A retrospective study on intensity-modulated radiation therapy combined with chemotherapy after D2 radical surgery for gastric carcinoma

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Abstract. In order to investigate the clinical value of different chemotherapies, the efficacy of intensity-modulated radiation therapy with concurrent chemotherapy following D2 radical surgery for gastric carcinoma was evaluated in this study. A total of 102 patients who underwent D2 radical surgery for gastric carcinoma followed by concurrent chemoradiotherapy (CRT) between January, 2008 and March, 2012, were selected. The 5/7 field intensity-modulated radiation therapy was used, with a planning target volume dose of 45 Gy in 25 fractions over 5 weeks. Among these patients, 45 were administered 400 mg/m²/day fluorouracil and 20 mg/m²/day tetrahydrofurfuryl alcohol through intravenous infusion 4 days before and 3 days after the radiotherapy (F-CRT group), while 57 patients received 825 mg/m² capecitabine orally twice a day (C-CRT group). The 3-year overall and the disease-free survival rates were 75.5 and 70.5%, respectively. The overall 3-year survival rates of the F-CRT and C-CRT groups were 72.2 and 78.5% (P>0.05), respectively, and the 3-year disease-free survival rates were 67.7 and 72.8% (P>0.05), respectively. No significant differences were observed between the two groups. However, during the concurrent CRT, significant differences were found in the incidence of grade 1-2 haematological toxicity between the F-CRT and C-CRT groups (73.3 vs. 50.9%, respectively; χ^2=5.320, P=0.021). Significant differences were also found in the incidence of grade 1-2 gastrointestinal reactions between the two groups (77.8 vs. 57.9%, respectively; χ^2=4.474, P=0.034). Therefore, intensity-modulated radiation therapy combined with concurrent chemotherapy following D2 radical surgery for gastric cancer was found to be safe and effective.

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In addition, radiotherapy was better tolerated and more likely to be completed using C-CRT rather than F-CRT.

Introduction

Gastric carcinoma, a common malignant tumor of the digestive tract, is the fourth more common cause of morbidity and the second cause of mortality among all malignant tumors worldwide, and is particularly common in Latin America, Eastern Europe and East Asian countries (1,2). The radical therapy of gastric carcinoma mainly relies on surgical resection; however, local recurrence and distant metastasis may still occur, even in patients who have undergone complete surgical resection (3-5). Among patients with failed surgical intervention, ~90% experienced local recurrence, which led to death in ~80% of these patients, particularly those with serosal invasion or lymphatic metastasis (6,7). The prognosis with surgery alone is poor for patients with locally advanced gastric carcinoma, while the 5-year survival rate is only ~8-34% (8). In order to improve the survival rate of patients with gastric carcinoma and reduce the recurrence rate, adjuvant therapy following gastrectomy has become a consensus (9). However, chemotherapy alone after surgery did not confer an obvious survival benefit to such patients in the majority of studies (9,10).

Since the results of the INT-0116 study (11) were published in 2001, adjuvant concurrent chemoradiotherapy (CRT) after surgery has been commonly used by oncologists for the treatment of gastric carcinoma; therefore, certain European and American guidelines have included adjuvant CRT and recommend it as the standard treatment following surgery. Among selected patients, the proportion of those receiving limited lymph node dissection (D0 or D1) is ≤90%, whereas the proportion of those receiving extended D2 lymph node dissection (D2) is only ~10% (11). However, in some Asian countries, patients with gastric carcinoma are more likely to receive D2 radical surgery, which limits the significance of this study for Asian patients. Thus, Kim *et al* compared patients who had received adjuvant concurrent CRT following D2 radical surgery for gastric carcinoma with those who had received surgery alone, and demonstrated that adjuvant concurrent CRT following D2 radical surgery may improve the survival rate and reduce the recurrence rate (12). The ARTIST trial further compared patients who had received concurrent

CRT following D2 surgery for gastric carcinoma with those who had received chemotherapy alone, and demonstrated that the overall 3-year disease-free survival rate was marginally higher compared with that of the group with concurrent CRT, although the difference was not statistically significant (13).

Intensity-modulated radiation therapy (IMRT) is a more advanced radiotherapy technique, which is able to concentrate high doses of radiation on the target area, while better protecting the adjacent normal tissue and has a dose advantage compared with conventional radiotherapy and three-dimensional conformal radiation therapy (3DCRT) following surgery for gastric carcinoma (14,15).

