RESEARCH ARTICLE

Impact of Adjuvant Chemotherapy Cycles on Prognosis of Resectable Stomach Cancer: A Retrospective Analysis

Wen-Ying Zhang[1&], Wen-Jun Zhang[2&], Yu Bai[1], Hai-Hua Yuan[3], Feng Liu[3], Jun Gao[1], Yan-Fang Gong[1], Bin Jiang[3*]

Abstract

Aims: The aim of this study was to investigate the effects of adjuvant chemotherapy cycles on the prognosis of patients with post-operative stomach cancer through retrospective analysis. Methods: A total of 128 patients with gastric cancer who underwent gastrectomy, followed by adjuvant chemotherapy consisting of epirubicin, cisplatin or oxaliplatin, leucovorin, and 5-fluorouracil, according to a defined schedule, were divided into three groups according to the number of chemotherapy cycles: Group I (<6 cycles); Group II (6 cycles); and Group III (>6 cycles). Results: The 5-year overall survival (OS) was 20.8% in Group I, 45.0% in Group II, and 42.9% in Group III, with a median follow-up of 43 months. The 5-year relapse-free survival (RFS) was 15.1% in Group I, 40% in Group II, and 40% in Group III. The OS and RFS in Groups II and III were significantly better than in Group I (OS, p = 0.002 and p=0.003; RFS, P<0.001 and P=0.002). There was no difference in OS (p = 0.970) or in RFS (p = 0.722) between Groups II and III. Multivariate Cox hazard analysis determined that the number of adjuvant chemotherapy cycles was an independent factor that influenced OS and RFS. Conclusion: Six cycles of adjuvant chemotherapy gave encouraging outcomes in patients with resectable gastric cancer. Further prospective randomized controlled investigations are warranted in a multi-center setting.

Keywords: Adjuvant chemotherapy - stomach cancer - gastrectomy

Asian Pacific J Cancer Prev, **14 (1)**, 381-386

Introduction

Stomach cancer is one of the leading causes of cancer-related deaths in the world, especially in Eastern Asia, with 736,000 cases per year (Jemal et al., 2011). Although surgery is the first-line treatment for stomach cancer, the recurrence rate is high and the survival rates remain low, even after extended surgery (Degiuli et al., 2006; Oba, 2009). In order to prevent relapse and improve overall response rates, adjuvant therapies have been administered to patients with stomach cancer after radical resection, including adjuvant chemotherapy and chemoradiotherapy (Macdonald et al., 2001; Lim et al., 2005). Adjuvant chemotherapy is recommended as the standard of care in Japan (Sakuramoto et al., 2007), and chemoradiotherapy or perioperative chemotherapy is first-line in the Western world (Cunningham et al., 2006; Okines et al., 2010). Recent studies have shown that adjuvant chemotherapy after radical resection improves overall survival and disease-free survival of gastric cancer patients (Sakuramoto et al., 2007; Zhao et al., 2008; Paoletti et al., 2010). The Global Advanced/Adjuvant Stomach Tumor Research International Collaboration (GASTRIC) group published results of meta-analysis of 17 randomized controlled trials of adjuvant chemotherapy in gastric cancer. The study demonstrated that adjuvant chemotherapy produced a modest but statistically significant benefit associated with 5-fluorouracil based adjuvant chemotherapy after radical gastrectomy of gastric cancers (Paoletti et al., 2010). Increased acceptance of adjuvant chemotherapy raises new questions about the optimum number of cycles of adjuvant chemotherapy for patients with operable gastric cancer. To date, no prospective studies have been implemented to compare different adjuvant chemotherapy cycles on the prognosis of resectable stomach cancer. The purpose of this study was to retrospectively review our experience in regard to the impact of adjuvant chemotherapy cycles on the prognosis of postoperative stomach cancer.

Materials and Methods

Patients

In this retrospective study, patients with stomach cancer undergoing radical gastrectomy were screened between January 2000 and December 2006 at the Department of

*[1]Department of Gastroenterology, [2]Department of Gerontology, Changhai Hospital, Second Military Medical University, [3]Department of Oncology, No. 3 People's Hospital, School of Medicine, Shanghai Jiaotong University, Shanghai, China [&]Equal contributors *For correspondence: bin_jiang@yeah.net*

Gastroenterology of Changhai Hospital (Shanghai, China). Together, 128 patients were enrolled in accordance with the following inclusion criteria: complete medical files, D1 gastrectomy and R0 resection, histologically confirmed gastric adenocarcinoma, a minimum performance status of 2 according to Eastern Cooperative Oncology Group (ECOG) (Oken et al., 1982), which includes normal organ function as well as normal bone marrow, liver, kidney, and heart status. Each patient was restaged retrospectively using the American Joint Committee on Cancer staging system revised in 2010 (7th edition) (Kim et al., 2012). Patients that received prior radiotherapy or targeted therapy were excluded. Toxicity was graded according to the World Health Organization (WHO) scoring system. Due to the retrospective nature of the study, informed consent was waived. However, the study was approved by the Ethics committee of Changhai Hospital, Shanghai, China.

