Original article

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Adjuvant chemotherapy in gastric cancer: 5-year results of a randomised study by the Italian Trials in Medical Oncology (ITMO) Group

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Background: The aim of this study was to determine the efficacy of the EAP regimen (etoposide, adriamycin and cisplatin) followed by the Machover schedule (fluorouracil and folinic acid) given as adjuvant treatment to patients with poor prognostic factors (N+ or T3/4).

Patients and methods: Before randomisation, the subjects were stratified on the basis of node involvement (N+ or N–) and the time from surgery to randomisation (≤21 days or >22 days). The surgical procedures for sub-total or total gastrectomy with D2 dissection were standardised among the participating centres.

Results: Between December 1992 and December 1997, 274 patients were enrolled: 137 in the treatment arm and 137 in the control arm. The majority of the patients (90%) were N+. After a median follow up of 66 months (range 2–83), the 5-year overall survival (OS) was 52% in the treatment arm and 48% in the control arm [hazard ratio (HR) 0.93; 95% confidence interval (CI) 0.65–1.34]; the 5-year disease-free survival (DFS) was 49% and 44%, respectively (HR: 0.83; 95% CI 0.59–1.17). Among the patients with N–/N+ (1–6), the 5-year OS was 61% in the treatment group and 60% in the control group; in those with N+ (1–6), it was 42% and 22%. The treatment was completed by 87% of patients. Drug-related grade 3/4 WHO toxicities included leukopenia (21%), nausea and vomiting (14%), mucositis (9%), neutropenia (3%) and thrombocytopenia (2%). There were two deaths due to sepsis.

Conclusions: Although our results are not statistically significant, there was a limited relative risk reduction in the patients receiving adjuvant therapy (17% in DFS and 7% in OS). The data suggest that D2 surgery may have a favourable impact on OS.

Key words: adjuvant chemotherapy, gastric cancer, polychemotherapy

Introduction

Although declining in incidence in many industrialised countries, gastric cancer remains a major cause of mortality, accounting for 10% of all new cancer diagnoses and 12% of all cancer-related deaths [1]. Furthermore, the diagnosis is often made when the disease is advanced and unresectable, thus contributing to the high rate of morbidity and mortality.

Surgery is the treatment of choice and, in early stages, can usually be performed with curative intent; however, the 5-year survival rate of 20–30% is disappointing [2]. In an attempt to improve post-surgery survival, various adjuvant chemotherapy regimens have been proposed and evaluated in clinical trials.

When this study was started in the early 1990s, the majority of adjuvant chemotherapy trials had failed to show a clear survival benefit over surgery alone; only the high-dose mitomycin C and immunochemotherapy trials had demonstrated a real benefit for the patients in the experimental treatment arms

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[3, 4]. Subsequently, a number of meta-analyses have shown a borderline significant effect in favour of adjuvant therapy [5–8].

Cisplatin-containing chemotherapy regimens have been investigated in advanced gastric cancer since 1983, and the drug is considered active in gastric cancer [9, 10]. In 1989, Wilke et al. reported a high response rate using an 8-day etoposide, adriamycin and cisplatin (EAP) regimen [11, 12]. This regimen, which does not use fluorouracil (FU), gained attention because of a relatively high complete response rate (CR 10%). The results were confirmed by an Italian Trials in Medical Oncology (ITMO) Group multicentre study in metastatic gastric cancer patients, which found a response rate of 37% with 12% of patients achieving CR. The regimen was well tolerated and had no significant side effects [13], although other published data have indicated that EAP has a high morbidity rate [14]. Nevertheless, this schedule has been extensively used in the clinical practice of our institution and found to be well tolerated.

Following our 1992 results, we designed a randomised study to test the efficacy of the regimen in the adjuvant treatment of resectable gastric cancer with negative prognostic factors. Given that the toxicity of the EAP schedule might be cumulative, we planned a limited number of EAP cycles followed by an FU-containing regimen according to the Machover schedule [15]. This therapeutic sequence was chosen because of the proven activity of these regimens in advanced disease and the possibility of improving patient compliance by sequentially combining two regimens with different toxicity profiles.

