a statistically significant difference in overall response rates (38% vs 21%, respectively, P = 0.009) but no improvement in median time to progression (5.9 vs 3.5 months, respectively; P = .34) or median overall survival (7.7 vs 6.9 months, respectively; P = .19) (12).

On the basis of the activity of the PELF treatment in advanced gastric cancer, GOIRC designed a clinical trial to evaluate in an adjuvant setting the efficacy of PELF compared with surgery alone in terms of overall survival and disease-free survival (DFS). Because some molecular markers (eg, p53, c-erbB2, epidermal growth factor receptor [EGFR], E-cadherin, thymidilate synthase [TS]) have recently been associated with a poor prognosis and more aggressive gastric cancer (13–17), GOIRC also carried out an exploratory analysis of the prognostic value of some of them using a univariate Cox proportional hazards model.

Methods

Patient Eligibility and Surgical Procedures

The criteria for inclusion in this study were: a histologically proven diagnosis of gastric cancer; radical resection of the tumor not more than 8 weeks before the date of random assignment with no evidence of residual disease as determined by staging exams; gastric cancer of stages IB, II, IIIA–B, or IV (T4N2M0) according to the American Joint Committee on Cancer—Cancer Staging 1992 (18); Eastern Cooperative Oncology Group performance status (ECOG-PS) less than 2; age 75 years or younger; no previous malignancies other than superficial skin cancer or in situ cervical carcinoma; no previous treatments such as neoadjuvant chemotherapy or radiotherapy; and no evidence of abnormal hepatic, renal, or cardiac function. Written informed consent and approval by the local ethics committee was obtained for all patients in the study before random assignment.

Surgical procedures were not standardized among participating centers. In the protocol, the minimum surgical recommendations included total or subtotal gastrectomy with negative resection margins with at least D_1 lymphadenectomy dissection.

CONTEXT AND CAVEATS

Prior knowledge

The effectiveness of adjuvant therapy for patients who are surgically treated for gastric cancer was not clear. A combination of epirubicin, leucovorin, 5-fluorouracil, and cisplatin, the PELF regimen, had shown some benefit over other regimens in terms of patient response.

Study design

Randomized clinical trial comparing PELF chemotherapy and follow-up alone in patients with completely resected gastric cancer.

Contribution

The PELF regimen was not effective at improving patient survival in an adjuvant setting.

Implications

New strategies and further study will be required to improve survival in patients who are surgically treated for gastric cancer.

Limitations

This study was not powered to detect very modest differences in patient outcomes between the two treatment arms.

Study Design

The study was designed as a multicenter randomized open-label phase III trial. After surgery, patients were randomly assigned to receive adjuvant chemotherapy or no further treatment. Random assignment was centrally managed at the GOIRC data center. Computer-generated permuted-block randomization lists were stratified by institution, stage (IB or II vs III or IV), and tumor site (upper third vs middle or inferior third of stomach).

Treatment Plan

In the chemotherapy arm, patients received four cycles of cisplatin (40 mg/m^2 given intravenously as a 30-minute infusion on days 1 and 5), epirubicin (30 mg/m^2 by intravenous bolus injection on days 1 and 5), L-leucovorin (100 mg/m^2 by intravenous bolus injection on days 1–4), and 5-fluorouracil (300 mg/m^2 by intravenous bolus injection on days 1–4). Cycles were repeated at 21-day intervals. As antiemetic therapies, ondansetron (8 mg by intravenous injection on days 1 and 5) and dexamethasone (8 mg by intravenous injection on days 1 and 5) were administered before and after cisplatin and epirubicin treatment.

Before and 7–10 days after each cycle of chemotherapy, clinical evaluation and hematology (white and red blood cell count and platelet count) and biochemistry (total bilirubin, aspartate amino transferase and alanine amino transferase, creatinine or creatinine clearance, blood urea nitrogen, calcium, sodium, potassium electrolytes) examinations were performed to evaluate toxicity, which was graded according to the World Health Organization scoring system.

Baseline Assessment and Follow-up

Baseline assessment included taking a complete medical history and performing a physical examination. Hematologic evaluation included white and red blood cell counts and platelet count. Biochemical evaluation consisted of measurement of total plasma bilirubin concentration; aspartate amino transferase; alanine amino

transferase; creatinine or creatinine clearance; blood urea nitrogen; and calcium, sodium, and potassium electrolytes. Tumor markers (CEA and CA-19.9) were measured in the blood of patients before treatment. Either an abdominal ultrasound or computed tomography (CT) scan and a chest x-ray were required after surgery and before random assignment.

Follow-up consisted of clinical examination and hematologic (white and red blood cell count and platelet count) plus biochemical (total bilirubin; aspartate amino transferase; alanine amino transferase; creatinine or creatinine clearance; blood urea nitrogen; and calcium, sodium, and potassium electrolytes) evaluation and was performed every 4 months for the first 3 years, then every 6 months until the fifth year, and thereafter at the investigator's discretion.

Endoscopy was performed every 6 months after surgery in the first 2 years and thereafter if clinically indicated. Disease recurrence (locoregional recurrence and/or metastases) was determined by clinical, radiologic, and, whenever possible, histologic examination. Treatment after relapse was not standardized and was left to the discretion of the investigators.

Clinical Prognostic Factors and Immunohistochemical Markers

In all 258 randomly assigned patients, we analyzed the association of clinical prognostic factors (age; sex; ECOG-PS; stage according to the American Joint Committee on Cancer tumor, node, metastasis staging system; tumor site; tumor histotype; tumor grading according to WHO classification (19); lymph node dissection; total number of lymph nodes excised; number of pathologic lymph nodes; gastric resection) with overall survival and disease-free survival. Because the American Joint Committee on Cancer Tumor (AJCC)-International Union Against Cancer node stage changed in 1997, we used the new classification of lymph nodes in the analyses of prognostic factors.

An ancillary study was designed to evaluate which molecular prognostic factors (p53, c-erbB2, Mib1, TS, or Herg1) were associated with the risk of relapse and death after curative resection. These factors were analyzed in tissues obtained from 145 randomly assigned patients (75 in PELF arm and 70 in follow-up arm).

Staining procedures for p53, TS, Ki-67, and c-erbB2 were conducted using an automated immunostainer (Ventana NexES; Ventana Medical Systems, Tucson, AZ) on 4-μm thick sections of paraffin-embedded tissue. Sections were deparaffinized in xylene and rehydrated in a descending ethanol series. Microwave-based heat induced epitope retrieval was performed. Endogenous peroxidase activity was blocked by immersion for 10 minutes in 0.3% hydrogen peroxide in methanol solution, followed by a single wash in phosphate-buffered saline (PBS; pH 7.4). The immunohistochemical staining was developed for the following primary antibodies: anti-p53 (clone DO-7 monoclonal prediluted; Ventana), anti-Ki-67 (Mib1 monoclonal, dilution 1:40; Dako Corporation, Carpinteria CA), anti-TS (clone TS106 dilution 1:50; Zymed, South San Francisco, CA), and c-erbB2 (polyclonal, dilution 1:500; Dako SA, Glostrup, Denmark). Immunohistochemical studies were performed on representative paraffin-embedded tissue sections from each patient by using the streptavidin-biotin immunoperoxidase complex method. The immunostaining was developed using 3,3′-diaminobenzidine as the chromogen.

