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Short-term curative effect of S-1 plus oxaliplatin as perioperative chemotherapy for locally advanced gastric cancer: a prospective comparison study

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This research aimed to investigate the efficacy of S-1 plus oxaliplatin (SOX) as perioperative chemotherapy for locally advanced gastric cancer. We enrolled 102 patients with preoperative clinical stage T3–4N×M0 gastric cancer who were then randomly assigned to receive SOX as either perioperative chemotherapy (group A, 50 patients) or postoperative adjuvant chemotherapy (group B, 52 patients). Short-term curative efficacy and adverse effects of perioperative chemotherapy were analyzed. The rates of R0 resection, surgical complications, combined multiple organ resection, overall survival (OS), and disease-free survival (DFS) were compared between the groups. Results showed an overall response rate in group A of 42%, with a disease control rate of 94% and a tumor down-staging rate of 50%. An R0 resection rate of 90% was achieved in group A, which was significantly higher than that in group B (75%). No surgical mortality was observed, and the differences in surgical complications and combined multiple organ resection rates between the groups were not significant. The postoperative pathological examination of 4 patients in group A did not show any cancer cells in the tumor bed, resulting in a histological complete remission rate of 8%. The average OS and DFS for group A patients were 17.928 and 16.134 months, respectively, which were both longer than that of group B patients. However, the differences were not significant. In all, our results shows that in locally advanced gastric carcinoma, SOX perioperative chemotherapy is effective and results in a significantly improved R0 resection rate compared to postoperative SOX administration. Perioperative SOX does not cause additional surgical complications and has low adverse reaction rates; moreover, it appears to prolong survival.

1. Introduction

Gastric cancer is one of the most common malignancies, and ranks second after lung cancer in China. Although the incidence of gastric cancer has slowly decreased, it remains the third leading cause of death. Early detection and diagnosis of gastric cancer remain challenging; with, 84% of all diagnosed cases being advanced (Chen et al. 2008). Although surgical resection is the primary treatment for advanced gastric cancer, a biologically radical cure cannot be achieved with surgery alone. Even after extended radical resection and lymphadenectomy, recurrence and metastasis still occur in the majority of gastric cancer patients, and can lead to death. Therefore, investigation with multimodal therapy (e.g., surgery, chemotherapy, and radiotherapy) is clinically valuable to improve the radical resection rate and extend the overall survival (OS) in patients with locally advanced gastric cancer. A series of previous studies have shown that perioperative chemotherapy is effective in improving complete tumor resection rates and prognosis (Li et al. 2010). However, lacking a large phase III trial, there is little clinical evidence from China as well as other countries; such evidence is required to establish the safety and efficacy of perioperative chemotherapy in the treatment of advanced gastric cancer. Additionally, a standard regimen for perioperative chemotherapy has not been determined for advanced gastric cancer. Therefore, the present study aims to investigate the curative effect of S-1 plus oxaliplatin (SOX) as perioperative chemotherapy for locally advanced gastric cancer, and to explore its potential as a standard regimen. We hypothesized that perioperative chemotherapy would improve outcomes over postoperative therapy in these patients.

2. Investigations and results

2.1. General data of enrolled patients

From November 2011 to May 2013, 102 patients with locally advanced gastric cancer at preoperative clinical stage of T3–4N×M0 were enrolled. They were randomly assigned to receive SOX as either perioperative chemotherapy (group A, 50 patients) or postoperative adjuvant chemotherapy (group B, 52 patients). Group A included 40 men and 10 women, aged 39–77 years (median, 59 years). Group B included 42 men and 10 women, aged 34–77 years (median, 58.5 years). There was no significant difference in preoperative baseline characteristics between the groups (Table 1). Fifty patients in group A completed a minimum of two cycles of preoperative chemotherapy for a total of 106 cycles. The median period of time to surgery after chemotherapy was 23 days. Curative efficacy evaluation before surgery revealed that 2% of the patients achieved CR (1/50), 50% achieved PR (20/40), 52% achieved SD (26/50), and 6% had PD (3/50). The overall response rate was 42% (21/50), and the DCR was 94% (47/50). The tumors of 25 patients were down-staged, resulting in a down-staging rate of 50% (25/50). However, the overall tumor clinical stage was significantly higher (Fig. 1).

