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Concurrent Neoadjuvant Chemoradiotherapy for Siewert II and III Adenocarcinoma at Gastroesophageal Junction

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Abstract: *Objective:* This study was conducted to investigate the efficacy and safety of using a concurrent neoadjuvant chemoradiotherapy (a XELOX regimen) to treat adenocarcinoma of the gastroesophageal junction. *Methods:* Seventy-six patients having resectable adenocarcinoma at the gastroesophageal junction (T3/4, N+, M0) were recruited to participate and randomly assigned to either a chemoradiotherapy group or a surgery group. Patients in the chemoradiotherapy group were orally given capecitabine (1,000 mg/m^2, twice daily for 14 days, days 1–14) and intravenous oxaliplatin (130 mg/m^2 on day 1) for 2 cycles. Radiotherapy was performed with a total of 45 Gy administered in 25 sessions for 5 weeks. Patients in the surgery group received only surgical intervention. *Results:* In the concurrent chemoradiotherapy group, the overall response rate was 55.6% (20/36), tumor control rate was 100% and a pathological complete response was achieved in 16.7% (6/36). The entire chemoradiotherapy group had R0 resections as did 80% of the surgery group (32/40) ($P < 0.05$). In the concurrent chemoradiotherapy group, 6 patients developed grade 3 side effects. Treatment was either discontinued or the dose adjusted. Major hematological side effects in the chemoradiotherapy group included leukopenia, neutropenia, anemia and thrombocytopenia. Nonhematological side effects included nausea, vomiting and appetite loss. Chemoradiotherapy-related death was not observed. *Conclusions:* Concurrent neoadjuvant chemoradiotherapy administration increased the rate of R0 resection and demonstrated favorable safety in patients with Siewert II or III adenocarcinoma at the gastroesophageal junction. These results support the use of neoadjunctive chemoradiotherapy in the treatment of adenocarcinoma of the gastroesophageal junction.

Key Indexing Terms: Neoadjuvant chemoradiotherapy; Gastroesophageal junction; Treatment. **[Am J Med Sci 2015;349(6):472–476.]**

Therapeutic modalities for esophageal cancer have progressed from surgery alone to surgery combined with radiotherapy, chemotherapy and/or targeted therapy. Compared with surgery alone, concurrent neoadjuvant chemoradiotherapy may significantly increase the radical resection rate and improve the prognosis of esophageal[1,2] and rectal cancer patients.[3] However, debate still exists regarding gastroesophageal junction adenocarcinoma therapy selection.[4,5] Some clinical studies[6,7] show that preoperative concurrent neoadjuvant chemoradiotherapy may result in increased pathological complete response and R0 resection rates with tolerable side effects, such as lower negative pathological nodes.[6] However, most of these studies were conducted in the United States and Europe.[8] Researchers in Western countries found that obesity and frequent reflux in combination were associated with considerably higher risk for gastroesophageal junction adenocarcinoma than either single factor alone. Comparing with Eastern countries, shifts in dietary practices in recent decades toward increased fat intake and consumption of meats in Western countries may have contributed in part to the rising incidence of gastroesophageal junction adenocarcinoma.[9] Therefore, few studies have investigated the efficacy of neoadjuvant chemoradiotherapy in Asians with adenocarcinoma gastroesophageal junction adenocarcinomas. In this study, patients having adenocarcinoma located at the gastroesophageal junction were recruited from Hebei Province, China, and received concurrent neoadjuvant chemoradiotherapy. The therapeutic efficacy and safety of this regimen was evaluated.

MATERIALS AND METHODS

General Information

A total of 76 patients with resectable adenocarcinoma at the gastroesophageal junction (T3/4, N+, M0) were recruited at the Fourth Hospital of Hebei Medical University, China, between August 2012 and August 2013. Each was randomly assigned to one of 2 groups: a concurrent chemoradiotherapy group (n = 36) or a surgery group (n = 40). Patients in the concurrent chemoradiotherapy group (32 men and 4 women, median age: 61 years, range: 46–73 years) received concurrent chemoradiotherapy and subsequent surgery. Patients in the surgery group (32 men and 8 women, median age: 57 years, range: 42–72 years) were treated with surgery alone. The general clinical characteristics of patients in the 2 groups are shown in Table 1. This study was approved by the Ethics Committee of the Fourth Hospital of Hebei Medical University and was registered at ClinicalTrials.gov (NCT01962246).

