Oncology and Translational Medicine
DOI 10.1007/s10330-018-0261-1

June 2018, Vol. 4, No. 3, P85–P92

ORIGINAL ARTICLE

Postoperative sequential chemotherapy and radiotherapy for locally advanced gastric cancer

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Abstract

Objective The aim of the study was to evaluate the role of postoperative sequential chemotherapy and radiotherapy in patients with locally advanced gastric cancer.

Methods From January 2003 to December 2010, 146 gastric cancer patients at our institution (Department of Oncology, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China) received postoperative sequential chemotherapy and radiotherapy after radical surgery. Radiotherapy was administered as a dose of 4500 cGy in 25 fractions. For patients with positive margins, the dose was raised to 5040 cGy in 28 fractions. Three cycles of mFOLFOX or PF (cisplatin, 5-fluorouracil) chemotherapy regimen were applied before and after radiotherapy. Three- and 5-year survival rates were analyzed; any adverse effects with respect to hematology, hepatic and renal function, or the gastrointestinal tract that occurred during the treatment were evaluated.

Results This cohort consisted of non-metastatic patients: 104 men and 42 women with a median age of 51.0 years. The full course of sequential chemotherapy and radiotherapy (4500–5040 cGy) was completed by 129 patients (88.4%). Seventeen regional relapses (9.8%) and 46 distant relapses (23.8%) were recorded. Fifty patients (34.2%) died during follow-up. The 3- and 5-year overall survival rates (OS) were 60% and 54%, and disease-free survival rates (DFS) were 53% and 47%, respectively. There were no significant differences in survival rate with respect to age, sex, histopathology, N stage, site of the tumor, or margin status. Multivariate analysis showed that only the depth of tumor invasion (T stage) was an independent prognostic factor for OS (P = 0.009) and DFS (P = 0.006). The rates of grades 3 and 4 neutropenia and vomiting were 9.6% and 3.4%, respectively, during the treatment.

Conclusion Postoperative sequential chemotherapy with an mFOLFOX or PF regimen and radiotherapy were found to be an effective means of treating advanced gastric cancer patients with T3–T4 disease. The adverse effects of this treatment were tolerable.

Received: 22 March 2018
Revised: 16 April 2018
Accepted: 20 May 2018

Key words: advanced gastric cancer; sequential chemotherapy; radiotherapy; survival rate

Gastric cancer ranks second among the most common cancers with respect to morbidity rate and third with respect to the mortality rate in China. In 2015, approximately 679 100 new upper gastrointestinal cancer cases were reported in China, and these were responsible for 498 000 deaths [1]. China is a high-incidence area for gastric cancer, and the situation shows no sign of improvement except in a few local areas. The mortality rate of gastric cancer can be attributed contributes more to more than 20% of all the cases of cancer metastasis in China [2]. Complete surgical resection is currently the most effective and potentially curative treatment available to patients with gastric cancer; however, only 25%–40% of first-time gastric cancer patients are eligible for radical surgery [3]. The overall 5-year survival rate has been only 20%–30% over the past 30 years [4–5].

Even after complete resection with negative margins, the risk of T3–4 and N1–3 local recurrence (local lymph node, peritoneum) remains high. Postoperative chemotherapy showed benefits for Asian patients; however, the recurrence rate was not reduced. This suggests that it is important to consider postoperative

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adjuvant therapy for patients with gastric cancer. In the INT0116 studies, postoperative chemoradiotherapy was shown to reduce local recurrence and promote survival [6–8]. In these studies, more than 90% of the patients were treated with D0- or D1-resection, but some studies have shown that chemoradiotherapy (CRT) can also decrease the rate of local recurrence in patients with D2-resection. The recently updated analysis of the INT0116 reveals that adjuvant CRT also potentiates the treatment benefit on overall survival (OS) in a subset of patients with D2 dissection [9], similar to a Korean retrospective study [10]. In the ARTIST trial [11], the largest phase III trial comparing CRT versus chemotherapy in patients with D2 gastrectomy, no statistical difference in 3-year disease-free survival (DFS) was observed between the two arms. Furthermore, the addition of radiotherapy (RT) to chemotherapy did not positively impact the pattern of relapse (locoregional or distant). In a subgroup analysis of 396 patients with positive pathologic nodes, however, there was a significant prolongation of 3-year DFS for CRT over chemotherapy (77.5% vs. 72.3%; P = 0.0365). However, a recent meta-analysis showed that postoperative CRT could benefit the survival of gastric cancer patients, especially regarding 5 year DFS, independent of surgical procedure [12]. Therefore, many controversies remain over the role of RT for gastric cancer after surgery.

