

Adjuvant FOLFOX-4 in patients with radically resected gastric cancer: Tolerability and prognostic factors

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Abstract. The aim of the present study was to evaluate the toxicity and efficacy of the FOLFOX-4 regimen as adjuvant chemotherapy in patients with gastric cancer after radical surgery. Fifty-four patients (1 stage Ib, 6 stage II, 22 stage IIIa, 14 stage IIIb and 11 stage IV) received 8-12 cycles of FOLFOX-4 (oxaliplatin 85 mg/m², Day 1; leucovorin 100 mg/m² i.v., Days 1 and 2; 5-fluorouracil 400 mg/m² i.v. bolus, Days 1 and 2 and 600 mg/m² in 22 h i.v. continuous infusion, Days 1 and 2; every 14 days). Toxicity was recorded at each cycle according to the National Cancer Institute Common Toxicity Criteria. Disease-free (DFS) and overall survival (OS) were calculated according to the Kaplan-Meier method. Thirty-eight patients (70.4%) completed the prescribed number of cycles of chemotherapy. The toxicity was mild. Grade 3-4 neutropenia occurred in 57% of patients, thrombocytopenia and anemia in 2% of cases. Peripheral neuropathy was experienced by 46% of the patients (grade 4 in 2% of cases). Five patients experienced grade 3 gastrointestinal toxicity. After a median follow-up of 33.1 months, 17 patients relapsed and 17 succumbed to the disease. The mean observed DFS and OS were 49.7 months (range 40.7-58.8) and 57.9 months (range 49.6-66.2), respectively. At univariate analysis, females and patients who had received <8 cycles of chemotherapy had a significantly worse probability of DFS and OS. The Cox model showed gender to be independent of the factors affecting DFS. Adjuvant FOLFOX-4 is feasible and well-tolerated in patients radically resected for gastric cancer. Receiving <4 months of adjuvant FOLFOX-4 could be detrimental to prognosis.

Introduction

Gastric cancer is the fourth most common malignancy and the second leading cause of cancer-related death in the world (1). Incidence rates vary across continents, being higher in Asia, Central and South America and Europe (1). At least in developed countries, both incidence and death rates have been constantly decreasing in the last 50 years. Furthermore, according to the Surveillance, Epidemiology and End Results database, the 5-year survival for all gastric cancer patients treated in the US increased by 50% from 1975 to 2003 (from 16 to 24%). However, in 2008 21,500 new diagnoses of gastric cancer were estimated in the US (2) and 12,600 in Italy (<http://www.tumori.net/stime>).

As expected, patients with localized disease have a higher 5-year survival rate (82%) compared to patients with regional (24%) or distant metastases (3%) (2). In Western countries, only 25-40% of the patients have localized disease at diagnosis, whereas such a subgroup is much larger in Japan and in countries that adopt aggressive screening programs.

Surgical resection of the primary tumor and regional lymph nodes is the fundamental treatment for gastric cancer. Although extensive lymphadenectomy (D2 resection) is the standard procedure in Japan since the 1980's (3), four prospective randomized trials that assessed the role of D1 (peri-gastric lymph nodes along the lesser and the greater curvature) vs. D2 (including lymph nodes along the left gastric artery, the common hepatic artery, the celiac trunk, the splenic hilum and the splenic artery) resection in the management of gastric cancer failed to demonstrate any advantage in terms of survival in favor of extended surgery (4-7).

In Western countries, more than 50% of the radically resected patients experience local or distant recurrence, thus prompting the evaluation of the best surgical procedure and the best complementary strategy to surgery. The role of chemotherapy as adjuvant treatment has been controversial for a long time. Several randomized trials run in Western countries during the '80s and '90s failed to demonstrate a clear survival benefit for post-operative chemotherapy as compared to surgery alone, mostly because they were underpowered and had a small sample size (8-21).