Patient-inclusion criteria for this study were as follows: (1) confirmation, by gastroscopy and CT, of Siewert II or III adenocarcinoma of the gastroesophageal junction with a presurgery tumor long diameter of ≤8 cm; (2) presurgery classification as progressive gastric cancer (T3/4, N+, M0) using the American Joint Committee on Cancer (American Joint Committee on Cancer, AJCC) 2010 patient classification with no evidence of metastasis to the liver, lung, brain, bone or other organs; (3) no prior antitumor therapy; (4) no contraindications for chemotherapy or surgery; (5) a Karnofsky Performance Status (KPS) score of >60 and an Eastern Cooperative Oncology Group (ECOG) score of 0 to 2 and (6) informed consent obtained before enrollment.

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TABLE 1. General clinical characteristics of the subjects

	Concurrent chemoradiotherapy (n = 36)	Surgery alone (n = 40)
Age, yr		
Median	61	57
Range	46–73	42–72
Gender, n (%)		
M	32 (88.9)	32 (80)
F	4 (11.1)	8 (20)
Degree of tumor differentiation, n (%)		
Moderately differentiated	14 (38.9)	18 (45)
Poorly differentiated	16 (44.4)	18 (45)
Mucinous adenocarcinoma	6 (16.7)	4 (10)
Vertical axis diameter of the tumor, cm		
Median	4	4
Range	3–6	3–7
HER2 expression		
0	10 (27.8)	16 (40)
1+	14 (38.9)	16 (40)
2+ (FISH: negative)	10 (27.8)	6 (15)
3+ (or FISH: positive)	2 (5.5)	2 (5)
Clinical T stage, n (%)		
cT3	14 (38.9)	16 (40)
cT4	22 (61.1)	24 (60)
Clinical N stage, n (%)		
cN0	12 (33.3)	16 (40)
cN1	18 (50)	18 (45)
cN2	6 (16.7)	6 (15)
ECOG score, n (%)		
0	4 (11.1)	8 (20)
1	28 (77.8)	24 (60)
2	4 (11.1)	8 (20)

Chemotherapy Regimen

The following XELOX regimen was used. Capecitabine was administered 1,000 mg/m^2 twice daily for 14 days (days 1–14), and oxaliplatin was given intravenously 130 mg/m^2 on day 1 for 2 cycles. Two chemotherapy cycles were administered before surgery and 6 cycles after.

Radiotherapy Regimen

Concurrent CT-based 3-dimensional conformal radiotherapy was delivered by a linear accelerator as multiple shaped beams of 6 to 20 MV X-rays in 5 daily fractions of 1.8 Gy per week for 5 weeks (total dose: 45 Gy). The biologically effective dose, calculated using the linear-quadratic formalism and an α/β ratio of 10 for early responding-tissues (tumor), was 51.1 Gy. According to tolerance of different patients, the chosen dosage ranged from 50 to 52 Gy.

Radiation targets included the entire adenocarcinoma of gastroesophageal junction, any perigastric extension and lymph nodes (gastric, celiac, porta hepatis, gastroduodenal, splenic-suprapancreatic and retropancreatic-duodenal), with adequate margins. The distal margins of the esophagus (3–5 cm) were included when the tumor involved the gastroesophageal junction.

Therapeutic Efficacy Determinations

Therapeutic efficacy was determined according to the Response Evaluation Criteria In Solid Tumors (RECIST Version 1.1) and included the following categories: complete response (CR), partial response (PR), stable disease (SD) and progressive disease. The response rate (RR) was calculated as the sum of CR and PR. The tumor control rate was calculated as the sum of CR, PR and SD. Tumor node metastasis (TNM) staging was performed according to the criteria developed by American Joint Committee on Cancer (7th edition).

