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Adjuvant chemotherapy with 5-fluorouracil and cisplatin compared with surgery alone for gastric cancer: 7-year results of the FFCD randomized phase III trial (8801)

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Background: The aim of this study was to evaluate the efficacy of adjuvant chemotherapy after resection for gastric cancer in a randomized controlled trial.

Patients and methods: After curative resection, stage II-III-IVM0 gastric cancer patients were randomly assigned to postoperative chemotherapy or surgery alone. 5-Fluorouracil (5-FU) 800 mg/m^2 daily (5-day continuous infusion) was initiated before day 14 after resection. One month later, four 5-day cycles of 5-FU (1 g/m^2 per day) plus cisplatin (100 mg/m^2 on day 2) were administered every 4 weeks.

Results: The study was closed prematurely after enrollment of 260 patients (79.7% N+), owing to poor accrual. At 97.8 months median follow-up, 5- and 7-year overall survival were 41.9% and 34.9% in the control group versus 46.6% and 44.6% in the chemotherapy group ($P = 0.22$). Cox model hazard ratios were 0.74 [95% confidence interval (CI) 0.54–1.02; $P = 0.063$] for death and 0.70 (95% CI 0.51–0.97; $P = 0.032$) for recurrence. An invaded/removed lymph nodes ratio >0.3 was the main independent poor prognostic factor identified by multivariate analysis ($P = 0.0001$). Because of toxicity, only 48.8% of patients received more than 80% of the planned dose.

Conclusion: There was no statistically significant survival benefit with this toxic cisplatin-based adjuvant chemotherapy, but a risk reduction in recurrence was observed.

Key words: adjuvant chemotherapy, cisplatin, gastric cancer, lymph nodes ratio, prognostic factor, randomized controlled trial

Introduction

Although the incidence of gastric cancer has decreased in Western countries [1], it still remains a significant problem in global health terms. In USA and French population-based studies its prognosis after curative resection remains poor [2–4]. Even though a significant improvement has been recently achieved by using an adjuvant combination of chemotherapy and radiotherapy [5], the 5-year overall survival (OS) rates remain lower than 30% to 40% [2–5].

Surgery is the sole potentially curative treatment for localized gastric cancer and during past 20 years a worldwide effort has been made to develop effective adjuvant therapies to reduce the risk of recurrence. Nevertheless, chemotherapy for metastatic gastric cancer has made some progress, but the efficacy of adjuvant chemotherapy still remains under discussion despite more than 30 years of investigation. When this study was initiated, the majority of Western trials using monochemotherapy and then second generation chemotherapy combinations were disappointing [6, 7]. A first meta-analysis published in 1993 showed no conclusive value of adjuvant chemotherapy [8].

In the late 1980s, a third generation of chemotherapy (cisplatin-based regimens) was investigated for advanced gastric cancer [9, 10]. We reported a 40% response rate

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and an acceptable level of toxicity with the use of cisplatin combined with a 5-day infusion of 5-fluorouracil (5-FU) (FUP) in a phase II trial [10]. On the other hand, preclinical studies have suggested that an early initiation of chemotherapy, at a time when the tumor burden is smallest, is more effective [11].

This was the rationale to evaluate the efficacy of early 5-FU followed by FUP in the adjuvant setting. In 1989, the Fédération Francophone de Cancérologie Digestive (FFCD) therefore initiated a multicenter randomized phase III study to compare surgery followed by chemotherapy or surgery alone in patients with gastric or cardial adenocarcinoma after curative resection (R0) and stage II, III or IVM0.

Patients and methods

Patients

The study was conducted according to the principles of the Declaration of Helsinki and Good Clinical Practice guidelines. All the patients provided informed consent prior to inclusion in the trial, which was approved by the Bicêtre University Ethics Committee. The eligibility criteria included histologically confirmed adenocarcinoma of the stomach or gastro-esophageal junction; complete resection of the neoplasm defined as resection of all tumor with the margins of the resection testing negative for carcinoma (R0); lymph node (LN) metastases (pN+) and/or serosal invasion (pT3 or pT4) with no distant metastases [stage II through IVM0 according to the 2002 staging criteria of the Union International against Cancer (UICC)] [12]; a WHO performance status <2; adequate hematological (neutrophils $\geq 2\times10^9$/l; platelets $\geq 150\times10^9$/l), hepatic (bilirubin ≤ 25 μmol/l; aspartate aminotransferase and alanine aminotransferase $\leq 5\times$ the upper normal limit), renal (creatinine ≤ 130 μmol/l) and cardiac function; no post-operative complications; and early registration with treatment beginning before 14 days after surgery. The exclusion criteria were linitis plastica and concurrent active malignancy.

Study design and randomization

The study was a multicenter, prospective, randomized, controlled phase III trial with two treatment arms. After undergoing gastrectomy, patients were randomly assigned to the control (surgery alone) or treatment (post-operative chemotherapy) arm. Eligible patients were all registered at the FFCD center and randomized with stratification according to the institution and tumor site (stomach versus gastro-esophageal junction).