To evaluate the efficacy of IMRT combined with concurrent chemotherapy following D2 radical surgery for gastric carcinoma and investigate the clinical value of its combination with different chemotherapies, we conducted a study including 102 patients who had received IMRT combined with concurrent chemotherapy with intravenous infusion of fluorouracil (F-CRT) or oral capecitabine (C-CRT) following D2 radical surgery for gastric carcinoma.

Patients and methods

Patient eligibility. A total of 102 patients treated with D2 radical surgery for gastric carcinoma were enrolled from January, 2008 to March, 2012. The characteristics of the patients are shown in Table I. The criteria for inclusion were as follows: Pathologically proven diagnosis of gastric adenocarcinoma; radical surgical resection (R0) of the tumor ≤4 weeks prior; D2 lymph node dissection; age ≥18 and ≤70 years; World Health Organization performance status score ≤2; TNM stage T3, T4 or N+ (IB-III) according to the American Joint Committee on Cancer (AJCC), 7th edition (16); normal cardiac, hepatic and renal function; normal bone marrow function (neutrophil count ≥1,500/μl, blood platelet 100,000/μl, hemoglobin level ≥10 g/dl); no malignant tumor at other sites; no intolerance of CRT due to various systemic diseases; no residual tumor or positive surgical margins after surgery; no TNM stage T1-2N0; no distant metastasis (M1); and no D0/D1 lymph node dissection. The present study was approved by the Ethics Committee of Anhui Provincial Hospital (Hefei, China) and all participating patients provided written informed consent.

Radiotherapy. Radiotherapy was initiated within 4 weeks after surgery. All the patients were required to fast for at least 4 h, and were scanned after orally taking 20 ml compound diatrizoate meglumine solution and 500-800 ml water to highlight the gastric stump and part of the intestinal loop structure. The patients were maintained at the supine position by a restraining device to undergo computed tomography (CT) enhancement scanning, which required a 5-mm stratum depth. The scanning range included the section between the fourth thoracic vertebra and the fourth lumbar vertebra, and the images were transferred to a treatment planning system after restructuring as 2.5 mm per stratum. First, the clinical target volume (CTV), which includes the preoperative tumor bed, anastomotic stoma, duodenal stump and high-risk lymphatic drainage area, was delineated on the restructured CT images by combining contrast agent development, postoperative silver clips and preoperative imaging data (17,18). Planning target volume (PTV) included

CTV taking into consideration organ excursion, with the enlarged irradiation area caused by repeatability error of the patient's position during positioning and treatment, as well as taking into account a change of target positions and target volumes to ensure the irradiation dose of CTV. Accordingly, PTV usually included a 7-10-mm margin around CTV, with a 10-mm craniocaudal margin. The organs at risk included the spinal cord, liver, heart, kidney and small intestine.

The number of the beams and incidence angle were adjusted according to the ray path and the association of the tumor target volume with surrounding normal tissue, while the dose of each beam was weighted with the limits of the organs at risk calculated. The treatment plan was formulated through automatic optimization by a computer reverse planning system. Isocenter irradiation was conducted using 5 or 7 intensity-modulated irradiation fields, which were coplanar and non-through. The 5-field IMRT beam orientation was usually at the following gantry angle: 0, 72, 144, 216 and 288°; the 7-field IMRT beam orientation was usually at the following gantry angle: 0, 51, 103, 154, 206, 257 and 309°. Based on the patient's target shape and the dose to target volume and normal tissue, adjustments were made until the plan requirements were met. The prescription dose of 95% PTV was 45 Gy in 25 fractions (1.8 Gy/fr). The doses to each organ at risk were as follows: Maximum dose to the spinal cord ≤45 Gy; liver V30 <30%; mean dose to each kidney <18 Gy, V15 ≤50%; small intestine V50 ≤10%; heart dose V40 ≤30%, V30 ≤40%; whole-lung dose V20 ≤25%, V5 ≤60%.