The aims of the present study were to verify whether two cycles of EAP regimen followed by two cycles of the Machover schedule increase overall (OS) and disease-free survival (DFS) in radically resected patients with nodal involvement (N+) or pT3/4.

Materials and methods

Patient population

Between December 1992 and December 1997, a total of 274 patients were recruited in 32 Italian institutions. The study was approved by the Institutional Review Board of Milan's Istituto Nazionale per lo Studio e la Cura dei Tumori, which was the reference centre. All patients had to have undergone a radical resection of stomach adenocarcinoma within the previous 8 weeks and have at least one of the following unfavourable characteristics according to the TNM system of the Joint Committee for Cancer Staging of 1992 [16]: serosa invasion (pT3); extension to adjacent organs (pT4); or metastases to regional lymph nodes (N1 or N2). No macroscopic or microscopic evidence of residual disease was allowed. The patients were considered eligible if they were aged <70 years. The exclusion criteria were a WHO performance status of >2, previous malignancies other than superficial skin cancer or *in situ* cervical carcinoma, any indication of metastasis elsewhere in the body, abnormal liver tests, high serum blood urea nitrogen (BUN) or creatinine levels (>1.25 times the upper normal limit), a leukocyte count of $<3 \times 10^3/mm^3$ or a platelet count of $<100 \times 10^3/mm^3$.

Surgical procedures

The surgical procedures suggested in the protocol were total or sub-total gastrectomy with free resection margins, and the 'en bloc' resection of the greater and lesser omentum. A D2 lymphadenectomy according to the rules of the Japanese Research Society for Gastric Cancer [17] was advocated in the protocol. If the records from the Pathology Department and the operative report did not specify the pathological status of second level nodes, the patients were considered inelegible for the study.

Trial design

After surgery and staging, all of the surgical and pathological reports from each participating institution were reviewed by a central surgical committee in order to validate the depth of invasion and the stage of nodal involvement. For each patient, an evaluation of regional lymphadenectomy was made on the basis of histological and surgical data. Informed consent was obtained from all participating patients.

The randomisation of the patients was centrally managed by the ITMO scientific office: the clinical investigators contacted the data manager by fax and, after the inclusion and exclusion criteria had been checked, eligible patients were registered and assigned to receive chemotherapy or simply to be followed up according to computer-generated permuted-block randomisation lists. The lists were stratified by centre, nodal involvement (N– or N+) and the time from surgery to randomisation (≤21 days or 22–60 days). The first cycle had to begin soon after randomisation, and the investigators did not know the allocation before it occurred. No blinding procedure was used for treatment administration or the follow-up assessments.

Protocol chemotherapy and follow-up evaluation

The patients included in the treatment group started chemotherapy within 60 days. The EAP regimen consisted of etoposide 120 mg/m^2/day (100 mg/m^2 in patients ≥60 years old) administered by means of a 30 min i.v. infusion on days 4, 5 and 6; adriamycin 20 mg/m^2/day i.v. on days 1 and 7; and cisplatin 40 mg/m^2/day i.v. on days 2 and 8. After two cycles of EAP, the patients received two cycles of FU and L-leucovorin as reported by Machover: L-leucovorin 100 mg/m^2 i.v. on days 1–5 and FU 375 mg/m^2 on days 1–5. The cycles were restarted after 28 days.

Cisplatin was delivered by means of a slow i.v. infusion in 250 ml of saline solution, with adequate hydration being given before and after administration.

Toxicity was graded according to the WHO scoring system. If grade 1/4 myelotoxicity was observed before starting a new chemotherapy cycle, the treatment was delayed by 1 week; in the case of persistent grade 1/3 myelotoxicity, the dose was reduced by 20% and, if grade 4 myelotoxicity persisted after 2 weeks of delay, the treatment was definitively stopped. In the presence of symptoms related to haematological toxicity (bleeding or infections), a complete blood count was performed, and the cycle was administered with a 20% dose reduction upon recovery.

