Translational Oncology
www.transonc.com

Volume 7 Number 2 April 2014 pp. 277–283 277

# Adjuvant Chemotherapy with Docetaxel, Cisplatin, and Continuous-Infusion 5-Fluorouracil for Gastric Cancer: A Phase II Study[1]

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## Abstract

*PURPOSE*: This study evaluated the efficacy and safety of adjuvant chemotherapy with the docetaxel plus cisplatin and 5-fluorouracil (5-FU) (DCF) regimen in patients with gastric cancer. *PATIENTS AND METHODS*: Thirty-two patients with gastric or gastroesophageal junction cancer were enrolled in this study after undergoing radical resection. The patients received the following chemotherapy: docetaxel (60 mg/m$^2$) on day 1, cisplatin (12 mg/m$^2$ per day) on days 1 to 5, and 5-FU (2500 mg/m$^2$) continuous infusion for 120 hours, repeated every 3 weeks for six cycles. The primary end point was disease-free survival (DFS). *RESULTS*: The median DFS was 17.0 months. The 1-year DFS was 72%, and the 2-year DFS was 37.5%. The median overall survival was 28.0 months. Using univariate analysis, the technique of lymph node dissection was a predictor for postoperative relapse. The median DFS was 15.0 months in the D1 group and 18.0 months in the D2 group ($P = .043$). The most frequent grade 3/4 adverse events were neutropenia (56.25%), diarrhea (9.38%), nausea (6.25%), and vomiting (6.25%); 12.5% of patients developed febrile neutropenia. There were no chemotherapy-related deaths. *CONCLUSIONS*: The modified DCF regimen is an effective adjuvant chemotherapy in gastric cancer. Hematologic toxicity was frequent but manageable. This regimen merits further investigation.

*Translational Oncology (2014) 7, 277–283*

## Introduction

Worldwide, gastric cancer is the fourth most common cancer and the second most common cause of cancer deaths [1]. China has a high incidence of gastric carcinoma. The incidence of gastric cancer has been increasing in China. In 2008, Chinese cases of gastric cancer accounted for more than 42% of the worldwide incidence [2]. According to the Chinese National Office for Cancer Prevention and Control (Beijing, China), gastric cancer incidence is still the most common cause of cancer death in China, and gastric cancer mortality accounted for nearly one fourth of all cancer deaths [3].

Complete surgical eradication of a gastric tumor represents the best chance for long-term survival. Nevertheless, nearly half of patients will develop recurrence or metastasis in a short period after radical surgery. In the United States, adjuvant chemoradiotherapy is the standard treatment for resectable gastric cancer. In much of Europe, neoadjuvant chemotherapy has become the preferred treatment strategy. However, the standard of care in Asia is still adjuvant chemotherapy. Many randomized trials have compared adjuvant systemic chemotherapy to surgery alone, with variable results. Some meta-analyses have shown that adjuvant chemotherapy has a significant survival benefit [4]. To date, outcomes of adjuvant treatment in gastric cancer remain disappointing. For locally advanced gastric cancer (AGC), the 5-year survival rate reported in the Japanese literature is approximately 50% [5] and is only 8% to 20% in the United States [6].

With the development of new chemotherapy agents, gastric cancer survival has improved. However, the question of which regimen is most effective for gastric cancer remains unresolved. This study was a single-center prospective phase II trial. In this study, we evaluated the efficacy and safety of docetaxel plus cisplatin and 5-fluorouracil (5-FU) (DCF) regimen as adjuvant chemotherapy for gastric cancer.

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[1] This work was supported by grants from the National Natural Science Foundation of China (No. 81101588).

Received 20 January 2014; Revised 9 February 2014; Accepted 10 February 2014

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http://dx.doi.org/10.1016/j.tranon.2014.02.014

## Patients and Methods

### *Patients*

Eligibility criteria for this study included the following: age of 18 years or older, histologically confirmed gastric or gastroesophageal junction adenocarcinoma, complete resection of the tumor, enrollment between 3 and 6 weeks after radical resection, American Joint Committee on Cancer (AJCC) (version 7.0) stage of IB to IIIC, no prior treatment for gastric cancer, Eastern Cooperative Oncology Group performance status of 0 to 1, and adequate hepatic, renal, and hematologic function [as indicated by serum bilirubin ≤1.5× upper limit of normal (ULN), serum aspartate aminotransferase ≤2.5× ULN, alkaline phosphatase ≤2.5× ULN, creatinine ≤1.5× ULN, hemoglobin ≥80 g/l, platelets $\geq 75\times10^9$ per liter, and absolute neutrophil count $\geq 1.5\times10^9$ per liter]. Patients were ineligible if distant metastases or severe/uncontrolled medical comorbidities were present. Patients were enrolled after signing an informed consent form that was approved by the Ethics Committee of Peking Union Medical College Hospital.