Adjuvant chemotherapy

Patients with histologically confirmed gastric adenocarcinoma were divided into three groups according to different cycles of adjuvant chemotherapy: Group I (<6 cycles), Group II (6 cycles) and Group III (>6 cycles, maximum 10 cycles). Systemic adjuvant chemotherapy was given in 3 or 4 weeks after curative resection of stomach cancer. Regimens and dose schedules of adjuvant chemotherapy were epirubicin (50 mg/m^2, a short i.v. infusion given on day 1), cisplatin (60 mg/m^2) or oxaliplatin (130 mg/m^2, i.v. infusion given on day 1), leucovorin (200 mg/m^2, i.v. infusion given on days 1–5) plus 5-fluorouracil (450 mg/m^2/day, continuous infusion, given on days 1–5). The cycle was repeated every 3 weeks. Intravenous hydration was administered before and after receiving cisplatin. Antiemetic prophylaxis therapy was administered as needed. Drug doses were modified in response to toxicity.

Follow-up assessments

Patients were followed-up at the end of the planned systemic adjuvant chemotherapy. The follow-up program consisted of history, physical examination, a complete blood count, liver or renal function, and tumor markers, including CEA and CA19-9, chest computed tomography (CT), abdominopelvic CT, and gastroscopy. These evaluations were performed every 3 months for 2 years, and every 6 months thereafter for 5 years.

Definition of relapse and end points

Relapse included local, regional relapse, and distant metastasis. The definition of relapse has been previously stated (Dikken et al., 2010). In short, local relapse is defined as relapse in the gastric bed, regional gastric lymph nodes, or at the anastomosis. Regional relapse involves

Table 1. Patient Characteristics

	Cycles of chemotherapy						
	<6 cycles		=6 cycles		>6 cycles		
Characteristics	n	%	n	%	n	%	P
Total	53	100	40	100	35	100	
Sex							0.959
Male	34	64.2	25	62.5	23	65.7	
Female	19	35.8	15	37.5	12	34.3	
Age, years							0.012
<60	24	45.3	23	57.4	27	77.1	
≥60	29	54.7	17	42.5	8	22.9	
Histological Grade							0.01
Well/moderately differentiated	24	45.3	14	35.0	5	14.3	
Poor / Undifferentiated	29	54.7	26	65.0	30	85.7	
Histological type							0.304
Mucinous adenocarcinoma	5	9.4	2	5.0	6	17.1	
Signet ring cell carcinoma	4	7.5	1	2.5	3	8.6	
Other adenocarcinoma	44	83.0	37	92.5	26	74.3	
T stage							0.119
T2	7	13.2	9	22.5	8	22.9	
T3	42	79.2	28	70.0	23	65.7	
T4 [a]	2	3.8	0	0.0	4	11.4	
T4 [b]	2	3.8	3	7.5	0	0.0	
N stage							0.374
N0	13	24.5	14	35.0	7	10.0	
N1	12	22.6	6	15.0	3	8.6	
N2	13	24.5	11	27.5	12	34.3	
N3	15	28.3	9	22.5	13	37.1	
Type of gastrectomy							0.395
Subtotal gastrectomy	44	83.0	29	72.5	39	82.9	
Total gastrectomy	9	17.0	11	27.5	6	17.1	
Location							0.243
proximal 1/3	6	11.3	9	22.5	2	5.7	
Middle 1/3	32	60.4	22	55.0	25	71.4	
distal 1/3	15	28.3	9	22.5	8	22.9	