The post-operative baseline and follow-up investigations were standardised. The baseline assessments included a complete history and physical examination, with performance status, weight and blood pressure measurements, a haemogram, and renal and hepatic function tests. An abdominal ultrasound or computed tomography (CT) scan and chest X-ray were performed before randomisation. At each chemotherapy cycle, the haemogram and the renal and hepatic tests were repeated. During the follow-up, the patients underwent upper gastrointestinal radiography, ultrasonography or CT scan, endoscopy and chest X-ray every 4 months for the first 3 years, and then every 8 months or whenever it was considered necessary.

Disease recurrence was ascertained by means of clinical, radiological and (whenever feasible) histological examinations.

Statistical methods

The primary endpoint of the study was to evaluate treatment efficacy on the basis of OS, including all-cause mortality. Another main endpoint was DFS. OS was computed from the date of randomisation to the date of death, or the last available follow-up assessment in the case of living patients; DFS was computed from the date of randomisation to the date of death or a neoplastic event, or the last available follow-up assessment in the case of living patients with no evidence of disease. All of the recorded events were included in the analysis, regardless of treatment duration and compliance levels, according to the intention-to-treat principle.

The planned sample size was 250 patients, equally divided into two groups. This number was calculated using Friedman's formula on the basis of an expected 5-year survival in the control group (surgery alone) of 30%, a minimum detectable difference in the treatment arm of 15%, a statistical power of 80% and a type I error probability level of 5%.

The OS and DFS curves in the two arms were estimated using the Kaplan–Meier method and compared by means of the log rank test (unadjusted analysis).

The two study arms were also statistically compared using Cox's proportional hazard regression model, allowing for the following covariates (adjusted analysis): T stage, N stage and tumour location. These covariates were chosen because they have been recognised as risk factors for gastric cancer recurrence and mortality [18].

Treatment, the above covariates and the first-order interaction terms between the treatment and the covariates were entered in the Cox model using 0–1 indicator variables. The interaction terms made it possible to assess whether the treatment effect was modified by the considered disease characteristics. The proportional hazard assumption implied by the Cox's model was checked by means of the analysis of scaled Schoenfeld residuals.

The Cox model results are reported as hazard ratio (HR) estimates, together with the corresponding 95% confidence intervals (CIs) and *P* value at Wald's test. An HR of 1 denotes the absence of a difference between the two arms (or the two categories of a compared covariate), whereas an HR of >1 or <1 denotes, respectively, an increased or decreased risk in a given patient group or stratum in comparison with the reference.

For each considered endpoint, a joint test of the interaction terms in the Cox's model was carried out. The interactions were also analysed using the empirical Bayesian method described by Dixon and Simon [19], which is intended to reduce the probability of false-positive results implied by the multiple testing of single interaction terms or their linear combinations. As the method requires binary covariates, the prognostic factors were categorised as follows: T stage: 1/2, 3/4; N stage: N–, N+ (1–6), N+ (>6); tumour site: middle/distal third, upper third/whole stomach. N– cases were too few to be considered as a separate category, and were therefore grouped with N+ 1–6 cases. The T-stage stratification reflected consolidated and widely applied criteria.

The computations were made using SAS™ software [20]. The Bayesian analyses were made using the SAS™ macro kindly supplied by D. O. Dixon and R. Simon.

Results

Two hundred and seventy-four patients were randomised: three (two in the treatment arm and one in the control arm) could not be included in the analysis because they were lost to follow-up soon after randomisation.

The trial flow chart is shown in Figure 1. Eleven patients (eight in the control and three in the treatment arm) refused to accept their study arm assignment. The median duration of the follow-up was 66 months (range 2–83), with all of the patients being monitored for at least 3 years or until death. Three patients in each arm were lost during the follow-up.