With the latest clinical data providing convincing evidence of the link between D2 dissection and lower recurrence rates in patients with resected gastric cancer, both the European Society for Medical Oncology and the US National Comprehensive Cancer Network (NCCN) have recommended D2 dissection for those patients, leading to a worldwide consensus [13–14]. However, due to the difference between Eastern and Western surgical methods and the race of the patients, it has been difficult to determine which treatment is the most beneficial. Although the INT0116 trial was initiated in the early nineties, the concept of concurrent CRT has not become widespread in China. The biggest obstacle to its application comes from its adverse hematological and gastrointestinal effects. In the INT0116 study, 17% of the patients did not complete the treatment because of side effects [6]. As our previous studies showed, the adverse effects of postoperative sequential CRT were no greater than those of chemotherapy alone [15]. Therefore, we have designed a postoperative CRT sequence, aimed at reducing toxicity while maintaining curative effects similar to concurrent CRT.

Patients and methods

This is a retrospective analysis of a series of patients identified in our database from Department of Oncology, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China. Between January 2003 and December 2010, 168 patients with pathologically confirmed adenocarcinoma of the gastroesophageal junction or stomach were treated with sequential chemotherapy and RT. Among them, 146 patients who underwent surgery with curative intent received adjuvant sequential chemotherapy and RT, and 22 patients received palliative CRT. The patients included in this study met the following criteria: staging done according to the 7th edition of the American Joint Commission on Cancer Staging Manual; no metastatic disease; Eastern Cooperative Oncology Group performance status (PS) score of 0–1; serum creatinine (mg/dL) ≤ 1.5× the upper limit of normal; total bilirubin (mg/dL) ≤ 1.5× the upper limit of normal; alanine aminotransferase ≤1.5× the upper limit of normal; and no preoperative chemotherapy. Treatment began as soon as possible and no later than 4 weeks after surgery. The pretreatment evaluations included physical examination, tumor markers, and computed tomography (CT) to rule out metastatic disease.

In our investigation, 146 patients received the regimen of RT and sequential chemotherapy. Chemotherapy consisting of oxaliplatin, 5-fluorouracil (5-FU) and leucovorin (mFOLFOX) was administered to 113 patients. Chemotherapy consisting of 5-FU/cisplatin (PF) was administered to 33 patients during the same treatment period. Postoperative CRT was performed sequentially after surgery. First, three cycles of chemotherapy were administrated to patients, followed by radiotherapy. Subsequently, the patients underwent another three cycles of chemotherapy.

Postoperative chemotherapy regimen: The mFOLFOX regimen was as follows: oxaliplatin 130 mg/m^2 d1; 5-FU 425 mg/m^2 d1–5; leucovorin 200 mg/m^2 d1–5 every 3 weeks. The PF regimen was as follows: cisplatin 80 mg/m^2 d1; 5-FU 800 mg/m^2 d1–5 every 3 weeks.

Radiotherapy was delivered following the recommendations outlined in INT0116 [11]. All patients were treated using a standardized 3D conformal technique. When available, the preoperative and postoperative scans and endoscopic, surgical, and pathological reports were reviewed. Patients had CT simulations performed at least 1 week before the beginning of radiotherapy. The CT simulation slice thickness was 5 mm. Patients were scanned in the supine position with their arms above their heads. A total radiation dose of 45 Gy was delivered in 25 fractions at 1.8 Gy per fraction, 5 days per week over 5 weeks. The patients with positive margins were given booster doses of 5.4 Gy to a total radiation dose of 50.4 Gy. Dose variation in the planning target volume (PTV) was kept within +7% and –5% of the prescribed dose in accordance with ICRU 50/62 recommendations.