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A great number of meta-analyses has been performed, including published trials comparing adjuvant chemotherapy to surgery alone (22-33). Most of them have suggested a small survival advantage for adjuvant treatment, but such data were considered unconvincing due to the different selection of the considered trials, the inconsistent surgical and medical treatment and, in some cases, the questionable methodology. Moreover, evidence from large, well-designed, randomized trials is more conclusive and easier to translate into clinical practice than suggestions from meta-analyses of small, under-powered trials. Thus, in the 1990's the effort of researchers worldwide was focused on large-sized, sufficiently powered trials designed to evaluate the benefit of adjuvant therapy over surgery alone.

In recent years, three pivotal studies carried out in the US, Europe and Japan, respectively, demonstrated the efficacy on survival of three different strategies of adjuvant treatment. The INT-0116 trial showed that post-operative chemoradiotherapy with 5-fluorouracil + leucovorin (5FU-LV) prolonged the survival of patients radically resected for adenocarcinoma of the stomach or gastroesophageal junction (34). The MAGIC trial demonstrated an improvement in disease-free survival (DFS) and overall survival (OS) when 3 cycles of ECF (epirubicin, cisplatin, 5FU) were administered before and after surgery in patients with gastric or lower esophageal cancer (35). The ACTS-GC group in Japan found that 1 year of treatment with the oral fluoropyrimidine S-1 prolonged the survival of Asian patients who had undergone a D2 dissection for stage II-III gastric cancer (36).

Cisplatin and 5FU are the most commonly used drugs for gastric cancer and are considered milestones for chemotherapy both in metastatic and in an adjuvant setting. However, the best regimen for adjuvant treatment remains under evaluation, as the best duration is undefined. Oxaliplatin was recently demonstrated to be as active as cisplatin in metastatic gastric disease (37), less toxic and more manageable. Thus, it may replace cisplatin in multi-drug regimens.

The association of 5FU-LV and oxaliplatin is a very active regimen in metastatic colorectal cancer and is the standard adjuvant chemotherapy for stage III colon cancer, since it demonstrated clear survival advantages over 5FU-LV alone (38,39).

Based on this evidence, patients with stage II-III-IV gastric cancer who had undergone radical surgery were treated with adjuvant FOLFOX-4; here, we report our experience.

Materials and methods

Fifty-four patients referred to our institution between October 2002 and June 2008 were enrolled for the present study. All patients, after radical surgery for gastric cancer, received adjuvant FOLFOX-4 (oxaliplatin 85 mg/m², Day 1; LV 100 mg/m² i.v., Days 1 and 2; 5FU 400 mg/m² i.v. bolus, Days 1 and 2; 5FU 600 mg/m² in 22 h i.v. continuous infusion, Days 1 and 2; every 14 days) for 8 or 12 cycles.

Patients were monitored at each cycle of chemotherapy by history, physical examination and complete biochemistry; blood count was performed once a week during chemotherapy. Toxicity was graded according to the National Cancer Institute Common Toxicity Criteria, version 3.0.

Table I. Patients and tumor characteristics.

	n	Percentage
Gender		
Male	41	75.9
Female	13	24.1
Age (median/range)	61	33-77
Primary tumour site		
Cardia	4	7.4
Fundus	3	5.6
Body	33	61.1
Antrum/pylorus	12	22.2
Gastric stump	2	3.7
Gastrectomy		
Total	30	55.6
Partial	24	44.4
Basal hemoglobin (n=51)		
<11 mg/ml	14	27.5
≥11 mg/ml	37	72.5

Staging procedures performed prior to the beginning of the treatment included blood cell count, biochemistry, blood CEA level and thorax-abdomen-pelvis CT scan. Follow-up visits were scheduled every 4 months during the first year and every 6 months thereafter. Esophagogastroduodenoscopy and thorax-abdomen-pelvis CT scan were performed yearly, and hematology, biochemistry and blood CEA levels were repeated every 4 or 6 months. Bone scan, PET/CT scan or magnetic resonance were executed only when clinically required.