Table 1 shows the main characteristics of the 271 evaluated subjects (135 in the treatment arm and 136 in the control group); the two arms were well balanced. A large proportion of cases (78%) had 15 or more resected nodes, with a median of 25 (range 2–87) per patient. It should be noted that the eligibility criteria required at least second-level pathological node, but only one case reported two resected nodes. This means that most of the patients would be classified as having undergone a D2 lymphadenectomy according to the latest TNM (tumour–node–metastasis) stage classification [22].

Of the randomised patients, 26 (10%) had T1; 102 (38%) T2; 136 (50%) T3 and seven (3%) T4; 244 (90%) had nodal metastases, of whom 144 (59%) were N+ (1–6) and 100 (41%) N+ (>6). There were 123 N+ patients in the treatment group (91%) and 121 in the control group (89%).

Three of the patients allocated to the treatment arm refused chemotherapy from the very beginning, 10 (7%) received one or two courses, five received three courses and 117 (87%) completed the protocol programme. The reasons for not completing the programme were adverse events in seven cases, treatment-related deaths in two, disease relapse during chemotherapy in two, and a refusal to continue in four cases. Of the 132 patients who started chemotherapy, 21 required a dose reduction in etoposide, 15 a reduction in adriamycin and 17 a reduction in cisplatin; the FU dose was reduced in 25 patients. Full-dose chemotherapy was given to >80% of the patients receiving each cycle.

Treatment was started within 21 days of surgery in eight cases, between 22 and 42 days in 91 cases, and after 43 days in 30 cases; no information is available about the date of the first cycle of chemotherapy for three patients.

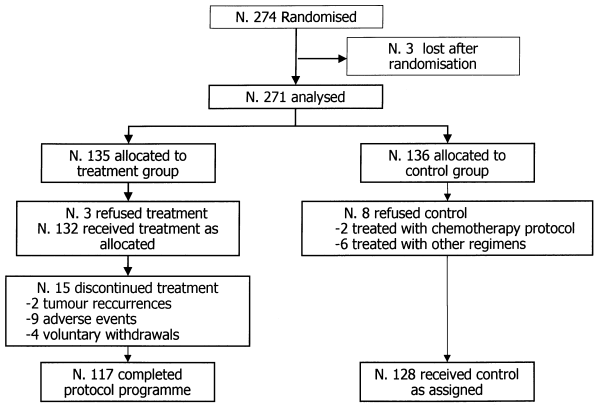

Figure 1. Study flow chart.

Table 1. Main patient characteristics

	Treatment		Control	
	No. of patients (135)	%	No. of patients (136)	%
Median age (range)	57 (23–70)		57 (31–70)	
Male/female	81/54	59/39	93/43	68/31
PS ECOG scale				
0–1	101–29	74–21	97–32	71–23
2–missing	5	4	2–5	1–4
Primary localisation				
Upper third	19	14	25	18
Middle third	30	22	30	22
Lower third	83	61	78	57
Whole stomach	3	2	3	2
Primary tumour stage[a]				
T1/2 N+ (1–6)	37	27	42	30
T1/2 N+ (7–15)	23	17	13	10
T1/2 N+ (>15)	5	4	8	6
T3/4 N+ (1–6)	32	23	33	24
T3/4 N+ (7–15)	22	16	19	14
T3/4 N+ (>15)	4	3	6	4
T3/4 N0	12	9	15	11
Surgical procedures				
Sub-total gastrectomy	67	49	56	41
Total gastrectomy	62	45	71	52
Not recorded	6	4	9	6
No. of resected lymph nodes				
≤14	31	23	22	16
15–24	48	36	47	35
≥25	50	37	66	48
Not specified	5	4	2	–
Surgical complications	16	12	14	10
Time from surgery to randomisation				
≤21 days	11	8	11	8
>21 days/≤42 days	99	72	102	74
>42 days/≤60 days	25	18	23	17

[a]International Union Against Cancer TNM (TNM classification 1997).

The first events observed during the follow-up are shown in Table 2. Of the 271 patients analysed, 124 relapsed: 57 of 135 in the treatment arm and 67 of 136 in the control group. Among the relapsing patients, distant metastases were the most frequent (60%), whereas a locoregional relapse occurred in 33% and both occurred in 7%. The causes of death are also shown in Table 2.