Radiation was delivered using 6–15 MV photons with a linear accelerator. The clinical target volume (CTV) and the design of the radiation treatment fields were individualized depending upon the extent and location of the primary tumor and involved lymph nodes and on the type of surgery performed. Lymph node stations in the radiation fields included perigastric, coeliac, splenic hilar, suprapancreatic, porta hepatis, pancreaticoduodenal, and local paraaortic nodes. In patients with tumors of the gastroesophageal junction, paracardial and paraesophageal lymph nodes were included in the radiation fields, but pancreaticoduodenal radiation was not required. The PTV consisted of the CTV with a 1-cm margin. The organs at risk were contoured, which included the kidneys, liver, heart, and spinal cord. At least two-thirds of one kidney was spared. No more than 30% of the heart received more than 40 Gy, and no more than two-thirds of the liver received more than 30 Gy. The maximum spinal cord dose was less than 45 Gy. A dose-volume histogram was used to ensure that the dose tolerances were met for the nearby critical organs.

Acute toxicity data were graded according to the Radiation Therapy Oncology Group Acute Radiation Morbidity Scoring Criteria. Hematologic toxicity was graded using the National Cancer Institute Common Toxicity Criteria version 3. Postoperative follow-up by the treating oncologist was scheduled every 3 to 6 months for the first 2 years and every 6 months thereafter. Follow-up included taking detailed patient histories and performing physical examinations. Neither routine endoscopy nor CT scans (chest, abdomen, or pelvis) were performed unless clinically warranted. Patients were followed with routine complete blood count (CBC), chemistry, carcinoembryonic antigen (CEA), and CA 19-9 at every follow-up (as per GAST-5 NCCN guidelines). Sites of first failure (locoregional or distant) were also documented.

Locoregional recurrence was defined as any recurrence in the tumor bed, anastomosis site, gastric remnant, duodenal stump, or regional nodes within the irradiated volume.

Distant metastases were defined as any recurrence outside of the irradiated field, including metastases to the liver, lower paraaortic lymph nodes, and extra-abdominal sites, and peritoneal seeding. DFS was measured from the date of radical surgery to the date of the first recurrence of the disease. OS was also recorded from the date of radical surgery until death from any cause.

Statistical analysis

The data were analyzed using SPSS version 13.0 (SPSS Inc., Chicago, IL). Patient survival was calculated using the Kaplan-Meier method. To assess the importance of potential prognostic factors, we performed univariate and multivariate analyses using log-rank testing and a Cox proportional hazards regression model. *P*-values < 0.05 were considered significant.

Results

The cohort consisted of 146 patients; 104 men and 42 women. Patient and tumor characteristics are outlined in Table 1. The mean age was 51.0 years (range, 24–66 years) and the median age was 50.0 years. All of the patients had a PS score of 0 or 1. Hundred and twelve (76.7%) underwent subtotal gastrectomy, and 34 underwent total gastrectomy (23.3%). Hundred and thirty-one patients (89.7%) had negative margins, whereas 15 had infiltrated surgical margins. Hundred and seventeen patients (81.3%) had T3–T4 primary tumors. Ninety-three patients (76.2%) had regional nodal involvement. Thirty-four patients had a D1 nodal clearance, and 112 patients had D2 surgery. Refer to Table 1 for detailed patient characteristics.

Table 1 Characteristics of patients selected

Characteristics	No.	%
Sex		
Male	104	71.2
Female	42	28.8
Median age (range, years)	51 (24–66)	
Pathological type		
Well differentiated adenocarcinoma	11	7.5
Moderately differentiated adenocarcinoma	21	14.4
Poorly-undifferentiated differentiated adenocarcinoma	114	78.1
Surgery		
Subtotal gastrectomy	112	76.7
Total gastrectomy	34	23.3
Tumor location		
Gastroesophageal junction (cardia)	38	26.0
Gastric body	24	16.4
Antrum / pylorus	76	52.1
The broader areas beyond the range of the above requirements	8	5.5
Lymph node dissection		
D1	34	23.3
D2	112	76.7
pT stage*		
T1	10	6.9
T2	18	13.0
T3	85	58.2
T4	32	21.9
pN stage*		
N0	32	21.9
N1	28	19.2
N2–3	86	58.9
Margin		
R0	131	89.7
R1	15	10.3

*According to AJCC staging manual (seventh edition)

As of December 2016, the median follow-up was 47.5 months. Twenty patients were lost to follow-up, and the follow-up ratio was 86.3%. The full course of CRT was completed by 129 patients (88.4%). Of the patients who could not complete the sequence as planned, 17 patients interrupted it for grade 4 gastrointestinal toxicity. Fifteen patients with positive margins were administered the booster dose of 540 Gy and a total radiation dose of 5040 Gy. Thirty-three and 113 patients received PF and mFOLFOX, respectively. Acute toxicity was recorded during the CRT regimen and throughout the adjuvant chemotherapy cycles (Table 2). The most common acute adverse effect was gastrointestinal side effects in 103 patients (70.5%) with only 3.4% experiencing grade 3 or 4 toxicity. Hematologic toxicity was the second most common side effect, with 9.6% of patients developing grade 3 or 4 neutropenia. Six episodes of febrile neutropenia were recorded.