2.2. Surgery results of both groups

All patients in both groups underwent surgical treatment. In group A, the R0 resection rate was 90% (45/50). All 5 non-R0 resection cases in group A had pathologic upper residual positivity. The R0 resection rate for group B patients was 75% (39/52). The 13 non-R0 resection cases included 3 with gastrojejunostomy, 4 with incomplete resection due to infiltrated surrounding organs, 3 with remnant metastatic lymph node, 2 with upper residual positivity,

Table 1: Baseline clinical characteristics of enrolled patients

Clinical pathological data	Perioperative chemotherapy group (n = 50)	Postoperative chemotherapy group (n = 52)	X^2	*P*
Age				
Median (years)	59	58.5		
Range (years)	39–77	34–77		
18–59 years, number (%)	26 (54.0)	30 (57.7)	4.050	0.132
60–69 years, number (%)	18 (36.0)	21 (40.4)		
≥70 years, number (%)	6 (12.0)	1 (1.9)		
Sex, number (%)				
Male	40 (80)	42 (80.8)	0.01	0.922
Female	10 (20)	10 (19.2)		
Body surface area				
Average (m^2)	1.78	1.73		
Range (m^2)	1.60–2.24	1.43–2.19		
1.25–1.9 m^2, number (%)	39 (78)	45 (86.5)	1.279	0.258
≥2 m^2, number (%)	11 (22)	7 (13.5)		
ECOG grade, number (%)				
0	20 (40)	17 (32.7)	0.589	0.443
1–2	30 (60)	35 (67.3)		
Tumor position, number (%)				
Cardia	17 (34)	17 (32.7)	1.385	0.709
Stomach body	11 (22)	13 (25)		
Pylorus	16 (32)	19 (36.5)		
Total stomach and multifocal	6 (12)	3 (5.8)		
Pathological staging, number (%)				
High and moderate differentiation	27 (54)	32 (61.5)	1.203	0.548
Low differentiation	16 (32)	16 (30.8)		
Poor differentiation#	7 (14)	4 (7.7)		
TNM staging, number (%)				
IIB	8 (16)	15 (28.8)	2.518	0.284
IIIA	20 (40)	19 (36.5)		
IIIB–IIIC	22 (44)	18 (34.6)		

ECOG, Eastern Cooperative Oncology Group
#Poorly differentiated cells, signet ring cell carcinoma, mucinous adenocarcinoma, undifferentiated carcinoma
TNM, tumor-node-metastasis staging in the present study was in accordance with the standards stated in the Union for International Cancer Control 2010 TNM staging manual for gastric cancer

Table 2: Comparison of R0 resection rate between group A and group B

	Total # of cases	Number of resections					
	(n)	R0: n (%)		Non-R0: n (%)		X^2	*P*
Group A	50	45	90.0	5	10.0	4.136	0.047
Group B	52	39	75.0	13	25.0		

and 1 with lower residual positivity. No simple exploratory surgery was performed in either group. The R0 resection rate in group A was significantly better than that in group B ($\chi^2 = 4.136$, $P = 0.047$; Table 2). In group A, all the non-R0 resections showed pathological upper residual positivity after surgery; no obvious tissue edema was observed during surgery. Tumors and surrounding organs were anatomically clear. In group A patients, local lesions and adhesions of surrounding tissues or adjacent organs were identified and considered infiltrating tumors. However, postoperative pathological examination revealed no cancer cell infiltration. In some surgically obtained tumor samples, no obvious lesion was even visible. In contrast, non-R0 resection (due to infiltrating residuals in the surrounding tissues, lymph nodes, or the solid tumor itself) accounted for 76.9% of group B patients (10/13). No death occurred in either group.

In group A, the rate of surgical complications was 14% (7/50), including 2 cases of postoperative abdominal infection, 1 of postoperative abdominal hemorrhage, 1 of postoperative acute renal failure, and 3 of postoperative incision infection. The complication rate was 15.4% (8/52) in group B, including 1 case of postoperative ileus, 1 of abdominal hemorrhage, 1 of postoperative respiratory failure, and 5 of surgical wound infection. No significant difference was observed between the groups ($P = 0.844$).