Chemotherapy. For comparison, during concurrent CRT the patients were separated into two groups: 45 patients received intravenous infusion of 400 mg/m^2/day 5-fluorouracil and 20 mg/m^2/day tetrahydrofolic acid (THFA) 4 days before and 3 days after radiotherapy; and 57 patients received 825 mg/m^2 oral capecitabine twice each day (morning and evening) during radiotherapy, and four cycles of XELOX chemotherapy (capecitabine 1,000 mg/m^2 on days 1-14 + oxaliplatin 130 mg/m^2 on day 1, repeated every 3 weeks) 4 weeks after the end of radiotherapy.

Evaluation of toxicity. The Common Terminology Criteria for Adverse Events v3.0 (19) of the National Cancer Institute were used for the evaluation of toxicity.

Statistical analysis. Statistical analysis was performed using SPSS 19.0 software (Armonk, NY, USA). The Chi-square test was used for the comparison of rates and the Student's t-test was used for the comparison of means. The survival rate was calculated by non-parametric Kaplan-Meier test, while the log-rank test was used to compare survival curve distribution between the two groups and to determine whether the difference was statistically significant. The multivariate Cox regression model was used to perform multivariate analysis of prognosis. P<0.05 was considered to indicate statistically significant differences.

Results

Patients. A total of 102 patients who met the aforementioned criteria were enrolled in this study. The characteristics of these patients are listed in Table I. There were no significant

Table I. Clinicopathological characteristics of the 102 patients.

Characteristics	Total number (n=102)	F-CRT, n (%) (n=45)	C-CRT, n (%) (n=57)
Gender			
Male	69	31 (68.9)	38 (66.7)
Female	33	14 (31.1)	19 (33.3)
Age, years			
≤55	56	24 (53.3)	32 (56.1)
>55	46	21 (46.7)	25 (43.9)
Tumor site			
Esophagogastric junction	22	9 (20.0)	13 (22.8)
Gastric body	24	11 (24.4)	13 (22.8)
Gastric antrum	56	25 (55.6)	31 (54.4)
Pathological type			
Canalicular and papillary adenocarcinoma	62	27 (60.0)	35 (61.4)
Poorly differentiated adenocarcinoma	21	10 (22.2)	11 (19.3)
Others	19	8 (17.8)	11 (19.3)
Lymph node metastasis			
Yes	66	30 (66.7)	36 (63.2)
No	36	15 (33.3)	19 (36.8)
TNM stage			
IB	11	5 (11.1)	6 (10.5)
II	38	17 (37.8)	21 (36.8)
III	53	23 (51.1)	30 (52.7)
Vascular cancer embolus or neural invasion			
Positive	25	11 (24.4)	14 (24.6)
Negative	77	34 (75.6)	43 (75.4)

F-CRT, concurrent chemoradiotherapy with intravenous infusion of fluorouracil; C-CRT, concurrent chemoradiotherapy with oral capecitabine.

differences in gender distribution, age, tumor site, pathological type, TNM stage, or the extent of neurovascular invasion between the F-CRT and C-CRT groups. Overall, 98 patients completed the concurrent CRT; 4 patients only completed radiotherapy but not chemotherapy, due to the toxic side effects, including 3 patients from the F-CRT group who only completed the first 4-day concurrent chemotherapy without the subsequent 3-day chemotherapy, and 1 patient from the C-CRT group who received concurrent capecitabine for only 2 weeks. A total of 6 patients did not complete the subsequent 4-cycle XELOX chemotherapy, of whom 4 patients were from the F-CRT group (2 patients only received two cycles of chemotherapy, 1 received only one cycle, and 1 patient did not receive any subsequent chemotherapy) and 2 patients were from the C-CRT group (1 received only two cycles of chemotherapy, and 1 did not receive any subsequent chemotherapy).

Safety evaluation. The individual toxic side effects in the F-CRT and C-CRT groups during the entire course of treatment are shown in Table II. Overall, the incidence of grade 3 hematological toxicities (leukopenia, anemia and thrombocytopenia) was 23.5%; grade 3 gastrointestinal reactions (nausea, vomiting and diarrhea) 13.7%; grade 1-2 hepatic and renal function impairment 9.8%; and grade ≥3 hepatic and renal function impairment 0%. The most common grade 1-2 hema-

