

# Phase II Study of Adjuvant Chemoradiotherapy Using Docetaxel/Cisplatin/5-Fluorouracil Before and After Intensity-modulated Radiotherapy With Concurrent Docetaxel in Patients With Completely (R0) Resected Gastric Carcinoma

Yong Liu, MD, PhD,\* Guoqi Zhao, MD,\* Yi Xu, MD,\* Tiening Zhang, MD,\*  
Zhixiao Chen, MD,\* Ge Yan, MD,\* Wenzhi Tu, PhD,\* Ye Hu, MD,\*  
Ying Chen, MD,\* Xia He, MD,† Xiaodong Li, MD,‡ Hui Chen, MD,§  
Shengyu Yao, MD,\* Zhekai Hu, MD,\* Xuming Chen, MD,\*  
and Tingfeng Chen, MD, PhD\*

**Objectives:** The Intergroup 0116 study has demonstrated a significant survival benefit for completely resected (R0) gastric cancer patients treated with a fluorouracil/leucovorin chemoradiotherapy regimen. However, this regimen is also toxic and less effective in terms of distant disease control. Therefore, a more efficacious and safer regimen is urgently needed.

**Methods:** Patients with R0 resected gastric carcinoma received up to two 21-day cycles of postoperative adjuvant preradiation and post-radiation DCF chemotherapy (docetaxel 37.5 mg/m<sup>2</sup> on days 1 and 8, cisplatin 25 mg/m<sup>2</sup> on days 1 to 3, and a continuous infusion of fluorouracil 750 mg/m<sup>2</sup> on days 1 to 5), respectively. Chemoradiotherapy between preradiation and postradiation chemotherapy was initiated on day 43 and consisted of intensity-modulated radiotherapy (45 Gy) plus concurrent docetaxel 20 mg/m<sup>2</sup> weekly for 5 weeks.

**Results:** A total of 55 patients were evaluated and 76% (42) of patients completed the prescribed therapy. With a median follow-up of 61 months, the 3- and 5-year progression-free survival rates were 67% (95% confidence interval [CI], 54%-80%) and 59% (95% CI, 46%-72%), respectively; and the 3- and 5-year overall survival rates were 72% (95% CI, 60%-84%) and 61% (95% CI, 48%-74%), respectively. The most common grade 3 or greater toxicity, during the chemotherapy phase, was neutropenia (24%). Common grade 3/4 toxicities during

concurrent chemoradiotherapy were nausea (32%), vomiting (26%), fatigue (15%), and anorexia (19%).

**Conclusions:** These results demonstrate that this adjuvant regimen is active with an acceptable toxicity profile. A randomized phase 3 trial comparing the Intergroup 0116 chemoradiotherapy regimen with this regimen is underway.

**Key Words:** docetaxel, fluorouracil, cisplatin, adjuvant chemoradiotherapy, gastric cancer

(*Am J Clin Oncol* 2018;41:619–625)

Complete surgical R0 resection has traditionally been considered the only curative treatment in localized gastric cancer. However, both local and distant relapses are common after surgical R0 resection alone, resulting in suboptimal 5-year overall survival (OS) rates of approximately 20%.<sup>1–3</sup> These poor survival outcomes provide a strong rationale for adjuvant or neoadjuvant treatment.

The landmark Intergroup 0116 trial was the first to demonstrate that adjuvant postoperative chemoradiotherapy offers a significant survival benefit.<sup>4</sup> In this study, the 3-year OS and relapse-free survival rates were improved from 41% and 31%, respectively, in the surgery only group to 50% and 48%, respectively, in the chemoradiotherapy group. However, despite this improved survival, half of these patients will die within 3 years of R0 resection. Notably, the patients receiving chemoradiotherapy had a higher rate of distant metastasis. Furthermore, the toxicity rate observed in the Intergroup 0116 trial was substantial. Thus, it is reasonable to optimize the Intergroup 0116 chemoradiotherapy regimen.

Docetaxel, administered as monotherapy, is active in both the first-line and second-line treatment of advanced stage gastric cancer.<sup>5,6</sup> In addition, *in vitro* and *in vivo* studies demonstrated that docetaxel is a potent radiosensitizer in human cancer cell lines, making it an attractive agent when combined with radiation.<sup>7</sup> A phase I study identified the phase II recommended dose of docetaxel as 20 mg/m<sup>2</sup> weekly for 6 weeks when administered with concurrent chest radiation of 60 Gy.<sup>8</sup>

Furthermore, it was demonstrated that docetaxel together with standard cisplatin and infused 5-fluorouracil (FU) (DCF regimen) prolonged survival and resulted in a higher response rate (RR) than cisplatin and 5-FU (CF) alone, but the regimen

From the \*Department of Radiation Oncology, Shanghai General Hospital, Shanghai Jiaotong University, Shanghai; †Department of Radiation Oncology, Jiangsu Cancer Hospital; ‡Department of Radiation Oncology, Nanjing BenQ Medical Center; and §Department of Radiation Oncology, Nanjing Jiangning Hospital, Nanjing Medical University, Nanjing, P.R. China.

This research was supported by the Scientific Research Foundation for the Returned Overseas Chinese Scholars (No. N130204) from the China State Education Ministry, by the National Natural Science Foundation of China (Nos. 81202148, 31370838), and by National Key Clinical Discipline-Oncology.

The authors declare no conflicts of interest.

Reprints: Tingfeng Chen, MD, PhD, Department of Radiation Oncology, Shanghai General Hospital, Shanghai Jiaotong University, 650 New Songjiang Road, Shanghai 201620, P.R. China. E-mail: tingfeng138138@163.com.