Among the total 146 patients in the cohort, 63 (43.1%) experienced relapse during the follow-up period. Isolated locoregional recurrence was observed in 17 patients and relapsed distant disease in 46 patients. One hundred and four patients were followed up for survival. The median OS time has not yet been reached for the entire cohort. Fifty patients (34.2%) died during follow-up. All 48 patients who experienced relapse died. Two patients died during remission, probably due to renal failure. The 3-year and 5-year OS rates were 60% and 54%, and DFS rates were 53% and 47%, respectively (Fig. 1). There were no significant differences in 5-year survival rate after postoperative CRT with respect to age, sex, history, pathology, N stage, tumor location and size, lymph node dissection, or the presence of a positive incisal margin (Tables 3 and 4). By multivariate analysis, only the depth of tumor invasion (T stage) remained a statistically significant factor for survival (Fig. 2).

Table 2 Acute toxicity of sequence chemoradiotherapy (*n*)

Acute toxity	Sequence chemoradiotherapy group			
	I (%)	II (%)	III (%)	IV (%)
Leucopenia	60 (41.1)	14 (9.6)	11 (7.5)	2 (1.4)
Neutropenia	68 (46.6)	10 (6.8)	12 (8.2)	2 (1.4)
Anemia	9 (6.2)	15 (10.3)	4 (2.7)	0 (0)
Thrombocytopenia	0 (0)	6 (4.1)	5 (3.4)	0 (0)
Nausea, vomiting	58 (31.5)	40 (27.4)	4 (2.7)	1 (0.7)
Liver function	11 (7.5)	2 (1.4)	2 (1.4)	0 (0)
Kidney function	0 (0)	1 (0.7)	2 (1.4)	0 (0)

Table 3 Cox model analysis for OS

	B	SE	Wald	*P*	Exp (B)	95.0% CI for Exp (B)	
						Lower	Upper
Age	–0.090	0.393	0.053	0.818	0.914	0.423	1.975
Gender	–0.291	0.332	0.771	0.380	0.747	0.390	1.432
Smoking history	–0.249	0.375	0.442	0.506	0.779	0.374	1.625
Drinking history	–0.543	0.427	1.621	0.203	0.581	0.252	1.340
Pathology	0.101	0.282	0.128	0.721	1.106	0.636	1.921
Tumor location	0.003	0.168	0.000	0.985	1.003	0.722	1.394
Tumor size	0.105	0.150	0.490	0.484	1.110	0.828	1.489
Lymph node dissection	–0.455	0.387	1.386	0.239	0.634	0.297	1.354
pT stage	0.551	0.212	6.760	0.009	1.736	1.145	2.630
pN stage	0.085	0.138	0.379	0.538	1.088	0.831	1.426
Margin	0.823	0.432	3.630	0.057	2.277	0.977	5.307

Table 4 Cox model analysis for DFS

	B	SE	Wald	*P*	Exp (B)	95.0% CI for Exp (B)	
						Lower	Upper
Age	0.034	0.362	0.009	0.925	1.035	0.509	2.102
Gender	0.057	0.306	0.034	0.853	1.058	0.581	1.928
Smoking history	0.031	0.312	0.010	0.920	1.032	0.560	1.901
Drinking history	–0.647	0.352	3.384	0.066	0.524	0.263	1.043
Pathology	0.182	0.255	0.505	0.477	1.199	0.727	1.978
Tumor location	0.128	0.155	0.686	0.408	1.137	0.840	1.539
Tumor size	0.078	0.137	0.328	0.567	1.081	0.827	1.413
Lymph node dissection	–0.232	0.313	0.552	0.458	0.793	0.429	1.463
pT stage	0.545	0.200	7.447	0.006	1.724	1.166	2.550
pN stage	0.171	0.128	1.784	0.182	1.186	0.923	1.525
Margin	0.661	0.397	2.775	0.096	1.936	0.890	4.212