tological toxicity was anemia (76.5%), and the most common grade 3 toxicity was leukopenia (21.6%). Grade 1-2 gastrointestinal reactions included nausea (71.6%), vomiting (34.3%) and diarrhea (26.5%), and grade 3 gastrointestinal reactions included nausea (10.8%), vomiting (3%) and diarrhea (1%). During the entire course of treatment, the incidence of grade 3 hematological toxicities (leukopenia, anemia and thrombocytopenia) in the F-CRT and C-CRT groups was 28.9 and 19.3%, respectively, and the incidence of grade 3 gastrointestinal reactions (nausea, vomiting and diarrhea) was 17.8 and 10.5%, respectively. Grade 3 hematological toxicities and gastrointestinal reactions were more common in the F-CRT group, but the difference was not statistically significant. The incidence of grade 1-2 hepatic and renal function impairment in the F-CRT and C-CRT groups was 11.1 and 8.8%, respectively, but the difference was again not statistically significant. The incidence of grade 1-2 hand-foot syndrome was 35.6 and 40.4%, respectively, with 1 patient in each group experiencing grade 3 hand-foot syndrome, without statistically significant differences between the two groups (Table II).

As shown in Table III, during the concurrent CRT, the incidence of grade 1-2 hematological toxicities in the F-CRT group was significantly higher compared with that in the C-CRT group (73.3 and 50.9%, respectively; P=0.021). The incidence of grade 1-2 gastrointestinal reactions in the F-CRT group was

Table II. Toxicities in the F-CRT and C-CRT groups during the entire course of treatment.

| | F-CRT (n=45) | | C-CRT (n=57) | |
| | Grade 1-2 | Grade 3-4 | Grade 1-2 | Grade 3-4 |
Toxicities	n (%)	n (%)	n (%)	n (%)
Nausea	34 (75.6)	6 (13.3)	39 (68.4)	5 (8.8)
Vomiting	17 (37.8)	2 (4.4)	18 (31.2)	1 (1.8)
Diarrhea	12 (26.7)	1 (2.2)	15 (26.3)	0 (0.0)
Leukopenia	28 (62.2)	11 (24.4)	34 (59.6)	10 (17.5)
Anemia	35 (77.8)	2 (4.4)	43 (75.4)	2 (3.6)
Thrombocytopenia	13 (28.9)	1 (2.2)	17 (29.8)	0 (0.0)
HFS	16 (35.6)	1 (2.2)	23 (40.4)	1 (1.8)
ALT	4 (8.9)	0 (0.0)	5 (8.8)	0 (0.0)
GFR	1 (2.2)	0 (0.0)	0 (0.0)	0 (0.0)

F-CRT, concurrent chemoradiotherapy with intravenous infusion of fluorouracil; C-CRT, concurrent chemoradiotherapy with oral capecitabine; HFS, hand-foot syndrome; ALT, alanine aminotransferase; GFR, glomerular filtration rate.

Table III. Toxicities in the F-CRT and C-CRT groups during the concurrent radiochemotherapy.

| | F-CRT (n=45) | | C-CRT (n=57) | |
| | Grade 1-2 | Grade 3-4 | Grade 1-2 | Grade 3-4 |
Toxicities	n (%)	n (%)	n (%)	n (%)
Gastrointestinal	35 (77.8)	1 (2.2)	33 (57.9)	0 (0.0)
Hematological	33 (73.3)	1 (2.2)	29 (50.9)	1 (1.8)

F-CRT, concurrent chemoradiotherapy with intravenous infusion of fluorouracil; C-CRT, concurrent chemoradiotherapy with oral capecitabine.
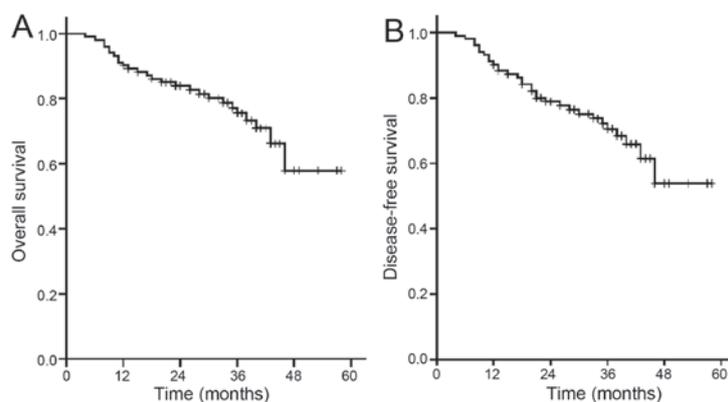

Figure 1. (A) Overall survival rate and (B) disease-free suvival rate of the 102 gastric cancer patients in this study.

also significantly higher compared with that in the C-CRT group (77.8 and 57.9%, respectively; P=0.034). However, during the concurrent CRT, no statistically significant difference was observed in grade 3-4 hematological toxicities and gastrointestinal reactions between the F-CRT and the C-CRT groups.