Immunohistochemistry for Herg1 was performed on 7-μm thick sections of paraffin-embedded tissue mounted on polylysine-coated slides. After dewaxing and blocking of endogenous peroxidase, sections were treated with proteinase K (Roche, Mannheim, Germany; 5 μg/mL in PBS) and UltraVBlock solution (LabVision, Fremont, CA) containing 0.1% Triton X-100 and then incubated with the primary antibody (anti-pan Herg1 antibody (Alexis Corporation, Lausanne, Switzerland) diluted 1:200 in PBS) overnight at 4°C. Immunostaining was carried out using a commercially available kit (PicTure Plus kit; Zymed).

Appropriate positive and negative controls were included on each immunohistochemistry run to confirm antibody specificity. After immunostaining, the entire section was examined with a light microscope at the magnification of ×100 by two independent examiners.

For p53, TS, c-erbB2, and Herg1, immunoreactivity was scored as negative (no immunostaining) or positive. A semiquantitative system was used, and the percentage of immunostained cells was recorded as follows: 1+ (1%–25%); 2+ (26%–50%); 3+ (51%–100%). The Ki-67 labeling index was determined by randomly counting 1000 tumor cells, and the results were expressed as the percentage of positive cells.

Statistical Methods

The treatment (PELF) and control (follow-up alone) arms were compared according to overall survival (the primary endpoint) and disease-free survival. Survival time was defined as the interval from the date of random assignment to the date of death from any cause or the date of last follow-up. Disease-free survival was the interval from the date of randomization to the date of the first observation of a neoplastic event (relapse or second malignancy) or the date of death from any cause. If no progression was reported and no death occurred, data on disease-free survival were censored from the date when the absence of relapse was last confirmed.

The planned sample size was calculated using Lachin's (20) approach assuming a 5-year survival in the control group of 30% and a relative mortality reduction of 42% (this corresponds to an absolute increase of 20% in overall survival at 5 years). Under these assumptions, in a sample of 250 patients (125 in each arm), there would be 145 events over 8 years (including the accrual period of 5 years) and thus a statistical power of 90% and a type I error probability of 5% in a two-sided comparison.

Primary statistical analysis was performed according to the intention-to-treat principle. Cumulative overall and disease-free survival curves were constructed as time-to-event plots by the Kaplan–Meier method. Differences between the curves were tested for statistical significance using log-rank statistics (unadjusted analysis). The two study arms were also compared using a Cox proportional hazards regression model that allowed for the following covariates in the adjusted analysis: tumor stage, lymph node stage, number of examined lymph nodes (≤15 or >15), site of disease, and age (in decades) (21). The proportionality assumption was tested by the method of Grambsch and Therneau (22). Treatment, the covariates that were statistically significantly

associated with the outcome, and the first-order interaction terms between the treatment and the covariates were entered into the final Cox model. The interaction terms made it possible to assess whether the treatment effect was modified by the considered covariates. For age (considered as a continuous variable), if there was statistically significant interaction with treatment, a cut point of reasonable clinical interest (such as 60 years) was chosen for descriptive purposes. Exploratory analysis of the association of selected biologic markers (p53, c-erbB2, Mib1, TS, Herg1) with overall survival and disease-free survival was also carried out in the subgroup of 145 patients for whom molecular data was obtained, and clinical (age, sex, ECOG-PS, stage, tumor site, grading, surgical type, lymphadenectomy type, total number of lymph nodes excised, number of pathologic lymph nodes) and biologic markers were considered in the univariate model. The variables were categorized according to criteria reported previously (23–25). Results were reported as hazard ratio (HR) estimates together with the corresponding 95% confidence intervals (CIs) and the *P* value obtained from the Wald test. Relative and absolute frequencies of adverse events and their severity were also calculated. For all the computations, we used the SAS software (26).

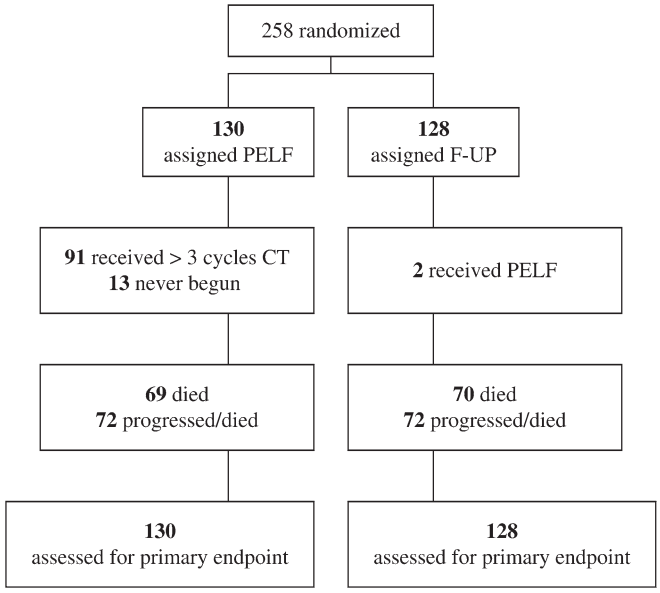


Figure 1. CONSORT flow chart of the Italian Oncology Group for Cancer Research phase III trial of cisplatin, epirubicin, 5-fluorouracil, and leucovorin (PELF) vs surgery (ie, follow-up) alone. Enrollment and treatment of patients included in the adjuvant randomized phase III trial in resected gastric cancer. F-UP = follow-up; CT = chemotherapy.

Results

From January 1995 through September 2000, 258 patients were randomly assigned by 33 Italian centers, 130 to the chemotherapy arm and 128 to no further treatment (follow-up arm; Figure 1). Seven patients were considered to be ineligible: one had stage IA gastric cancer, two had not undergone radical resection of the primary tumor, three had metastatic disease, and one was not randomly assigned until 56 days after the date of surgery. The yearly accrual rate was similar in the two groups, and the two arms were also similar in terms of the distribution of follow-up time for survivors: for the chemotherapy arm, the median follow-up was 5.6 years (interquartile range [IQR] = 4.9–6.8 years), whereas for the control arm, it was 5.9 years (IQR = 3.9–6.6 years).

Patient and Surgical Procedures

In each arm, the median age was 59 years (Table 1) and 61% of patients were male; 57% and 54% of patients were surgically treated with total gastrectomy in the control and treatment arms, respectively. Among all patients, 55% underwent D_2, D_3, or D_4 extended nodal dissection. The median number of removed lymph nodes per patient was 16 (range = 4–77) in the chemotherapy arm and 18 (range = 2–68) in the follow-up arm.