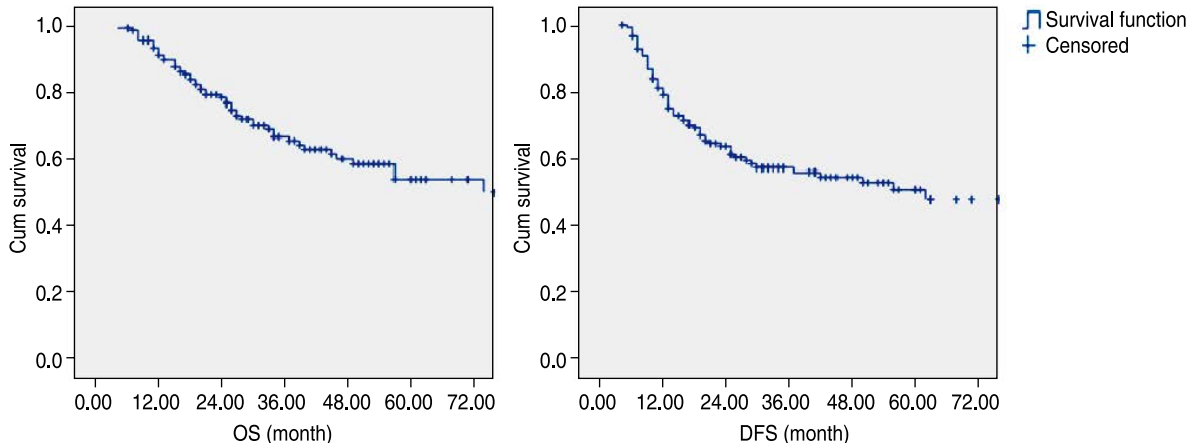

Fig. 1 OS and DFS of 146 patients with advanced gastric cancer. The 3-year and 5-year OS were 60% and 54% and DFS were 53% and 47%, respectively.

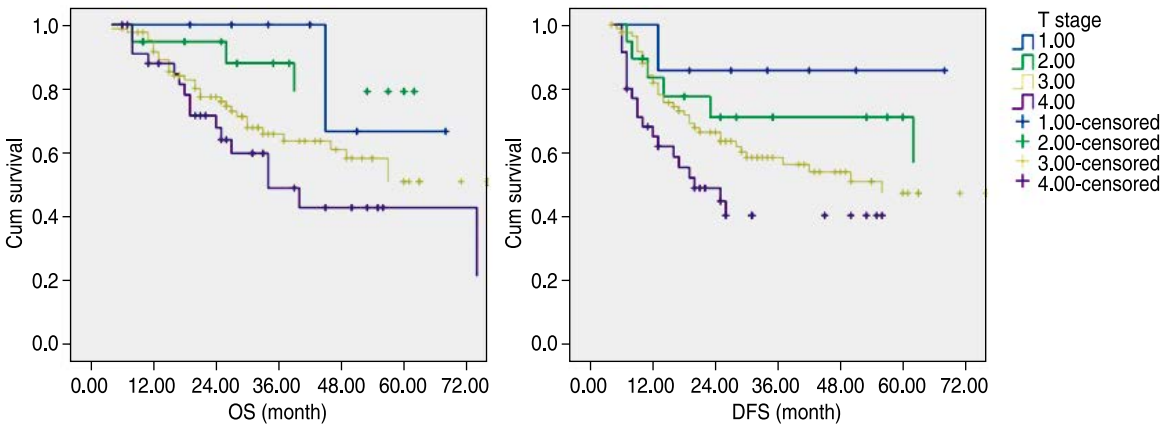

Fig. 2 Comparision of OS and DFS in the subgroup of patients with T stage. Depth of tumor invasion (T stage) was the independent prognostic factors for OS (P = 0.009) and DFS (P = 0.006).

