Combined perioperative EOX chemotherapy and postoperative chemoradiotherapy for locally advanced gastric cancer

QIUSHAN HE[1,2], JUAN ZHAO[1], JIA YUAN[1], ZHIMIN GONG[1] and TIENAN YI[2]

[1]Department of Oncology, Affiliated Hospital of Medical College, [2]Institute of Oncology, Hubei Arts and Science University, Xiangyang, Hubei 441000, P.R. China

Received January 16, 2016; Accepted February 17, 2017

DOI: 10.3892/mco.2017.1300

Abstract. Currently, adjunctive therapy for gastric cancer is not standardized worldwide and the most effective combination of different modalities has not been clearly determined. The aim of the present study was to retrospectively analyze the efficacy and toxicity of the combination of perioperative epirubicin, capecitabine and oxaliplatin (EOX) chemotherapy and postoperative concurrent chemoradiotherapy in the treatment of locally advanced gastric cancer. A total of 41 patients with locally advanced gastric cancer who had undergone perioperative EOX chemotherapy and surgical resection followed by chemoradiotherapy, were assessed. The perioperative EOX regimen consisted of 50 mg/m^2 epirubicin and 130 mg/m^2 oxaliplatin on day 1, with 625 mg/m^2 capecitabine administered twice daily on days 1-21. The perioperative regimen was repeated 2-3 times every 3 weeks. After complete resection following the perioperative EOX regimen, concurrent chemoradiotherapy with capecitabine (4,500 cGy in daily fractions of 180 cGy administered 5 days per week for 5 weeks, with 625 mg/m^2 capecitabine twice daily during radiotherapy) and 2 cycles of the EOX regimen 4 weeks after radiotherapy, were performed. In total, 30/41 patients (73.2%) completed all the planned treatments, including perioperative chemotherapy, surgical resection and chemoradiotherapy. The effective rate of preoperative chemotherapy (partial and complete response) was 56.1%; 30/41 patients received R0 resection, and the overall 3-year survival rate was 57.7%. Grade 3/4 gastrointestinal toxicity (nausea/vomiting) occurred in 22% of the patients, while 18 patients (43.9%) developed grade 3/4 hematological toxicity (granulocytopenia). The results of the present study indicated that the combination of perioperative EOX chemotherapy and postoperative concurrent chemoradiotherapy is feasible and effective for locally advanced gastric cancer.

Correspondence to: Dr Qiushan He, Department of Oncology, Affiliated Hospital of Medical College, HuBei Arts and Science University, 136 JinZhou Street, Xiangyang, Hubei 441000, P.R. China
E-mail: 849050146@qq.com

Key words: gastric cancer, perioperative chemotherapy, chemoradiotherapy, capecitabine

Introduction

Gastric cancer is the most common malignancy in China and the second leading cause of tumor-related mortality worldwide (1). Surgery is the main treatment for gastric cancer; however, even for patients suitable for radical resection, high local recurrence and distant metastasis commonly affect postoperative survival (2). A large number of evidence-based medical findings have indicated that adjuvant chemotherapy or postoperative concurrent chemoradiotherapy significantly improve the survival of patients with advanced gastric cancer (3). Currently, adjunctive therapy for gastric cancer is not standardized worldwide. After a study published in 2006 (4), perioperative epirubicin, cisplatin and 5-fluorouracil (5-FU) (ECF) chemotherapy was adopted as the preferred treatment in Europe, while postoperative combined treatment with radiotherapy and chemotherapy, as suggested by the 0116 trial (5), is more frequently applied in the US, and postoperative chemotherapy based on the CLASSIC trial (6) is the preferred treatment in Asia. Studies assessing the effects of combinations of these three types of therapy are scarce (7), the main concern being toxicity. Advancements in chemotherapy and radiotherapy for treating gastric cancer have provided novel therapeutic options. Indeed, ECF therapy is effective as a perioperative treatment in advanced gastric tumors. In the MAGIC trial (4), the total survival rate improved from 23 to 36% following perioperative ECF treatment. According to the REAL-2 trial (8), epirubicin, capecitabine and oxaliplatin (EOX) treatment was found to be better compared with ECF in patients with late-stage gastric cancer in terms of effectiveness as well as hematological toxicity: The response rate to chemotherapy was 47.9 vs. 40.7%; the progression-free survival was 7 vs. 6.2 months; and the incidence of grade 3 neutropenia was 27.6 vs. 41.7%, respectively (all $P<0.01$). In theory, substituting ECF with EOX may improve the chemotherapeutic efficacy and also has the potential to reduce treatment-related toxicity. Moreover, application of postoperative chemoradiotherapy was based on the 0116 trial published in 2001 (5), which was the first to show that postoperative chemoradiotherapy provided a survival benefit, achieving an increase in the 3-year overall survival (OS) of patients with advanced gastric cancer from 41 to 50% compared with surgery alone. With the techniques available at that time, only anteroposterior/posteroanterior illumination was applied, with only 64% of the patients receiving