Survival analysis. The median follow-up time in the overall population was 40 months (range, 18-61.2 months), the follow-up rate was 98%, and loss to follow-up was considered as death. The 3-year survival rate was 75.5% and the disease-free survival rate was 70.5% (Fig. 1), while the survival rate was 84.3% in a local group.

As shown in Fig. 2, the total 3-year survival rate of the F-CRT and C-CRT groups was 72.2 and 78.5%, respectively (P>0.05), and the 3-year disease-free survival rate was 67.7 and 72.8%, respectively (P>0.05). No statistically significant differences were observed.

Table IV. Prognostic univariate analysis in the overall population.

Variables	Number	3-year survival rate	χ^2	P-value
Gender				
Male	69	76.8	2.613	0.116
Female	33	72.7		
Age, years				
≤55	56	73.2	1.436	0.217
>55	46	78.3		
Tumor site				
Esophagogastric junction	22	68.2	5.129	0.078
Gastric body	24	75.0		
Gastric antrum	56	78.6		
Pathological type				
Canalicular and papillary adenocarcinoma	62	79.0	5.682	0.062
Poorly differentiated adenocarcinoma	21	71.4		
Others	19	68.4		
Lymph node metastasis				
Yes	66	63.8	8.055	0.005
No	36	84.4		
TNM stage				
IB	11	90.9	7.420	0.024
II	38	86.8		
III	53	64.2		
Vascular cancer embolus or neural invasion				
Positive	25	70.2	4.426	0.038
Negative	77	82.4		
Chemotherapy				
5-FU+CF	45	72.2	3.204	0.085
Capecitabine	57	78.5		

5-FU, 5-fluorouracil; CF, leucovorin.

Analysis of prognostic factors. Lymph node metastasis, TNM stage, vascular cancer embolus and neural invasion are usually the factors that affect survival. In our study, as shown in Table IV, the 3-year survival rate of patients with and without lymph node metastasis was 63.8 vs. 84.4%, respectively (P=0.005; Fig. 3). The 3-year survival rate of patients with stage IB, II and III disease was 90.9, 86.8 and 64.2%, respectively (P=0.024; Fig. 4). The 3-year survival rate of patients with positive and negative neurovascular invasion was 70.2 and 82.4%, respectively (P=0.038; Fig. 5). In accordance with previous studies (11,12), lymph node metastasis, TNM stage and vascular cancer embolus or neural invasion are statistically significant prognostic factors, while factors such as gender, age, tumor site, pathological type and different chemotherapies were not significantly associated with prognosis.

To determine the independent prognostic factors, multivariate Cox regression analysis was used. As shown in Table V,
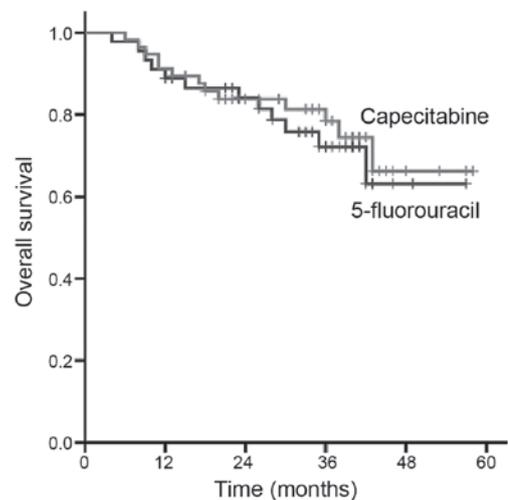

Figure 2. Overall survival rate with the two different chemotherapies.

Table V. Multivariate Cox regression analysis of prognosis after surgery for gastric cancer.