Chemotherapy

The median time from surgery to the beginning of chemotherapy was 46 days (range = 5–92). In the chemotherapy arm, 13 patients (9.8%) never started chemotherapy, and in the follow-up arm, two patients were erroneously treated with chemotherapy.

A total of 119 patients were treated with adjuvant chemotherapy. In the chemotherapy arm, 75 patients (58%) completed treatment and in 52 patients (40%) there was some modification of dose and/or time. Twenty patients (15% of patients properly assigned to chemotherapy) did not receive four complete cycles of treatment due to toxic effects during treatment, 15 patients (11%) stopped treatment for refusal, and seven patients (5%) stopped for other causes (Table 2).

Toxicity

Data on toxicity were available for 118 of the 119 patients who received at least one cycle of chemotherapy (Table 3). Grade 3–4 nausea and vomiting were experienced by 25 (21%) of these patients, diarrhea by 14 (12%), mucositis by 10 (8%), and alopecia by 29 (25%). Grade 3–4 leukopenia was experienced by 24 patients (20%). Other toxic effects were rare. One patient death (due to cardiovascular complications and electrolytic imbalance after grade 4 vomiting) was observed.

Overall and Disease-Free Survival

After a median follow-up of 73 months, 139 patients (54%) had died. There were 69 (53%) deaths in the chemotherapy arm and 70 (55%) deaths in the follow-up arm. There were 11 deaths not related to disease progression or second neoplasm, eight in the chemotherapy arm (one due to toxicity) and three in the control arm.

One hundred twenty-eight patients (50%) experienced recurrence: 66 (52%) in the follow-up arm and 62 (48%) in the chemotherapy arm. There was no difference in the pattern of first sign of recurrence (locoregional or systemic) between the two arms. In both arms, the most common site of recurrence was the liver (27% in the follow-up arm and 29% in the chemotherapy arm), followed by the peritoneum (25% in the follow-up arm vs 31% in the chemotherapy arm) and the lymph nodes (16% in the follow-up arm and 17% in the chemotherapy arm).

Kaplan–Meier estimates of 5-year overall survival rates were 47.6% in the chemotherapy arm and 48.7% in the follow-up arm, and median overall survival was 56.7 months and 57.6 months,

Table 1. Patient and tumor characteristics*

Characteristic	Follow-up alone, N = 128 n (%)	Chemotherapy, N = 130 n (%)	Total n (%)
Sex			
Male/female	78/50 (61/39)	79/51 (61/39)	157/101 (61/39)
WHO PS			
0	116 (90.6)	118 (90.8)	234 (90.7)
1	12 (9.4)	11 (8.5)	23 (8.9)
2	–	1 (0.8)	1 (0.4)
Primary localization†			
Upper third	11 (8.6)	10 (7.7)	21 (8.1)
Middle third	64 (50)	58 (44.61)	122 (47.3)
Lower third	52 (40.6)	60 (46.1)	112 (43.4)
Grading			
G1 and G2	23 (18)	30 (23)	53 (20.5)
G3 and G4	74 (57.8)	65 (50)	139 (53.8)
Not specified	31 (24.2)	35 (26.9)	66 (25.6)
Stage‡			
T3/T4	60/8 (46.8/6.2)	64/6 (49.2/4.6)	124/14 (48.6/5.4)
No/N+	22/104 (17.1/81.2)	20/109 (15.3/83.8)	42/213 (16.3/82.5)
I/II	12/36 (9.4 / 28.1)	19/32 (14.6/24.6)	99 (38.9)
III/IV	75/3 (58.6 / 2.3)	71/7 (54.6/5.4)	156 (60.5)
Surgery§			
Total gastrectomy	73 (57)	70 (53.9)	143 (55.4)
Subtotal	54 (42.2)	59 (45.4)	113 (43.8)
Lymphadenectomy‖			
D1	44 (34.4)	49 (37.7)	93 (36)
D2	57 (44.5)	53 (40.8)	110 (42.7)
D3	13 (10.1)	15 (11.5)	28 (10.8)
D4	2 (1.6)	3 (2.3)	5 (1.9)
No. of lymph nodes examined¶			
≤15	59 (46)	62 (47.7)	121 (46.9)
>15	63 (49.2)	65 (50)	128 (49.6)
No. of pathologic nodes#			
≤6	91 (71)	83 (63.9)	174 (67.4)
7–15	25 (19.5)	36 (27.7)	61 (24)
>15	11 (8.6)	11 (8.5)	22 (8.9)

* WHO = World Health Organization; PS = performance status. Median age of patients in the both chemotherapy and follow-up arms was 59 years; ranges were 32–73 and 18–71, respectively.

† Data were missing for one and two patients in the follow-up alone and chemotherapy arms, respectively.

‡ Staging according to the American Joint Committee on Cancer tumor, node, metastasis staging system. Data was missing for two patients and one patient in the follow-up alone and chemotherapy arms, respectively.

§ Data missing for one patient in each arm.

‖ Data missing for 12 and 10 patients in the follow-up alone and chemotherapy arms, respectively.

¶ Data missing for six and three patients in the follow-up alone and chemotherapy arms, respectively; median (range) was 16 (4–77) and 18 (2–68) in the follow-up and chemotherapy arms, respectively.

Data missing for one patient in the follow-up arm; median (range) was 4 (0–29) and 4 (0–45) in the follow-up and chemotherapy arms, respectively.

respectively (Figure 2). Five-year disease-free survival rates were 42.3% in the chemotherapy arm and 41.6% in the follow-up arm, and median disease-free survival was 41.2 months and 34.3 months, respectively (Figure 3). Chemotherapy did not lead to an increase in either disease-free survival (HR of recurrence in the PELF arm vs the follow-up arm = 0.92, 95% CI = 0.66 to 1.27) or overall survival (HR of death in the PELF arm vs the follow-up arm = 0.90, 95% CI = 0.64 to 1.26) relative to the control arm.