Surgical procedures

The surgical procedures suggested in the protocol were total or subtotal gastrectomy with curative intent and *en bloc* resection of the tumor with negative margins. A D2 lymphadenectomy according to the rules of the Japanese Research Society for the study of Gastric Cancer [13], was recommended. This procedure entails the resection of all perigastric LN, and some celiac, splenic or splenic-hilar, hepatic-artery and cardial LN, depending on the location of the tumor in the stomach. The operating surgeon completed an assessment form defining the extent of lymphadenectomy that was sent to the pathologist along with the surgery report, but no quality control was performed on surgery and pathology.

Chemotherapy administration and dose adjustments

The patients assigned to the treatment group received a two-stage post-operative chemotherapy. The first stage consisted of intravenous (i.v.) 5-FU 800 mg/m^2 per day in continuous infusion for 5 days initiated not later than 14 days after surgery. The second stage, which began 4 weeks later in the absence of WHO grade 4 toxicity, was the administration of four cycles of the FUP regimen, consisting of a 5-day continuous infusion of 5-FU 1 g/m^2 per day combined with cisplatin 100 mg/m^2 i.v. over 1 h on day 2. On day 2, prophylactic medication consisted of i.v. antiemetics and hydration (2 l over 3 h before and after cisplatin). The cycles of FUP were repeated every 4 weeks (one cycle = 28 days). Routine blood analyses were carried out before each cycle of treatment.

In the event of WHO toxicity, the following dose reductions and treatment delays were planned. In cases of insufficient hematological function (neutrophil count $<1.5\times10^9$/l or platelet count $<100\times10^9$/l) on day 28 of any cycle, treatment was delayed. For grade 3–4 gastrointestinal toxicities, thrombocytopenia and neutropenia, there were 25% 5-FU and cisplatin dose reductions. For grade 2 or greater cardiotoxicity, 5-FU treatment was discontinued. Cisplatin administration was discontinued in cases of grade 2 or greater neurological toxicity or if creatinine levels were >130 μmol/l.

Follow-up of patients

The postoperative baseline and follow-up investigations were standardized. The baseline assessments included a complete medical history and physical examination, a hemogram, and renal and hepatic function tests. An abdominal ultrasound or computed tomography (CT) scan and a chest X-ray were required before or after surgery. Before each chemotherapy cycle, the hemogram and the renal tests were repeated. All adverse events were graded using the WHO Toxicity Criteria.

Follow-up of both groups occurred at 3-month intervals for 2 years, then at 6-month intervals for 3 years, and yearly thereafter. This consisted of physical examination, complete blood count, liver-function tests, determination of CEA and CA19-9, and abdominal ultrasonography or CT scan. The patients also underwent chest X-ray every 12 months and upper endoscopy as clinically indicated. The site and date of the first recurrence and the date of death, if the patient died, were recorded. Disease recurrence was ascertained by means of clinical, radiological and (whenever feasible) histological examinations.

Statistical analysis

The primary end point was OS. Secondary end-points were disease-free survival (DFS) and safety. DFS was measured from the date of randomization to the date of the first occurrence of a neoplasic event (relapse or second malignancy) or the date of death from any cause. If no progression was reported and if no death occurred, data on DFS were censored as from the date when the absence of relapse was confirmed. OS was measured from the date of randomization to the date of death from any cause or the date of the last follow-up.

The planned sample size was 400 patients, with 200 patients in each arm. The planned duration of accrual was 5 years and the planned follow-up time was 2 years. This sample size was designed to provide the study with 80% power to detect a difference between 5-year OS of 40% in the surgery-alone arm and 55% in the chemotherapy arm [hazard ratio (HR) for death of 0.65], with two-sided type I error of 0.05.

At inclusion, the clinical variables were described as means or frequencies. Comparison of two groups based on patient characteristics was performed using the Student's *t*-test and the χ^2-test. DFS and OS curves were estimated using the Kaplan–Meier method and compared using the log-rank test (unadjusted analysis) for all the eligible patients on an intention-to-treat basis.

An uni- and multivariate prognostic analysis was also prospectively planned. The two study arms were compared using Cox's proportional

hazards model with results reported as relative HR of death and relapse with corresponding 95% confidence interval (CI) and *P* value. The following covariates were included in a multivariate analysis: age, gender and all clinical variables significant at $P<0.15$ in the univariate analysis. Adjustment was routinely performed on the investigator centers, the tumor site and the type of treatment attributed. At the end of the study, centers were defined according to the number of patients included by institution: large if 20 or more patients, medium if six to 19 patients and small if five or less patients. For each end point considered, a joint test of the interaction terms in the final Cox's model was carried out. The main prognostic factors were categorized as follows: pT1 or pT2 versus pT3 or pT4; invaded/removed LN ratio ≤0.3 versus LN ratio >0.3; gastro-esophageal junction versus whole stomach; centers: large versus small and large versus medium. N0 cases were too limited to be considered as a separate category, and were therefore grouped with LN ratio ≤0.3 cases.