Discussion

Currently, the benefits of adjuvant therapy for gastric adenocarcinoma are disputed due to conflicting results from trials. Western studies have shown that it offers either no or minimal benefits. Hermans *et al* analyzed 11 relevant randomized trials from 1980 to 1991 in which postoperative adjuvant chemotherapy was compared to surgery alone for patients with gastric cancer [odds ratio (OR) = 0.88; 95% confidence interval (CI), 0.78 to 1.08] [16]. They concluded that postoperative chemotherapy, in general, offers no additional survival benefit for patients. Earle *et al* revisited a meta-analysis of 13 randomized trials in non-Asian countries and found that adjuvant chemotherapy may produce a small survival benefit with borderline statistical significance [17]. In a randomized trial in Japan that analyzed studies of stage II and III gastric cancer (ACTSGC), patients underwent extended (D2) lymph node dissection followed by adjuvant therapy with S-1 treatment. The 3-year OS rate was 80.1% in the adjuvant group and 70.1% in the surgery-only group [18]. Janunger *et al* performed a meta-analysis of 21 randomized studies and found a small survival benefit for the patients with postoperative adjuvant chemotherapy relative to patients who had undergone surgery alone (OR = 0.84, 95% CI 0.74 to 0.96) [19]. They found that the survival benefit was only apparent in Asian and not in Western patients. Therefore, they recommended adjuvant chemotherapy for Asian patients only. In the MAGIC trial, perioperative chemotherapy was found to benefit Western patients significantly [20]. These studies suggest that postoperative and perioperative chemotherapy may have survival benefits relative to surgery alone.

In our study, the 3-year and 5-year OS rates after postoperative sequential CRT were found to be 60% and 54%, respectively. This improved survival rate may

primarily be the result of the more extensive surgical methods (D2 lymph node resection). In the sequential CRT group, 76.7% of patients underwent D2 lymph node resection; whereas only 10% of the patients in the INT0116 trial underwent any kind of D2 dissection. Of these, 54% had a D0 dissection. In an analysis of variations in surgical treatment in an INT0116 trial, Hundahl *et al* pointed out that surgical undertreatment can undermine survival in gastric cancer patients [21]. Although the INT0116 study with its low D2 resection rate could not show whether postoperative CRT was better than surgery, other studies in Korea and Europe revealed that postoperative CRT could significantly reduce the rate of local recurrence and promote OS [22–23]. Another cause of this improved survival rate may have been the different races of the patients studied. Some Asian studies showed the OS rate of Asian patients with postoperative CRT to be higher than that of Western patients as mentioned above [19]. The main explanation may be that more cases of distal gastric cancer occur in Asian patients. Our study is a good example of this (68.5% distal gastric cancer). The use of new chemotherapeutic drugs, such as oxaliplatin, may have also contributed to the higher survival rate observed in sequential CRT treatment for advanced gastric cancer patients. Oxaliplatin was 10 times more quickly and tightly combined with DNA than cisplatin. Furthermore, the toxic effects of oxaliplatin were also lower than those of cisplatin. The toxicity of oxaliplatin in the gastrointestinal tract and kidneys has been shown to be significantly lower than that of cisplatin; therefore, oxaliplatin is more easily accepted by gastrointestinal cancer patients. Literature has shown chemotherapy with oxaliplatin and 5-FU for metastatic gastric cancer to be effective and highly tolerable [24–25]. A REAL-2 study showed that oxaliplatin could promote survival in gastric cancer [26]. In recent years, exploratory research has confirmed that docetaxel, oxaliplatin, and 5-FU along with concurrent CRT can improve the survival rate of locally advanced gastric cancer patients [27–28].

In this study, univariate analysis showed no statistically significant differences in survival. However, in multivariate analysis, the degree of tumor infiltration was affected in patients with gastric cancer. With the depth of tumor invasion increasing, from T1 to T4, the survival period of the patients decreased gradually. It will significantly shorten the survival time of patients when tumor penetrates serosa or invades serosa tissue.

Subgroup analysis revealed that the survival rate of patients with stage T3–T4 was lower than that of patients with stage T1–T2, and in multivariate analysis, the degree of tumor infiltration (T staging) affected OS and DFS of patients with gastric cancer. From stage T1 to T4, the survival rate decreased, especially for tissues of the serous or outer serous invaded by the tumor. This differs from the results of previous studies [9–11]. There was no difference in 3-year and 5-year survival rate by N stage or margins status (positive or negative). D2 lymph node dissection and CRT appeared to improve local-regional control and survival in N1–3 patients whose 3-year and 5-year survival rates were near the level of survival for early gastric cancer patients. Radiation might minimize the effects of stage on survival in locally advanced gastric cancer patients. However, the size of the sample examined in our study was small. These principles should be reevaluated through further study. After the 45 Gy radiotherapy, we boosted radiation to 50.4 Gy using small-field intensity-modulated radiation for positive margin patients. No difference in survival was observed between patients with positive and negative margins. Stiekema *et al* found that CRT significantly improved survival after a microscopically non-radical (R1) resection [29]. These results indicate that RT might be a suitable postoperative supplementary treatment.