Figures 2 and 3 show the OS and DFS curves. The 5-year OS rate was 52% in the treatment group and 48% in the control group (P = 0.869); DFS was 49% and 44% (P = 0.421). Neither of these differences are statistically significant. In the patients with N–/N+ (1–6), the 5-year OS rate was 61% in the treatment group and 60% in the control group; the corresponding figures for the patients with N+ (>6) were 42% and 22%. The Cox's model results are shown in Table 3. Significant results were obtained for T and N stage in relation to both endpoints, whereas the prognostic effect of tumour location was significant on DFS but not OS. As expected, the risk was greater in the case of widespread nodal involvement (N >6), T stage T3/4 and a tumour location in the upper third of the

Table 2. Site of first event and cause of death

	No. of events	
	Treatment (n = 135)	Control (n = 136)
Disease relapse		
Locoregional[a]	18	23
Distant	34	40
Both	5	4
Death		
Tumour related	52	58
Treatment related	2	–
Cardiovascular disease	2	–
Intercurrent disease	2	4
Second malignancy	–	1

[a]Including peritoneal carcinosis.

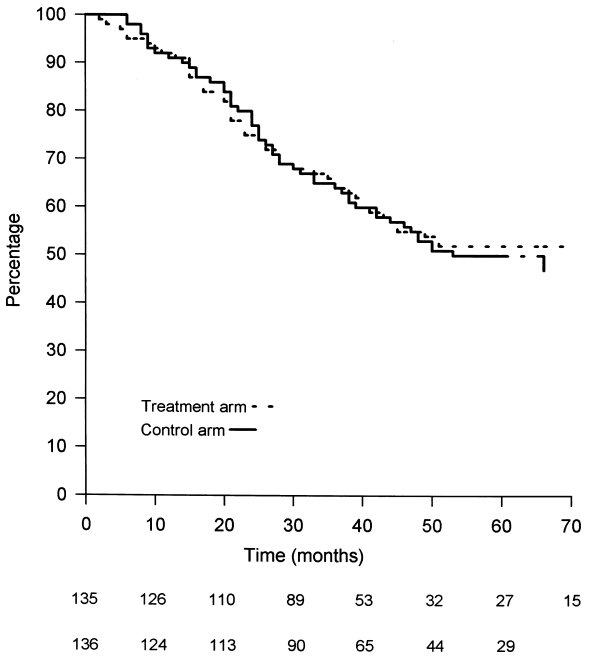

Figure 2. Intention-to-treat analysis of all randomised patients. Kaplan–Meier survival by treatment. Bottom: number of patients at risk by treatment arm.

stomach. After adjustment for T stage, N stage and tumour location, the Cox's HR estimates for the treated patients compared with controls were 0.93 (95% CI 0.65–1.34; P = 0.704) for OS, and 0.83 (95% CI 0.59–1.17; P = 0.296) for DFS. These figures indicate a relative risk reduction in the patients receiving adjuvant therapy of ~7% for OS and 17% for DFS, but univariate analysis showed that this reduction is not statistically significant.

The results of the Bayesian analysis of the interactions between the treatment and the considered covariates are shown