### *Treatment*

After undergoing gastrectomy, patients began postoperative chemotherapy. The regimen consisted of docetaxel (60 mg/m$^2$) on day 1, cisplatin (12 mg/m$^2$ per day) on days 1 to 5, and 5-FU (2500 mg/m$^2$) continuous infusion for 120 hours. Chemotherapy was repeated every 3 weeks for a total of six cycles.

Dose reductions or interruptions were allowed to manage potentially serious or life-threatening adverse events. Full doses of antineoplastic agents were given for the first cycle. If an episode of grade 2 neutropenia, thrombocytopenia, or nonhematologic toxicity was recorded, the treatment was delayed until the toxicity resolved to baseline or grade 1. If grade 3 or 4 adverse events occurred, subsequent doses of cytotoxic drugs were reduced to 75% of the planned dose until the toxicity resolved to baseline or grade 1. After dose reduction, if grade 3 or 4 toxicities still occurred, patients were removed from the study.

### *Follow-Up*

Postoperatively, all of the patients underwent a systematic baseline assessment. Chest and abdominal computed tomography scan and whole-body bone scan were required to exclude patients with postoperative recurrence and/or distant metastasis. During and after adjuvant chemotherapy, follow-up visits were required at 3-month intervals for 2 years, then at 6-month intervals for 3 years, and yearly thereafter. Follow-up consisted of a physical examination, a complete blood count, liver function testing, and chest/abdominal computed tomography scan as clinically indicated. If signs or symptoms indicated a possible recurrence, further tests were then conducted to verify whether the patient was disease free. The same assessment paradigm was used for each patient.

### *Statistical Analysis*

The primary end point of the study was disease-free survival (DFS). Secondary end points were overall survival (OS) and toxicity. DFS was defined as the time from enrollment to recurrence, second cancer, or death from any cause, whichever came first. OS was defined as the time from enrollment to death from any cause or to the last follow-up visit. Patients who were still alive were censored on the date of the last follow-up visit for the purposes of statistical analysis.

Adverse events were graded according to the National Cancer Institute's Common Terminology Criteria for Adverse Events (version 3.0) (Bethesda, MD). Adverse events were recorded during chemotherapy and for 4 weeks after the last dose of study medication. Statistical analyses were performed using SPSS version 17.0 (SPSS Inc., Chicago, IL). Estimates of values were calculated using 95% confidence intervals (CIs). DFS and OS were analyzed using the Kaplan-Meier method. A $P$ value of less than .05 was considered to be statistically significant.

## Results

### *Patient Characteristics*

From November 2006 to June 2011, 32 patients with gastric cancer were enrolled in this study. The median age was 50 years (range = 24-68). The TNM stages according to the AJCC system (version 7.0) were as follows: stage I, 2 patients (6.25%); stage II, 8 patients (25.0%); and stage III, 22 patients (68.75%). Table 1 shows details of the patients' profiles.

### *Treatment*

*Surgical Procedures.* All patients underwent radical surgery. Most of the patients underwent a D2 lymphadenectomy (22 patients, 68.75%). D1 lymphadenectomy was performed in 10 patients (31.25%).

*Chemotherapy.* All patients received adjuvant DCF chemotherapy after radical resection. Twenty-four patients (75%) completed the planned six cycles of treatment, and 8 patients (25%) stopped chemotherapy because of toxicity ($n$ = 7) or disease progression ($n$ = 1) (Table 2). The median number of cycles received was 5.3 (range = 1-6).