all the planned treatments (5). Newly developed techniques for radiotherapy, including three-dimensional conformal and intensity-modulated radiation therapy (IMRT), are able to provide effective treatment, while reducing treatment-related toxicity (9-11). In the present study, the clinical efficacy and toxicity of combined perioperative EOX chemotherapy and enhanced postoperative chemoradiotherapy was assessed by retrospectively analyzing 41 patients with locally advanced gastric cancer, in order to provide a basis for further clinical research and application.

Patients and methods

Patient information. A total of 41 patients treated at the tumor center of the Affiliated Hospital of Hubei University of Arts and Science (Xiangjang, China) between November 2010 and August 2014 were assessed. The selection criteria were as follows: Gastric adenocarcinoma or signet ring cell cancer diagnosed pathologically; no previous radio/chemotherapy; an Eastern Cooperative Oncology Group performance status (ECOG-PS) of 0-2; normal function of main organs (hemoglobin >90 g/l, absolute neutrophil count >1.5x10^9/l, platelet count >100x10^9/l, aspartate aminotransferase and alanine aminotransferase <1.5 upper limit of normal (ULN), serum bilirubin <1.5 ULN and serum creatinine <0.15 mmol/l); and T3 and T4 clinical stage or positive lymph nodes. The present study was approved by the Ethics Committee of the Affiliated Hospital of Hubei University of Arts and Science and informed consent was obtained from the patients for combining perioperative EOX chemotherapy and postoperative concurrent chemoradiotherapy.

Perioperative chemotherapy and concurrent chemotherapy. Perioperative EOX treatment was first administered to all eligible subjects. The EOX regimen consisted of 50 mg/m^2 epirubicin and 130 mg/m^2 oxaliplatin on day 1; furthermore, 625 mg/m^2 capecitabine was administered twice daily on days 1-21. The perioperative regimen was repeated every 3 weeks for 2-3 cycles. Surgery was then performed based on the patient's condition. Concurrent chemoradiotherapy was performed 4-6 weeks after surgery (capecitabine, 625 mg/m^2, twice daily) for 5 weeks. The EOX regimen was then administered twice in 4 weeks after chemoradiotherapy.

Postoperative radiotherapy. Based on the tumor stage and the patient's postoperative status, IMRT was delivered to the targeted region, which mainly included the tumor bed, stoma (including gastrointestinal and duodenal stump anastomoses), gastric stump (for T4 patients diagnosed by preoperative ultrasonic gastroscopy or postoperative pathological examination) and associated lymph drainage area. Reverse modulation was adopted with a prescribed radiation dose at 95% planning target volume of 45 Gy delivered in 25 fractions of 1.8 Gy. The fitness of the target area and normal tissue limits were assessed using a dose-volume histogram and verified by image-guided radiotherapy once weekly.

Assessment of chemotherapeutic effects. There are currently no clearly defined criteria for assessing the effect of gastric cancer treatments. In the present study, enhanced computed tomography (CT) and ultrasonic endoscopy were combined to assess the therapeutic effects after two preoperative chemotherapy cycles by comparing gastric wall thickness, tumor size, and number and size of lymph nodes according to the Response Evaluation Criteria In Solid Tumors (8).