DFS was defined as the time elapsed between the date of surgery and the occurrence of local relapse, distant metastases or death without recurrence; OS was defined as the time elapsed between the date of surgery and the date of death. Estimation of likelihood events for relapse or death was calculated according to the Kaplan-Meier method (40). Statistical differences between curves were calculated using the log-rank test (41). Multivariate analysis was performed using the Cox proportional hazard model (42) to estimate the hazard ratio and relative 95% confidence intervals (95% CI) for each covariate. A p-value of ≤0.05 was considered statistically significant. Statistical analysis was performed with SPSS (version 16.0; SPSS, Inc., Chicago, IL, USA).

Results

The main patient characteristics are reported in Table I. They were mostly male, with a median age of 61 years. More than half of the patients received a total gastrectomy. The median value of pre-chemotherapy hemoglobin was 12.1 g/dl in men and 11.7 g/dl in women. Thirteen patients started adjuvant chemotherapy having <11 g/dl of hemoglobin.

The primary tumor was located mostly in the mid-lower part of the stomach; ~75% were poorly differentiated. The median number of the examined lymph nodes was 19 (range 2-40); 92.6% of the patients had positive lymph nodes and

Table II. Pathological characteristics of the primary tumor.

	n	Percentage
T primary ^a		
1	1	1.8
2	5	9.3
3	38	70.4
4	10	18.5
N primary ^a		
N-	4	7.4
N1	31	57.4
N2	14	25.9
N3	5	9.3
UICC-TNM stage ^a		
Ib	1	1.8
II	6	11.1
IIIa	22	40.7
IIIb	14	25.9
IV ^b	11	20.4
Examined lymph nodes		
≤15	23	42.6
>15	31	57.4
Histology		
Adenocarcinoma	44	81.5
Signet ring cell	5	9.3
Mucinous adenocarcinoma	4	7.4
Other	1	1.8
Grading		
Well differentiated	6	11.1
Intermediate	7	13.0
Poorly differentiated	41	75.9

^aUICC-TNM classification, 6th edition, 2002; ^bT4 or N3.

87% of the cases were stage III or IV (T4 primary or N3 nodal status). Detailed pathological tumor characteristics are listed in Table II.

The median time elapsed from surgery to the commencement of adjuvant chemotherapy was 6 weeks (range 3-14); 14 (25.9%) patients started chemotherapy ≥8 weeks from surgery.

A total of 463 cycles of chemotherapy were administered; the median number of the received cycles of FOLFOX-4 was 8 (range 1-12). Twenty-two and 16 patients completed the 8 or 12 prescribed cycles, respectively; 3 patients progressed during chemotherapy, 1 patient died 14 days after the 4th cycle of chemotherapy, in 7 cases FOLFOX-4 was stopped due to toxicity (3 due to hematological, 1 for severe mucositis and 3 due to both hematological and gastrointestinal adverse events) and 5 patients refused to complete the scheduled number of cycles.

Overall chemotherapy was well tolerated, and registered adverse events were comparable to those reported with adjuvant FOLFOX-4 in colorectal cancer. Grade 3-4 hematological toxicity was observed in 57% (neutropenia), 2% (thrombocytopenia) and 2% (anemia) of the patients. One patient received 5 blood transfusions because of grade 4 anemia. Peripheral neuropathy was experienced by 46% of the patients, but it was grade 4 only in 2% of the cases. Grade 3 gastrointestinal toxicity occurred only in 5 cases. Table III presents in detail the worse adverse events experienced per patient.

After a median follow-up of 33.1 months (range 3.5-79.4) from surgery, 17 (31.5%) patients relapsed (4 peritoneal carcinoma, 2 liver, 2 perianastomotic, 2 lung, 1 suprarenal gland and 6 multiple sites) and 17 (31.5%) succumbed to the disease. The mean observed DFS and OS were 49.7 months (range 40.7-58.8) and 57.9 months (range 49.6-66.2), respectively. The estimated 3-year DFS and 3-year OS were 57 and 67%, respectively. The causes of death were metastatic disease in 12 cases, cardiovascular event in 4 and sudden death in 1 case. The median number of days elapsed from the end of chemotherapy and the date of the 5 deaths without recurrence was 428 days (range 14-1,104); 2 patients died of myocardial infarction and icus, respectively, within 60 days from the end of chemotherapy.