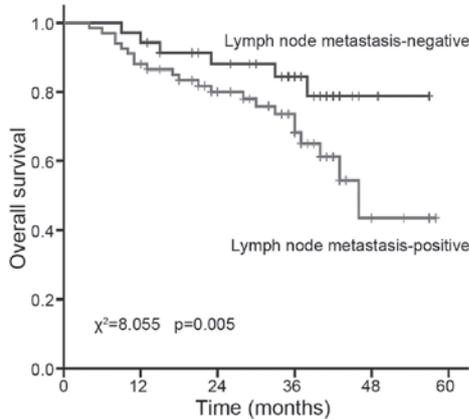| Variables	Regression coefficient (B)	Standard error	Statistics (Wald) value	P-value	95% confidence interval
TNM stage	0.304	0.121	5.136	0.032	1.084-1.843
Lymph node metastasis	0.362	0.146	6.523	0.010	1.097-1.965
Vascular/nerve invasion	0.148	0.092	2.385	0.138	0.984-1.764

Figure 3. Effect of lymph node status on overall survival rate.

Figure 4. Effect of TNM stage on overall survival rate.
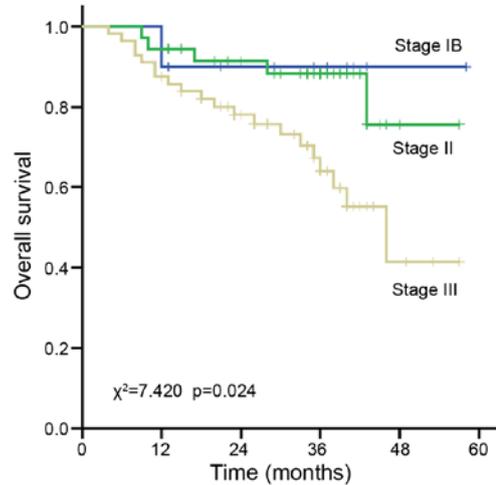

Figure 5. Effect of vascular cancer embolus and neural invasion status on overall survival rate.

lymph node metastasis and TNM stage were independent prognostic factors, while vascular and/or neural invasion was not identified as an independent prognostic factor.

Discussion

The majority of previous studies have compared adjuvant concurrent CRT after surgery with surgery alone in patients with gastric carcinoma undergoing D0/D1 surgery (11,20,21), while only a limited number of studies compared CRT after D2 radical surgery with surgery alone (12). As D2 resection (surgery with an enlarged range of lymph node dissection) is common in Asia, particularly in Eastern Asia, this study was focused on such patients in order to estimate the effects of concurrent CRT following D2 resection in gastric carcinoma.

The clinical SWOG 9008/INT-0116 study (11) was a milestone study designed to observe the effects of surgery and postoperative concurrent CRT in patients with resectable gastric and gastroesophageal junction carcinoma. The study included two groups, the R0 resection with concurrent CRT group (281 patients) and the surgery alone group (275 patients). All the patients had stage IB-IV (M0) gastric or gastroesophageal junction carcinoma, of whom 68% had stage T3 or T4 lesions, and 85% had lymph node metastasis (11). In the concurrent CRT group, the local recurrence rate was significantly reduced compared with that in the surgery alone group (19 vs. 29%, respectively), the median survival was significantly prolonged (36 vs. 27 months, respectively), the 3-year disease-free rate was significantly improved (48 vs. 31%, respectively), the survival rate was significantly improved (50 vs. 41%, respectively; P=0.005) and the incidence of grade 3-4 adverse reactions was 41 and 32%, respectively (11). Moreover, concurrent CRT
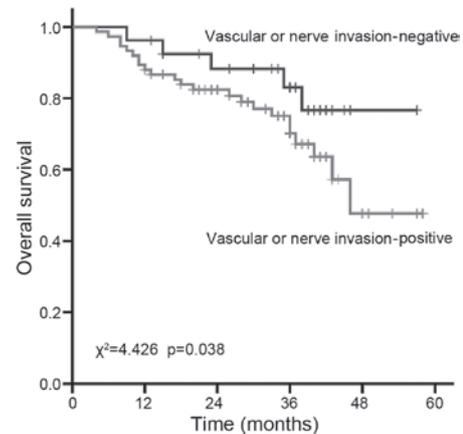
after surgery was shown to benefit patients with stage IB-IV (M0) gastric cancer without increasing chronic toxicity in a follow-up study (20). The INT-0116 study established the use of concurrent CRT as standard postoperative adjuvant treatment of gastric carcinoma in the US and several European countries (21). However, a major disadvantage of that study was that only 10% of the selected patients received D2 resection, while 36% of the patients received D1 resection, and over half of the patients (54%) received <D0 resection.