Evaluation of side effects. The acute side effects of preoperative chemotherapy, postoperative concurrent chemoradiotherapy and postoperative chemotherapy were evaluated. Staging was performed following the National Cancer Institute's Common Terminology Criteria for Adverse Events, version 4.0 (8).

Follow-up. Side-effects were recorded and CT imaging was performed for all patients during hospitalization. Follow-up was performed by outpatient visits, telephone communication and text messages and the times of recurrence and death were recorded. Follow-up was performed from the 1st of November 2010 to the 1st of April 2015 (8-50 months), with OS as the primary endpoint.

Statistical analysis. SPSS 16.0 (SPSS, Inc., Chicago, IL, USA) was used for statistical analysis. Survival rates were calculated using the Kaplan-Meier method and significance was assessed using the log-rank test (α=0.05). Toxicities were compared using the χ^2 test (Fisher's exact test based on data). P<0.05 was considered to indicate a statistically significant difference.

Results

Baseline characteristics of the patients. The patient cohort (n=41) comprised 26 men and 15 women aged 23-72 years, with a median age of 54 years; 22% of the patients had T3 disease, and 85% had positive lymph nodes; 43 and 54% of the patients had clinical stage II and III, respectively. The ECOG PS was <2 at enrolment. The patient characteristics are summarized in Table I.

Therapeutic effects. The 41 patients received ≥2 chemotherapy cycles. A total of 18 patients were administered 2 cycles of preoperative treatments in total [2 treatment cycles did not produce an overt effect in patients with stable disease (SD) or progressive disease, who were operated immediately thereafter]. The remaining 23 patients received 3 cycles of preoperative treatment (the patients received the third cycle after the first two produced an obvious effect). In total, 39 patients underwent surgery with D2 postoperative lymphadenectomy performed in 8 patients, D1 in 17 and D0 in 2 patients; furthermore, 9 patients received palliative operations, indicating an overall R0 resection rate of 73.2%. Two patients did not receive surgery, as one had liver metastasis and the other one ascites; these 2 patients were received palliative chemotherapy with docetaxel. Of the 39 patients who received surgery, 36 received postoperative concurrent radio/chemotherapy; the 3 remaining patients declined radiotherapy: 2 patients received paclitaxel monotherapy after two cycles of EOX chemotherapy, and 1 patient was administered a third cycle of EOX. A total of 30 patients received two cycles of EOX. Of the patients who did not receive two cycles of EOX, 2 received one cycle of EOX, and treatment was discontinued in 4 subjects. In total, 73.2% of the patients completed all the

Table I. Clinical characteristics of the patients (n=41).

Characteristics	No. (%)
Gender	
Male	26 (63)
Female	15 (37)
T stage	
T1-2	7 (17)
T3-4	34 (83)
N stage	
N0	6 (12)
N1-3	35 (85)
Tumor location	
Gastroesophageal junction	10 (24)
Gastric fundus	4 (10)
Gastric body	18 (44)
Pylorus	9 (22)
Pathological type	
Highly differentiated adenocarcinoma	12 (30)
Poorly differentiated adenocarcinoma	16 (39)
Mucinous adenocarcinoma	4 (10)
Signet ring cell cancer	7 (17)
Others	2 (4)

Table II. Preoperative and operative parameters (n=41).

Parameters	No. (%)
Type of surgery	
D2 lymphadenectomy	8 (19.5)
D1 lymphadenectomy	17 (41.5)
D0 lymphadenectomy	5 (12.2)
Palliative	9 (22.0)
None	2 (4.9)
Effect of preoperative chemotherapy	
Complete response	1 (2.4)
Partial response	22 (53.7)
Stable disease	13 (31.7)
Progressive disease	5 (12.2)

planned treatments (Table II). Of the 41 patients who were followed up, 15 succumbed to the disease (36.6%). The 1- and 3-year OS rates were 92.4 and 57.7%, respectively, with a median survival time of 41 months (Fig. 1).