The resection rate of combined multiple organs was 6% (3/50) in group A, including 1 case of distal splenectomy and pancreatectomy, 1 of splenectomy, and 1 of partial liver resection. This rate was 3.8% (2/52) in group B, including 1 case of distal splenectomy and pancreatectomy and 1 of partial liver resection. No significant difference of resection rate was observed between the groups ($P = 0.675$).

Pathological tumor regression grading was evaluated in the 50 group A patients; the results were as follows: 4 cases of grade 0, 10 of grade 1, 14 of grade 2, and 22 of grade 3. The pathological response rate was 56% (28/50). Among these patients, 4 had no residual cancer cells observed in the pathological tumor bed after surgery. Thus, the pathologically complete remission rate was 8% (4/50).

Incidences of adverse events were evaluated for all group A patients. Non-hematological adverse events comprised gastrointestinal reaction, fatigue, abnormal hepatorenal function, neurotoxicity,

Table 3: Adverse effects associated with perioperative chemotherapy (n = 50)

Event	Grade 1	Grade 2	Grade 3	Grade 4	Total
Hematological toxicity, number (%)					
Leukopenia	13 (26)	4 (8)	3 (6)	0	20 (40)
Neutropenia	11 (22)	4 (8)	3 (6)	0	18 (36)
Thrombocytopenia	1 (2)	1 (2)	0 (0)	0	2 (4)
Anemia	5 (10)	3 (6)	1 (2)	0	9 (18)
Non-hematological toxicity, number (%)					
Nausea	17 (34)	8 (16)	3 (6)	0	28 (56)
Vomiting	10 (20)	6 (12)	2 (4)	0	18 (36)
Anorexia	15 (30)	8 (16)	5 (10)	0	28 (56)
Diarrhea	11 (22)	5 (10)	0 (0)	0	16 (32)
Fatigue	12 (24)	3 (6)	0 (0)	0	15 (30)
Hepatic function abnormality	5 (10)	3 (6)	1 (2)	0	9 (18)
Renal function abnormality	0 (0)	1 (2)	0 (0)	0	1 (2)
Stomatitis	3 (6)	1 (2)	0 (0)	0	4 (4)
Skin effect	5 (10)	2 (4)	0 (0)	0	7 (14)
Neurotoxic effect	6 (12)	5 (10)	0 (80)	0	11 (22)