Copyright © 2017 The Author(s). Published by Wolters Kluwer Health, Inc. This is an open-access article distributed under the terms of the Creative Commons Attribution-Non Commercial-No Derivatives License 4.0 (CCBY-NC-ND), where it is permissible to download and share the work provided it is properly cited. The work cannot be changed in any way or used commercially without permission from the journal.

ISSN: 0277-3732/18/4107-0619

DOI: 10.1097/COC.0000000000000373

also resulted in significant toxicity.<sup>9</sup> In addition, a favorable RR and median OS for DCF over epirubicin, cisplatin, and protracted venous infusion fluorouracil (ECF) was demonstrated in a randomized phase II trial.<sup>10</sup>

We therefore designed a phase II trial to evaluate the impact of a novel adjuvant chemoradiotherapy regimen on the survival of patients with curatively resected gastric cancer. This regimen consisted of radiotherapy and concurrent weekly docetaxel plus preradiation and postirradiation chemotherapy with modified DCF. Intensity-modulated radiation treatment (IMRT) was used on the basis of data illustrating that IMRT protects the surrounding normal tissues better than both conventional techniques and 3-dimensional conformal radiotherapy.<sup>11,12</sup> The primary endpoint of the study was the progression-free survival (PFS) rate, and the second objective was to evaluate toxicity, OS, and patterns of failure.

## METHODS

### Statement of Ethics Approval

This study was approved by the ethics committee of each hospital and was performed in accordance with the Declaration of Helsinki. Patients provided written informed consent before study entry.

### Patients

The eligibility criteria included histologically confirmed adenocarcinoma of the stomach or gastroesophageal junction, complete resection of the tumor defined as surgical resection performed with curative intent and resulting in negative resection margins, disease stage IB through IV (M0) according to the 2002 American Joint Commission for Cancer Staging System, age of 20 to 75 years, Zubrod performance status (PS) of 0 to 2, a platelet count  $\geq 100 \times 10^9/L$ , an absolute granulocyte count  $\geq 2 \times 10^9/L$ , a hemoglobin level  $\geq 10$  g/dL, adequate renal and hepatic function (serum creatinine  $\leq 1.5 \times$  the upper limit of normal, bilirubin and aspartate transaminase  $\leq 1.5 \times$  the upper limit of normal), a caloric intake of at least 1500 kcal/d, and initiation of adjuvant treatment within 6 weeks of surgery. The exclusion criteria included a history of prior upper abdominal radiotherapy or chemotherapy, any metastatic disease, active inflammatory bowel disease, and ischemic heart disease. The protocol was reviewed and approved by the institutional review board. When a patient was enrolled, surgery and pathology reports were reviewed to confirm the completeness of the resection and the extent of the lymphadenectomy. The latter was classified as follows. A D1 dissection included perigastric lymph nodes along the right and left cardiac, the lesser and larger curvature, suprapyloric area along the right gastric artery, and infrapyloric area. A D2 dissection entailed a D1 dissection plus lymph nodes along the left gastric artery, common hepatic artery, celiac artery, splenic hilum, and splenic artery. A D0 dissection was less than a D1 dissection.

At baseline, the initial evaluation included a detailed clinical history and complete physical examination, assessment of Zubrod PS, weight and height measurements, a complete blood cell count with differential and platelet count, a chemistry panel, and computed tomography (CT) of the chest, abdomen, and pelvis. Nutritional counseling was offered to all patients.

### Treatment Plan

#### Chemotherapy

The treatment scheme is illustrated in Figure 1. The patients received preradiation chemotherapy for 2 cycles and

postirradiation chemotherapy for 2 cycles. Each 21-day cycle consisted of the DCF regimen based on the V325 study but modified due to the significant toxicity observed. This involved the administration of docetaxel (37.5 mg/m<sup>2</sup>, 1-h intravenous [IV] infusion on days 1 and 8), cisplatin (25 mg/m<sup>2</sup>, 2-h IV infusion on days 1 to 3), and 5-FU (750 mg/m<sup>2</sup>/d by continuous infusion with a central venous access over 5 d). All patients received appropriate hydration, premedication, and dose reduction for individual drugs based on the worst toxicity experienced, as previously described.<sup>13</sup>