Association of Clinical Variables and Molecular Factors With Survival

To explore the potential prognostic and predictive value of clinical variables, a multivariable Cox proportional hazards regression analysis was performed using the data from all randomly assigned patients. Analysis of overall and disease-free survival showed that increasing age in decades (HR for death = 1.38, 95% CI = 1.12 to 1.70, $P = .002$; HR for recurrence = 1.32, 95% CI = 1.08 to 1.61, $P = .008$), fewer examined lymph nodes (HR for death = 0.47, 95% CI = 0.32 to 0.37, $P < .001$; HR for recurrence = 0.48, 95% CI = 0.34 to 0.68, $P < .001$), increasing tumor stage (HR for death = 1.69, 95% CI = 1.19 to 2.37, $P = .003$; HR for recurrence = 1.88, 95% CI = 1.34 to 2.64, $P < .001$), and more positive lymph nodes (HR for death = 2.96, 95% CI = 2.05 to 4.26, $P < .001$; HR for recurrence = 2.80, 95% CI = 1.96 to 3.99; $P < .001$) were statistically significantly associated with poorer overall survival and disease-free survival (Table 4). Moreover, a statistically significant ($P = .022$) interaction

Table 2. Compliance with treatment*

Treatment characteristic	No. (%)
Completed treatment	75 (58)
Stopped for toxicity	20 (15)
Stopped treatment for refusal	15 (12)
Stopped for other	7 (5.4)
Never started	13 (10)
No. of cycles	
0	13 (10)
1	15 (12)
2	11 (8.5)
3	16 (12)
4	75 (58)

* The treatment arm consisted of 130 patients.

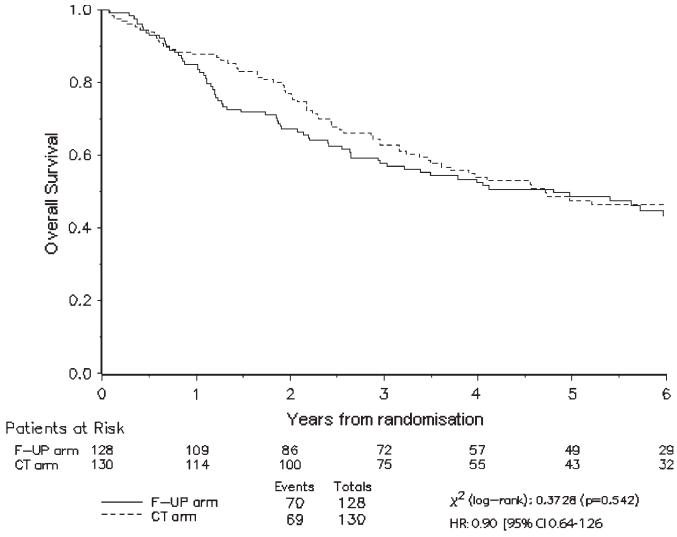
between age (considered as continuous variable) and treatment was detected when we split the sample in two subgroups according to age for descriptive purposes. Among younger (<60 years) patients, the HR for recurrence in the chemotherapy arm vs follow-up was 0.94 (95% CI = 0.58 to 1.52), and in the older group, it was 0.58 (95% CI = 0.35 to 0.96) (Figure 4). Similar patterns were observed for overall survival: HR for death = 0.93 (95% CI = 0.57 to 1.53) and 0.62 (95% CI = 0.37 to 1.01) for younger and older groups, respectively (Table 4).

In the subgroup of 145 patients (75 in the PELF arm and 70 in follow-up arm) for whom data on biologic factors were also available, there was no statistical evidence of a relationship between p-53, c-erbB2, Mib1, TS, or Herg1 expression and prognosis in the univariate model. However, a statistically significant association with mortality and disease-free survival was confirmed for N_2-N_3–stage lymph node involvement (according to AJCC-1997) and the number of examined lymph nodes (Table 5).

Discussion

This randomized trial did not show any statistically significant benefit in terms of overall survival or disease-free survival in patients with radically resected gastric cancer treated with PELF adjuvant chemotherapy relative to those treated by follow-up alone. This study was powered to detect larger differences in survival than the ones observed here based on very promising results obtained in previous randomized trials in advanced gastric cancer (11–12). Higher than expected survival rates may have decreased the power of our study; nevertheless, the results (HR = 0.9) show that the best estimate of the absolute risk reduction in terms of overall survival at 5 years is less than 3%.

These disappointing results are in agreement with those of other recently published trials that showed a higher than anticipated survival in the control group and no statistical evidence of improvement with chemotherapy. For example, Bajetta et al. (27) randomly assigned 274 gastric cancer patients who had been treated with surgery and found to have poor prognostic factors (N+ or T3/4) to either adjuvant treatment with a combination of etoposide, adriamycin, and cisplatin followed by treatment with 5-fluorouracil and leucovorin according to the Machover schedule or follow-up alone. After a median follow-up of 66 months (range = 2–83), the 5-year overall survival was 52% in the treatment arm and 48% in the control arm, whereas the 5-year disease-free survival was 49% and 44%, respectively. De Vita et al. (28), after treating patients in a randomized trial with radically resected gastric cancer with the epirubicin, leucovorin, 5-fluorouracil, and etoposide regimen for six cycles, reported a 5-year overall survival rate of 48% in the chemotherapy arm and 43.5% in the control



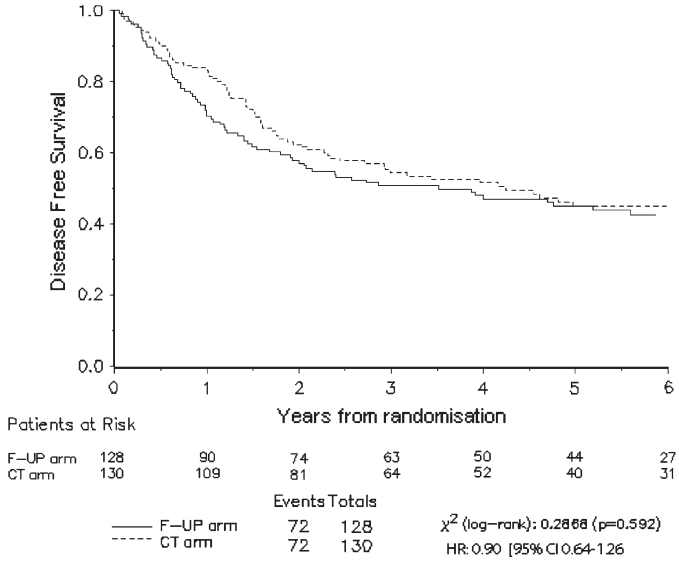
	OVERALL SURVIVAL					
	PELF			Follow-up		
Years	EST	*95% CI*		EST	*95% CI*	
1	**0.877**	*0.820*	*0.933*	**0.852**	*0.790*	*0.913*
2	**0.769**	*0.697*	*0.842*	**0.672**	*0.591*	*0.753*
3	**0.628**	*0.544*	*0.711*	**0.577**	*0.491*	*0.663*
4	**0.540**	*0.452*	*0.628*	**0.525**	*0.438*	*0.613*
5	**0.476**	*0.384*	*0.567*	**0.487**	*0.398*	*0.576*
6	**0.464**	*0.372*	*0.556*	**0.432**	*0.339*	*0.526*

Figure 2. Overall survival in patients treated with cisplatin, epirubicin, 5-fluorouracil, and leucovorin (PELF, **dashed line**) or surgery alone (**solid line**). Overall survival for all patients randomly assigned to chemotherapy (CT) arm with PELF (**dashed line**) or follow-up (F-UP) arm (**solid line**) was estimated using the Kaplan–Meier method. Survival time was defined as the interval from the date of random assignment to the date of death from any cause or the date of last follow-up. Overall survival curves were constructed as time-to-event plots by the Kaplan–Meier method. Differences between the curves were tested for statistical significance using log-rank statistics. HR = hazard ratio; CI = confidence interval; EST = estimated fraction of patient alive.