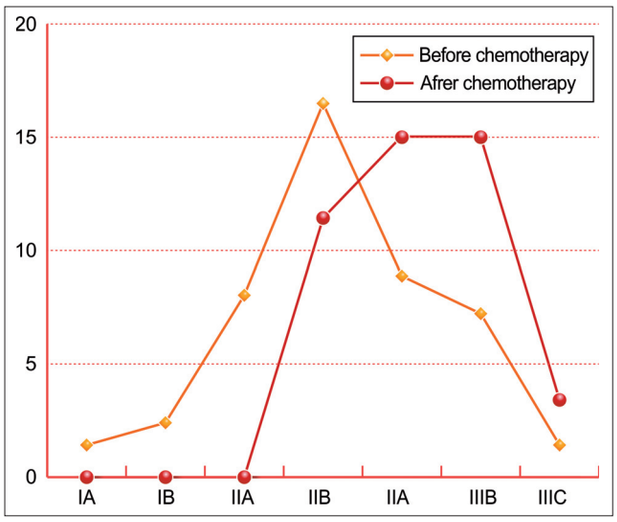

Fig. 1: Changes in tumor staging before and after chemotherapy in group A

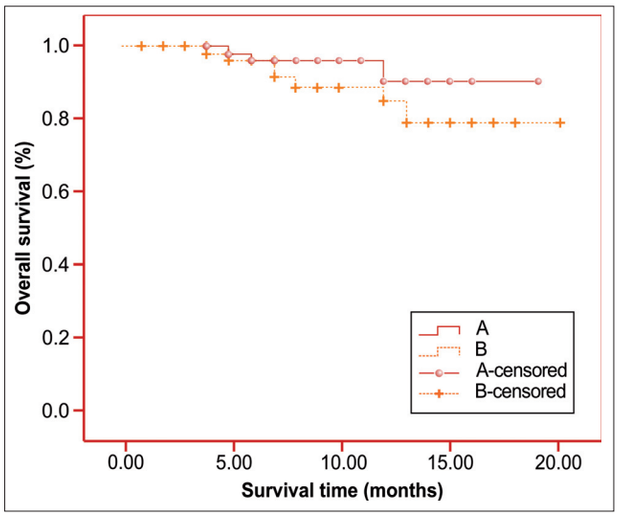

Fig. 2: Comparison of overall survival between groups A and B

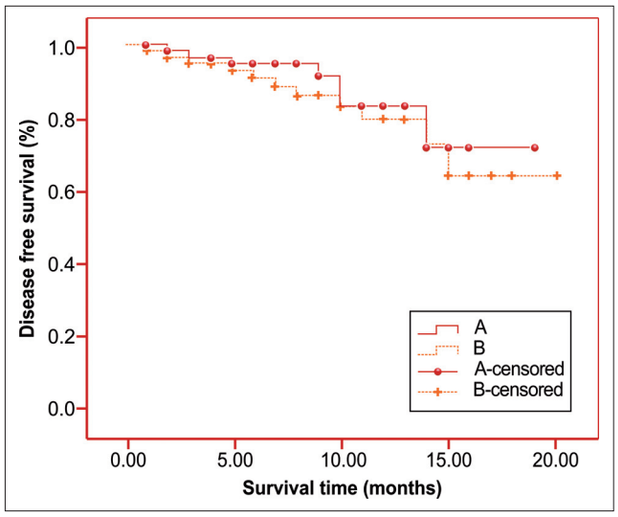

Fig. 3: Comparison of disease-free survival between groups A and B

and skin pigmentation. Hematological toxic adverse events were mostly neutropenia, anemia, and thrombocytopenia. The adverse events were not severe, as most were constrained to grades 1 or 2, and were improved with active symptomatic management. No chemotherapy related deaths were observed (Table 3).

2.3. Follow-up results of both groups

By the follow-up deadline, 98 of the 102 patients in both groups had completed all follow-up visits. Two patients each from groups A and B missed the follow-up, resulting in a follow-up absence rate of 4% (2/50) and 3.85% (2/52), respectively; this was a statistically insignificant difference (P= 0.986). The median follow-up time of all patients was 9.6 months (range, 1.7–20.5 months). The average OS was 17.928 months (95% CI: 16.752–19.10 months) in group A and 17.433 months (95% CI: 15.711–19.155 months) in group B. No significant difference in the average OS was observed between the groups (p = 0.239). The mean DFS was 16.134 months (95% CI: 14.214–18.055 months) in group A and 15.846 months (95% CI: 13.791–17.901 months) in group B. Similarly, no significant difference in the mean DFS was observed between the groups (p = 0.536) (Figs. 2 and 3).

3. Discussion

Gastric cancer is a global disease; its incidence and mortality rates in China are 48.6% and 47.8%, respectively. Although the mortality rate has been decreasing according to Chinese national figures, the incidence rate still ranks third among all diagnosed cancers (Shi et al. 2012). Because there are no specific symptoms in Chinese patients with gastric cancer, and medical care in China is limited, early detection is challenging. Therefore, most patients are diagnosed with the disease at advanced stages. Although the importance of curative surgery and standardization of surgery have been constantly emphasized in recent years, the overall survival rate of gastric cancer patients has not improved significantly; one of the main reasons for this is that micro-metastasis are present in most patients after surgery. Therefore, relapse or metastasis inevitably occurs, resulting in an overall poor prognosis (Yu et al. 2010).

For patients with locally advanced gastric cancer, only those with R0 resection have a favorable survival rate (Biondi et al. 2010), while the prognosis for those with R1/R2 resection is poor. Therefore, perioperative chemotherapy offers a number of benefits, including: 1) the reduction of tumor volume and tumor infiltration/adhesion to the surrounding tissues, thus relieving tissue edema and leading to tumor down-staging and improved R0 resection rate; 2) the reduction of circulating cancer cells and tumor activity, which decreases intra-operative spreading; 3) the reduction of potential postoperative micro-metastasis and relapse; and 4) the opportunity to preoperatively evaluate tumor sensitivity to chemotherapy to determine whether the same agent is appropriate for postoperative adjuvant chemotherapy (Díaz-González et al. 2011).