Toxicity. Gastrointestinal reactions and hematological toxicity were the main side effects (Tables III-V). The most common type of hematological toxicity was reduced white blood cell count (neutrophils and granulocytes). The grade 3/4 toxicities mainly included reduced white blood cell and granulocyte count (43.9%), and nausea and vomiting (17.1%) (Table III).

Table III. Grade 3/4 toxicities in the 41 patients.

Toxicities	No. (%)
Hematological	
Reduced white blood cell count	15 (36.6)
Reduced granulocyte count	18 (43.9)
Anaemia	5 (12.2)
Thrombocytopenia	3 (7.3)
Gastrointestinal	
Nausea/vomiting	7 (17.1)
Diarrhea	3 (7.3)

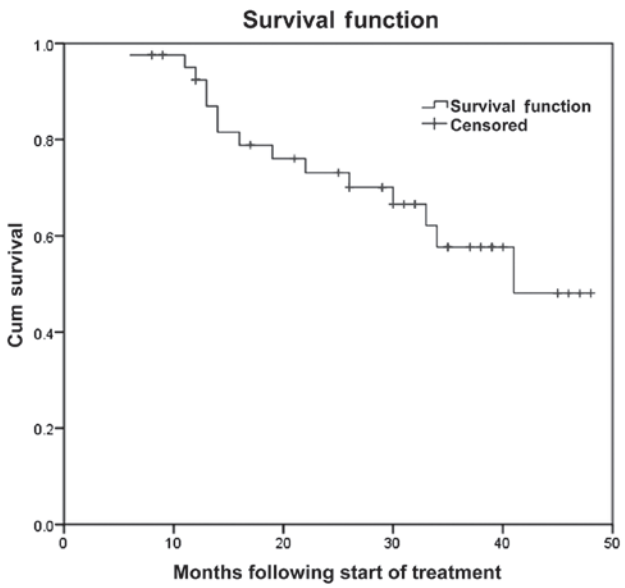

Figure 1. Overall survival of the 41 patients. Cum, cumulative.

In addition, the acute toxicities associated with preoperative, concurrent and postoperative chemotherapy were analyzed. Of note, the overall side effects increased with treatment; however, grade 3/4 side effects did not differ significantly among stages (P>0.05). Regarding grade 1/2 side effects, nausea and vomiting differed significantly between concurrent chemoradiotherapy (56%) and pre-/postoperative chemotherapy (80%; P=0.027).

Discussion

Radical surgery combined with adjuvant therapy is the standard treatment for locally advanced gastric cancer. Adjunctive therapies include perioperative chemotherapy with ECF, fluorouracil-based postoperative concurrent radiochemotherapy and capecitabine/cisplatin- or XELOX-based postoperative adjuvant chemotherapy (4-6,9). Treatment selection by gastrointestinal oncologists may be difficult. There are solid, evidence-based data for all three types of treatment; however, it remains unclear which is more effective. Furthermore, as all three treatments are beneficial, they may provide added advantages when combined, but relevant studies are scarce. The present study aimed to investigate the clinical feasibility of periopera-

Table IV. Grade 1/2 toxicity (NCI CTC-AE 4.0).

Toxicities	Pre-chemo (n=41), n (%)	Post-radio/chemo (n=36), n (%)	Post-chemo (n=30), n (%)	χ^2	P-value
Hematological					
Reduced white blood cell count	21 (51.2)	17 (47.2)	22 (73.3)	4.877	0.087
Reduced granulocyte count	16 (39.0)	14 (38.9)	19 (63.3)	5.166	0.076
Anaemia	26 (63.4)	14 (38.9)	18 (60.0)	5.209	0.074
Thrombocytopenia	20 (48.8)	17 (47.2)	16 (53.3)	0.260	0.878
Gastrointestinal					
Nausea/vomiting	33 (80.5)	20 (55.6)	24 (80.0)	7.240	0.027
Diarrhea	8 (19.5)	5 (13.9)	8 (26.7)	1.694	0.429

NCI CTC-AE, National Cancer Institute Common Terminology Criteria for Adverse Events. Pre-chemo, preoperative chemotherapy, post-radio/chemo, postoperative concurrent chemoradiotherapy; post-chemo, postoperative chemotherapy.