Table 3. Toxicity in patients receiving chemotherapy*

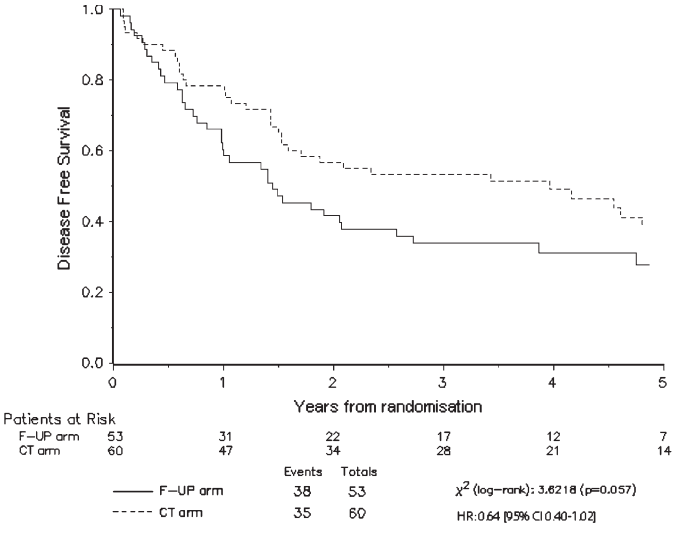
Type of toxicity	Grades 1 + 2, n (%)	Grades 3 + 4, n (%)
Hematologic		
Leukopenia	47 (39.8)	24 (20.3)
Thrombocytopenia	14 (11.8)	5 (4.2)
Anemia	41 (34.7)	4 (3.3)
Nonhematologic		
Nausea/vomiting	65 (55)	25 (21.1)
Diarrhea	39 (33)	14 (11.8)
Mucositis	43 (36.4)	10 (8.4)
Ototoxicity	4 (3.3)	0 (0)
Alopecia	34 (28.8)	29 (24.5)
Neurotoxicity	7 (5.9)	1 (0.8)

* Data on toxicity were available on 118 of 119 patients who received at least one cycle of chemotherapy.



	DISEASE FREE SURVIVAL					
	PELF			Follow-up		
Years	EST	*95% CI*		EST	*95% CI*	
1	**0.838**	*0.775*	*0.902*	**0.703**	*0.624*	*0.782*
2	**0.623**	*0.540*	*0.706*	**0.602**	*0.517*	*0.686*
3	**0.551**	*0.465*	*0.637*	**0.523**	*0.436*	*0.609*
4	**0.515**	*0.427*	*0.602*	**0.477**	*0.389*	*0.565*
5	**0.450**	*0.359*	*0.540*	**0.448**	*0.360*	*0.536*
6	**0.450**	*0.359*	*0.540*	**0.423**	*0.333*	*0.513*

Figure 3. Disease-free survival in patients treated with cisplatin, epirubicin, 5-fluorouracil, and leucovorin (PELF; **dashed line**) or surgery alone (**solid line**). Disease-free survival for all patients randomly assigned to chemotherapy (CT) arm with PELF (**dashed line**) or follow-up arm (F-UP; **solid line**) was estimated using the Kaplan–Meier method. Disease-free survival was the interval from the date of randomization to the date of the first observation of a neoplastic event (relapse or second malignancy) or the date of death from any cause. If no progression was reported and no death occurred, data on disease-free survival were censored from the date when the absence or relapse was last confirmed. Disease-free survival curves were constructed as time-to-event plots by the Kaplan–Meier method. Differences between the curves were tested for statistical significance using log-rank statistics. HR = hazard ratio; CI = confidence interval; EST = estimated fraction of patient alive.



	DISEASE FREE SURVIVAL PTS > 60 YRS					
	PELF			Follow-up		
Years	EST	*95% CI*		EST	*95% CI*	
1	**0.783**	*0.679*	*0.888*	**0.585**	*0.452*	*0.718*
2	**0.567**	*0.441*	*0.692*	**0.472**	*0.337*	*0.606*
3	**0.533**	*0.407*	*0.660*	**0.376**	*0.241*	*0.510*
4	**0.490**	*0.361*	*0.620*	**0.328**	*0.194*	*0.463*
5	**0.384**	*0.247*	*0.521*	**0.269**	*0.135*	*0.404*
6	**0.384**	*0.247*	*0.521*	**0.231**	*0.096*	*0.365*

Figure 4. Disease-free survival in patients older than 60 years treated with cisplatin, epirubicin, 5-fluorouracil, and leucovorin (PELF, **dashed line**) or surgery alone (**solid line**). In this analysis, a statistically significant (P = .022) interaction between age (considered as continuous variable) and treatment was detected when we split the sample in two subgroups according to age for descriptive purposes. Among younger (<60 years) patients, the hazard ratio for disease-free survival in the chemotherapy arm vs follow-up arm was 0.94 (95% CI = 0.58 to 1.52), and in the older group, it was 0.58 (95% CI = 0.35 to 0.96). HR = hazard ratio; CI = confidence interval; EST = estimated fraction of patient alive; pts = patients.

(surgery alone) arm and a 5-year disease-free survival rate of 44% in the chemotherapy arm and 39% in the control arm. In another randomized trial (29), a French group compared treatment with 5-fluorouracil administered as a continuous infusion started before day 14 after resection and followed by four subsequent cycles of 5-fluorouracil plus cisplatin and treatment with surgery alone. They reported a 5-year overall survival rate of 46.6% (median OS = 44.8 months) in the chemotherapy group vs 41.9% (median OS = 42.1 months) in the group treated with surgery alone. The 5-year disease-free survival rates were 39.8% in the control group vs 47.6% in the chemotherapy group (P = .19). Finally, a randomized trial by the European Organization for Research and Treatment of Cancer–Gastrointestinal and International Collaborative Cancer Group (30) that compared surgery alone vs adjuvant FEMTX reported a 5-year overall survival of 44% in the control arm and 43% in the treatment arm, with a 5-year disease-free survival of 42% and 41%, respectively. Long-term survival after adequate surgical treatment has also been reported in other studies.

It is well known that the effectiveness of surgery in promoting long-term survival depends on the extension of disease and the adequacy of surgery (ie, whether all margins are histologically free of tumor) (31). In our trial, a large number of patients (51.4%) had 15 or more resected nodes (median = 17 [range = 2–77] per patient). About 55% of the patients received a D_2 or more lymphadenectomy. However, there is controversy about the benefit of extended (D_2 or more) lymphadenectomy, as reported in the two European trials that compared D_1 vs D_2 lymphadenectomy (32,33). There is no doubt that the goal in gastric cancer treatment is the complete removal of primary tumor and the affected regional lymph nodes. At present, in a considerable part of Europe, surgery alone is the standard of care.