After relapse, 11 (64.7%) patients received further treatment (chemotherapy or radiotherapy); 4 patients received 2 or more lines of chemotherapy for metastatic disease.

Table III. Worse experienced toxicity among the 54 treated patients.

Adverse event	G0		G1		G2		G3		G4	
	n	%	n	%	n	%	n	%	n	%
Nausea	33	61.1	20	37.0	1	1.8	-	-	-	-
Vomiting	39	72.2	9	16.7	4	7.4	2	3.7	-	-
Diarrhea	27	50.0	20	37.0	5	9.3	2	3.7	-	-
Stomatitis	43	79.6	6	11.1	4	7.4	1	1.8	-	-
Neutropenia	15	27.8	5	9.3	3	5.6	21	38.9	10	18.5
Anemia	12	22.2	28	51.8	13	24.1	-	-	1	1.8
Thrombocytopenia	18	33.3	31	57.4	4	7.4	1	1.8	-	-
Peripheral neuropathy	29	53.7	21	38.9	3	5.6	-	-	1	1.8
Asthenia	38	70.4	12	22.2	3	5.6	1	1.8	-	-

Table IV. Univariate analysis.

Variable	Probability of DFS (%) ^a	P-value	Probability of OS (%) ^a	P-value
Age, in years		0.20		0.10
≤65	61.1		75.0	
>65	50.0		55.6	
Gender		0.01		0.02
Male	65.8		78.1	
Female	30.7		38.5	
Primary tumor		0.80		0.60
pT1	100.0		100.0	
pT2	60.0		60.0	
pT3	57.9		71.1	
pT4	50.0		60.0	
Nodal status		0.40		0.09
pN0	75.0		100.0	
pN1	64.5		74.2	
pN2	42.9		57.1	
pN3	40.0		40.0	
UICC-TNM stage		0.50		0.10
I-II	71.4		85.7	
III	58.3		72.2	
IV	45.4		45.5	
No. of examined nodes		0.08		0.20
≤15	69.6		73.9	
>15	48.4		64.5	
Grading		0.50		0.90
G1-G2	69.2		69.2	
G3	53.7		68.2	
Basal hemoglobin		0.90		0.90
<11 mg/ml	46.1		61.5	
≥11 mg/ml	53.0		71.1	
Interval surgery-chemotherapy		0.90		0.90
≤8 weeks	55.5		65.0	
>8 weeks	64.3		78.6	
No. of received cycles of CT		0.05		0.007
≥8	63.4		78.1	
<8	38.5		38.5	

^aCalculated for the entire period of observation.

Upon univariate analysis (Table IV), females and patients who received <8 cycles of adjuvant chemotherapy had a significantly worse probability of DFS and OS. Kaplan-Meier curves for DFS and OS, according to delivered cycles of FOLFOX-4, are depicted in Fig. 1A and B. The interval between surgery and the initiation of adjuvant treatment did not affect the long-term outcome.

Upon multivariate analysis, in a model including age, gender and TNM stage as adjusting covariates, females showed a 2.6-fold risk of recurrence and death ($p=0.04$). The risk of death was significantly affected by age ($HR=4.1$, $p=0.01$) and the number of delivered cycles of chemotherapy ($HR=2.78$, $p=0.04$). However, in a model excluding the patients

who died for causes other than the tumor, age lost significance (Table V). The interactions gender-stage and gender-number of delivered cycles were not significant in the Cox model.

Discussion

The optimum regimen and the optimal duration of adjuvant or neo-adjuvant chemotherapy after radical surgery of patients with gastric cancer remains in debate. The three pivotal trials demonstrated that 5 cycles of 5FU-FA + radiotherapy (34), or 1 year of oral fluoropyrimidine (36), or 6 cycles of poly-chemotherapy (ECF) (35), produce survival benefit over surgery alone.