Table 2. Assessment of Prognostic Factors Based on Multivariate Analyses

Variable	OS		RFS	
	HR*(95%CI)	P	HR*(95%CI)	P
Univariate analysis				
Sex	1.368 (0.886-2.112)	0.157	1.379 (0.904-2.102)	0.136
Age	1.149 (0.747-1.768)	0.527	1.183 (0.780-1.793)	0.429
Histological Grade	0.956 (0.602-1.519)	0.850	0.983 (0.629-1.536)	0.939
Histological type	0.927 (0.678-1.266)	0.633	0.991 (0.726-1.354)	0.957
T stage	1.701 (1.112-2.604)	0.014	1.627 (1.084-2.442)	0.019
N stage	1.391 (1.114-1.691)	0.001	1.343 (1.115-1.618)	0.002
Type of gastrectomy	1.518 (0.918-2.511)	0.104	1.350 (0.821-2.222)	0.237
Location	0.818 (0.573-1.168)	0.270	0.862 (0.603-1.233)	0.416
Cycles of chemotherapy	0.649 (0.490-0.861)	0.003	0.611 (0.466-0.801)	0.000
Multivariate analysis				
T stage	1.352 (0.849-2.152)	0.204	1.288 (0.828-2.005)	0.261
N stage	1.429 (1.159-1.761)	0.001	1.380 (1.130-1.686)	0.002
Cycles of chemotherapy	0.600 (0.454-0.793)	0.000	0.576 (0.442-0.752)	0.000

*HR, hazard ratio

peritoneal carcinomatosis. Distant metastasis is defined as metastasis to systemic organs such as the liver, lung, bone, brain, and ovaries. Recurrence was confirmed through imaging including CT, magnetic resonance imaging (MRI), positron emission tomography-CT (PET-CT), biopsies, or cytology. Overall survival (OS) was calculated from the time of surgery to death for any reason, or to the last follow-up that ended without death (censored). Relapse-free survival (RFS) was measured from the day of surgery to gastric cancer relapse, or the last day at which the patient was still free of recurrence (censored).

Statistical Analysis

All statistical analyses were performed using SPSS for Windows version 17.0 (SPSS, Inc., Chicago, IL). Comparison of categorical variables was analyzed using Pearson chi-squared test. OS or RFS curves were plotted using the Kaplan–Meier method. Comparisons of different groups were performed using the log-rank test. Prognostic factors were assessed by the Cox proportional hazards method. All P values were two-sided and statistical significance was defined as $P < 0.05$.

Results

Patient Characteristics

A total of 128 patients with gastric cancer were enrolled in this study. Patients were divided into the following three treatment groups: Group I, < 6 cycles, 53 patients (41.4 %); Group II, 6 cycles, 40 patients (31.3%); and Group III, >6 cycles, 35 patients (27.3%). The median follow-up time was 43 months (range 8-60). Patient characteristics are displayed in Table 1. There were no statistically significant differences in the three groups, except in regard to age and histological grade.

Impact of the number of adjuvant chemotherapy cycles on OS and RFS

Median survival time was 37 months (95% CI 30.01–43.99) in Group I, 54 months (95% CI 45.53–62.47) in Group II, and 55 months (95% CI 49.34–60.65) in Group III. The 5-year OS was 20.8% in Group I, 45.0% in Group II, and 42.9% in Group III .The median duration of relapse-free survival was 19 months (95% CI 11.22–26.78) in Group I, 40 months (95% CI 29.03–50.97) in Group II, and 43 months (95% CI 38.81–47.19) in Group III. The 5-year RFS was 15.1% in Group I, and 40% in Groups II and III. Figure 1 shows that the number of adjuvant chemotherapy cycles had a significant effect on both the OS and RFS (OS, $p = 0.001$; RFS, $P<0.001$). The OS and RFS for patients who received >6 cycles were significantly better than in those who received <6 cycles (OS, $p = 0.002$;