Equally important, sequential CRT was designed to decrease the high levels of acute toxicity of normal concurrent CRT. It has been reported that the incidence rates for blood and gastrointestinal toxicities of postoperative CRT in gastric cancer were 10%–30% [30]. Changes in blood cells and gastrointestinal adverse effects were monitored closely in the sequential CRT group. The most common side effects were leucopenia, neutropenia, and gastrointestinal effects. Overall, sequential CRT treatment showed a decreased toxicity profile. The incidence of grade 3/4 leucopenia and granulopenia was below 10%. That of other types of toxicity was low (< 5%). Adverse effects were found to continue for 6 months to 1 year. Toxicity was tolerable after aggressive treatment, and no treatment-related deaths occurred. The 3D-CRT technique in our treatment resulted in equivalent CTV coverage with significantly decreased doses to the left kidney, liver, and gastrointestinal tract relative to the two anteroposterior fields in the INT0116 trial. No significant abnormal liver or kidney function was observed, despite the radiation doses administered to the liver and kidney during the current study. No delayed complications of the gastrointestinal tract, liver, or kidneys were observed after 3 years of follow up. We believe that this low toxicity was the most important reason why the curative effect of our trial was better than that of INT0116. Only 11.6% (17/146) of the patients were unable to complete the treatment due to gastrointestinal adverse effects.

Due to the lack of any postoperative chemotherapy-only group to use as a control, we could not ultimately determine whether the higher 3-year survival rate was the sole result of RT or whether RT and chemotherapy had equal effects. Although tumor staging did not turn out to be significant in our database, these results may

reflect that in a higher proportion of patients, poorly differentiated adenocarcinoma was in stage Ib–II; some patients may have had signet-ring cell carcinoma. Another reason for obtaining such unconventional results might be due to the fact that we had a 13.7% loss in the follow-up. If we assume all of them are alive, the survival rates could be substantially higher in patients with stage Ib–II disease. Therefore, the results of this study may not be representative of all gastric cancer cases in stage Ib–II but could demonstrate the fact that the majority of patients in stage III–IVa gastric cancer at our institution have similar survival to those in stage Ib–II after postoperative sequential chemotherapy and RT. We also acknowledge the necessity of enrolling more patients for further study. Meanwhile, it would be valuable to know whether intensity modulated radiation therapy (IMRT) is a better technique than 3D-CRT with respect to RT technology. The optimal regimen for postoperative CRT has not yet been established. Further studies on this topic must explore optimization of the chemotherapy regimen, define the role of RT, establish ways of integrating it into treatment schema (pre- vs. postoperative), and explore the effects of treatment timing (preoperative, postoperative, or both) [31–32]. Targeted therapies have recently made their way into the treatment of gastric cancer with the approval of trastuzumab for the treatment of metastatic gastric cancer with human epidermal growth factor receptor 2 positive [33]. Anti-angiogenics (bevacizumab) and anti-epidermal growth factor receptor agents (cetuximab) are also being studied in adjuvant settings.

In conclusion, for all patients with high-risk gastric cancer, especially pT3–T4 stage, the combination of postoperative local-regional radiation with systematic chemotherapy applied to patients in a sequential fashion is a feasible option. The effects of sequential CRT appear promising. The treatment was well tolerated with few grade 3 to 4 toxicities. Thus, further investigation into the role of postoperative sequential chemotherapy and RT in gastric cancer treatment is merited.

Conflicts of interest

The authors indicated no potential conflicts of interest.

Ethics statement

This study was approved by the Ethics Committee of Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China (Approval ID: TJ-C20091211) and written informed consent was obtained from every participant. The study was conducted in compliance with the Declaration of Helsinki.

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DOI 10.1007/s10330-018-0261-1
Cite this article as: Fu Q, Yu SY, Hu GQ, *et al*. Postoperative sequential chemotherapy and radiotherapy for locally advanced gastric cancer. Oncol Transl Med, 2018, 4: 85–92.