Table V. Grade 3/4 toxicity (NCI CTC-AE 4.0).

Toxicities	Pre-chemo (n=41), n (%)	Post-radio/chemo (n=36), n (%)	Post-chemo (n=30), n (%)	χ^2	P-value
Hematological					
Reduced white blood cell count	6 (14.6)	7 (19.4)	7 (23.3)	0.883	0.643
Reduced granulocyte count	10 (24.4)	8 (22.2)	9 (30.0)	0.550	0.760
Anaemia	3 (7.3)	3 (2.7)	3 (6.7)	0.162	0.922
Thrombocytopenia	2 (4.8)	1 (2.8)	2 (6.7)	0.562	0.755
Gastrointestinal					
Nausea/vomiting	3 (7.3)	3 (8.3)	5 (16.7)	1.865	0.394
Diarrhea	2 (4.9)	1 (2.8)	2 (6.7)	0.562	0.755

NCI CTC-AE, National Cancer Institute Common Terminology Criteria for Adverse Events. Pre-chemo, preoperative chemotherapy, post-radio/chemo, postoperative concurrent chemoradiotherapy; post-chemo, postoperative chemotherapy.

tive treatment combined with postoperative radio/chemotherapy in the treatment of late-stage gastric cancer. Of note, perioperative EOX treatment and postoperative concurrent IMRT exerted a certain curative effect, with acceptable toxicity.

As mentioned above, the overall effectiveness rate [complete response (CR) + partial response (PR) + SD] of 2-3 cycles of EOX treatment was 87.8%, with CR and PR rates of 2.4 and 53.7%, respectively. The PR obtained in the present study was similar to that reported by the REAL-2 trial (47.9%) (8), indicating that EOX produces similar effects in local early gastric cancer as in this study and late stage gastric tumors. In the present study, the radical resection rate in patients receiving perioperative EOX treatment was 73.2%, which is similar to that reported by the MAGIC trial (69.3%) (4), indicating that the perioperative EOX treatment used in the present study may be able to increase the percentage of patients eligible for radical resection compared with perioperative ECF treatment.

Although postoperative concurrent radio/chemotherapy was shown to improve the OS of patients with gastric cancer in the 0116 trial (5), radiotherapy after postoperative D2 lymphadenectomy was not associated with a survival benefit in the ARTIST trial, and may only be beneficial for patients with positive lymph nodes (12). The differences between the two trials mainly resulted from the difference in the recruited patients: Patients subjected to D2 lymphadenectomy accounted for ~10% in the 0116 trial vs. 100% in the ARTIST trial. D2 radical resection is the standard treatment for advanced gastric cancer, while in clinical practice, only 20% of the patients are eligible for this treatment in the clinical setting. The status of the patients assessed in the present study was similar to that of the subjects of the 0116 trial, and the majority were not eligible for D2 resection; therefore, in principle it is feasible to apply postoperative concurrent radio/chemotherapy. Based on the follow-up data over 8-50 months, the 1-, 2- and 3-year OS rates of 92.4, 73.1 and 57.7%, respectively, with a median survival time of 41 months. The 3-year survival rate was significantly lower compared with the DFS in the ARTIST trial (77.5%), which may have been due to the fact that all the patients in the ARTIST trial, but only 20% of the patients in the present study, received D2 radical resection; furthermore, 26.8% of the patients in the present study received palliative surgery or no surgery, all of which are factors likely to affect patient survival. Compared with the median survival time reported by the 0116 trial (36 months), the 41 months observed in the present

study indicate the superiority of the combined treatment. In the MAGIC trial, although 42.5% of the patients received D2 resection, the 3-year OS rate was 41%, which was significantly lower compared with the 57.7% observed in the present study, suggesting that application of concurrent radio/chemotherapy following perioperative chemotherapy may provide a further survival benefit for the patients.