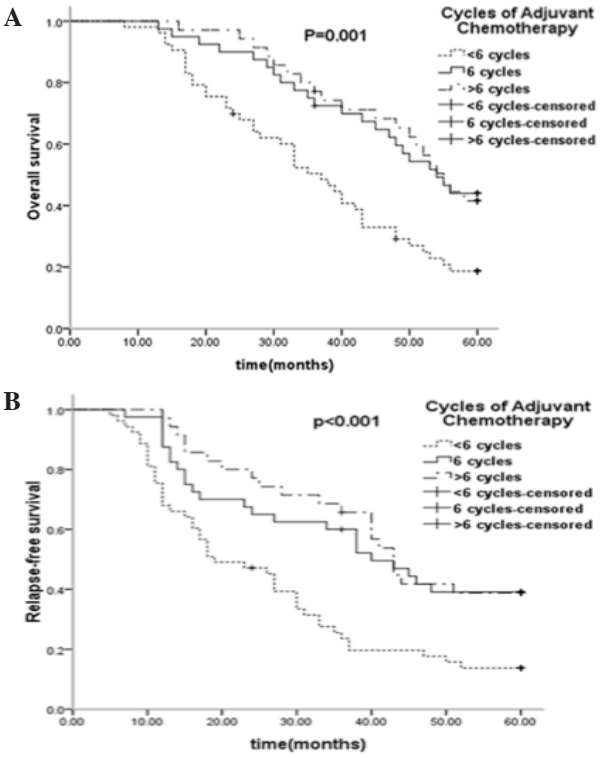

Figure 1. Kaplan-Meier Evaluates the Impact of the Number of Adjuvant Chemoradiation Cycles on OS (A) and RFS (B). The number of adjuvant chemotherapy cycles had a significant effect on both the OS and RFS .The OS and RFS for patients who received 6 or > 6 cycles were significantly better than for those who received < 6 cycles (OS, $p = 0.002$ and $p=0.003$; RFS, $P<0.001$ and $P=0.002$), but there was no difference in OS ($p = 0.970$) or in RFS ($p = 0.722$) for patients who received 6 cycles and > 6 cycles

RFS, $P<0.001$). In addition, the OS and RFS for patients who received 6 cycles were also significantly better than for those who received <6 cycles (OS, $p=0.003$; RFS, $P=0.002$), but there was no difference in OS ($p = 0.970$) or RFS ($p = 0.722$) for patients who received 6 cycles and >6 cycles.

Analysis of Prognosticators for OS and RFS

Five years after surgery, prognosticators for OS and RFS were analyzed in the enrolled patients. A detailed explanation is shown in Table 2. In univariate analysis, T stage, N stage, and cycles of chemotherapy were the major prognostic factors that influenced OS and RFS. Significant factors in the univariate analysis were analyzed in the multivariate analysis. Multivariate analysis showed that N stage demonstrated an increased risk, whereas cycles of chemotherapy demonstrated a reduced risk as independent factors that influence OS and RFS.

Recurrence in the Three Patient Groups

Recurrence data among the three groups are shown in Table 3. Recurrence rates were higher in Group I (84.9%) than in Groups II and III (60% and 60%, $P=0.007$ and $P=0.008$, respectively) 5 years post-surgery. Relapse rates of local, distant, and peritoneal recurrence were 13.2, 56.6, and 15.1%, respectively in Group I (<6 cycles), and 17.5, 30.0, and 12.5%, respectively in Group II (6 cycles), and 14.3, 20.0, and 25.7%, respectively in Group III (>6 cycles). No significant differences were seen in patterns of recurrence between these three groups ($P=0.079$).

Toxicity of Chemotherapy

The main toxicities are listed in Table 4. The major grade 3/4 hematologic toxicities were leukopenia (3.8%), anemia (0.0%), and thrombocytopenia (1.9%) in Group I, leukopenia (2.5%), anemia (10.0%), and thrombocytopenia (5.0%) in Group II, and leukopenia (8.6%), anemia (5.7%), and thrombocytopenia (5.7%) in Group III. The major grade 3/4 non-hematologic toxicities were nausea and vomiting at rates of 3.8% in Group I, 10.0% in Group II, and 17.1% in Group III.

Table 3. Recurrence Patterns of Different Chemotherapy Cycles after Surgery

	<6 cycles (n=53)		=6 cycles (n=40)		>6cycles (n=35)	
Recurrence patterns	n	%	n	%	n	%
Total numbers of recurrence	45	84.9	24	60	21	60
Local recurrence	7	13.2	7	17.5	5	14.3
Distant recurrence	30	56.6	12	30	7	20
Peritoneal recurrence	8	15.1	5	12.5	9	25.7

Discussion

Adjuvant chemotherapy has recently become one of the standard treatments after resection of gastric cancers in some Asian countries (Sakuramoto et al., 2007; Bang et al., 2012). Meta-analyses indicated that patients with resectable gastric cancer could actually benefit from adjuvant chemotherapy (Oba, 2009; Paoletti et al., 2010). To date, there is no single, global standard for adjuvant chemotherapy regimens for stomach cancer after radical resection (Oh, 2012). We selected patients who were amenable to epirubicin, cisplatin or xaliplatin, and leucovorin plus 5-fluorouracil on the basis of preliminary results of some studies that indicated that these agents were effective and well-tolerated for patients with advanced gastric cancer (Jeen et al., 2001; Karacetin et al., 2004; Neri et al., 2007; Zhang et al., 2007). Cunningham et al. (2008) found that epirubicin, with oxaliplatin plus fluorouracil was as effective as epirubicin, with cisplatin plus fluorouracil for the treatment of advanced gastric cancer. There is no defined standard that addresses the number of cycles of adjuvant chemotherapy that are required for the maximal response after gastric cancer resection. Previous studies have reported that patients with stomach cancer had no survival benefit from 3 to 5 courses of adjuvant chemotherapy after radical gastrectomy (De Vita et al., 2007; Di Costanzo et al., 2008; Kulig et al., 2010). Neri et al. (2001) investigated whether 7 cycles of adjuvant chemotherapy led to a longer median survival time than the surgery-only group. Kang et al. (2011) reported that 6 cycles of adjuvant S-1 plus cisplatin was feasible for patients with stomach cancer undergoing surgical resection. Bang et al. (2012) showed that 8 cycles of chemotherapy after D2 gastrectomy increased 3 year disease-free survival rates and lowered the risk of recurrence. Five-year outcomes of a randomized phase III trial by Sasako et al. (2011) showed that patients with gastric cancer undergoing D2 gastrectomy could benefit from 8 cycles of postoperative adjuvant chemotherapy with S-1. The 5-year OS and RFS rates were 71.7% and 65.4%, respectively in the adjuvant chemotherapy group. Our retrospective analysis showed a significant impact on the 5-year RFS in patients who received 6 or >6 cycles of adjuvant chemotherapy compared to those who received <6 cycles adjuvant chemotherapy (40%, 40%, and 15.1% respectively; $p < 0.001$). We also saw an improvement in 5-year OS in patients who received 6 or >6 cycles of adjuvant chemotherapy compared to those who received <6 cycles adjuvant chemotherapy (45.0%, 42.9%, and 20.8%, respectively; $p=0.001$). Our findings of 5-year OS and RFS rates were lower than those of other studies