#### Chemoradiotherapy

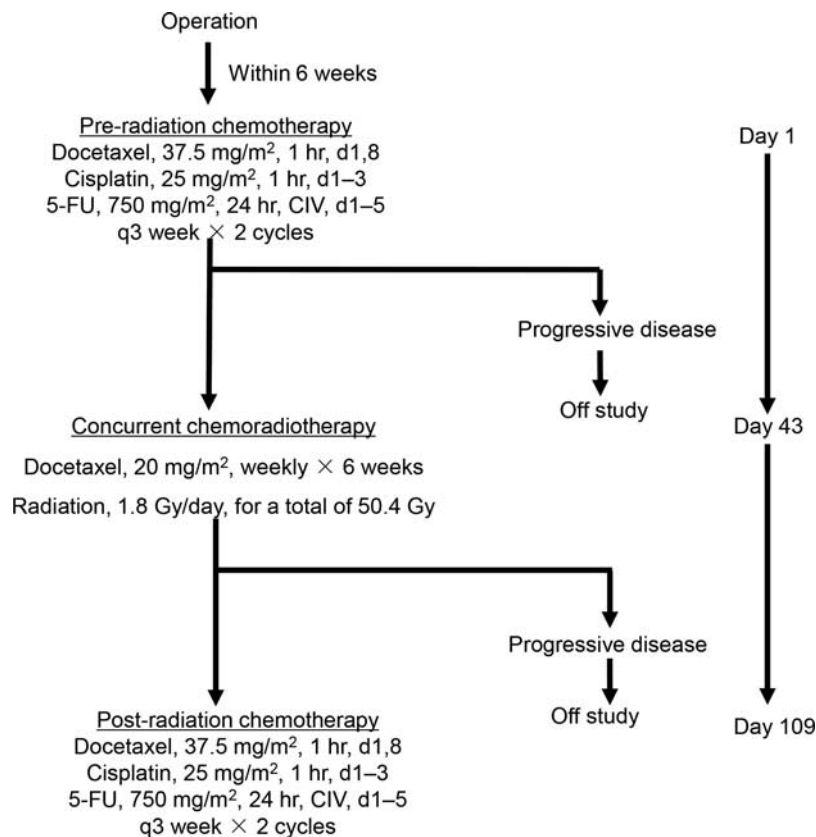
Chemoradiotherapy began on day 43. Radiotherapy was administered through a linear accelerator with 6 to 15 MV photons, and IMRT treatment planning was performed in all cases. Patients were immobilized in a vacuum pad in a supine position with their arms above their head and 5-mm-thick treatment planning. CT images were acquired on a CT simulator (Philips Medical Madison, WI). The clinical tumor volume (CTV) included the tumor bed, anastomoses and stumps, regional draining lymph nodes (perigastric, celiac, portahepatis, gastroduodenal, splenic-suprapancreatic, retropancreaticoduodenal, and para-aortic), and 3 cm beyond the proximal and distal margins of surgical resection, as described in the Intergroup 0116 study. The tumor bed was determined by preoperative CT imaging and surgical clips in some cases. It was necessary to include the medial left hemidiaphragm in the CTV, in the case of a proximal T3 lesion.

For proximal lesions involving the cardia or gastroesophageal junction, paracardial and paraesophageal lymph nodes were included in the radiation fields, but pancreaticoduodenal radiation was not required. Exclusion of the splenic nodes was permitted in cases of antral lesions. The planning target volume (PTV) consisted of the CTV plus a 0.5-cm margin in all directions to account for daily patient set-up variation. IMRT plans were generated and optimized using commercial planning software (Eclipse; Varian, Palo Alto, CA). Typically, a 6-field nonaxial beam arrangement was used. The PTV received a total dose of 45 Gy in 25 fractions at 1.8 Gy per fraction delivered once daily for 5 weeks. Treatment planning was performed with the isocenter calculated at 100%, with at least 95% of the PTV receiving the prescribed dose. The dose constraints for critical organs were as follows: mean liver dose,  $<28$  Gy; spinal cord dose,  $\leq 45$  Gy; at least two thirds of 1 kidney received  $<20$  Gy; and maximum dose to the duodenum,  $\leq 45$  Gy.

Concurrent chemotherapy consisted of 5 docetaxel doses of 20 mg/m<sup>2</sup> delivered through a 1-hour IV infusion on days 1, 8, 15, 22, and 29 of radiation. Radiation was delivered 2 hours after completion of the docetaxel infusion. Best supportive care including nutritional support, antiemetics, and antacid was provided as clinically indicated. No dose modifications were planned for radiation and docetaxel. In cases of grade 3 or greater nonhematological or grade 4 hematological toxicity, chemoradiotherapy could be delayed by up to 2 weeks until these symptoms resolved to no worse than grade 1 for nonhematological toxicity or no worse than grade 2 for hematological toxicity.

#### Patient Follow-up

Patients were observed weekly during treatment. Complete blood counts and serum chemistries were assessed weekly. Acute toxicities were graded according to the National Cancer Institute-Common Toxicity Criteria Version 3.0. Follow-up evaluations were conducted at 3-month intervals for the first 2 years, every



**FIGURE 1.** Treatment schema. CIV indicates continuous intravenous; FU, fluorouracil.

6 months for 3 years, and yearly thereafter together with a physical examination, a complete blood count, serum chemistries, and CT scanning. Late radiation toxicities were graded according to the Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer Late Radiation Morbidity Scoring Schema.

### Statistical Analysis

This single-stage phase II trial was designed to have 93% power to detect a 20% improvement in the 20-month PFS rate from 50% to 70% with a 2-sided significance level of exactly 0.05. The present 20-month PFS was based on a median PFS of 19 months for 275 patients in the surgery-alone arm of the Intergroup 0116 study. The accrual goal was 61 patients, assuming 55 patients would be eligible. If at least 34 of 55 evaluable patients were progression-free at 20 months, then the regimen would be considered worthy of further investigation. PFS was measured from the date of study entry to the first event (ie, local-regional relapse or progression, distant recurrence, or death from any cause), and OS was defined as the time from the date of study entry to the date of death or the last follow-up. Data on patients who were event-free were censored on the date they were last reviewed. The Kaplan-Meier method was used to generate the OS and PFS curves. All statistical analyses were performed using IBM SPSS statistics 19.0.

## RESULTS

### Patient Characteristics

A total of 61 patients were enrolled between April 2004 and January 2007, of whom 55 were evaluable. Of the

6 ineligible patients, 3 patients had a Zubrod PS of 3, 2 were registered more than 6 weeks after the date of surgical resection, and 1 withdrew from the trial before initiating protocol therapy. The baseline characteristics of these assessable patients are listed in Table 1. The median age was 59 years (range, 28 to 75 y). The majority of patients had locally advanced disease (stage T3 or T4, 71%; N1-3, 93%).