Surgery

Surgical treatment consisted of either (1) proximal subtotal gastrectomy or (2) total gastrectomy and a subsequent extended lymph node dissection (D2 resection).

Pathological Analysis

Pathological examinations included detecting tumor; invasion depth; number of metastatic lymph nodes; surgical margins; human epidermal growth factor receptor-2 HER-2 expression and tumor regression grade (TRG).

Tumor regression grades were defined as follows: grade 0 (complete remission) is no cancer cells. Grade 1 (partial remission) is single cells or small groups of cancer cells. Grade 2 (low efficacy) is residual cancer outgrown by fibrosis. Grade 3 (poor efficacy) is minimal or no treatment effect and extensive residual cancer cells.

Statistical Analysis

Statistical analysis was performed using SPSS version 19.0 software. Quantitative data comparisons were made using the χ^2 test. Qualitative data were expressed as the mean ± SD and compared using the t test. A P value <0.05 was considered statistically significant.

RESULTS

Clinical Efficacy

RECIST1.1 evaluation of the concurrent chemoradiotherapy group evaluation showed CR in 0 patients, PR in 20 patients, SD in 16 patients and progressive disease in 0 patients. RR in the concurrent chemoradiotherapy group was 55.6% (20/36). The tumor control rate was 100%. A clinical stage reduction was noted in 61.1% (22/36) of patients.

Safety Evaluation

Toxic Effects of Concurrent Chemoradiotherapy

Concurrent chemoradiotherapy toxic effects were evaluated using the National Cancer Institute Common Toxicity Criteria (NCI-CTC) version 4.0. Nonhematologic toxic effects included nausea, vomiting, loss of appetite, abnormal liver function, neurological toxicity and radiation dermatitis. Hematologic toxic effects included leukopenia, neutropenia, anemia and thrombocytopenia. These toxic effects were graded 1 to 2 primarily and resolved after symptomatic therapy. There were no chemotherapy-related deaths (Table 2). Treatment was temporarily discontinued for 6 patients due to grade 3 toxic effects and restarted after the toxic effects had lessened or resolved. Chemotherapeutic dosages was reduced for 4 patients.

Perioperative Complications

One patient in a concurrent chemoradiotherapy group developed a lymphatic fistula which resolved after 5 days of conservative therapy. One developed moderate pleural effusion and ascites. These symptoms were significantly improved after

TABLE 2. Toxic effects of concurrent chemoradiotherapy in 36 patients, n (%)

Toxic effects	Grade 1	Grade 2	Grade 3	Grade 4	Grand total
Hematologic					
Leukopenia	16 (44.4)	6 (16.7)	2 (5.6)	0	24 (66.7)
Neutropenia	8 (22.2)	6 (16.7)	0	0	14 (38.9)
Anemia	4 (11.1)	2 (5.6)	0	0	6 (16.7)
Thrombocytopenia	2 (5.6)	4 (11.1)	4 (11.1)	0	10 (27.8)
Abnormal liver function	6 (16.7)	0	0	0	6 (16.7)
Nonhematologic					
Nausea	4 (11.1)	8 (22.2)	0	0	12 (33.3)
Vomiting	8 (22.2)	2 (5.6)	0	0	10 (27.8)
Loss of appetite	8 (22.2)	8 (22.2)	0	0	16 (44.4)
Neurological toxicity	2 (5.6)	0	0	0	2 (5.6)
Radiation dermatitis	2 (5.6)	0	0	0	2 (5.6)

13 days of conservative therapy. One surgery group patient developed an esophageal jejunal anastomotic fistula that resolved after 52 days of conservative therapy. One patient had a wound dehisce, which resolved after symptomatic therapy. In the concurrent chemoradiotherapy group, a jejunal tube was indwelt for a month after surgery to ensure early and smooth enteral nutrition.