Currently, there are 2 reported phase III studies of perioperative chemotherapy of gastric cancer, the Medical Research Council Adjuvant Gastric Infusional Chemotherapy (MAGIC) trial (Cunningham et al. 2006) and the French FFCD-9703 study (Ychou et al. 2011). In the MAGIC trial, known as a milestone in gastric cancer perioperative therapy, both the curative resection rate and the OS rate in the perioperative chemotherapy group was higher than that in the surgery-only group. As the exact curative effect of perioperative chemotherapy was demonstrated in this clinical study, it was recommended as first-level evidence by the *NCCN Treatment Guidelines* in 2008. Similarly, in the FFCD-9703 trial, both the curative resection rate and the 5-year survival rate in the chemotherapy group were significantly higher compared to those in the group with surgery alone. Other clinical studies have also demonstrated the efficacy of perioperative chemotherapy for gastric cancer (van et al. 2012; Pechačová et al. 2013; Reece-Smith et al. 2012). In the present study, an R0 resection rate of 90% was achieved in the perioperative chemotherapy group, significantly higher than that of the group receiving postoperative adjuvant chemotherapy. No significant differences in the rates of operative complications and multiple organ resections were observed between these two groups, and the overall outcomes were similar to those previously reported. Therefore, our results suggested that the SOX regimen improved the curative resection rate and reduced intra-operative residual cancer cell spreading without enlarging the surgical wound. The benefits of perioperative chemotherapy in locally advanced gastric cancer were thus further confirmed in this study.

Although impressive efficacy was achieved at the preoperative stage in our study, there remains a lack of adequate evidence from a large phase III clinical trial to establish the efficacy of the SOX regimen as perioperative chemotherapy in the treatment of gastric cancer. In a Japan phase II study, patients with recurrent or metastatic gastric cancer received first-line treatment with a SOX regimen, resulting in overall response and disease control rates of 59% and 84%, respectively (Kim et al. 2012). Koizumi et al. demonstrated that SOX achieved an overall response rate of 53–59% in their studies (Koizumi et al. 2008; Koizumi et al. 2010; Park et al. 2010; Rosati et al. 2009). A Chinese study reported that the overall response and disease control rates of the SOX regimen in the treatment of advanced gastric cancer were 46.6% and 93.3%, respectively (Yang et al. 2013). The overall response rate in the present study was lower than that in previously published studies. However, the patients in the above-mentioned studies were mostly at an advanced disease stage or with relapse and metastasis, while those in this study were at the preoperative clinical stage of T3–4, NX, and M0. The evaluation criteria for the chemotherapy curative effect were also different. Therefore, it cannot be concluded that the overall response rate to the SOX regimen in Chinese gastric cancer patients is different from those reported elsewhere. These results were close to those obtained in our study, which further verified the curative effect of SOX regimen chemotherapy.

Another critical issue is that it is often challenging to accurately determine the curative effect of chemotherapy by conventional imaging examination. Pathological complete response (pCR), as a histopathologically curative effect is referred to, is considered the most reliable index for preoperative chemotherapy evaluation. Becker et al. (2011) demonstrated that pCR, as an independent prognostic indicator, was positively correlated with patients' survival rates. In our study, 4 patients (8%) achieved pCR after surgery, but only 1 had CR based on the preoperative RECIST criteria (Zhao et al. 2013). This inconsistency was similar to that in the studies conducted by Chen et al. in China and Cascinu et al. in Italy (Chen et al. 2014; Cascinu et al. 2004); this indicates that the aforementioned evaluation criteria are mutually inconsistent, and that the clinical evaluation method requires improvement. In our opinion, preoperative RECIST evaluation of measurable lesions combined with postoperative pathological results could be more adequate for the evaluation of the curative effect of chemotherapy.