The main side effects were gastrointestinal and hematological toxicities. Acute toxicities were analyzed for the preoperative, concurrent and postoperative chemotherapies, to determine undesired reactions to each adjunctive therapy. Postoperative concurrent radio/chemotherapy was expected to produce more severe side effects; however, although ≥grade 3 side-effects did not differ significantly among the various stages, the incidence of grade 1/2 nausea and vomiting was significantly lower with concurrent radiochemotherapy compared with the postoperative adjunctive therapy. This may be associated with the IMRT and manipulation during target-volume selection to include the gastric stump in patients <T3, minimizing the irradiated volume. A contribution of cumulative postoperative side effects following postoperative adjunctive therapy cannot be excluded. Furthermore, there was no major hematological toxicity observed during concurrent radio/chemotherapy or adjunctive therapy. In the present study, 43.9% of the patients exhibited a grade 3/4 reduction of the granulocyte count, while the incidence of grade 3/4 nausea and vomiting was 17.1%. These rates were markedly lower compared with the adverse event rates reported in the 0116 trial (54 and 33%, respectively). The EOX treatment used in the present study was more potent compared with CF+5-FU, with fewer side effects, which may be associated with the IMRT also used in this study. In a study applying ECF as postoperative concurrent radio/chemotherapy (7), grade 3 hematological toxicities were observed in 66% of the patients, while the rate of gastrointestinal toxicities was 28%, which was higher compared with the present study. Although three-dimensional conformal radiation was also used, ECF treatment produced more severe side effects compared with EOX therapy. Furthermore, gastric stump tumors were included as radiation targets when ECF, but not EOX, was applied; thus, the radiation volume may be reduced to decrease side effects according to our paradigm. Moreover, the proportion of patients receiving all planned treatments was 64% in the 0116 trial and 67% in a study using ECF (7), while it was 73.2% in the present study, further demonstrating the tolerability of combined perioperative EOX chemotherapy and concurrent IMRT. However, compared with solely administered postoperative chemotherapy, whether the side effects are reduced with our perioperative treatment requires further investigation.

In the present study, combining perioperative EOX chemotherapy and concurrent IMRT produced not only tolerable side effects, but also exhibited curative efficacy. By combining postoperative adjuvant 5-FU-based chemotherapy and concurrent radio/chemotherapy, Leong *et al* (7) obtained an OS rate of 61.6% (7), which is similar to that observed in the present study (57.7%). Of note, all the patients in the abovementioned study, but only 73.2% in the present study, received R0 resection. As resection of gastric cancer exerts a significant beneficial effect on patient survival, there may be certain curative advantages to the treatment used in the present study. A recent meta-analysis also found that, for gastric cancer patients suitable for surgery, perioperative chemotherapy is superior to postoperative adjuvant chemotherapy (13). In addition, whether other widely used effective adjuvant chemotherapies (14-17) are superior to EOX as perioperative chemotherapy when combined with other treatments also requires further investigation.

In summary, combining perioperative EOX chemotherapy and concurrent IMRT may be useful in the treatment of gastric cancer.