### Treatment Delivery

Of the 55 evaluable patients, 54 (98%) completed both cycles of preradiation chemotherapy; conversely, the other patient received only 1 cycle due to disease progression, and this patient was removed from the study per the protocol, but included in the analysis on an intention-to-treat basis. No dose reduction or treatment delay was required for toxic effects. Of the 54 patients who started concurrent chemoradiotherapy (CCRT), 46 completed all 5 doses of weekly docetaxel and the planned 45-Gy radiotherapy. Meanwhile, 1 patient had a 2-week break due to vomiting, and 4 patients had a 1-week delay due to vomiting, anorexia, or diarrhea. Eight patients did not complete the planned CCRT; of these, 2 patients completed 5 doses of weekly chemotherapy and 43.2 Gy of radiation, 4 patients received 5 doses of chemotherapy and 41.4 Gy of radiation, and 2 patients received 4 doses of chemotherapy and 36 Gy of radiation. Failure to complete the planned CCRT was due to vomiting (4 patients), deteriorating health (2 patients), diarrhea (1 patient), and patient refusal (1 patient). Of the 46 patients who completed the planned CCRT, 42 completed both cycles of postradiation chemotherapy. Conversely, 1 patient withdrew from the study due to peritoneal carcinomatosis, 1 patient did not receive postradiation chemotherapy due to

**TABLE 1.** Patient Characteristics (N=55)

Characteristics	No Patients (%)
Sex	
Male	41 (76)
Female	14 (24)
Age (y)	
Median	59
Range	28-75
Eastern Cooperative Oncology Group PS	
0	32 (58)
1	17 (31)
2	6 (11)
Location of the primary tumor	
Antrum/pylorus	19 (34)
Cardia/fundus	13 (23)
Body	8 (15)
Lesser curvature	9 (16)
Greater curvature	3 (6)
Linitis plastica	2 (4)
Not specified	1 (2)
Node dissection	
D0	5 (9)
D1	39 (71)
D2	11 (20)
T stage	
1	2 (4)
2	14 (25)
3	35 (64)
4	4 (7)
N stage	
0	4 (7)
1	30 (55)
2	18 (33)
3	3 (5)
Stage group	
IB	2 (4)
II	13 (23)
IIIA	23 (42)
IIIB	10 (18)
IV(M0)	7 (13)

PS indicates performance status.

deteriorating health, and 2 patients completed only 1 cycle of chemotherapy. Dose reductions and/or treatment delays were required for 3 patients because of toxic effects. Overall, 76% of the patients completed the prescribed therapy.

### Toxicity

The grade 3 and 4 toxicities observed in this study are listed in Table 2. During the preradiation and postradiation chemotherapy phase, the most common grade 3 and 4 hematological toxicity was neutropenia, which was observed in 13 patients (24%) during preradiation chemotherapy and 10 patients (23%) during postradiation chemotherapy. Maximum grade 3 or 4 nonhematological toxicities occurred mainly during the postradiation chemotherapy phase, consisting of nausea (18%), and vomiting (14%).

Of the 54 patients for whom toxicity could be assessed during the CCRT phase, grade 3 or 4 hematological toxicities consisted of neutropenia in 7 patients (13%) and lymphocytopenia in 18 patients (33%). The most significant nonhematological toxicities were nausea and vomiting. Grade 3 or greater nausea and vomiting occurred in 17 (32%) and 14 patients (26%), respectively. Nausea and vomiting generally began in the third week of CCRT, peaked in the last 2 weeks, and resolved within 2 to 3 weeks of CCRT completion. Other

significant nonhematological toxicities included anorexia in 10 patients (19%) and fatigue in 8 patients (15%). Parenteral or enteral support was required for most of these patients, especially those with grade 3 or 4 nausea or vomiting. No cases of grade 2 or greater hepatic or renal toxicity were observed, and there were no treatment-related deaths.

Only 1 patient developed late toxicity. This patient developed a duodenal ulcer with severe bleeding 7 months after the completion of radiotherapy that required surgical intervention. There was 1 patient with second tumor, who was diagnosed as lung cancer 58 months after the study entry.

### Survival and Relapse

The median follow-up time for all 55 evaluable patients was 61 months, with 21 patients dying during this period. The 20-month PFS rate was 75% (95% confidence interval [CI], 64%-86%). The 3- and 5-year PFS rates were 67 (95% CI, 54%-80%) and 59% (95% CI, 46%-72%), respectively (Fig. 2), and the 3- and 5-year OS rates were 72 (95% CI, 60%-84%) and 61% (95% CI, 48%-74%), respectively (Fig. 3). Of 21 documented sites of first treatment failure, local-regional relapse occurred in 5 patients, distant relapse including peritoneal carcinomatosis was observed in 13 patients, and 3 patients had both local-regional and distant recurrences.