S-1 is a fourth-generation derivative of oral fluorouracil (FU). The major cytotoxic component of S-1 is tegafur, which is metabolized by liver enzymes to active 5-FU. Another component, gimeracil, prevents the degradation of 5-FU to enhance its antitumor effect. S-1 also contains oteracil potassium to protect the gastrointestinal mucosa and reduce gastrointestinal reaction. Metabolized tegafur produces 5-FU, which is sustained for longer periods in the blood stream. Thus, a curative effect similar to that of continuous intravenous injection of 5-FU was achieved. Adverse effects of S-1 mostly include gastrointestinal adverse effects and myelosuppression. In our study, the adverse effects observed in patients were mostly mild. All patients demonstrated good tolerance, with adverse effects relieved after receiving symptomatic treatment. S-1 toxicity exerted no negative impact on subsequent surgery and postoperative chemotherapy.

The survival analysis indicated that both the OS and DFS rates in the perioperative chemotherapy group were higher than those in the postoperative adjuvant chemotherapy group, although no significant difference was observed. The results were consistent with those obtained from previously reported clinical studies (Misra et al. 2012; Schuhmacher et al. 2010). However, the total median follow-up time for both groups was only 9.6 months, and only a small sample size was enrolled for observation. A longer follow-up period is therefore necessary.

In conclusion, our SOX regimen was highly effective as perioperative chemotherapy for locally advanced gastric carcinoma, which offered adequate tolerability and significantly improved the curative resection rate without increasing operative complications. Additionally, patients receiving SOX as perioperative chemotherapy showed a trend towards prolonged survival. However, the study cohort was limited, and the follow-up time was short. Thus, a larger sample size and longer follow-up period are necessary to further evaluate the impact of perioperative chemotherapy on survival. Additionally, its curative significance should be assessed using RECIST combined with postoperative pathology.

4. Experimental

4.1. Enrollment of patients

Patients were selected based on the following eligibility criteria: gastric cancer pathologically confirmed prior to surgery; advanced stage according to the staging guidelines by the Union for International Cancer Control 7th edition, no distant metastasis to the liver, lungs, brain, or bone; no anti-tumor therapy administered before enrollment; no contraindications for chemotherapy and surgery; a physical status rating of ≤2 points according to the Zubrod-Eastern Cooperative Oncology Group-World Health Organization (WHO) (ZPS, 5-point scale) standard; and the providing of informed consent.

4.2. Research procedures

Patients in group B immediately underwent surgery, whereas those in group A received 2–4 cycles of SOX chemotherapy prior to surgery. Each 21-day cycle consisted of S-1 at 40–60 mg/m^2 (administered orally, twice a day, from day 1 to day 14 of each cycle) and oxaliplatin at 130 mg/m^2 (administered intravenously on day 1). The administered dose of S1 was calculated according to the patients' body surface areas as follows: <1.25 m^2, 40 mg; 1.25–1.5 m^2, 50 mg; and >1.5 m^2, 60 mg. The efficacy of the perioperative therapy was evaluated via computed tomography 7 days after the last chemotherapy cycle. Subsequently, surgical treatment was performed 21 days after the end of chemotherapy.

Surgical procedures: The same group of surgeons with individual experience of over 100 cases of gastric cancer D2 radical resections each conducted all surgical procedures. If a tumor was located at the pylorus, distal subtotal gastrectomy, Billroth II gastroenterostomy, and Braun's anastomosis were performed. If the tumor was located at the cardia and gastric fundus, proximal subtotal gastrectomy and jejunal interposition were performed. Total gastrectomy and Roux-en-Y esophagojejunostomy were performed if a tumor was located in the total stomach or gastric body. Per convention, D2 lymphadenectomy was also performed. After surgery, all patients continued to receive the SOX regimen as adjuvant chemotherapy until a total of 8 cycles of perioperative chemotherapy was ensured.

Before surgery, all patients were evaluated according to the *Response Evaluation Criteria in Solid Tumors* (RECIST 1.1) recommended by the WHO. The evaluation outcomes included complete remission (CR), partial remission (PR), stable disease (SD), and progressive disease (PD). The overall response rate (ORR) was calculated as the sum of CR and PR, whereas the disease control rate (DCR) was the sum of CR, PR, and SD. Postoperatively, patients were evaluated according to the grading standard of pathological tumor regression recommended by the 2012 National Comprehensive Cancer Network (NCCN) *Clinical Practice Guideline in Oncology-Gastric Cancer*. The results included grade 0 (complete remission), grade 1 (partial remission), grade 2 (minor effect), and grade 3 (poor effect). Toxicity analysis of patients receiving perioperative chemotherapy was evaluated according to the United States' *National Cancer Institute-Common Toxicity Criteria (version 3.0)*. All patients received follow-up visits every month beginning at the time they were randomized until July 31, 2013.