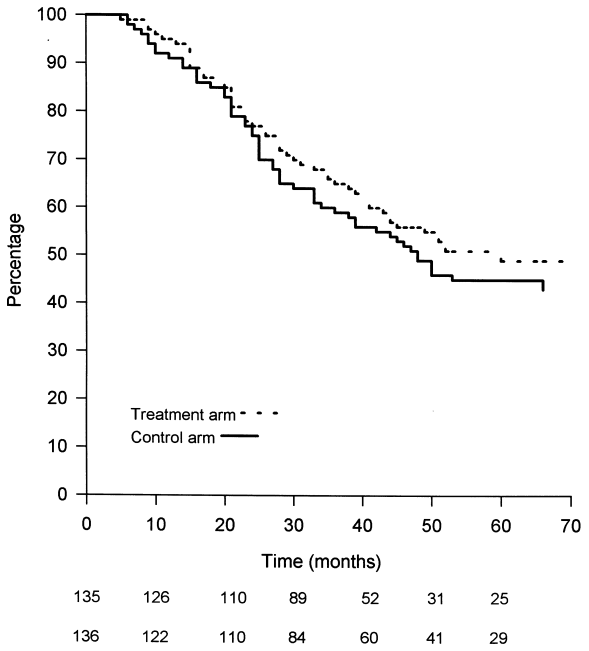

Figure 3. Kaplan–Meier DFS by treatment arm. Bottom: number of patients at risk by treatment arm.

in Table 4 for OS and Table 5 for DFS. The patient categories that seemed to benefit more from adjuvant treatment were those characterised by a tumour location in the middle/distant third of the stomach, a small tumour size (pT1/pT2), or >6 metastatic nodes. However, the joint test of the interactions failed to yield significant results for either OS (P = 0.072) or DFS (P = 0.089).

The Kaplan–Meier overall and event-free survival rates by N stage and treatment group are shown in Figures 4 and 5.

Toxicity

The toxic effects are listed in Table 6. EAP treatment induced grade 4 leukopenia in 9% of the cases; no episodes of grade 4 neutropenia or thrombocytopenia were observed. One patient experienced an infection that required hospitalisation and specific therapy. Twenty-one patients received chemotherapy without experiencing any toxic events, whereas 11 patients had one grade 1 event, five had one grade 2 event, six had one grade 3 event and one had one grade 4 event. Gastrointestinal toxicity was mild: one patient experienced grade 4 diarrhoea and six had grade 4 vomiting. There were two treatment-related deaths due to sepsis during the myelosuppression period: one patient died 1 week after starting therapy, and the other after the second cycle given at full doses after grade 4 toxicity (protocol violation).

Discussion

The present trial was designed to detect a 15% difference in 5-year survival between the two arms, from 30% in the control

Table 3. Cox model results in terms of hazard ratio (HR), 95% confidence intervals (95% CI) and Wald's *P*

Variable	Reference category	HR	95% CI	*P*
Overall survival				
Treatment arm: adjuvant therapy	Control	0.932	0.649–1.339	0.704
T stage: T3/4	T1/2	2.347	1.636–3.368	0.014
N stage: N+ >6	N–/N+ ≤6	1.593	1.100–2.307	<0.001
Tumour site: upper third, whole	Middle, distal third	1.443	0.936–2.224	0.097
Disease-free survival				
Treatment arm: adjuvant therapy	Control	0.834	0.593–1.172	0.296
T stage: T3/4	T1/2	2.347	1.667–3.304	<0.001
N stage: N+ >6	N–/N+ ≤6	1.609	1.138–2.276	0.007
Tumour site: upper third, whole	Middle, distal third	1.562	1.038–2.351	0.033

Table 4. Effect of treatment effect on OS in different patient categories defined by tumour size, nodal status and tumour site, estimated using the Dixon and Simon Bayesian approach[a]

Stratum			HR	95% CI
T1/2			0.845	0.459–1.319
T3/4			1.038	0.689–1.652
N–/N+ ≤6			0.975	0.638–1.537
N+ >6			0.852	0.512–1.303
Middle, distal third			0.890	0.590–1.307
Upper third, whole			1.036	0.644–2.259
T1/2	N–/N+ ≤6	Middle, distal third	0.868	0.435–1.409
		Upper third, whole	0.984	0.537–2.268
	N+ >6	Middle, distal third	0.803	0.325–1.273
		Upper third, whole	0.913	0.427–1.775
T3/4	N–/N+ ≤6	Middle, distal third	1.025	0.654–1.840
		Upper third, whole	1.084	0.678–3.391
	N+ >6	Middle, distal third	0.913	0.546–1.461
		Upper third, whole	1.030	0.619–2.535

[a]Table shows the hazard ratio (HR) for treated patients versus controls and the corresponding 95% confidence intervals (95% CI) for each stratum.