Table 4. Major Toxic Effects of Chemotherapy

	<6 Cycles (n =53)				=6 Cycles (n=40)				>6 Cycles (n=35)			
toxic effects	Grade1/2		Grade3/4		Grade1/2		Grade3/4		Grade1/2		Grade3/4	
	n	%	n	%	n	%	n	%	n	%	n	%
Leukopenia	31	58.5	2	3.8	28	70	1	2.5	23	65.7	3	8.6
Anemia	25	47.2	0	0	18	45	4	10	13	37.1	2	5.7
Thrombocytopenia	7	13.2	1	1.9	8	20	2	5	3	8.6	2	5.7
Nausea/Vomiting	25	47.2	2	3.8	29	72.5	4	10	22	62.9	6	17.1

from Asia, presumably due to differences in operation procedures (Sasako et al., 2011). In our follow-up study, patients with gastric cancer received D1 gastrectomy.

Many studies reported various prognostic indicators for post-operative stomach cancer at 5 years, such as stage, histology, and treatments such as chemotherapy (Neri et al., 2001; Moon et al., 2007; Aoyama et al., 2011). In our study, a multivariate prognostic analysis was performed in order to evaluate whether patients had survival benefits from multiple cycles of chemotherapy. Our results demonstrated two potentially prognosticators that influence OS and RFS: N stage and number of cycles of adjuvant chemotherapy. Multivariate prognostic analyses showed that 6 or more cycles of adjuvant chemotherapy might be more useful for improving 5-year OS or RFS compared to less than 6 cycles (OS, $P<0.001$; RFS: $P<0.001$). Our follow-up data demonstrated that there was a higher incidence of relapse in Group I (84.9%) than in Groups II or III (60.0% vs. 60.0%, $P=0.007$ and $P=0.008$, respectively). Although the relapse patterns in the three groups also failed to reach statistical difference, it was noted that the rate of distant metastasis in groups II or III (30% vs.20%) was lower than in group I (56.6%). The toxic effects of adjuvant chemotherapy have been reported in previous studies, and include leukopenia, anemia, thrombocytopenia, nausea, vomiting, and other rare toxic effects (Saletti et al., 2007; Di Costanzo et al., 2008; Bang et al., 2012). In our study, the toxic events of grade 3 or 4 were more frequent in group III than in the other groups. The major toxicities were leucopenia, nausea, and vomiting. Although grade 3 or 4 toxicities were uncommon, some patients needed to dose modify to reduce adverse effects.

The major limitation of our study is the small sample size and selection bias of the samples. Some patients with stage 4a or 4b received <6 cycles of adjuvant chemotherapy because they could not tolerate the side effects of chemotherapy. In addition, the majority of 60 or over 60-year-old patients received <6 cycles of adjuvant chemotherapy, also due to intolerance of adverse effects.

In conclusion, our retrospective analysis showed that 6 cycles of adjuvant chemotherapy might improve outcomes in patients with resectable gastric cancer. These results provide a rationale to conduct a large multi-centered controlled trial to investigate the optimal number of chemotherapy cycles to help improve treatment outcomes in patients with postoperative gastric cancer.

Acknowledgements

This work was supported by Shanghai Science and Technology Committee Foundation grant (No. 10JC 1409200). We thank Mei Zhao for her assistance in telephone visit.

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