Owing to low recruitment 7 years after the start of the study, the data monitoring committee recommended to stop enrollment and to perform the final analysis, after a median follow-up of at least 7 years, in order to increase statistical power. The power of the final analysis performed with the reduced accrual was 47%.

Results

Patient characteristics

Between April 1989 and December 1997, 278 patients were randomized by 64 centers in France. Eighteen patients (6.5%) were considered ineligible: three had linitis plastica, two had pT2-N0 stage tumor, two had a positive surgical margin, five had metastatic disease and six had missing data (Figure 1). Therefore, the analyses were carried out on an intention-to-treat basis with the remaining 260 enrolled eligible patients (133 in the control arm and 127 in the chemotherapy arm).

The patient and tumor characteristics, summarized in Table 1, were similar between the two arms except for the extent of the cancer; the proportion of advanced tumors was higher in the chemotherapy arm than in the surgery-alone arm, with a different distribution between stages IIIA, IIIB and IV ($P=0.01$).

Most tumors were in the distal stomach. The tumor was located at the gastroesophageal junction in 15.8% of the patients. The patients were at high risk for recurrence; 77.3% had stage pT3 or pT4 tumors, 79.7% had LN metastases and more than one-third had invaded/removed LN ratio >0.3.

Surgical procedures

Distribution of the surgical procedures across the two groups was well balanced (Table 1). Among 260 patients, only 70 (26.9%) underwent a formal D2 lymphadenectomy. A D0 lymphadenectomy was performed in 105 patients (40.4%), and at least D1 lymphadenectomy in the remaining patients (55.8%) (more than 15 LN removed). The median number of removed LN per patient was 18. The frequency of postoperative

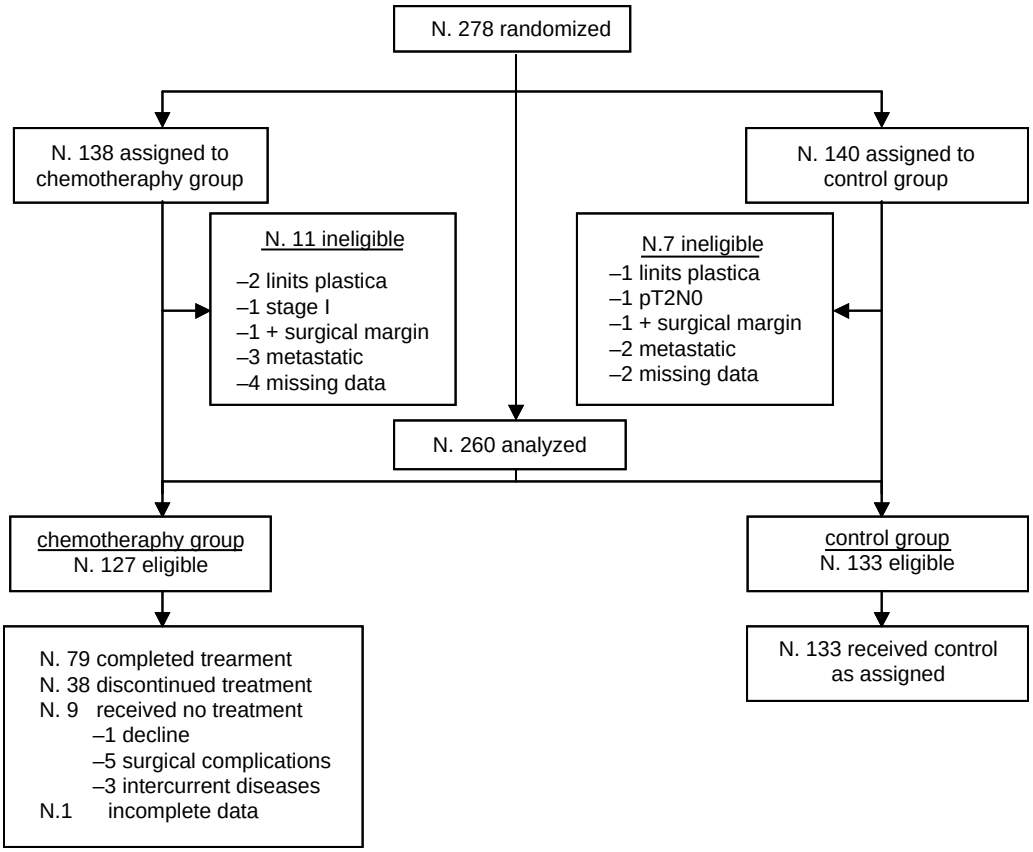

Figure 1. Study flow chart.