arm to 45% in the treated patients, corresponding to a 40% reduction in mortality. However, analysis of the study results showed that the sequential regimen led to a 7% reduction in mortality and a 17% reduction in the rate of disease relapse rate, neither of which were statistically significant. Furthermore, 5-year OS in both groups (control 48%; treatment 52%) was significantly better than that expected on the basis of previously published data. This may be related to the fact that our patients underwent sub-total or total gastrectomy with a lymphadenectomy that was also usually extended to the extra-perigastric nodes; long-term survival after adequate surgical treatment has been reported in other studies [21–23].

The results of previous trials of adjuvant treatment in gastric cancer patients are conflicting. Most studies have failed to show any clear survival benefit in favour of adjuvant treatment over surgery alone [24–29]. However, unlike our trial, these studies were stratified by stage rather than TNM classification, and many did not define a homogeneous surgical approach or pathological quality control. In 1994, Hermans et al. reported a meta-analysis showing an estimated common odds ratio for mortality of 0.82 with a 95% CI of 0.68–0.98, corresponding to a marginally significant effect in favour of adjuvant therapy [5, 6]. Similar results were obtained in a more recent meta-analysis of non-Asian randomised trials,

Table 5. Effect of treatment on DFS in different patient categories defined by tumour size, nodal status and tumour site, estimated using the Dixon and Simon Bayesian approach[a]

Stratum			HR	95% CI
T1, T2			0.777	0.455–1.177
T3, T4			0.908	0.621–1.395
N–/N+ ≤6			0.878	0.592–1.350
N+ >6			0.771	0.477–1.150
Middle, distal third			0.801	0.550–1.154
Upper third, whole			0.922	0.591–1.952
T1/2	N–/N+ ≤6	Middle, distal third	0.795	0.436–1.254
		Upper third, whole	0.886	0.522–2.022
	N+ >6	Middle, distal third	0.737	0.325–1.139
		Upper third, whole	0.828	0.421–1.578
T3/4	N–/N+ ≤6	Middle, distal third	0.905	0.592–1.545
		Upper third, whole	0.955	0.615–2.798
	N+ >6	Middle, distal third	0.810	0.491–1.251
		Upper third, whole	0.908	0.559–2.071

[a]Table shows the hazard ratio (HR) for treated patients versus controls and the corresponding 95% confidence intervals (95% CI) for each stratum

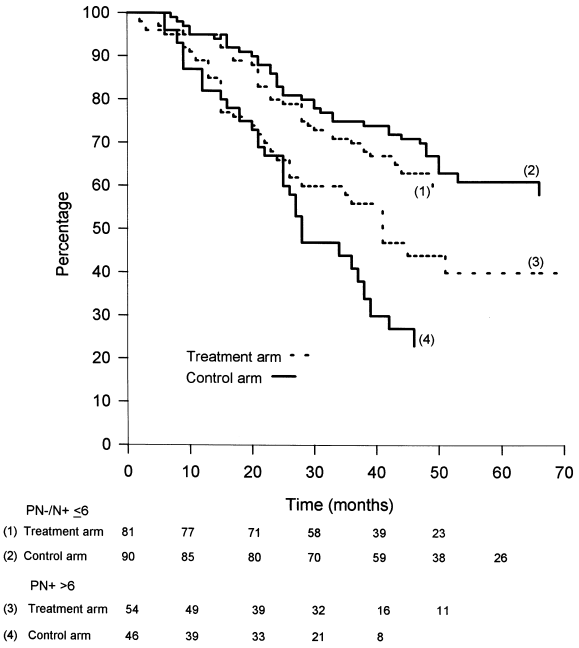

Figure 4. OS by number of involved nodes (N–/N+ <6 and N+ >6). Bottom: number of patients at risk by treatment arm.