4.3. Statistical analyses

All data were analyzed using the Statistical Packages for the Social Sciences (SPSS) version 17.0 (IBM, Armonk, New York, USA). Data were compared using the χ^2 test. The Kaplan-Meier method was used for univariate survival and survival curve analysis. All tests were performed bilaterally, and a P value of <0.05 was considered a significant difference.

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All authors declare that they have no competing interests.

References

Becker K, Langer R, Reim D, Novotny A, Meyer zum Buschenfelde C, Engel J, Friess H, Hofler H (2011) Significance of histopathological tumor regression after neoadjuvant chemotherapy in gastric adenocarcinomas: a summary of 480 cases. Ann Surg 253:934-939.

Biondi A, Persiani R, Cananzi F, Zoccali M, Vigorita V, Tufo A, D'Ugo D (2010) R0 resection in the treatment of gastric cancer: Room for improvement. World J Gastroenterol 16:3358-3370.

Cascinu S, Scartozzi M, Labianca R, Catalano V, Silva RR, Barni S, Zaniboni A, D'Angelo A, Salvagni S, Martignoni G, Beretta GD, Graziano F, Berardi R, Franciosi V; Italian Group for the Study of Digestive Tract Cancer (GISCAD) (2004) High curative resection rate with weekly cisplatin, 5-fluorouracil, epidoxorubicin, 6S-leucovorin, glutathione, and filgastrim in patients with locally advanced, unresectable gastric cancer: a report from the Italian Group for the Study of Digestive Tract Cancer (GISCAD). Br J Cancer 90:1521-1525.

Chen W, Shen J, Pan T, Hu W, Jiang Z, Yuan X, Wang L (2014) FOLFOX versus EOX as a neodjuvant chemotherapy regimen for patients with advanced gastric cancer. Exp Ther Med 7:464-467.

Chen XZ, Jiang K, Hu JK, Zhang B, Gou HF, Yang K, Chen ZX, Chen JP (2008) Cost-effectiveness analysis of chemotherapy for advanced gastric cancer in China. World J Gastroenterol 14:2715-2722.

Cunningham D, Allum WH, Stenning SP, Thompson JN, Van de Velde CJ, Nicolson M, Scarffe JH, Lofts FJ, Falk SJ, Iveson TJ, Smith DB, Langley RE, Verma M, Weeden S, Chua YJ, MAGIC Trial Participants (2006) Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. N Engl J Med 355:11-20.

Díaz-González JA, Rodríguez J, Hernández-Lizoain JL, Ciérvide R, Gaztañaga M, San Miguel I, Arbea L, Aristu JJ, Chopitea A, Martínez-Regueira F, Valentí V, García-Foncillas J, Martínez-Monge R, Sola JJ (2011) Patterns of response after preoperative treatment in gastric cancer. Int J Radiat Oncol Biol Phys 80:698-704.

Kim GM, Jeung HC, Rha SY, Kim HS, Jung I, Nam BH, Lee KH, Chung HC (2012) A randomized phase II trial of S-1-oxaliplatin versus capecitabine-oxaliplatin in advanced gastric cancer. Eur J Cancer 48:518-526.

Koizumi W, Narahara H, Hara T, Takagane A, Akiya T, Takagi M, Miyashita K, Nishizaki T, Kobayashi O, Takiyama W, Toh Y, Nagaie T, Takagi S, Yamamura Y, Yanaoka K, Orita H, Takeuchi M (2008) S-1 plus cisplatin versus S-1 alone for first-line treatment of advanced gastric cancer (SPIRITS trial): a phase III trial. Lancet Oncol 9:215-221.

Koizumi W, Takiuchi H, Yamada Y, Boku N, Fuse N, Muro K, Komatsu Y, Tsuburaya A (2010) Phase II study of oxaliplatin plus S-1 as first-line treatment for advanced gastric cancer (G-SOX study). Ann Oncol 21:1001-1005.

Li W, Qin J, Sun YH, Liu TS (2010) Neoadjuvant chemotherapy for advanced gastric cancer: A meta-analysis. World J Gastroenterol 16:5621-5628.