Table 1. Characteristics of the patients and the tumors

Characteristics	Total ($n = 260$) [n (%)]	Surgery alone ($n = 133$) [n (%)]	Chemotherapy ($n = 127$) [n (%)]	P
Sex				
Male	186 (71.5)	93 (69.9)	93 (73.2)	0.55
Female	74 (28.5)	40 (30.1)	34 (26.8)	
Age, years				
Median (SE)	61.0 (0.9)	62.0 (1.2)	60.0 (1.4)	0.38
Range	31–83	31–83	32–82	
WHO performance status				
0	155 (59.6)	79 (59.4)	76 (59.8)	0.46
1	95 (36.5)	47 (35.3)	48 (37.8)	
2	10 (3.9)	7 (5.3)	3 (2.4)	
Center (patients/center)				
Large (≥20)	96 (36.9)	48 (36.1)	48 (37.8)	0.83
Medium (6–19)	65 (25.0)	32 (24.1)	33 (26.0)	
Small (≤5)	99 (38.1)	53 (39.8)	46 (36.2)	
Location of tumor				
Cardia	41 (15.8)	22 (16.5)	19 (15.0)	0.73
Stomach	219 (84.2)	111 (83.5)	108 (85.0)	
Surgical procedures				
Partial gastrectomy	93 (35.8)	49 (36.8)	44 (34.6)	0.71
Total gastrectomy	167 (64.2)	84 (63.2)	83 (65.4)	0.52
Splenectomy	45 (17.3)	25 (18.8)	20 (15.7)	0.91
Pancreatectomy	24 (9.2)	12 (9.0)	12 (9.4)	
Macroscopic type				
Infiltrative	111 (42.7)	59 (44.4)	52 (40.9)	0.31
Exophytic	147 (56.5)	72 (54.1)	75 (59.1)	
Unknown	2 (0.8)	2 (1.5)	0 (0.0)	
Histology differentiation				
Well differentiated	124 (47.7)	62 (46.6)	62 (48.8)	0.95
Poorly differentiated	62 (23.9)	33 (24.8)	29 (22.8)	
Signet-ring cell	63 (24.2)	33 (24.8)	30 (23.6)	
Other	11 (4.2)	5 (3.8)	6 (4.7)	
Depth of invasion				
pT1 or pT2	59 (22.7)	31 (23.3)	28 (22.1)	0.97
pT3	191 (73.4)	97 (72.9)	94 (74.0)	
pT4	10 (3.9)	5 (3.8)	5 (3.9)	
Extent of LN dissection				
≤15 LN removed	105 (40.4)	54 (40.6)	51 (40.2)	0.99
16–25 LN removed	75 (28.9)	38 (28.6)	37 (29.1)	
≥26 LN removed	70 (26.9)	36 (27.1)	34 (26.8)	
Unknown	10 (3.8)	5 (3.8)	5 (3.9)	
Median (SE)	18 (0.9)	17.5 (1.2)	18 (1.2)	
No. of invaded LN (stage)				
0 (pN0)	43 (16.5)	23 (17.3)	20 (15.8)	0.14
1–6 (pN1)	138 (53.1)	69 (51.9)	69 (54.3)	
7–15 (pN2)	48 (18.5)	30 (22.6)	18 (14.2)	
>15 (pN3)	21 (8.1)	6 (4.5)	15 (11.8)	

Table 1. (*Continued*)

Characteristics	Total ($n = 260$) [n (%)]	Surgery alone ($n = 133$) [n (%)]	Chemotherapy ($n = 127$) [n (%)]	P
Unknown	10 (3.8)	5 (3.8)	5 (3.9)	
Invaded/removed LN ratio				
0 (pN0)	43 (16.5)	23 (17.3)	20 (15.7)	0.84
1–20%	87 (33.5)	43 (32.3)	44 (34.7)	
21–30%	28 (10.8)	17 (12.8)	11 (8.7)	
>30%	92 (35.4)	45 (33.8)	47 (37.0)	
Unknown	10 (3.8)	5 (3.8)	5 (3.9)	
UICC stage[a]				
II	91 (35.0)	48 (36.1)	43 (33.9)	0.01
IIIA	104 (40.0)	48 (36.1)	56 (44.1)	
IIIB	33 (12.7)	24 (18.0)	9 (7.1)	
IV	29 (11.1)	10 (7.5)	19 (15.0)	
Unknown	3 (1.2)	3 (2.3)	0 (0.0)	

[a]Stages according to the sixth edition of the TNM classification manual (2002) [12].
SE, standard error; LN, lymph nodes; UICC, Union International against Cancer.

mortality was low: one death from pulmonary emboli occurred in each arm.

Chemotherapy

Among the 127 patients allocated to the chemotherapy group, 79 (62.2%) completed treatment as planned and 38 (29.9%) stopped chemotherapy because of toxicity (24 patients after three or four cycles and 14 patients after one or two cycles); data were incomplete in one patient (0.8%). Patients received a median of four cycles (range one to five) of treatment. Nine patients (7.1%) did not receive chemotherapy for the following reasons: one declined, five had postoperative complications and three developed intercurrent diseases (Figure 1).