### DISCUSSION

Although surgery is the standard of care for localized gastric cancer, the outcome remains poor due to local and distant failure after R0 resection. Many adjuvant therapies including chemotherapy, radiation, or a combination of the 2 modalities have been investigated to enhance surgical results.<sup>3,14,15</sup> The Intergroup 0116 study demonstrated that postoperative chemoradiotherapy can significantly improve OS and PFS compared with the effects of surgery alone.<sup>4</sup> An analysis of failure patterns suggests that this improvement was mainly attributable to improved local control, indicating that 5-FU/leucovorin, used as systemic treatment in the Intergroup 0116 study, had little effect on distant disease. Another landmark study, Medical Research Council Adjuvant Gastric Infusional Chemotherapy, reported a statistically significant survival benefit for patients with gastric cancer treated with perioperative ECF chemotherapy over surgery alone. Treatment consisted of three courses of ECF before and after surgery.<sup>16</sup> This survival benefit was believed to arise primarily from the effect of perioperative chemotherapy on micrometastatic disease. Therefore, we postulated that the combination of more effective local (ie, chemoradiotherapy) and systemic treatments (ie, chemotherapy) may further improve surgical outcomes.

The DCF chemotherapy regimen is more active in patients with advanced gastric cancer than the standard CF or ECF regimen based on the results of randomized trials.<sup>9,10</sup> Theoretically, this regimen may also have an excellent effect on micrometastases, but it has not yet been tested in the adjuvant setting. Hence, we chose the DCF regimen as a systemic treatment to improve the control of distant disease. To enhance local treatment efficacy, we substituted docetaxel for 5-FU as a radiosensitizing agent administered weekly with concurrent radiotherapy, as it has been reported that 5-FU-based chemoradiotherapy was less active and more toxic in the primary management of advanced gastric cancer.<sup>17-19</sup> Docetaxel, a relatively newer agent, is a potent radiosensitizer in addition to its significant antitumor activity as monotherapy or in combination with other agents. Docetaxel-based

**TABLE 2.** Grade III or IV Hematological and Nonhematological Toxicity Associated With Preradiation and Postradiation Chemotherapy and CCRT

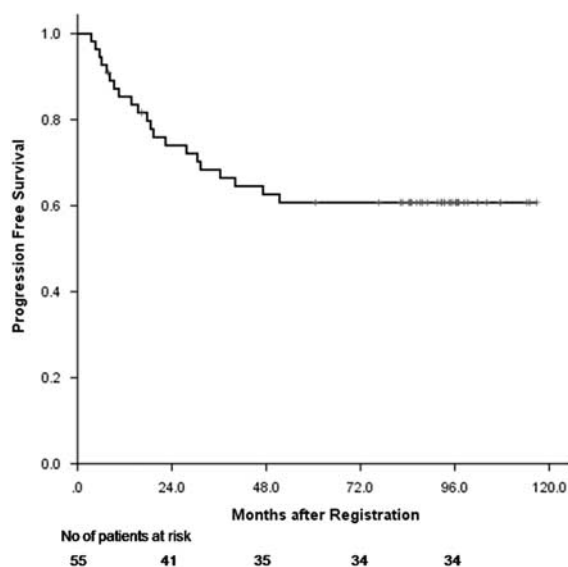
Toxicity Grade	Preradiation CT (N=55)			CCRT (N=54)			Postradiation CT (N=44)		
	Grade 3	Grade 4	Total (%)	Grade 3	Grade 4	Total (%)	Grade 3	Grade 4	Total (%)
<b>Hematological toxicity</b>									
Neutropenia	8	5	13 (24)	5	2	7 (13)	8	2	10 (23)
Lymphocytopenia	3	2	5 (9)	13	5	18 (33)	3	1	4 (9)
Thrombocytopenia	2	1	3 (6)	4	0	4 (7)	1	0	1 (2)
Hemoglobin	2	0	2 (4)	2	0	2 (4)	1	1	2 (5)
Febrile neutropenia	2	0	2 (4)	3	0	3 (6)	0	0	0
Worst hematological	9	6	15 (27)	14	5	19 (35)	8	3	11 (25)
<b>Nonhematological toxicity</b>									
Nausea	6	1	7 (13)	11	6	17 (32)	6	2	8 (18)
Vomiting	4	1	5 (9)	9	5	14 (26)	4	2	6 (14)
Diarrhea	2	1	3 (6)	2	0	2 (4)	1	0	1 (2)
Anorexia	3	0	3 (6)	8	2	10 (19)	3	1	4 (9)
Neuropathy	0	0	0	0	0	0	1	1	2 (5)
Dehydration	1	0	1 (2)	5	1	6 (11)	1	0	1 (2)
Fatigue	4	0	4 (7)	7	1	8 (15)	3	1	4 (9)
Infection (without neutropenia)	1	0	1 (2)	1	0	1 (2)	1	0	1 (2)
Worst GI	8	2	10 (18)	14	7	21 (39)	6	3	9 (21)
Worst overall toxicity	10	6	16 (29)	15	9	24 (44)	9	4	13 (30)

CCRT indicates concurrent chemoradiotherapy; CT, chemotherapy; GI, gastrointestinal.

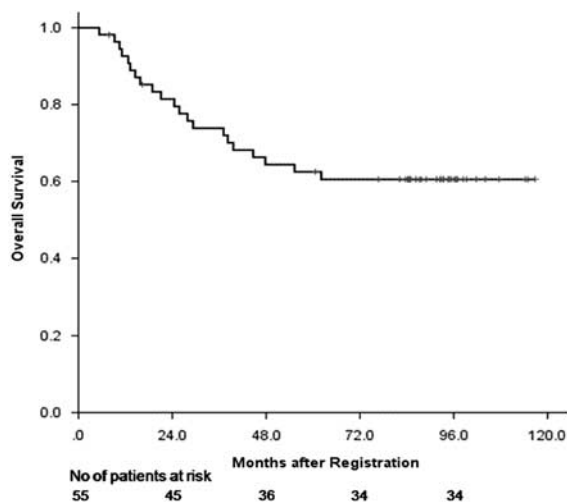
chemoradiotherapy has been used extensively in the treatment of many tumors including lung cancer and head and neck cancer,<sup>20</sup> but it has never been evaluated in gastric cancer. We recently reported that 36 patients with inoperable gastric cancer were treated using the same chemoradiotherapy regimen used in the present study, although the radiation dose was 50.4 Gy in 28 fractions as opposed to 45 Gy in 25 fractions, as used in this series. Overall and complete RRs of 83 (95% CI, 75%- 97%) and 36% (95% CI, 19%-53%), respectively, were achieved, and the median survival time and 3-year survival rate

