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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