### *Efficacy*

Median follow-up was 29.8 months (range = 6.0-61.0). No patients were lost to follow-up. Sixteen patients (50%) developed local recurrence or metastases. The median DFS was 17.0 months (95% CI = 13.7-20.3). In this study, the 1-year DFS rate was 72%,

**Table 1.** Patient Characteristics.

| Characteristics | *n* | % |
|---|---|---|
| Age | | |
| Median (yr) | 50 | |
| Range (yr) | 24-68 | |
| Sex | | |
| Male | 23 | 71.9% |
| Female | 9 | 28.1% |
| Primary site | | |
| GEJ | 6 | 18.8% |
| Fundus | 1 | 3.1% |
| Body | 6 | 18.8% |
| Antrum | 19 | 59.4% |
| Lymphadenectomy | | |
| D1 | 10 | 31.3% |
| D2 | 22 | 68.8% |
| Histology | | |
| Andenocarcinoma | 30 | 93.8% |
| Signet-ring cell carcinoma | 2 | 6.3% |
| Differentiation | | |
| Moderate | 5 | 15.6% |
| Low | 27 | 84.4% |
| TNM stage (AJCC 7.0) | | |
| I | 2 | 6.3% |
| II | 8 | 25.0% |
| III | 22 | 68.8% |

GEJ, gastroesophageal junction.

**Table 2.** Reasons For Discontinuation Chemotherapy.

| Received Cycles | *n* | % | Major Reasons |
|---|---|---|---|
| 1 | 1 | 3.2% | G3 gastrointestinal effect |
| 2 | 2 | 6.3% | First patient: hypertension and arrhythmia |
| | | | Second patient: change to XELOX because of medical condition |
| 4 | 3 | 9.4% | First patient: G2 bone marrow, GI, peripheral neuropathy |
| | | | Second patient: G2 arrhythmia |
| | | | Third patient: G2 neutropenia |
| 5 | 2 | 6.3% | First patient: GI toxicity |
| | | | Second patient: PD |

GI, gastrointestinal; PD, progressive disease.

and the 2-year DFS rate was 37.5%. The median OS was 28.0 months (95% CI = 19.7-36.3), as shown in Figure 1.

Using univariate analysis, the technique of lymph node dissection was a predictor for postoperative relapse. The median DFS was 15.0 months in the D1 group and 18.0 months in the D2 group ($P$ = .043), as shown in Figure 2*A*. No significant difference in DFS was observed on subgroup analyses of other factors such as sex, age, primary site, histology, differentiation, clinical stage, and cycles of adjuvant chemotherapy received. The median DFS was 28 months in stage I patients, 25.0 months in stage II patients, and 15.0 months in stage III patients ($P$ = .660), as shown in Figure 3*A*.

None of the factors analyzed were significant predictors of OS on univariate analysis. The median OS was 23.0 months (95% CI = 15.3-30.7) in the D1 group and 28.0 months (95% CI = 20.0-36.0) in the D2 group ($P$ = .786), as shown in Figure 2*B*. The median OS was 29.0 months (95% CI = 26.2-31.8) in the stage II group and 22.3 months (95% CI = 19.5-25.1) in the stage III group ($P$ = .983), as presented in Figure 3*B*.