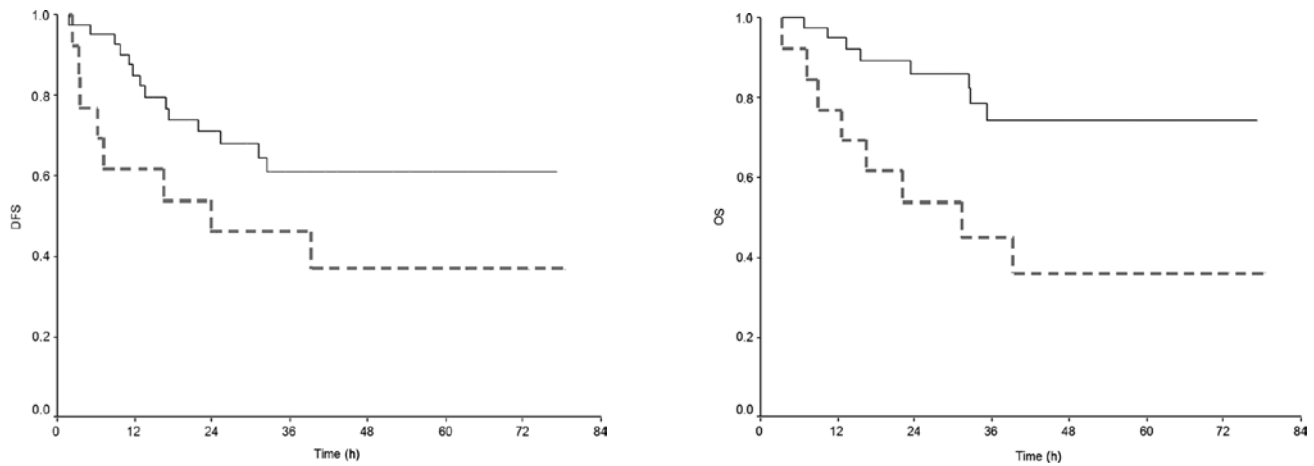


Figure 1. Disease-free (DFS) (A) and overall survival (OS) (B) according to the number of delivered cycles of adjuvant chemotherapy (≥ 8 cycles, solid line; < 8 cycles, dashed line).

Table V. Multivariate analysis.

Variable	Disease-free survival		Overall survival	
	Hazard ratio ^a	P-value (95% CI)	Hazard ratio ^a	P-value (95% CI)
Age, in years		0.10		0.01 ^b
≤ 65	1 ^c		1 ^c	
> 65	2.0	(0.8-5.2)	4.1 ^b	(1.3-12.6) ^b
Gender		0.04		0.04
Male	1 ^c		1 ^c	
Female	2.6	(1.1-6.4)	2.6 ^b	(1.0-7.0)
UICC-TNM stage		0.60		0.07
I-II	1 ^c		1 ^c	
III	1.6	(0.3-7.3)	2.3	(0.3-19.2)
IV	2.3	(0.4-13.8)	8.5	(0.8-90.5)
No. of examined nodes		0.10		0.35
$N^+ \leq 15$	1 ^c		1 ^c	
$N^+ > 15$	1.9	(0.8-4.7)	1.5	(0.6-4.2)
No. of received cycles of CT		0.20		0.04
≥ 8	1 ^c		1 ^c	
< 8	1.7	(0.7-4.2)	2.78	(1.1-7.1)

^aCox model including age, gender, IUCC TNM stage as adjusting covariates. ^bIn a model excluding deaths for causes other than the tumor, HR for age = 2.3 (95% CI, 0.6-8.3), $p=0.2$. ^cReference category. CT, chemotherapy.

Evidence suggests that the duration of adjuvant chemotherapy is considered an independent prognostic factor for DFS (43) or mortality risk (44) in colon and ovarian cancer (45). Our analysis suggested that a short duration of adjuvant chemotherapy (< 8 cycles) is detrimental for DFS and OS of patients surgically operated on for gastric cancer.