were 25.8 months (95% CI, 7.1-44.5 mo) and 42% (95% CI, 23%-59%), respectively.<sup>21</sup> These outcomes are encouraging, and thus, it is logical to evaluate this regimen in the adjuvant setting.

In this phase II trial, the estimated 20-month PFS rate of 75% achieved the primary end point of a regimen considered for further investigation. The 3- and 5-year estimated PFS rates were 67% and 59%, respectively, and the 3- and 5-year estimated OS rates were 72% and 61%, respectively. Although the main prognostic factors such as T stage and N stage are comparable, our results appear superior to those obtained in the Intergroup 0116 trial.



**FIGURE 2.** The Kaplan-Meier plot of progression-free survival for 55 assessable patients treated in the phase II trial using postoperative adjuvant docetaxel/cisplatin/5-fluorouracil before and after intensity-modulated radiotherapy with concurrent docetaxel weekly. The progression-free survival was 67% (95% confidence interval, 54%-80%) at 3 years and 59% at 5 years (95% confidence interval, 46%-72%).



**FIGURE 3.** The Kaplan-Meier plot of overall survival for 55 assessable patients treated in the phase II trial using postoperative adjuvant docetaxel/cisplatin/5-fluorouracil before and after intensity-modulated radiotherapy with concurrent docetaxel weekly. The overall survival was 72% (95% confidence interval, 60%-84%) at 3 years and 61% (95% confidence interval, 48%-74%) at 5 years.

**TABLE 3.** Main Trials With Adjuvant Chemoradiotherapy in Completely Resected Gastric Cancer

References	CRT Regimen	N	Stage (%)		Node Dissection (%)	3-Year PFS (%)	≥ Grade III HT and GT (%)
Macdonald et al <sup>4</sup>	Pre-RT CT: FU 425 mg/m <sup>2</sup> , LV 20 mg/m <sup>2</sup> for 5 d × 1 cycle CRT: FU 400 mg/m <sup>2</sup> , LV 20 mg/m <sup>2</sup> on the first 4 and last 3 d of RT, 1.8 Gy daily/45 Gy total Post-RT CT: FU 425 mg/m <sup>2</sup> , LV 20 mg/m <sup>2</sup> for 5 d × 2 cycles 1 mo apart	281	T1-2 T3 T4 N0 N1-3	31 62 6 14 85	D0: 54 D1: 36 D2: 10	48	HT: 54* GT: 33
Park et al <sup>15</sup>	Pre-RT CT: FU 400 mg/m <sup>2</sup> , LV 20 mg/m <sup>2</sup> for 5 d × 1 cycle CRT: FU 400 mg/m <sup>2</sup> , LV 20 mg/m <sup>2</sup> on the first 4 and last 3 d of RT, 1.8 Gy daily/45 Gy total Post-RT CT: FU 400 mg/m <sup>2</sup> , LV 20 mg/m <sup>2</sup> for 5 d × 2 cycles 1 mo apart	290	IB II IIIA IIIB IV(M0)	12 24 33 12 20	D2: 100	62	HT: 30 GT: 40
Schwartz et al <sup>22</sup>	Pre-RT CT: FU 600 mg/m <sup>2</sup> CI, D1-5, 29-33, D 15 mg/m <sup>2</sup> D1-5, 29-33, T 175 mg/m <sup>2</sup> D1, 29 CRT: FU 300 mg/m <sup>2</sup> CI, 5 d/wk × 5 wk, T 45 mg/m <sup>2</sup> , weekly for 5 wk; RT 1.8 Gy daily/45 Gy total	28	IB II IIIA IIIB	14 36 43 7	NA	NA	HT: 67 GT: 68
Schwartz et al <sup>22</sup>	Pre-RT CT: C 75 mg/m <sup>2</sup> D1, 29, T 175 mg/m <sup>2</sup> D1, 29 CRT: T 60 mg/m <sup>2</sup> CI, weekly for 5 wk, C 30 mg/m <sup>2</sup> , weekly for 5 wk, RT 1.8 Gy daily/45 Gy total	45	IB II IIIA IIIB	7 40 49 4	NA	52 (2 y PFS)	HT: 40 GT: 34
Leong et al <sup>23</sup>	Pre-RT CT: E 50 mg/m <sup>2</sup> D1, C 60 mg/m <sup>2</sup> D1, FU 200 mg/m <sup>2</sup> CI, D1-21 × 1 cycle CRT: FU 225 mg/m <sup>2</sup> CI, daily, RT 1.8 Gy daily / 45 Gy total Post-RT CT: the same regimen as Pre-RT CT × 2 cycles	54	IB II IIIA IIIB IV(M0)	9 20 41 15 15	<D1: 20 D1: 37 D2: 18 Unknown: 6 Others: 4	58.6	HT: 82 GT: 47

\*1% toxic deaths.