Misra S, Pedroso FE, DiPasco PJ, Solomon NL, Gennis E, Franceschi D, Ardalan B, Koniaris LG (2012) Does neoadjuvant chemotherapy improve outcomes for patients with gastric cancer? J Surg Res 178:623-631.

Park I, Lee JL, Ryu MH, Chang HM, Kim TW, Sym SJ, Lee SS, Jang G, Yoo C, Bae KS, Kang YK (2010) Phase I/II and pharmacokinetic study of S-1 and oxaliplatin in previously untreated advanced gastric cancer. Cancer Chemother Pharmacol 65:473-480.

Pechačová Z, Zemanová M, Haruštiak T, Vítek P, Fencl P (2013) Peri-operative chemotherapy in patients with oesophageal and gastro-oesophageal junction cancer-three years of experience. Prague Med Rep 114:57-71.

Reece-Smith AM, Saha S, Cunnell ML, Hameed K, Bessell EM, Duffy JP, Madhusudan S, Parsons SL (2012) MAGIC in practice: experience of peri-operative ECF/X chemotherapy in gastro-oesophageal adenocarcinomas. J Surg Oncol 106:748-752.

Rosati G, Ferrara D, Manzione L (2009) New perspectives in the treatment of advanced or metastatic gastric cancer. World J Gastroenterol 15:2689-2692.

Schuhmacher C, Gretschel S, Lordick F, Reichardt P, Hohenberger W, Eisenberger CF, Haag C, Mauer ME, Hasan B, Welch J, Ott K, Hoelscher A, Schneider PM, Bechstein W, Wilke H, Lutz MP, Nordlinger B, Van Cutsem E, Siewert JR, Schlag PM (2010) Neoadjuvant chemotherapy compared with surgery alone for locally advanced cancer of the stomach and cardia: European Organisation for Research and Treatment of Cancer randomized trial 40954. J Clin Oncol 28:5210-5218.

Shi WT, Wei L, Xiang J, Su K, Ding Q, Tang MJ, Li JQ, Guo Y, Wang P, Zhang JW(2012) Chinese patients with gastric cancer need targeted adjuvant chemotherapy schemes. Asian Pac J Cancer Prev 13:5263-5272.

Van Hagen P, Hulshof MC, van Lanschot JJ, Steyerberg EW, van Berge Henegouwen MI, Wijnhoven BP, Richel DJ, Nieuwenhuijzen GA, Hospers GA, Bonenkamp JJ, Cuesta MA, Blaisse RJ, Busch OR, ten Kate FJ, Creemers GJ, Punt CJ, Plukker JT, Verheul HM, Spillenaar Bilgen EJ, van Dekken H, van der Sangen MJ, Rozema T, Biermann K, Beukema JC, Piet AH, van Rij CM, Reinders JG, Tilanus HW, van der Gaast A; CROSS Group(2012) Preoperative chemoradiotherapy for esophageal or junctional cancer. N Engl J Med 336:2074-2084.

Yang L, Song Y, Zhou AP, Qin Q, Chi Y, Huang J, Wang JW(2013) A phase II trial of oxaliplatin plus S-1 as a first-line chemotherapy for patients with advanced gastric cancer. Chin Med J (Engl) 126:3470-3474.

Ychou M, Boige V, Pignon JP, Conroy T, Bouché O, Lebreton G, Ducourtieux M, Bedenne L, Fabre JM, Saint-Aubert B, Genève J, Lasser P, Rougier P. Perioperative chemotherapy compared with surgery alone for resectable gastroesophageal adenocarcinoma: an FNCLCC and FFCD multicenter phase III trial. J Clin Oncol 2011;29:1715-21.

Yu M, Zheng HC, Xia P, Takahashi H, Masuda S, Takano Y, Xu HM(2010) Comparison in pathological behaviours & prognosis of gastric cancers from general hospitals between China & Japan. Indian J Med Res 132:295-302.

Zhao Q, Li Y, Tian Y, Chen YN, Tan BB, Zhao XF, Jiao ZK, Zhang ZD, Chang SL(2013) Histological complete response after neoadjuvant XELOX in advanced gastric carcinoma. Hepatogastroenterology 60:638-640.