The higher than expected survival obtained with a good surgery in our study may reflect the fact that a large majority of patients underwent a D_1 or D_2 dissection, approaches more frequently used in European trials. These more extensive lymphadenectomies may have decreased the rate of disease recurrence and lengthened survival. It is also possible that patients with more complete lymph node dissections derive less value from current approaches to adjuvant therapy, and this may partially explain the modest efficacy of chemotherapy observed in our trial.

Table 4. Effect of patient variables on the risk of death and recurrence as determined by a Cox proportional hazards regression model*

		Overall survival			Disease-free survival		
Variables	**Reference category**	**HR**	**(95% CI)**	***P* value**	**HR**	**(95% CI)**	***P* value†**
Chemotherapy arm	Control arm	0.87	(0.62 to 1.22)	.41	0.84	(0.60 to 1.17)	.30
Age decades		1.38	(1.12 to 1.70)	.002	1.32	(1.08 to 1.61)	.008
Stage							
T3–T4	T1–T2	1.69	(1.19 to 2.37)	.003	1.88	(1.34 to 2.64)	<.001
N2–N3‡	N0–N1	2.96	(2.05 to 4.26)	<.001	2.80	(1.96 to 3.99)	<.001
>15 examined nodes	≤15 examined nodes	0.47	(0.32 to 0.67)	<.001	0.48	(0.34 to 0.68	<.001
Interaction chemotherapy/age	Treatment effect			.056			.022
Age ≤60 y		0.93	(0.57 to 1.53)	.77	0.94	(0.58 to 1.52)	.81
Age >60 y		0.62	(0.37 to 1.01)	.057	0.58	(0.35 to 0.96)	.033

* HR = hazard ratio; CI = confidence interval; T = tumor; N = node. The two study arms were compared using a Cox proportional hazard regression model that allowed for the following covariates in the adjusted analysis: tumor stage, lymph node stage, number of examined lymph nodes, and site of disease and age (in decades).

† From the Wald test.

‡ N2 = 7–15 involved lymph nodes; N3 = >15 involved lymph nodes.

The frailty of gastric cancer patients after surgery combined with toxicity of adjuvant chemotherapy could explain the poor compliance to chemotherapy and the lack of the treatment efficacy. In our study, only 58% of patients completed the planned treatment and 40% of this subgroup modified the dose and timing.

The potential value of having many different approaches to adjuvant treatment of gastric cancer has been underscored in several recent trials. For example, in a large US intergroup study, treatment with postoperative chemotherapy (5-fluorouracil plus leucovorin) combined with radiotherapy (34) led to an improvement on overall survival relative to surgery alone (27 months vs 36 months). This trial was the subject of debate because although a D_2 lymph node dissection was recommended, this procedure was performed in only 10% of patients and 54% did not undergo clearance of regional lymph nodes (N_1).

Another recent approach to adjuvant treatment of gastric cancer was the combination of pre- and postoperative active chemotherapy. Utilizing this approach in a randomized study of patients with operable gastric or lower esophageal adenocarcinomas, Cunningham et al. (35) reported decreased tumor size and stage and a statistically significant improvement in those who were treated with cisplatin, epirubicin, and 5-fluorouracil (ECF) compared with those treated with surgery alone in terms of progression-free survival (HR = 0.66, 95% CI = 0.53 to 0.81, $P < .001$) and overall survival (HR = 0.75, 95% CI = 0.60 to 0.93, $P = .009$; 5-year survival rate = 36% vs 23%). However, a recent systematic overview of neoadjuvant treatment for gastric cancer that included trials of preoperative chemotherapy only did not show any survival benefit. In the four clinical trials analyzed, among 250 patients who received preoperative chemotherapy and 332 patients who did not receive preoperative chemotherapy, there were 106 and 126

Table 5. Univariate analysis of clinical and biologic prognostic factors*

		Overall survival			Disease-free survival		
Variables	**Reference category**	**HR**	**(95% CI)**	***P* value**	**HR**	**(95% CI)**	***P*† value**
Chemotherapy	Follow-up alone	0.70	(0.37 to 1.32)	.256	0.73	(0.39 to 1.36)	.320
Age decades		2.02	(1.26 to 3.24)	.003	1.88	(1.17 to 3.00)	.008
T3–T4	T1–T2	1.41	(0.74 to 2.71)	.300	1.46	(0.76 to 2.78)	.253
N2–N3‡	N0–N1	1.23	(0.64 to 2.37)	.541	1.37	(0.72 to 2.63)	.336
>15 examined nodes	≤15 examined nodes	0.48	(0.25 to 0.92)	.028	0.51	(0.27 to 0.98)	.043
p53	Neg	1.18	(0.70 to 2.06)	.575	1.11	(0.63 to 1.93)	.721
c-erbB2	Neg	0.90	(0.44 to 1.83)	.775	0.85	(0.42 to 1.72)	.649
Mib1	<3	0.88	(0.45 to 1.70)	.696	0.76	(0.40 to 1.47)	.418
TS	Neg	1.17	(0.68 to 2.04)	.570	1.14	(0.66 to 1.96)	.652
Herg1	0–1	0.84	(0.44 to 1.60)	.602	0.76	(0.40 to 1.44)	.395

* HR = hazard ratio; CI = confidence interval; T = tumor; N = node; Neg = negative; TS = thymydilate synthase. Exploratory analysis of the association of selected biological markers (p53, c-erbB2, Mib-1, TS, and Herg1) with overall survival and disease-free survival was also carried out in the subgroup of 145 patients for whom molecular data were obtained and clinical (age, sex, ECOG-PS, stage, tumor site, grading, surgical type, lymphadenectomy type, total number of lymph nodes excised, number of pathological lymph nodes) and biological markers were considered in the univariate model. Results were reported as hazard ratio estimates, together with the corresponding 95% confidence intervals and the *P* value obtained from the Wald test. An HR of 1 denotes the absence of a difference between arms (or the two categories of compared covariates), whereas an HR greater than 1 or less than 1 denotes an increased or decreased risk, respectively, in a given patient group in comparison with the reference group.

† From the Wald test.

‡ N2 = 7–15 involved lymph nodes, N3 = >15 involved lymph nodes.

deaths at the end of follow-up in the preoperative chemotherapy and control group, respectively. For the outcome of death at the last follow-up, the odds ratio was 1.05 (95% CI = 0.73 to 1.50). The results showed no statistically significant differences ($P = .29$) between the two groups (36). These data suggest that the effect in the Cunningham trial may be due mainly to ECF chemotherapy given in the pre- and postoperative phase.