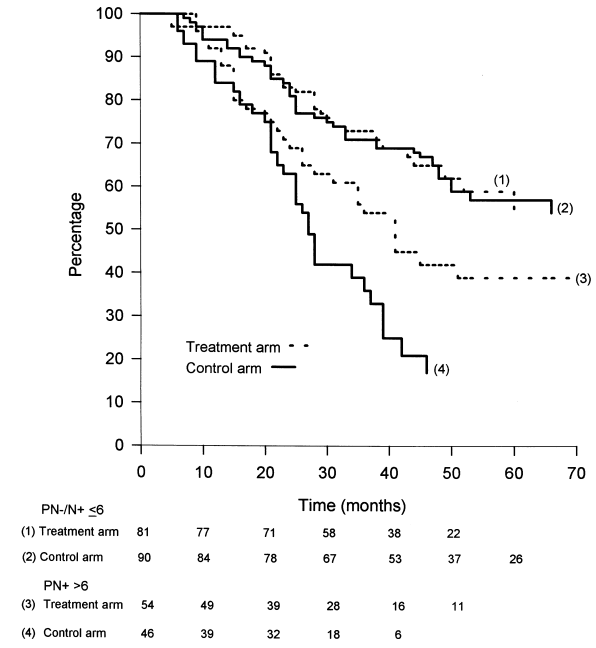

Figure 5. DFS by number of involved nodes (N–/N+ <6 and N+ >6). Bottom: number of patients at risk by treatment arm.

which showed a relative risk with adjuvant chemotherapy of 0.94 (95% CI 0.89–1.00) [7]. A third meta-analysis by an Italian group found clinically similar and highly significant results in terms of the reduction in the risk of death (HR 0.82; 95% CI 0.75–0.89; *P* <0.001) [8].

In light of the above findings, it is likely that the treatment regimen investigated in our trial is also effective, but the benefit appears to be smaller than that which the study was designed to detect, and this explains the lack of statistically significant results. A multivariate analysis was carried out in

Table 6. Side effects

Treatment	WHO grade							
	1		2		3		4	
	No.	%	No.	%	No.	%	No.	%
EAP treatment								
Leukopenia	12	9	20	15	16	12	12	9
Neutropenia	1	1	1	1	4	3	–	
Thrombocytopenia	3	3	5	4	2	2	–	
Nausea and vomiting	34	26	26	20	12	9	6	5
Diarrhoea	9	8	19	15	2	2	–	
Mucositis	12	11	7	5	10	8	2	1
FU + LV treatment[a]								
Diarrhoea	15	13	7	6	11	9	1	1
Mucositis	10	8	9	9	3	3	1	1

[a]FU, fluorouracil; LV, leucovorin.

order to assess whether patients might receive different benefits from adjuvant therapy depending on T stage, N stage or tumour location. Although this analysis also failed to reach statistical significance, it is interesting to note that in the presence of widespread nodal involvement (N+ >6), the overall survival of the patients treated with chemotherapy was better than that of the control patients (42% compared with 20%). Although this apparently encouraging result must be interpreted with caution, because it comes from a *post hoc* exploratory analysis of a small patient subgroup.

The other interesting findings of our study include the low incidence of locoregional relapses (13% in the treatment arm and 17% in the control arm), which suggests that patients undergoing D2 dissection may not benefit from adjuvant chemoradiation; the recent Intergroup 116 study has demonstrated that chemoradiation improves survival and local control in patients treated with limited surgery [29].

A second point is that our protocol treatment was well tolerated, as shown documented by the fact that full drug doses were administered in >80% of the cases. Many FU-based regimens, such as FU plus adriamycin and/or mitomycin, have been studied in clinical adjuvant trials that have found evidence of toxicity without any survival benefit [30]. Furthermore, this is the first study using a second-generation cisplatin-containing regimen in an adjuvant setting.

In conclusion, this randomised study shows a limited benefit of adjuvant chemotherapy in radically resected gastric cancer patients after adequate surgery. In such cases, more efficacious strategies are warranted, such as new drug combinations (with or without high quality radiotherapy), and research in the field of molecular markers might allow the identification of patients who are more likely to benefit from treatment.

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