References

1. Kelley JR and Duggan JM: Gastric cancer epidemiology and risk factors. J Clin Epidemiol 56: 1-9, 2003.
2. GASTRIC (Global Advanced/Adjuvant Stomach Tumor Research International Collaboration) Group, Paoletti X, Oba K, Burzykowski T, Michiels S, Ohashi Y, Pignon JP, Rougier P, Sakamoto J, Sargent D, *et al*: Benefit of adjuvant chemotherapy for resectable gastric cancer: A meta-analysis. JAMA 303: 1729-1737, 2010.
3. Schirren R, Reim D and Novotny AR: Adjuvant and/or neoadjuvant therapy for gastric cancer? A perspective review. Ther Adv Med Oncol 7: 39-48, 2015.
4. Cunningham D, Allum WH, Stenning SP, Thompson JN, Van de Velde CJ, Nicolson M, Scarffe JH, Lofts FJ, Falk SJ, Iveson TJ, *et al*: Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. N Engl J Med 355: 11-20, 2006.
5. Macdonald JS, Smalley SR, Benedetti J, Hundahl SA, Estes NC, Stemmermann GN, Haller DG, Ajani JA, Gunderson LL, Jessup JM and Martenson JA: Chemoradiotherapy after surgery compared with surgery alone for adenocarcinoma of the stomach or gastroesophageal junction. N Engl J Med 345: 725-730, 2001.
6. Noh SH, Park SR, Yang HK, Chung HC, Chung IJ, Kim SW, Kim HH, Choi JH, Kim HK, Yu W, *et al*: Adjuvant capecitabine plus oxaliplatin for gastric cancer after D2 gastrectomy (CLASSIC): 5-year follow-up of an open-label, randomised phase 3 trial. Lancet Oncol 15: 1389-1396, 2014.
7. Leong T, Joon DL, Willis D, Jayamoham J, Spry N, Harvey J, Di Iulio J, Milner A, Mann GB and Michael M: 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 79: 690-695, 2011.
8. Cunningham D, Starling N, Rao S, Iveson T, Nicolson M, Coxon F, Middleton G, Daniel F, Oates J and Norman AR; Upper Gastrointestinal Clinical Studies Group of the National Cancer Research Institute of the United Kingdom: Capecitabine and oxaliplatin for advanced esophagogastric cancer. N Engl J Med 358: 36-46, 2008.
9. Minn AY, Hsu A, La T, Kunz P, Fisher GA, Ford JM, Norton JA, Visser B, Goodman KA, Koong AC and Chang DT: Comparison of intensity-modulated radiotherapy and 3-dimensional conformal radiotherapy as adjuvant therapy for gastric cancer. Cancer 116: 3943-3952, 2010.
10. Chung HT, Lee B, Park E, Lu JJ and Xia P: Can all centers plan intensity-modulated radiotherapy (IMRT) effectively? An external audit of dosimetric comparisons between three-dimensional conformal radiotherapy and IMRT for adjuvant chemoradiation for gastric cancer. Int J Radiat Oncol Biol Phys 71: 1167-1174, 2008.
11. Trip AK, Nijkamp J, van Tinteren H, Cats A, Boot H, Jansen EP and Verheij M: IMRT limits nephrotoxicity after chemoradiotherapy for gastric cancer. Radiother Oncol 112: 289-294, 2014.
12. Lee J, Lim do H, Kim S, Park SH, Park JO, Park YS, Lim HY, Choi MG, Sohn TS, Noh JH, *et al*: Phase III trial comparing capecitabine plus cisplatin versus capecitabine plus cisplatin with concurrent capecitabine radiotherapy in completely resected gastric cancer with D2 lymph node dissection: The ARTIST trial. J Clin Oncol 30: 268-273, 2012.
13. Yang Y, Yin X, Sheng L, Xu S, Dong L and Liu L: Perioperative chemotherapy more of a benefit for overall survival than adjuvant chemotherapy for operable gastric cancer: An updated meta-analysis. Sci Rep 5: 12850, 2015.

14. Sakuramoto S, Sasako M, Yamaguchi T, *et al*: Adjuvant chemotherapy for gastric cancer with S-1, an oral fluoropyrimidine. N Engl J Med 357: 1810-1820, 2007.
15. Kulig J, Kolodziejczyk P, Sierzega M, Bobrzynski L, Jedrys J, Popiela T, Dadan J, Drews M, Jeziorski A, Krawczyk M, *et al*: Adjuvant chemotherapy with etoposide, adriamycin and cisplatin compared with surgery alone in the treatment of gastric cancer: A phase III randomized, multicenter, clinical trial. Oncology 78: 54-61, 2010.
16. Sasako M, Sakuramoto S, Katai H, Kinoshita T, Furukawa H, Yamaguchi T, Nashimoto A, Fujii M, Nakajima T and Ohashi Y: Five-year outcomes of a randomized phase III trial comparing adjuvant chemotherapy with S-1 versus surgery alone in stage II or III gastric cancer. J Clin Oncol 29: 4387-4393, 2011.
17. Di Costanzo F, Gasperoni S, Manzione L, Bisagni G, Labianca R, Bravi S, Cortesi E, Carlini P, Bracci R, Tomao S, *et al*: Adjuvant chemotherapy in completely resected gastric cancer: A randomized phase III trial conducted by GOIRC. J Natl Cancer Inst 100: 388-398, 2008.