Chemotherapy was initiated, as required, before day 14 after resection in 95 patients (80.5%) and before day 7 in 16 patients (13.6%).

Considering the planned dose/intensity, only half the patients (62 patients; 48.8%) received more than 80% of the cumulative planned dose of chemotherapy, and the main reason for dose reduction was toxicity.

Toxicity

Toxicities experienced during treatment are listed in Table 2. Gastrointestinal and hematological toxicities predominated. Grade 3–4 nausea/vomiting was experienced by 32.5% of the patients. The most common hematological toxic effect was neutropenia (27.4% of patients). Overall, one severe toxic episode (grade 3–4) was reported at least once in 55.6% of the patients.

One death occurred that was considered likely to be related to chemotherapy (sepsis complicating neutropenia).

OS and DFS

The median follow-up time was 97.8 months [standard error (SE) 3.0]. One hundred and sixty-one patients (61.9%) were dead at the end point date of 31 December 2002. Figures 2 and 3 show the OS and DFS curves according to treatment arm. The 5- and 7-year OS rates were 41.9% (SE 4.3) and 34.9% (SE 4.4) in the control group versus 46.6% (SE 4.5) and 44.6% (SE 4.5) in the chemotherapy group ($P = 0.22$) (Figure 2). The median OS duration was, respectively, 42.1 months (SE 16.7) versus 44.8 months (SE 7.8). The 5- and 7-year DFS rates were 39.8% (SE 4.5) and 37.2% (SE 4.5) in the control group versus 47.6% (SE 4.6) and 43.2% (SE 4.8) in the chemotherapy group ($P = 0.19$) (Figure 3). The median DFS duration was, respectively, 28.5 months (SE 16.3) versus 36.4 months (SE 7.8). Neither of these differences was statistically significant.

The site of first recurrence and the cause of death during the follow-up are shown in Table 3. In the relapsed patients, metastases were the most frequent (63.6%), whereas a loco-regional recurrence occurred in 18.3% and both occurred in 18.3%. There was no difference in the pattern of recurrence among the two groups. Death was tumor-related in 75.6% of the patients in the surgery alone group and in 73.3% in the chemotherapy group.

Univariate analysis showed an association of OS with size of center ($P = 0.003$), histological differentiation ($P = 0.03$), tumor size ($P = 0.007$), type of gastrectomy ($P = 0.0001$), splenectomy ($P = 0.0001$), location of tumor ($P = 0.005$), tumor UICC stage ($P = 0.0001$), depth of invasion ($P = 0.0001$), number of invaded LN ($P = 0.0001$) and invaded/removed LN ratio ($P = 0.0001$). In contrast sex, age, WHO performance status, number of LN removed and period of inclusion (1989–1993 versus 1994–1997) did not significantly influence the OS.

Table 2. Toxicity of chemotherapy (infusional 5-fluorouracil cycle 1 and 5- fluorouracil–cisplatin cycle 2–5) by patient according to WHO grade

Toxicity	% of patients					
	Cycle 1 ($n=117$)	Cycle 2 ($n=112$)	Cycle 3 ($n=103$)	Cycle 4 ($n=91$)	Cycle 5 ($n=79$)	Overall ($n=117$)
Hematological						
Grade 1 or 2	15.4	27.7	26.2	31.9	25.0	35.0
Grade 3 or 4	2.6	13.4	17.5	12.1	5.0	27.4
Nausea or vomiting						
Grade 1 or 2	30.8	44.6	43.7	42.9	32.5	47.9
Grade 3 or 4	6.8	20.5	15.5	7.7	3.8	32.5
Stomatitis						
Grade 1 or 2	10.3	14.3	17.5	6.6	2.5	17.1
Grade 3 or 4	4.3	9.8	7.8	4.4	1.3	18.8
Cardiovascular						
Grade 1	0.0	0.9	1.0	0.0	1.3	1.7
Grade 2	0.0	2.7	1.9	1.1	0.0	5.1
Maximal toxicity						
Grade 1 or 2	38.5	47.3	43.7	46.2	50.0	35.9
Grade 3 or 4	13.7	32.1	31.1	22.0	7.5	55.6
Toxic deaths						
No.			1[a]			1
%			1.0			0.9

[a]One patient died from sepsis complicating neutropenia.

The results of the Cox model are shown in Table 4. After adjustment, the Cox HR estimates for the treated patients compared with controls were 0.74 (95% CI 0.54–1.02; $P=0.063$) for OS and 0.70 (95% CI 0.51–0.97; $P=0.032$) for DFS. These figures indicate a relative risk reduction in the patients receiving adjuvant therapy of 26% for OS and 30% for DFS.