Several pathologic factors, including the presence of lymph node metastases, site of gastric tumor, depth of tumor invasion, and stage, have been considered to be important indicators of prognosis. Our exploratory analysis confirmed the association of extent of the primary tumor and the presence of regional lymph node metastases. Analysis of interaction between covariates and adjuvant treatment suggested that the benefit of treatment, if any, was related to older patients. This result suggesting a possible benefit of treatment in older patients must be interpreted with caution because it comes from an exploratory analysis. The question of whether age is a real predictive factor for response or a marker of other factors needs to be investigated further.

Our analysis indicated that additional biomolecular factors (p53, c-erbB2, Mib1, TS, and Herg1) previously implicated in progression and metastasis of gastric cancer were not associated with prognosis in older patients. Even in the relatively small subgroup of patients with available data, the power of the study was sufficient to rule out medium or large increases in risk associated with the presence of these biologic factors. Our results do not confirm findings of other groups (37) that suggested that immunohistochemical examination of biologic markers may be useful in predicting the clinical outcomes of gastric cancer patients.

Our study had several limitations: in the planning of the study, we estimated a 5-year survival of 30% in the control group in which we actually observed a 5-year survival of 50%. So, the objective of a 20% benefit with adjuvant chemotherapy was optimistic, and the sample size was too small to detect a smaller difference. Otherwise, the exploratory analysis of clinical prognostic factors showed a statistically significant difference in survival in older patients (>60 years), considering the age as continuous variable, treated with adjuvant chemotherapy. The analysis of molecular prognostic factors performed did not clarify these results in disease-free survival and overall survival obtained with chemotherapy in older patients.

In summary, this randomized study failed to demonstrate a statistically significant benefit of PELF as adjuvant chemotherapy in terms of overall survival and disease-free survival after curative surgery in patients with gastric cancer. Our study confirms that a dose-intense regimen like PELF, which showed very promising results in advanced gastric cancer, is not effective in an adjuvant setting. The absolute risk reduction that we observed is within the range of 4% suggested by the meta-analyses of more than 30 randomized trials (5–8). The same magnitude of effect was confirmed by a recent study by Cascinu et al. (38), which found that PELF administered in weekly cycles in an adjuvant setting was not superior to 5-fluorouracil plus leucovorin, thus confirming that PELF treatment is not better than 5-fluorouracil–based adjuvant chemotherapies.

Oral chemotherapy with fluoropyrimidines (UFT, Capecitabine, S-1) is used for adjuvant chemotherapy in gastric cancer in Asian countries. Recently, promising results have been reported for S-1 in the treatment of patients with advanced gastric cancer and in patients with radically resected gastric cancer treated with S-1 as adjuvant chemotherapy (39). In a randomized trial of 1059 patients with stage II and III gastric cancer who underwent gastrectomy plus extended (D_2) lymph node dissection, Sakuramoto et al. (40) reported a 3-year overall survival rate of 80.1% (95% CI = 76.0 to 84.0) in the patients treated with S-1 compared with 70.1% (95% CI = 65.5 to 74.6) in the group treated with surgery alone, with an HR for death of 0.68 (95% CI = 0.50 to 0.77, $P < .001$). The rate of relapse-free survival at 3 years was 72.2% (95% CI = 67.9 to 76.4) in S-1 group and 59.6% (95% CI = 54.9 to 64.3) in the control arm with an HR for relapse of 0.62 (95% CI = 0.50 to 0.77, $P = .001$). These results are promising, but the trial was conducted in East Asian patients and all patients received a D_2 dissection of lymph nodes. New strategies, such as combining neoadjuvant chemotherapy and adjuvant chemotherapy, appear to be promising (35), but the role of preoperative chemotherapy alone is still not clear. Therefore, for patients with gastric cancer that is resectable or has been treated by surigical resection, there are two viable options: pre- and postoperative chemotherapy or postoperative chemoradiotherapy. Adjuvant chemotherapy alone remains a controversial approach in operable gastric cancer, and it needs further testing in trials incorporating newer chemotherapy combinations including taxanes, irinotecan, and oral fluoropyrimidines.

References

1. Verdecchia A, Corazziari I, Gatta G, Lisi D, Faivre J, Forman D; EUROCARE Working Group. Explaining gastric cancer survival differences among European countries. *Int J Cancer.* 2004;109(5):737–741.
2. Peeters KCMJ, van de Velde CJ. Improving treatment outcome for gastric cancer: the role of surgery and adjuvant therapy. *J Clin Oncol.* 2003;(23 Suppl):272s–273s.
3. Hundahl SA, Phillips JL, Menck HR. The National Cancer Data Base Report on poor survival of U.S. gastric carcinoma patients treated with gastrectomy: Fifth Edition American Joint Committee on Cancer staging, proximal disease, and the "different disease" hypothesis. *Cancer.* 2000; 88(4):921–932.
4. Lim L, Michael M, Mann GB, Leong T. Adjuvant therapy in gastric cancer. *J Clin Oncol.* 2005;23(25):6220–6232.
5. 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(8):1441–1447.
6. 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(7):1059–1064.
7. Mari E, Floriani I, Tinazzi A, et al. Efficacy of adjuvant chemotherapy after curative resection for gastric cancer: a meta-analysis of published randomized trials. A study of the GISCAD (Gruppo Italiano per lo Studio dei Carcinomi dell'Apparato Digerente). *Ann Oncol.* 2000;11(7):837–843.
8. Panzini I, Gianni L, Fattori PP, et al. Adjuvant chemotherapy in gastric cancer: a meta-analysis of randomized trials and a comparison with previous meta-analyses. *Tumori.* 2002;88(1):21–27.
9. Van Cutsem E, Moiseyenko VM, Tjulandin S, et al. Phase III study of docetaxel and cisplatin plus fluorouracil compared with cisplatin and fluorouracil as first-line therapy for advanced gastric cancer: a report of the V325 Study Group. *J Clin Oncol.* 2006;24(31):4991–4997.
10. Bouché O, Raoul JL, Bonnetain F, et al. Randomized multicenter phase II trial of a biweekly regimen of fluorouracil and leucovorin (LV5FU2), LV5FU2 plus cisplatin, or LV5FU2 plus irinotecan in patients with previously untreated metastatic gastric cancer: a Fédération Francophone de Cancérologie Digestive Group Study—FFCD 9803. *J Clin Oncol.* 2004; 22(21):4319–4328.