The significance of the timing of the commencement of adjuvant chemotherapy in many solid tumors remains controversial. In colon cancer, a German study found a positive effect of early (< 27 days) administration of adjuvant chemotherapy on DFS, but not on survival (46). Chau *et al* (47) reported a significant OS advantage for patients who started adjuvant chemotherapy within 8 weeks from surgery; this latter

finding was confirmed by Hershman *et al* in elderly patients (> 65 years); however, disease-specific mortality was found to significantly worsen only after a longer than 3-month interval (48). In breast cancer, two large retrospective analyses (49,50) failed to demonstrate any effect of early initiation of adjuvant chemotherapy on survival. However, starting adjuvant chemotherapy within 21 days from surgery has been suggested to be favorable for pre-menopausal patients with receptor-negative tumors (51). One of the reasons why some oncologists prefer pre-operative chemotherapy is that surgery for gastric cancer is demanding, post-operative complications are frequent and convalescence is often long-lasting, not allowing for the timely commencement of chemotherapy. Most trials have 6 (36) or

8 weeks (19-21,34) from surgery as eligibility criteria for entry, thus they do not include patients who cannot be randomized within this time interval. Our results suggested that starting adjuvant chemotherapy more than 2 months after surgery does not affect long-term outcome and does not nullify the effect of adjuvant chemotherapy following radical surgery.

Patients who receive radical resection for gastric cancer usually have low values of hemoglobin due to pre-operative bleeding, prolonged fasting and impaired iron absorption. Anemia is frequently reported as a negative predictor of response to chemoradiotherapy (52-54). In early gastric cancer, pre-operative hemoglobin of less than 12 g/dl has been associated with poorer survival (55), and in a metastatic setting, hemoglobin of less than 10 g/dl has been correlated with worse response rate and increased risk of death (56). In our patients, starting adjuvant chemotherapy with hemoglobin values of less than 11.0 g/dl did not affect the number of delivered cycles of FOLFOX-4 or long-term prognosis. However, basal hemoglobin of less than 11 g/dl was associated with increased hematological toxicity, since 53.8% of these patients experienced grade ≥ 2 anemia during chemotherapy.

Although the combination of 5FU and oxaliplatin has been extensively studied in metastatic gastric cancer (57), there are a few reports regarding the adjuvant setting mainly in Chinese populations (58,59). To our knowledge, our series is the largest in the literature to address the feasibility and tolerability of FOLFOX-4 regimen in Caucasian patients surgically operated on for gastric cancer. Grade 3-4 hematological toxicity registered in our patients is comparable to that reported in the Mosaic study (38) in patients operated on for colon cancer, neutropenia being the most frequent adverse event. Gastrointestinal tolerability was good, since less than 4% of the patients experienced grade 3 vomiting or diarrhea. Severe peripheral neuropathy occurred in 1 patient, much less than reported in the Mosaic study (12.4%), probably because the median number of delivered cycles of chemotherapy was lower (8 vs. 12 cycles).

The prognostic role of gender in solid tumors is questionable and is often attributed to chance. However, in gastric cancer some experimental evidence suggests that estrogen-positive tumors are more frequent in women and more aggressive (60,61). The reason for such behavior remains poorly understood; however, it can be explained by a cross-talk between estrogen receptors and epidermal growth factor receptor pathways in gastric cancer cells (62). In our study, we confirmed that women have a significantly worse prognosis and that the increased risk of recurrence at multivariate analysis is independent from other prognostic factors (the interactions gender-stage and gender-number of delivered cycles were not significant). Thus, it may be speculated that it is due to intrinsic growth characteristics of the tumor cells.

In conclusion, our experience suggests that FOLFOX-4 is a feasible and manageable regimen as adjuvant treatment and represents a valid option when a platinum + fluoropyrimidine scheme is indicated for radically resected gastric cancer patients. Moreover, although demonstrated in a limited number of patients, the present study suggests that at least 4 months of adjuvant chemotherapy should be administered to obtain the most beneficial effect and that a short interval between surgery and the commencement of adjuvant chemotherapy is

not fundamental for the effect of adjuvant chemotherapy on prognosis.

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