Of all subgroups analyzed, only patient categories that seemed to benefit more from adjuvant treatment were those characterized by invaded/removed LN ratio >0.3. In the patients with invaded/removed LN ratio ≤0.3, the 5-year OS rate was 61.1% in the treatment group and 59% in the control group; the corresponding figures for the patients with invaded/removed LN ratio >0.3 were 25.4% and 14%. The Kaplan–Meier OS rate by LN ratio and treatment group are shown in Figure 4. However, the interaction test failed to yield significant results for either OS ($P=0.43$) or DFS ($P=0.35$).

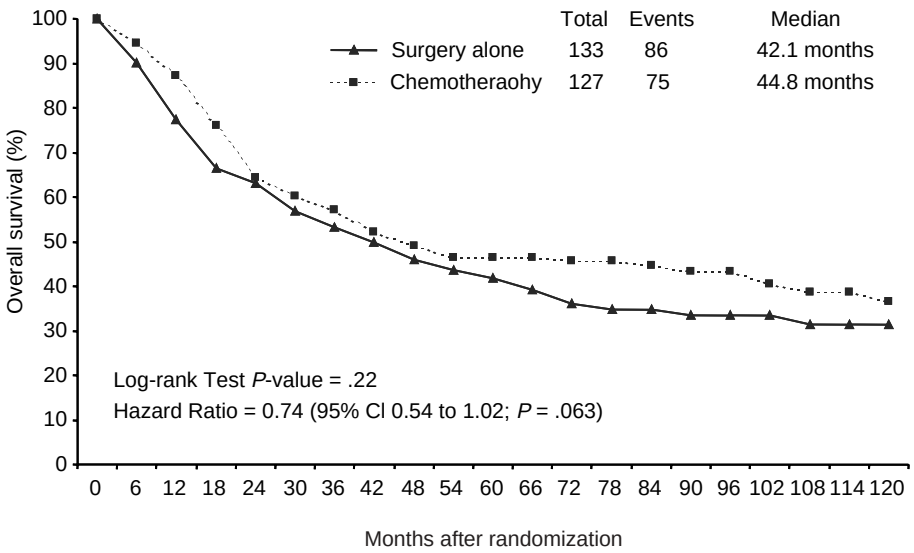

Figure 2. Overall survival according to treatment arm. The median overall survival times, log-rank test *P* value and hazard ratio in multivariate analysis are shown. CI, confidence interval.

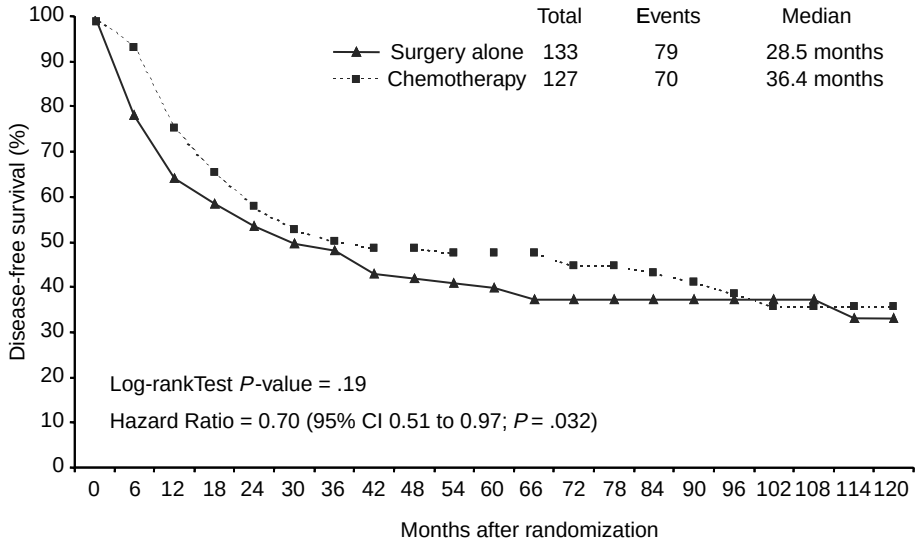

Figure 3. Disease-free survival according to treatment arm. The disease-free median survival times, log-rank test *P* value and hazard ratio in multivariate analysis are shown. CI, confidence interval.

Discussion

This study indicates a relative risk reduction of 26% for death ($P = 0.063$) and 30% for recurrence ($P = 0.032$) in the patients receiving adjuvant therapy. In designing the present trial, we set an absolute 15% difference (40% versus 55%) in 5-year OS (relative risk reduction of 35%) between the arms as clinically significant. The number of patients finally enrolled was not sufficient to detect the planned difference; however, the long follow-up (median 8 years) and the longer duration of the recruitment than planned gave us the opportunity to perform an analysis with more mature data and higher power than when the results were reported in 2000 [14]. Fewer patients had to be enrolled to obtain the same number of events [7]. However, as the observed survival difference was smaller than that planned, the fact that the results of our study did not reach statistical significance for OS is therefore not surprising. An absolute 15% improvement in survival due to chemotherapy was clearly too ambitious.