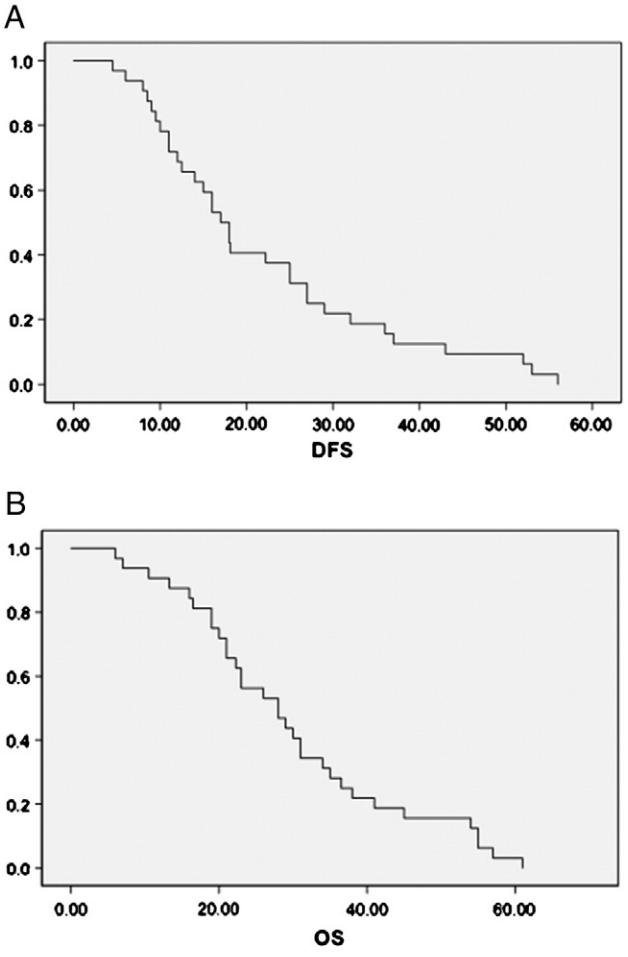


**Figure 1.** Median DFS and median OS for all patients. A) Median DFS was 17.0 months. B) Median OS was 28.0 months.

### *Toxicity*

The most commonly reported adverse events of any grade were neutropenia (90.6%), nausea (78.1%), vomiting (56.3%), and anemia (53.1%). Most of these toxicities were mild. The only grade 3/4 adverse event that occurred in more than 10% of patients was neutropenia.

The most frequent hematologic adverse events were grade 3/4 neutropenia, which occurred in 18 patients (56.3%), and febrile neutropenia, which developed in 4 patients (12.5%). The frequency of anemia was high at 53.13%, but all of these toxicities were grade 1/2. Grade 1/2 thrombocytopenia was recorded in eight patients (25.0%), but no grade 3/4 cases of thrombocytopenia occurred.

The most frequent grade 3/4 nonhematologic adverse events were diarrhea (9.4%; $n$ = 3), nausea (6.3%; $n$ = 2), and vomiting (6.3%; $n$ = 2). Cases of peripheral neuropathy were all grade 1/2 (15.6%; $n$ = 5). There were no chemotherapy-related deaths (Table 3).

## Discussion

Gastric cancer has a high risk of relapse and metastasis after radical resection. Early clinical studies failed to confirm that adjuvant chemotherapy prolongs survival. In 2009, a meta-analysis of 12 randomized clinical trials analyzed 3809 patients [7]. The hazard ratio for OS was 0.78 (95% CI = 0.71-0.85) in favor of chemotherapy. The most recently published meta-analysis evaluated data from 34 randomized trials that compared adjuvant systemic chemotherapy to surgery alone and were conducted in both Asian and Western populations [8]. The risk of death among patients receiving adjuvant chemotherapy was reduced by 15% [hazard ratio (HR) = 0.85). To date, two large-scale phase III clinical trials have demonstrated a benefit of adjuvant chemotherapy in patients with gastric cancer who underwent curative surgery with D2 lymphadenectomy. One was the Japanese adjuvant chemotherapy trial of TS-1 for gastric cancer (ACTS-GC) trial [9]. In the ACTS-GC trial, 1059 patients with stage II or III gastric cancer who had undergone a D2 lymphadenectomy were randomly assigned to 6 months of S-1 *versus* surgery alone. Five-year OS was significantly better with S-1 (72% *vs* 61%). Another study was the Asian multicenter capecitabine and oxaliplatin adjuvant study in stomach cancer (CLASSIC) trial, in which 1035 patients with stage II/III gastric cancer were randomly assigned to capecitabine plus oxaliplatin (XELOX) or observation after a D2 gastrectomy [10]. Adjuvant chemotherapy was associated with a significant improvement in 3-year DFS (74% *vs* 59%; HR = 0.56) and OS (78% *vs* 69%; HR = 0.66) [11].

The optimal adjuvant chemotherapy regimen has not yet been established. There are several choices, including S-1 (used in the ACTS-GC trial) [10], XELOX (used in the CLASSIC trial) [11], capecitabine plus cisplatin (used in the adjuvant chemoradiation therapy in stomach cancer trial) [12] or epirubicin, cisplatin, and infused fluorouracil (used in the Medical Research Council Adjuvant Gastric Infusional chemotherapy trial) [13]. However, it is unclear which regimen is best or whether a superior alternative approach exists.

Docetaxel is a novel antitumor drug that promotes microtubule assembly from tubulin dimers and inhibits the depolymerization of