C indicates cisplatin; CI, continuous infusion; CRT, chemoradiotherapy; E, epirubicin; FU, fluorouracil; GT, gastrointestinal toxicity; HT, hematological toxicity; LV, leucovorin; N, number of patients; NA, not available; PFS, progression-free survival; Post-RT CT, postirradiation chemotherapy; Pre-RT CT, preradiation chemotherapy; RT, radiotherapy; T, paclitaxel.

Several chemoradiotherapy regimens incorporating other chemotherapeutic agents have recently been examined as adjuvant therapies for resected gastric cancer.<sup>15,22,23</sup> Schwartz and colleagues evaluated 2 paclitaxel-containing and cisplatin-containing regimens, 1 with 5-FU (PCF) and the other without FU (PC), in the treatment of patients with resected gastric cancer. Patients received 2 cycles of postoperative chemotherapy followed by 45 Gy of radiation with either concurrent 5-FU and paclitaxel or paclitaxel and cisplatin. The PCF arm was closed early after the enrollment of 28 patients due to the higher rate of grade 3 or 4 gastrointestinal (GI) toxicity. The 2-year DFS rate was 52% (95% CI, 36%-68%) for the 45 patients in the PC arm.<sup>22</sup> It is worth noting that patients in Schwartz trial received only 2 cycles of preradiation chemotherapy, potentially resulting in suboptimal control of systemic disease. In another phase II trial, Leong et al<sup>23</sup> treated 54 patients with 1 cycle of ECF, followed by radiotherapy (45 Gy) with concurrent infusional 5-FU and then 2 additional cycles of ECF. Radiotherapy was delivered using 3-dimensional conformal techniques. The 3-year OS rate was estimated at 61.6%. The main trials evaluating different adjuvant chemoradiotherapy regimens are shown in Table 3. Although we acknowledge that comparisons between the trials are inappropriate, our 3-year PFS rate of 67% is promising in contrast to the PFS rate of 48% to 62% reported in these trials for resected gastric cancer. Nevertheless, the standard adjuvant chemoradiotherapy regimen for resected gastric cancer remains uncertain, and

subsequent prospective randomized controlled trials are required for clarification.

One of our concerns was the toxicity potentially associated with the treatment at the initiation of this study, considering the significant toxicity observed in the Intergroup 0116 trial, which reported grade 3 and 4 toxicities in 41% and 32% of patients, respectively. By contrast, the toxicity appears acceptable in the present study and comparable with that observed in other trials (Table 3). During the periradiation chemotherapy phase, the main toxicity was grade 3 or 4 neutropenia, which was observed in approximately a quarter of the patients. Significant GI toxicity was observed despite including only docetaxel in CCRT. The increased rate of GI toxicity may reflect the higher dose intensity and the relatively larger irradiation field. Despite significant GI toxicity, 76% of the assessable patients completed the protocol therapy. Our favorable toxicity profile may be attributable to the combination of the mDCF regimen chemotherapy (less aggressive), a single-agent radiosensitizer in docetaxel (in place of 5-FU), and sophisticated radiation techniques used.

In an attempt to improve outcomes for patients with gastric cancer, there is a trend to initially treat patient with chemoradiotherapy followed by surgery.<sup>24,25</sup> This approach is supposed to have a few advantages: (a) radiotherapy and systemic therapy are more effective due to the existence of intact tumor vasculature and oxygenation; (b) patients generally have better treatment compliance; (c) tumor downstaging after preoperative

chemoradiotherapy may facilitate surgical resection and decrease the risk of local relapse; and (d) during preoperative therapy, some patients may develop overt metastases due to their aggressive biological disease and avoid unnecessary surgery. Although preoperative chemoradiotherapy has not been evaluated in a phase III setting, several phase II trials were reported, with a pathologic complete response rate of 20% to 30%.<sup>24,25</sup> In addition, patients with a pathologic complete response or <10% residual cancer cells in the resected specimen can achieve long-term survival. Nevertheless, the survival outcomes achieved in this series seems more favorable as compared with the MAGIC trial and other trials using neoadjuvant strategies. The MAGIC trial demonstrated a 5-year survival rate of 36% among patients in the ECF perioperative-chemotherapy group although the tumor stage is similar to that of the present trial.<sup>16</sup> Ajani et al<sup>24</sup> reported a 2-year survival rate of 54% in 33 patients treated with preoperative chemoradiotherapy consisting of two 28-day cycles of FU, leucovorin, and cisplatin, followed by 45 Gy of radiation plus concurrent FU. Obviously, no definite conclusion can be drawn based on the outcomes achieved in this phase 2 series. A direct comparison of the postoperative chemoradiotherapy with this preoperative approach should be considered as well.

In conclusion, we demonstrated that a periradiation mDCF chemotherapy regimen plus docetaxel-based chemoradiotherapy can be delivered safely with acceptable toxicity in the postoperative adjuvant setting in patients who underwent R0 resection. The survival results appear favorable compared with those observed in the Intergroup 0116 trial. On the basis of our data, we have designed a randomized phase III trial directly comparing the Intergroup 0116 chemoradiotherapy regimen with our regimen in this series (<http://www.clinicaltrials.gov/NCT02640898>).