Table 3. Status at last follow-up and sites of recurrence

Characteristics	Total ($n = 260$) [*n* (%)]	Surgery alone ($n = 133$) [*n* (%)]	Chemotherapy ($n = 127$) [*n* (%)]
Death	161 (61.9)	86 (64.7)	75 (59.1)
Tumor-related[a]	120 (74.5)	65 (75.6)	55 (73.3)
Surgery-related[a]	2 (1.2)	1 (1.2)	1 (1.3)
Chemotherapy-related[a]	1 (0.6)	–	1 (1.3)
Intercurrent disease[a]	30 (18.6)	15 (17.4)	15 (20.0)
Second malignancy[a]	7 (4.4)	4 (4.7)	3 (4.0)
Unknown cause[a]	1 (0.6)	1 (1.2)	0 (0.0)
Site of first recurrence			
Locoregional[b]	22 (18.3)	15 (23.1)	7 (12.7)
Distant[b]	76 (63.3)	39 (60.0)	37 (67.3)
Both[b]	22 (18.3)	11 (16.9)	11 (20.0)

[a]Percentage related to number of deaths.

[b]Percentage related to number of tumor-related deaths.

Two other studies have also failed to demonstrate a significant efficacy of cisplatin-based adjuvant chemotherapy [15, 16]. The 5-year OS was 48% in the surgery-alone arm versus 52% in the chemotherapy arm in an Italian study [15], and 39% in both arms in another French study [16]. One result of our study was to demonstrate the feasibility of early postoperative systemic 5-FU, but required early registration could be an explanation for the insufficient recruitment.

The limited benefit may be related to an insufficient efficacy of FUP regimen, as was suggested by the low response rate reported in metastatic patients in a phase III trial [17] despite excellent results of earlier phase II studies [9, 10]. Another reason for the lack of efficacy may be the poor compliance due to the digestive toxicity of cisplatin. Indeed, a meta-analysis indicated a larger advantage of adjuvant chemotherapy for some subgroups of patients, when effective chemotherapeutic regimens with sufficient dose-intensity were used [18]. In our study only half of the patients received more than 80% of the cumulative planned dose of chemotherapy. The association of postoperative and chemotherapy side-effects was probably the main reason for this low compliance of treatment in gastrectomized patients [16].

This study suggests a small difference of at least 5% in OS and a role for chemotherapy in the prevention of recurrence. One early meta-analysis concluded that postoperative chemotherapy did not improve survival [8], whereas four more recent meta-analyses provided a marginal, but statistically significant, overall absolute risk reduction in 5-year OS between 3% and 5% (HR of death in the treated group ranging from 0.72 to 0.84) [18–21]. The results should, however, be considered with caution, as meta-analyses of published literature tend to overestimate treatment effects. However, several

Table 4. Multivariate Cox proportional hazard ratio analysis

Factors	Reference categories	Hazard ratio	95% CI	*P*
Overall survival				
Center size	Medium/large	1.49	0.98–2.26	0.06
	Small/large	1.79	1.23–2.59	0.002
Location of tumor	Cardia/stomach	1.42	0.95–2.13	0.10
Depth of invasion	pT3-T4/pT1-T2	2.25	1.41–3.58	0.0002
Invaded/removed LN ratio	>0.3/≤0.3	2.98	2.16–4.10	0.0001
Treatment arm	Chemotherapy/control	0.74	0.54–1.02	0.063
Disease-free survival				
Center size	Medium/large	1.60	1.04–2.46	0.03
	Small/large	1.89	1.29–2.79	0.001
Location of tumor	Cardia/stomach	1.61	1.06–2.44	0.03
Depth of invasion	pT3-T4/pT1-T2	2.46	1.51–4.00	0.0001
Invaded/removed LN ratio	>0.3/≤0.3	3.04	2.17–4.24	0.0001
Treatment arm	Chemotherapy/control	0.70	0.51–0.97	0.032

LN, lymph node; CI, confidence interval.