Surgery

In the neoadjuvant chemoradiotherapy group, surgery was performed after concurrent chemoradiotherapy. The median interval between concurrent chemoradiotherapy and surgery was 6.7 weeks (range: 5.7–8 weeks). Peritoneal cytology results were negative for both groups. The concurrent chemoradiotherapy group consisted of 36 participants who had the following interventions performed at the rates and number of participants indicated: proximal subtotal gastrectomy and jejunal interposition surgery 44.4% (16/36); proximal subtotal gastrectomy and an esophageal gastric remnant anastomosis was performed in 11.1% (4/36); total gastrectomy and Roux-en-Y anastomosis 33.3% (12/36); total gastrectomy and jejunal interposition 11.1% (4/36). The surgery group consisted of 40 patients. The following interventions were performed at the rates and number of participants noted: proximal subtotal gastrectomy and jejunal interposition surgery 45% (18/40); proximal subtotal gastrectomy and esophageal gastric remnant anastomosis 15% (6/40); total gastrectomy and Roux-en-Y anastomosis 40% (16/40).

Pathological Evaluation

R0 resection rates in the concurrent chemoradiotherapy group and the surgery group were 100% and 80% (32/40), respectively. This difference is statistically significant ($\chi^2 = 4.024$, $P = 0.045$). In the concurrent chemoradiotherapy group, the pathological complete RR was 16.7% (6/36), and the total pathological RR (grade 1 + grade 0) was 72.2% (26/36), which was statistically significant ($P < 0.05$). The number of resect lymph nodes in the concurrent chemoradiotherapy group and the surgery group was 26.9 ± 8.4 and 29.4 ± 9.2, respectively. This difference was not statistically significant ($t = 1.725$, $P > 0.05$). Lymph node metastasis occurred in 2.5% (24/968) of the concurrent chemoradiotherapy group and in 7.1% (84/1,176) of the surgery group. This difference is statistically significant ($\chi^2 = 12.070$, $P = 0.001$).

DISCUSSION

Siewert has 3 classifications of gastroesophageal junction adenocarcinomas.[10,11] The surgery recommended as treatment varies with each. Patient with Siewert II and III adenocarcinomas are less likely to have upper and middle mediastinal lymph node metastasis making surgery using the transabdominal approach by the diaphragmatic hiatus feasible. In neoadjuvant therapy, preoperative concurrent chemoradiotherapy efficacy in treating Siewert II and III gastric cancers has been previously confirmed in clinical trials conducted in Western countries. However, the necessity for neoadjuvant therapy has not been confirmed.[12–14] Patients with adenocarcinoma of the gastroesophageal junction were not separated from those with esophageal, or gastric, cancer in most of these studies. The authors were able to identify on a few studies that seem to have been conducted investigating adenocarcinoma at the gastroesophageal junction. This lack of clinical data might result in inappropriate use of combined chemotherapy drugs or radiotherapy dose.

The MAGIC trial, which compared the therapeutic efficacy of cisplatin-based neoadjuvant chemotherapy and surgery alone, resulted in encouraging findings regarding the utility of neoadjuvant therapy.[15] That study showed a 5-year survival rate for patients receiving neoadjuvant chemotherapy increased by 13% compared with a surgery group (36% versus 23%). Patients with type II and III adenocarcinoma of the esophagogastric junction accounted for only 11.5% (58/503) of the total subjects studied, but the findings relating to using neoadjuvant therapy to treat esophagogastric junction adenocarcinomas were encouraging.[16,17] As a result, focal radiotherapy was added to systemic chemotherapy with the goal of improving therapeutic efficacy. An RR of 55.6%, total tumor control rate of 100% and clinical stage reduction rate of 61.1% suggest that the therapeutic efficacy of concurrent chemoradiotherapy was superior to surgery alone.[18,19] These findings were consistent with those of De Paoli et al as an interim analysis of a phase II multicenter study presented at a European Society for Medical Oncology conference.[20]

The timely implementation of radical resection of the cancer is a key step toward a favorable therapeutic result. Radiotherapy may lessen the focal inflammatory edema and fibrous adhesion of the tumor after chemotherapy. Surgery was performed 6 weeks after chemoradiotherapy.