## REFERENCES

- Gunderson LL. Gastric cancer—patterns of relapse after surgical resection. *Semin Radiat Oncol*. 2002;12:150–161.
- Landry J, Tepper JE, Wood WC, et al. Patterns of failure following curative resection of gastric carcinoma. *Int J Radiat Oncol Biol Phys*. 1990;19:1357–1362.
- Zhang ZX, Gu XZ, Yin WB, et al. Randomized clinical trial on the combination of preoperative irradiation and surgery in the treatment of adenocarcinoma of gastric cardia (AGC)—report on 370 patients. *Int J Radiat Oncol Biol Phys*. 1998;42:929–934.
- Macdonald JS, Smalley SR, Benedetti J, et al. Chemoradiotherapy after surgery compared with surgery alone for adenocarcinoma of the stomach or gastroesophageal junction. *N Engl J Med*. 2001;345:725–730.
- Mavroudis D, Kourousis C, Androulakis N, et al. Frontline treatment of advanced gastric cancer with docetaxel and granulocyte colony-stimulating factor (G-CSF): a phase II trial. *Am J Clin Oncol*. 2000;23:341–344.
- Vanhoefer U, Wilke H, Harstrick A, et al. Phase II study of docetaxel as second-line chemotherapy (CT) in metastatic gastric cancer. *Proc Am Soc Clin Oncol*. 1999;18:303.
- Choy H, Rodriguez F, Koester S, et al. Investigation of taxol as a potential radiation sensitizer. *Cancer*. 1993;71:3774–3778.
- Mauer AM, Master GA, Haraf DJ, et al. Phase I study of docetaxel with concomitant thoracic radiation therapy. *J Clin Oncol*. 1998;16:159–164.
- Cutsem EV, Moiseyenko VM, Tjulandin S, et al. Phase III study of docetaxel and cisplatin plus fluorouracil compared with cisplatin and fluorouracil as first-line therapy for advanced gastric cancer: a report of the V325 Study Group. *J Clin Oncol*. 2006;24:4991–4997.
- Roth AD, Fazio N, Stupp R, et al. Docetaxel, cisplatin, and fluorouracil; docetaxel and cisplatin; and epirubicin, cisplatin, and fluorouracil as systemic treatment for advanced gastric carcinoma: a randomized phase II trial of the Swiss Group for Clinical Cancer Research. *J Clin Oncol*. 2007;25:3217–3223.
- Milano MT, Garofalo MC, Chmura SJ, et al. Intensity modulated radiation therapy in the treatment of gastric cancer: early clinical outcome and dosimetric comparison with conventional techniques. *Br J Radiol*. 2006;79:497–503.
- Minn AY, Hsu A, La T, et al. Comparison of intensity-modulated radiotherapy and 3-dimensional conformal radiotherapy as adjuvant therapy for gastric cancer. *Cancer*. 2010;116:3943–3952.
- Ajani JA, Fodor MB, Tjulandin SA, et al. Phase II multi-institutional randomized trial of docetaxel plus cisplatin with or without fluorouracil in patients with untreated, advanced gastric, or gastroesophageal adenocarcinoma. *J Clin Oncol*. 2005;23:5660–5667.
- Coombs RC, Schein PS, Chilvers CE, et al. A randomized trial comparing adjuvant fluorouracil, doxorubicin, and mitomycin with no treatment in operable gastric cancer. International Collaborative Cancer Group. *J Clin Oncol*. 1990;8:1362–1369.
- Park SH, Kim DY, Heo JS, et al. Postoperative chemoradiotherapy for gastric cancer. *Ann Oncol*. 2003;14:1373–1377.
- Cunningham D, Allum WH, Stenning SP, et al. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. *N Engl J Med*. 2006;355:11–20.
- Moertel CG, Childs DS Jr, Reitemeier RJ, et al. Combined 5-fluorouracil and supervoltage radiation therapy of locally unresectable gastrointestinal cancer. *Lancet*. 1969;2:865–867.
- The Gastrointestinal Tumor Study Group. A comparison of combination chemotherapy and combined modality therapy for locally advanced gastric carcinoma. *Cancer*. 1982;49:1771–1777.
- The Gastrointestinal Tumor Study Group. The concept of locally advanced gastric cancer. Effect of treatment on outcome. *Cancer*. 1990;66:2324–2330.
- Kim ES, Khuri FR. Docetaxel and radiation as combined-modality therapy. *Oncology (Williston Park)*. 2002;6(suppl 6):97–105.
- Chen T, Liu Y, Guoqi Z, et al. Multicenter phase II study of concurrent chemoradiotherapy plus peri-irradiation chemotherapy for inoperable nonmetastatic gastric cancer. *Int J Radiat Oncol Biol Phys*. 2016;96:S30.
- Schwartz GK, Winter K, Minsky BD, et al. Randomized phase II trial evaluating two paclitaxel and cisplatin-containing chemoradiation regimens as adjuvant therapy in resected gastric cancer (RTOG-0114). *J Clin Oncol*. 2009;27:1956–1962.
- Leong T, Joon DL, Willis D, et al. Adjuvant chemoradiation for gastric cancer using epirubicin, cisplatin, and 5-fluorouracil before and after three-dimensional conformal radiotherapy with concurrent infusional 5-fluorouracil: a multicenter study of the Trans-Tasman Radiation Oncology Group. *Int J Radiat Oncol Biol Phys*. 2011;79:690–695.
- Ajani JA, Mansfield PF, Janjan N, et al. Multi-institutional trial of preoperative chemoradiotherapy in patients with potentially resectable gastric carcinoma. *J Clin Oncol*. 2004;22:2774–2780.
- Ajani JA, Mansfield PF, Crane CH, et al. Paclitaxel-based chemoradiotherapy in localized gastric carcinoma: degree of pathologic response and not clinical parameters dictated patient outcome. *J Clin Oncol*. 2005;23:1237–1244.