11. Cocconi G, Bella M, Zironi S, et al. FAM combination versus PELF combination (cisplatin, epirubicin, leucovorin, 5-fluorouracil) in advanced gastric cancer. A prospective randomized trial of the Italian Oncology Group for Clinical Research (GOIRC). *J Clin Oncol.* 1994;12(12): 2687–2693.
12. Cocconi G, Carlini P, Gamboni A, et al. Italian Oncology Group for Clinical Research. Cisplatin, epirubicin, leucovorin and 5-fluorouracil (PELF) is more active than 5-fluorouracil, doxorubicin and methotrexate (FAMTX) in advanced gastric carcinoma. *Ann Oncol.* 2003;14(8): 1258–1263.
13. Thara E, Semba S, Thara H. Molecular biological observations in gastric cancer. *Semin Oncol.* 1996;23(3):307–315.
14. Aranda M, Naquira H, Karque R, Mendoza H, Sepulveda C, Silva C. Mutations of the p53 suppressor gene in gastric adenocarcinoma. *Rev Med Chil.* 1998;126(5):525–532.
15. Tsigris C, Karayiannakis AJ, Syrigos KN, et al. Clinical significance of soluble c-erbB-2 levels in the serum and urine of patients with gastric cancer. *Anticancer Res.* 2002;22(5):3061–3065.
16. Yeh KH, Shun CT, Chen CL, et al. High expression of thymidylate synthase is associated with the drug resistance of gastric carcinoma to high dose 5-fluorouracil-based systemic chemotherapy. *Cancer.* 1998;82(9): 1626–1631.
17. Wang H, Zhang Y, Cao L, et al. HERG K+ channel, a regulator of tumor cell apoptosis and proliferation. *Cancer Res.* 2002;62(17):4843–4848.
18. Sobin LH, Wittekind Ch, eds.; *TNM Classification of Malignant Tumors*. 5th ed. International Union Against Cancer (UICC). New York: John Wiley and Sons, Inc., 1997.
19. Hamilton SR, Aaltonen LA. *World Health Organization Classification of Tumors. Pathology and Genetics of Tumours of the Digestive System*. Lyon, France: IARC Press; 2000.
20. Rosemberger WF, Lachin JM. *Randomization in Clinical Trials*, *Theory and Practice*. 2002 Wiley Series in Probability and Statistics. New York: John Wiley and Sons; 2002.
21. Karpeh MS, Leon L, Klimistra D, Brennan M. Lymph node staging in gastric cancer: is location more important than number?. *Ann Surg.* 2000;232(3):362–371.
22. Grambsch P, Therneau T. Proportional hazards tests and diagnostics based on weighted residuals. *Biometrika.* 1994;81(3):515–526.
23. Maruyama K. The most important prognostic factors for gastric cancer patients: a study using univariate and multivariate analyses. *Scand J Gastroenterol Suppl.* 1987;22(2):63–68.
24. Adachi Y, Oshiro T, Mori M, Maehara Y, Sugimachi K. Prediction of early and late recurrence after curative resection for gastric carcinoma. *Cancer.* 1996;77(12):2445–2448.
25. Shiraishi N, Inomata M, Osawa N, Yasuda K, Adachi Y, Kitano S. Early and late recurrence after gastrectomy for gastric carcinoma. Univariate and multivariate analyses. *Cancer.* 2000;89(2):255–261.
26. SAS Institute Inc. *SAS/STATTM User's Guide*, *Version 6*. 4th ed. Vols 1 and 2. Cary, NC: SAS Institute Inc.; 1990.
27. Bajetta E, Buzzoni R, Mariani L, et al. Adjuvant chemotherapy in gastric cancer: 5-year results of a randomised study by the Italian Trials in Medical Oncology (ITMO) Group. *Ann Oncol.* 2002;13(2):299–307.
28. De Vita F, Giuliani F, Orditura M, Maiello E, Galizia G, Di Martino N. Adjuvant chemotherapy with epirubicin, leucovorin, 5-fluorouracil and etoposide regimen in resected gastric cancer patients: a randomized phase III trial by the Gruppo Oncologico Italia Meridionale (GOIM 9602 Study). *Ann Oncol.* 2007;18(8):1354–1358.
29. Bouché O, Ychou M, Burtin P, et al.; Federation Francophone de Cancerologie Digestive Group. Adjuvant chemotherapy with 5-fluorouracil and cisplatin compared with surgery alone for gastric cancer: 7-year results of the FFCD randomized phase III trial. *Ann Oncol.* 2005;16(9): 1488–1497.
30. Nitti D, Wils J, Guimaraes Dos Santos J, et al. Randomized phase III trials of adjuvant FAMTX or FEMTX compared with surgery alone in resected gastric cancer. A combined analysis of the EORTC GI Group and the ICCG. *Ann Oncol.* 2006;17(2):262–269.
31. Bozzetti F, Marubini E, Bonfanti G, Miceli R, Piano C, Gennari R. Subtotal versus total gastrectomy for gastric cancer: five-year survival rates in a multicenter randomized Italian trial. Italian Gastrointestinal Tumor Study Group. *Ann Surg.* 1999;230(2):170–178.
32. Bonenkamp JJ, Hermans J, Sasako M, et al.; Dutch Gastric Cancer Group. Extended lymph-node dissection for gastric cancer. *N Engl J Med.* 1999;340(9):9908–9914.
33. Degiuli M, Sasako M, Ponti A, Soldati T, Danese F, Calvo F. Morbidity and mortalità after D2 gastrectomy for gastric cancer: results of the Italian Gastric Cancer Study Group Prospective Multicenter Surgical Study. *J Clin Oncol.* 1998;16(4):1490–1493.
34. Macdonald J, Smalley S, 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(10):725–730.
35. Cunningham D, Allum W, Stenning S, et al. Perioperative chemotherapy vs surgery alone for resectable gastroesophageal cancer. *N Engl J Med.* 2006;355(1):1–20.
36. Wu AW, Xu GW, Wang HY, Ji JF, Tang JL. Neoadjuvant chemotherapy versus none for resectable gastric cancer. *Cochrane Database Syst Rev.* 2007;2:CD005047. doi:10.1002/14651858.
37. Bedikian AY, Chen TT, Khankhanian N, et al. The natural history of gastric cancer and prognostic factors influencing survival. *J Clin Oncol.* 1984;2(4):305–310.
38. Cascinu S, Labianca R, Barone C, et al. Adjuvant treatment of high-risk, radically resected gastric cancer patients with 5-fluorouracil, leucovorin, cisplatin, and epidoxorubicin in a randomized controlled trial. *J Natl Cancer Inst.* 2007;99(8):601–607.
39. Sakamoto AJ, Morita S, Kodera Y, Kobayashi M, Miyashitaand Y, Macdonald JS. A randomized phase III trial of post-operative adjuvant oral fluoropyrimidine versus sequential paclitaxel/oral fluoropyrimidine; and UFT versus S1 for T3/T4 gastric carcinoma: the Stomach Cancer Adjuvant Multi-institutional Trial Group (Samit) Trial. Jpn. *J Clin Oncol.* 2005;35(11):672–675.
40. Sakuramoto S, Sasako M, Yamaguchi T, et al. Adjuvant chemotherapy for gastric cancer with S-1, an oral fluoropyrimidine. *N Engl J Med.* 2007; 357(18):1810–1820.

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