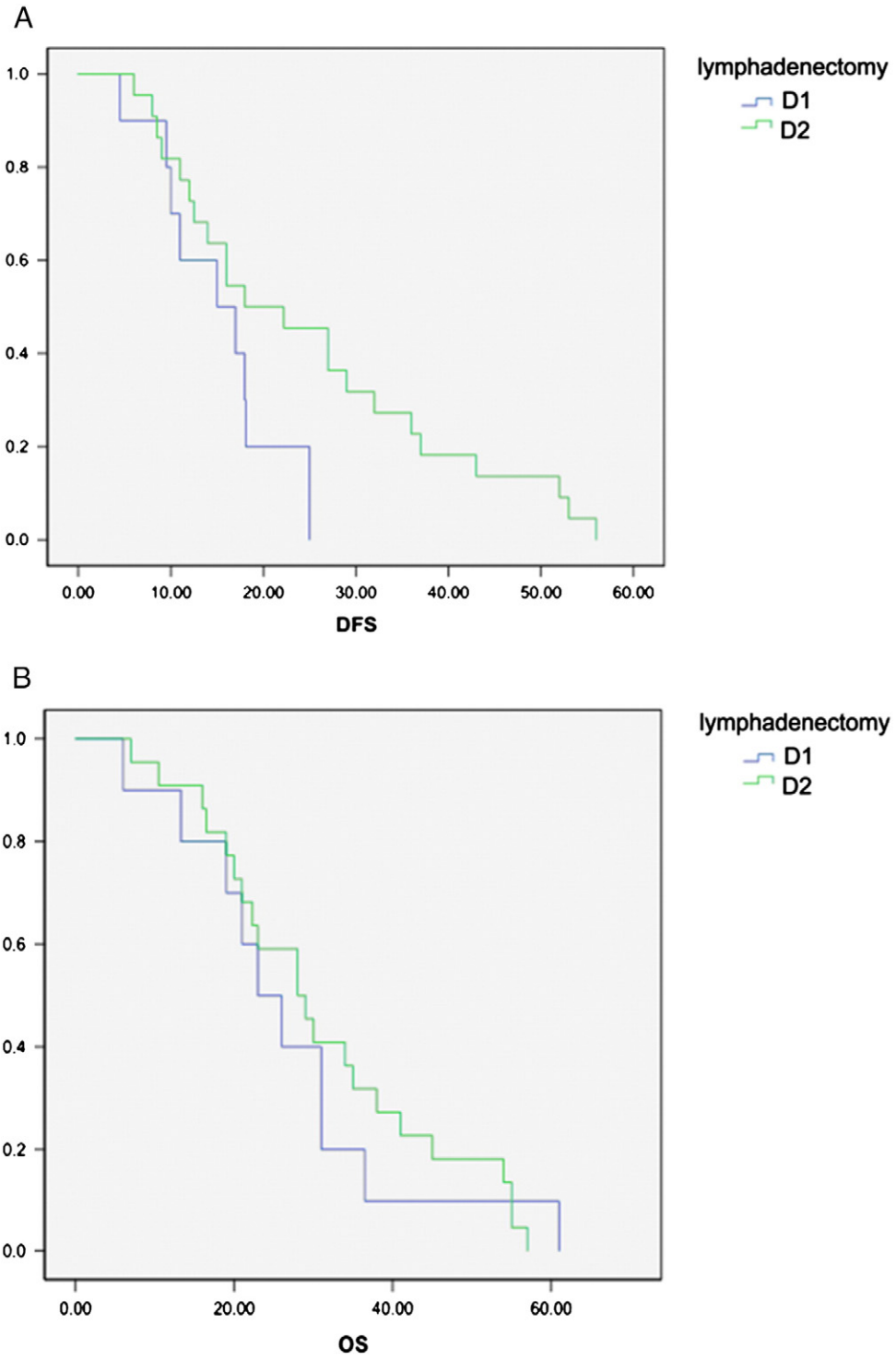


**Figure 2.** Median DFS and median OS in the D1 and D2 groups. A) Median DFS in the D1 group was 15.0 months and 18.0 months in the D2 group ($P$ = .043). B) Median OS in the D1 group was 23.0 months and 28.0 months in the D2 group ($P$ = .786). D1 group, D1 lymphadenectomy; D2 group, D2 lymphadenectomy.

tubulin, thereby stabilizing microtubules in the cell. This results in the inhibition of DNA, RNA, and protein synthesis [14]. The efficacy of docetaxel monotherapy in AGC is only 15% to 24% [15]. The response rate of 5-FU/platinum-based treatment is approximately 22% to 65% [16]. Cisplatin and 5-FU synergize with docetaxel. The DCF regimen was first shown to have efficacy for the treatment of patients with AGC in a multinational TAX-325 trial [17]. On the basis of these results, docetaxel was approved in the United States and Europe for AGC. The role of the DCF regimen in the adjuvant treatment of gastric cancer is not clear.