Among the surgical modalities available for resecting esophagogastric junction adenocarcinoma, proximal subtotal gastrectomy seems to have achieved the best radical resection of the cancer. Preoperative evaluation usually shows that the cancer to be localized at the esophagogastric junction. The choice of surgical modality should be made according to intraoperative exploration findings.[21,22] For example, if there is extensive lymph node enlargement at the lesser curvature of the stomach and the

lower borderline of the cancer is blurred, active total gastrectomy is the preferred method for achieving radical resection of the tumor. This is also an important factor in the favorable R0 resection rate for patients receiving concurrent chemoradiotherapy. All the patients in this study that received concurrent chemoradiotherapy also underwent surgical intervention and achieved an R0 resection. No other previous studies have found such results.[6,14,23,24] In addition, the pathological complete remission rate in this study was 16.7% and is consistent with previously reported results that ranged from 15% to 30%.[25–29]

Some investigators have questioned the efficacy of concurrent chemoradiotherapy preceding surgery of adenocarcinomas of the esophagogastric junction and have also expressed concerns about the toxic effects of such therapy. In the CROSS study,[6] 1 patient receiving chemotherapy, with carboplatin plus paclitaxel and concurrent radiotherapy at 41.4 Gy, developed grade 4 hematologic toxicity and neutropenic fever.[30] One other patient died of possible esophageal perforation, heavy bleeding or thrombocytopenia after chemoradiotherapy and before surgery. A Duke University Medical Center study examined the therapeutic efficacy of chemotherapy with fluorouracil in combination with platinum or taxane, and concurrent radiotherapy at 45 Gy, in the treatment of 48 patients with gastric adenocarcinoma or adenocarcinoma of the esophagogastric junction.[31] In that study, therapy was discontinued in 6 patients, 2 patients failed to complete the concurrent chemoradiotherapy and 1 patient developed gastric perforation and febrile neutropenia. In this study, 6 patients developed grade 3 hematologic toxicity. Two had leukopenia and 4 had thrombocytopenia. Fever and heavy bleeding were not observed. Chemoradiotherapy-related death was absent. During the perioperative period for patients in this study, 1 patient developed a lymphatic fistula that may have been attributable to an accidental lymphatic injury during the surgery. A single patient developed moderate plural effusion and ascites that might be attributable to abnormal liver function before surgery and also to postoperative stress. These symptoms were resolved after active therapy. Patients in the concurrent chemoradiotherapy group each had an indwelling jejunal feeding tube for 1 month to assure adequate enteral nutrition, and postoperative complications were reduced. The results of this study can be compared with those of the INT-0116 study in which postsurgical adjunctive concurrent chemoradiotherapy was performed.[32] In the INT-0116 study, 64% of patients completed the therapy. Three patients experienced chemoradiotherapy-related death. Forty-one percent developed grade 3 toxic effects and 32% had grade 4 toxic effects. This comparison suggests that preoperative concurrent chemoradiotherapy is relatively safe. The findings of this study suggest that the toxic effects of chemotherapy are tolerable. A XELOX regimen is administered in combination with radiotherapy at 45 Gy (25 sessions) that may contribute to the absence of highly toxic taxanes in the chemotherapeutic regimen.

It should be noted that the long-term survival of patients included in this study is unknown. On the basis of available findings, chemotherapy with the XELOX regimen administered in combination with radiotherapy at 45 Gy (25 sessions) seems to be a mildly toxic, but highly effective, therapeutic modality for patients with adenocarcinoma at the gastroesophageal junction. However, additional studies conducted with larger sample sizes and careful patient monitoring would be required to confirm these findings. The results of such studies could be used to significantly improve therapeutic efficacy in treatment of adenocarcinoma of the esophagogastric junction.

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