Kim *et al* compared the outcome of gastric carcinoma patients with or without CRT following D2 radical surgery (12), of whom 554 patients had CRT after D2 radical

surgery, while 446 patients had D2 radical surgery alone. A significant increase in the median survival time and median relapse-free survival time were observed in the concurrent CRT group compared with the surgery alone group. The 5-year survival rate (57.1 vs. 51.0%, P=0.0198) and relapse-free rate (54.5 vs. 4.9%, P=0.0161) of the concurrent CRT group were significantly higher compared with those in the surgery alone group, and the mortality risk was reduced by 20% (12). These data indicated that concurrent CRT following D2 gastric cancer surgery may improve the survival rate and reduce the recurrence rate.

In the ARTIST study (13), which aimed to compare the results of the gastric cancer patients who had received concurrent CRT with those of patients who had received chemotherapy alone, 228 patients were randomized into the 6-cycle adjuvant chemotherapy XP group (capecitabine plus cisplatin) and 230 patients were randomized to receive 2-cycle concurrent XP chemotherapy, sequential concurrent CRT (total dose of 45 Gy in 25 fractions + capecitabine), and sequential 2-cycle XP chemotherapy. After a median follow-up of 53.2 months, no significant differences were found in 3-year disease-free survival rate (78.2% for CRT vs. 74.2% for chemotherapy; P=0.0862), but only marginal differences were found in the 3-year disease-free survival rate in patients with positive lymph nodes (77.5 vs. 72.3%, respectively; P=0.0365) (13).

In our study, the 3-year survival rate in patients who received concurrent CRT following gastric cancer surgery was 75.5%, and the disease-free survival rate was 70.5%, while the local control rate was 84.3%. However, a limitation of our study was that we only investigated concurrent CRT after surgery, without setting up control groups to compare with surgery alone and postoperative chemotherapy alone. However, the 3-year disease-free survival rate was higher compared with that reported in the INT-0116 study, which may be explained by the fact that all our patients had received D2 radical surgery, suggesting a better prognosis with chemotherapy after D2 surgery rather than D0/D1 surgery in terms of disease-free survival. When compared to the ARTIST study, our study demonstrated a lower 3-year disease-free survival rate, possibly because all our patients were at advanced TNM stage, which is also the cause for the outcome differences with treatments between European patients and patients from Japan and Korea.

Since the adjuvant concurrent CRT was limited by the tolerance dose of major organs, such as the gastrointestinal tract, liver and kidney, the conventional radiotherapy usually led to the intolerable radiation reactions in the gastrointestinal tract, liver and other organs at risk. Compared with conventional radiotherapy and 3DCRT, IMRT had the advantage of three-dimensional conformity of high doses to the target volume, increasing the total dose delivered (14,15). Milano et al (14) also reported that the IMRT reduced the liver V30 (63.6 vs. 18.9%, P=0.010) and right kidney V20 (20.9 vs. 11.6%, P=0.027) compared with 2/3-field 3DCRT. Boda-Heggemann et al (22) observed that the V30 of the left and right kidneys was 26.8 vs. 19.5%, respectively (P=0.0015) when investigating 27 patients who received concurrent CRT with 3DCRT. A study conducted by Stanford University (23) also indicated that IMRT led to a reduction of the liver V30 from 28 to 16.1% compared with 3DCRT. Moreover, IMRT

also improved the postoperative gastric cancer treatment. Badakhshi et al (24) investigated 25 cases of patients who received concurrent CRT with IMRT after gastric cancer surgery, and observed that the incidences of grade 3 nausea and diarrhea during treatment were 4 and 8%, respectively, and the incidences of grade 3 decrease in hemoglobin level, leukocyte and platelet counts were 12, 25 and 4%, respectively.