In this study, we show that the DCF regimen may also have a survival benefit when used as adjuvant chemotherapy in gastric cancer. The median DFS was 17 months, and the 2-year DFS rate was 37.5%. According to the National Cancer Institute, Surveillance, Epidemiology, and End Results Program (Bethesda, MD) database, the 2-year survival rate was only 22% to 42% in patients with stage III

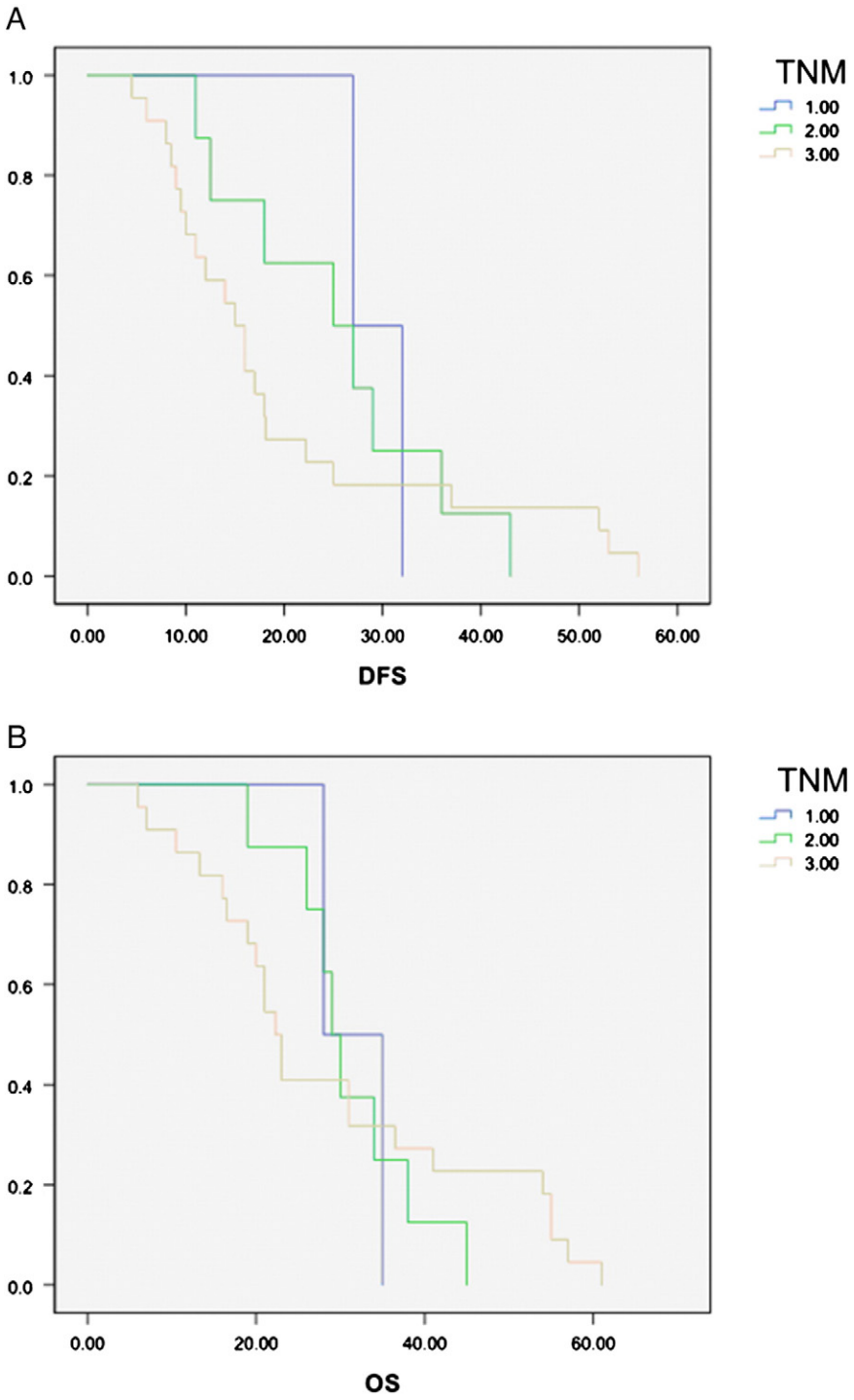


**Figure 3.** Median DFS and median OS by stage. A) Median DFS was 27.0 months in the stage I group, 25.0 months in the stage II group, and 15.0 months in the stage III group ($P = .660$). B) Median OS was 29.0 months in the stage II group and 22.3 months in the stage III group ($P = .983$).

gastric cancer [18], which appears to be shorter than the results of the ACTS-GC and the CLASSIC trials. However, almost 70% of patients enrolled in this study had AJCC stage III disease, which was more advanced than the characteristics of those two trials. This difference may influence survival times.