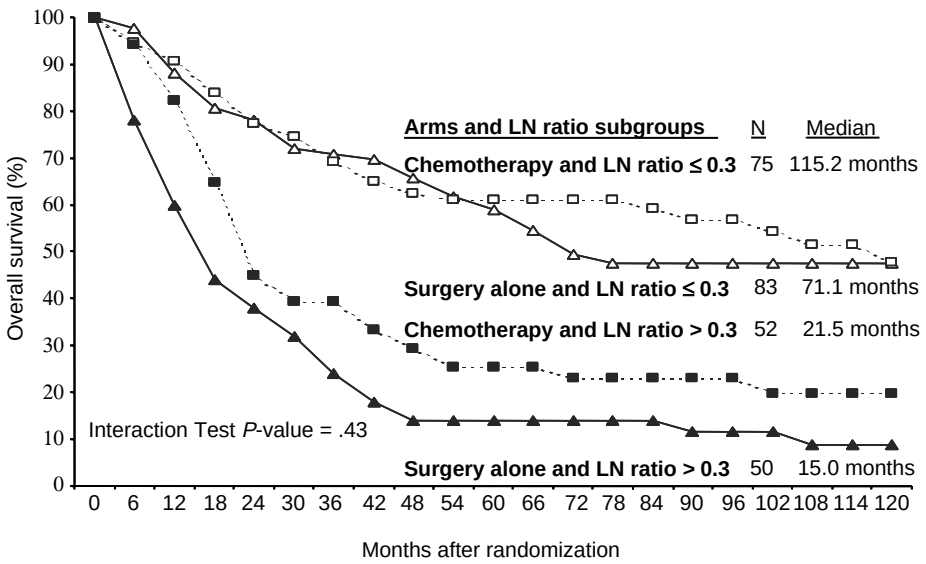

Figure 4. Overall survival by invaded/removed LN ratio (>0.3 and ≤0.3) according to treatment arm. The median overall survival times and interaction test *P* value are shown. LN, lymph nodes.

studies published recently, and therefore not included in meta-analyses, also suggested a moderate improvement of ∼5% in patients receiving different postoperative chemotherapy [15, 22, 23], although only one showed a significant effect [22]. Nevertheless, the positive effect of this study could be debatable given that median OS duration in the surgery alone group was 18 months [22].

The present trial was not designed specifically to consider subgroups; however, a multivariate prognostic analysis was carried out in order to assess whether patients might receive different benefits from adjuvant therapy. As in previously reported series [24–29], our multivariate analysis confirmed that main independent poor prognostic factor was the high invaded/removed LN ratio ($P = 0.0001$). This factor was of greater prognostic value than the TNM/UICC staging system [12], as it avoided the stage migration phenomenon; it should be incorporated in stratification factors of future trials. Our study suggested that the LN ratio cut-offs were ≤0.3 and >0.3, with significant differences in the prognosis of these two classes of patients. By comparison, other studies have selected different cut-offs for the LN ratio of 0.1 [24, 25], 0.2 [26, 27], 0.25 [24, 25, 28, 29], 0.5 [28] or/and 0.6 [25]. However, this result must be interpreted with caution, given the fact that 40% of patients had less that 15 LN removed, the chance of missing invaded LN increased. The influence of size of centers in term of recruitment also appeared important, reflecting, at

least in part, the favorable impact of experienced surgical teams.

Analysis of interaction between prognostic covariates and adjuvant treatment showed no significant difference. In an exploratory analysis, the only subgroup with a trend to benefit from chemotherapy was the LN ratio >0.3 group: the 5-year OS of the patients treated with chemotherapy was comparatively better than that of the control patients (25% versus 14%). This result must be interpreted with caution, because it is based on an *a posteriori* analysis of a subgroup of approximately one-third of patients. Bajetta et al. [15] also indicated a favorable trend in the more than six LN invaded subgroup. These results in fact provide a rationale for testing chemotherapy in these subgroups in future studies or meta-analyses.

The interest of many different approaches has been recently suggested. The first has been the demonstration of the efficacy of postoperative chemotherapy with 5-FU and leucovorin combined with radiotherapy reported by a large US Intergroup study [5]. This trial has been the subject of debate, because surgical undertreatment may possibly have undermined survival results [30]. The proportion of patients with more than 15 LN removed was slightly greater in our study than in US Intergroup [5] (56% versus 46%); in population-based studies, this rate was only $\sim$20% [2, 3]. In a US trial, the 3-year OS was 41% for the control group [5], which is inferior compared with 53% reported in our study. The second approach was the pre- and postoperative use of active chemotherapy. The preliminary results of a phase III perioperative chemotherapy clinical trial using epirubicin, cisplatin and 5-FU (ECF) demonstrated a statistically significant improvement in DFS and a potential improvement in OS [31]. Considering the promising results of phase II studies [32–34], preoperative radiochemotherapy also seems an attractive option. Otherwise, the promising efficacy of several newer drug-based combination such as docetaxel–cisplatin–5-FU [35, 36], docetaxel–5-FU [37], irinotecan–5-FU [38, 39] or oxaliplatin–capecitabine–epirubicine [40] supports their evaluation in the adjuvant setting.

In conclusion, although an improvement of 5% in 5-year survival was shown in our study, this result failed to reach statistical significance. Therefore, our highly toxic regimen of adjuvant chemotherapy cannot be recommended as adjuvant treatment for patients with resected gastric cancer. These limited survival advantages are considered to be of clinical relevance in other cancers, i.e. breast or colorectal cancers, but should be balanced against the toxicities [7]. Future trials should investigate more effective and less toxic strategies with new drugs or targeted biotherapies, combined with radiotherapy, in different settings, including neo-adjuvant and adjuvant. Furthermore, ongoing research in the field of molecular markers could permit more tailored treatment and the identification of patients who are more likely to benefit from treatment [41].

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