Both the INT-0116 study and ARTIST trial used front-back parallel opposed-field radiotherapy (11). In our study, we used 5/7-field IMRT, with an incidence of grade 3 hematological toxicities during treatment of 23.5%; grade 3 gastrointestinal reactions of 13.7%; grade 1-2 liver and kidney function impairment of 9.8%; and grade 3 liver and kidney function impairment of 0%; these findings were similar to the results reported by Badakhshi et al (24). In addition, we observed that grade 3 hematological toxicities and gastrointestinal reactions mostly occurred due to the cumulative effect of subsequent adjuvant chemotherapy, and the toxic effects were usually grade 1-2 during concurrent CRT. Moreover, all the patients were able to tolerate concurrent CRT after symptomatic treatment.

The concurrent chemotherapy used by the INT-0116 study was 5-fluorouracil + leucovorin, and the efficacy and safety of oral capecitabine as concurrent CRT following gastric cancer surgery had also been demonstrated (25-27). The CLASSIC trial (28) demonstrated the effectiveness and good tolerance of capecitabine plus oxaliplatin as adjuvant therapy after gastric cancer surgery. To determine the differences between 5-fluorouracil and capecitabine, we compared the F-CRT and C-CRT groups following concurrent CRT, with 45 patients receiving concurrent chemotherapy for the first 4 and last 3 days of radiotherapy with 400 mg/m^2/day fluorouracil and 20 mg/m^2/day THFA, and 57 patients receiving 825 mg/m^2/day capecitabine twice daily (in the morning and evening) during the radiotherapy. The 3-year overall survival rate of the F-CRT and C-CRT groups was 72.2 and 78.5%, respectively (P>0.05); and the 3-year disease-free survival rate was 67.7 and 72.8%, respectively (P>0.05); the differences were not statistically significant. During the entire therapy course, the grade 1-2 hematological toxicities and grade 1-2 gastrointestinal reactions were similar between the F-CRT and C-CRT groups; the incidence of grade 3 hematological toxicities was 28.9 and 19.3%, respectively; the incidence of grade 3 gastrointestinal reactions was 17.8 and 10.5%, respectively; there was no statistically significant difference. However, the incidences of grade 1-2 hematological toxicities in the F-CRT and C-CRT groups were 73.3 vs. 50.9%, respectively (χ^2=5.320; P=0.021) and the incidences of grade 1-2 gastrointestinal reactions 77.8 vs. 57.9%, respectively (χ^2=4.474; P=0.034) during concurrent CRT. Thus, concurrent chemotherapy with capecitabine reduced grade 1-2 hematological toxicities and grade 1-2 gastrointestinal reactions in the C-CRT group, and was able to help the patients tolerate and complete the radiotherapy.

As regards prognostic factors following gastric cancer surgery, most scholars consider the status of lymph node metastasis to be an important independent factor affecting the prognosis of gastric cancer (29,30). Other studies demonstrated that the prognosis of the patients was associated with the absolute number of positive lymph nodes when the lymph node sampling was sufficient (16 required by TNM, AJCC 7th edition); however, the metastatic lymph node ratio and

log odds of positive lymph nodes may be used to better assess prognosis when lymph node sampling was inadequate (31,32). In addition to the status of lymph node metastasis, the factors affecting the prognosis of gastric cancer also included TNM stage, depth of tumor infiltration, vascular invasion and nerve invasion (33,34). Histological classification (34) and tumor size (35,36) may also be used to predict the prognosis of patients with advanced gastric carcinoma. We also evaluated the prognostic factors of patients following gastric cancer surgery, with the single-factor analysis showing that lymph node metastasis, TNM stage and intravascular cancer emboli or perineural invasion were the factors affecting patient survival, while the other factors, including gender, age, tumor site, pathology and different chemotherapies, were not significantly correlated with prognosis. The multivariate Cox regression analysis indicated that lymph node metastasis and TNM stage were independent prognostic factors for the patients (Table V).

In conclusion, our study analyzed 102 cases of gastric carcinoma patients receiving CRT following D2 surgery, with similar overall survival rates observed compared with previous reports, while the toxic side effects were reduced by using IMRT. No significant difference in survival rates was observed between oral capecitabine or intravenous infusion of fluorouracil. However, concurrent chemotherapy with capecitabine was associated with fewer hematological toxicities and gastrointestinal reactions compared with intravenous infusion of fluorouracil; thus, the patients were able to better tolerate and complete the radiotherapy.

Acknowledgements

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