One controversial issue in the surgical management of gastric cancer is the optimal extent of lymph node dissection. Some large prospective clinical studies in western countries have shown that there was no difference in the 5-year survival rate among patients who underwent D1 *versus* D2 resection and that mortality related to surgery was higher in the D2 group [19–21]. However, in Japan and other Asian countries, clinical studies have shown that the D2 operation can reduce postoperative local recurrence rates compared with D1 resection and that complication and operative mortality rates are very low [22]. In this study, 22 patients (68.8%) received a D2 resection, and 10 patients (31.3%) underwent a D1 operation. The

**Table 3.** Adverse Events during Adjuvant Chemotherapy National Cancer Institute's Common Terminology Criteria for Adverse Events v3.0 (NCI-CTC v3.0).

| | Grade 1/2 | | Grade 3/4 | | All Grades | |
|---|---|---|---|---|---|---|
| | *n* | % | *n* | % | *n* | % |
| Hematology | | | | | | |
| Neutropenia | 11 | 34.4% | 18 | 56.3% | 29 | 90.6% |
| Anemia | 17 | 53.1% | 0 | 0% | 17 | 53.1% |
| Thrombocytopenia | 8 | 25.0% | 0 | 0% | 8 | 25.0% |
| Febrile neutropenia | 4 | 12.5% | 0 | 0% | 4 | 12.5% |
| Nonhematology | | | | | | |
| Liver function | | | | | | |
| ALT | 9 | 28.1% | 0 | 0% | 9 | 28.1% |
| Tbil | 9 | 28.1% | 0 | 0% | 9 | 28.1% |
| Gastrointestinal | | | | | | |
| Nausea | 23 | 71.9% | 2 | 6.3% | 25 | 78.1% |
| Vomiting | 16 | 50.0% | 2 | 6.25% | 18 | 56.3% |
| Stomatitis | 4 | 12.5% | 0 | 0% | 4 | 12.5% |
| Diarrhea | 8 | 25.0% | 3 | 9.4% | 11 | 34.4% |
| Constipation | 6 | 18.8% | 0 | 0% | 6 | 18.8% |
| Peripheral neuropathy | 5 | 15.6% | 0 | 0% | 5 | 15.6% |
| Arrhythmia | 1 | 3.1% | 0 | 0% | 1 | 3.1% |
| Skin rash | 3 | 9.4% | 0 | 0% | 3 | 9.4% |
| Fatigue | 5 | 15.6% | 0 | 0% | 5 | 15.6% |

ALT, Alanine aminotransferase; Tbil, total bilirubin.

median DFS of these two groups was significantly different (15 months for D1 and 18 months for D2 dissections; $P$ = .043), suggesting that D2 lymphadenectomy may provide a survival benefit. This result may also suggest that patients who undergo a radical D2 dissection may also benefit more from adjuvant DCF chemotherapy. For patients who have had a D1 resection, DCF adjuvant chemotherapy may not be effective enough. The addition of radiotherapy in these subgroups may be of paramount importance on the basis of the results of the US Intergroup trial INT0116 [23] and two recently published meta-analyses [24,25]. This study showed that neutropenia and febrile neutropenia occurred most frequently in patients treated with adjuvant DCF chemotherapy. The incidence of grade 3/4 neutropenia was high (at 56.4%), and febrile neutropenia occurred in 12.5% of patients. Other grade 3/4 adverse events developed in less than 10% of patients. There were no chemotherapy-related deaths in our study. The adverse events were manageable, and nonhematologic AE were more tolerable than in some previous studies. In TAX-325, the rates of any grade 3 or 4 toxicity during therapy were high when triple therapy was used (81%), and the most frequent grade 3/4 adverse events were neutropenia (30%) and diarrhea (20%) [17].

In summary, our results support the use of combination chemotherapy with DCF as a new approach to adjuvant treatment in patients with gastric cancer who have undergone radical surgery. We suggest further investigation of this adjuvant regimen.

## Conflict of Interest

The authors report no conflicts of interest.

## Acknowledgments

The authors thank all the patients who participated in this study.

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