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Retrospective Study

Adjuvant chemoradiotherapy ³ vs adjuvant chemotherapy in locally advanced Siewert type II/III adenocarcinoma of gastroesophageal junction after D2/R0 resection

Adjuvant chemoradiotherapy for AGE

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Abstract

BACKGROUND

For Siewert type II/III adenocarcinoma of gastroesophageal junction (AGE), the efficacy of adjuvant chemoradiotherapy after D2/R0 resection remains uncertain.

AIM

To determine whether chemoradiotherapy was superior to chemotherapy alone after D2/R0 resection for locally advanced Siewert type II/III AGE

METHODS

We identified 316 Locally advanced Siewert type II/III AGE patients who were treated with D2/R0 resection at National Cancer Center from 2011 to 2018. 57 patients received adjuvant chemoradiotherapy (CRT) and 259 patients received adjuvant chemotherapy (CT). We followed patients for overall survival (OS), relapse-free survival (RFS), and recurrence pattern.

RESULTS

Five-year overall survival rates of the CRT group and the CT group for all patients were 66.7% and 41.9% ($P = 0.010$). Five-year overall survival rates of the CRT group and the CT group for Siewert type III AGE patients were 65.7% and 43.9% ($P = 0.006$). Among the 195 patients whose recurrence information could be obtained, 18 cases (34.6%) and 61 cases (42.7%) were diagnosed as recurrence in the CRT group and CT group, respectively. The local and regional recurrence rates in the CRT group were lower than that in the CT group (22.2% *vs* 24.6%, 27.8% *vs* 39.3%). Multivariable cox regression analysis showed that vascular invasion, nerve invasion, and adjuvant chemoradiotherapy were important prognostic factors for Siewert type III AGE.

CONCLUSION

For locally advanced Siewert type III AGE, adjuvant chemoradiotherapy may prolong overall survival and reduce the regional recurrence rate.

Key Words: Siewert type II/III, Gastroesophageal Junction, Adjuvant Chemoradiotherapy, Adjuvant Chemotherapy, Survival, Recurrence

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Core Tip: This is a retrospective study to investigate the value of adjuvant chemoradiotherapy in locally advanced Siewert type II/III adenocarcinoma of gastroesophageal junction. We identified 316 such patients and followed their overall survival, relapse-free survival, and recurrence pattern. Our study found that for locally advanced Siewert type III AGE, adjuvant chemoradiotherapy may prolong overall survival and reduce the regional recurrence rate.

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INTRODUCTION

In recent years, the incidence of adenocarcinoma of the gastroesophageal junction (AGE) has been increasing^[1-3]. The Siewert type II/III type is the most common type of AGE in Asia^[4-6]. At present, treatment for this type of AGE is based on the principle of gastric cancer. However, due to the special anatomical site of Siewert type II/III AGE, it differs from middle-distal gastric cancer in terms of its biological characteristics and prognosis. An increasing number of researchers have recognized AGE as an independent tumor entity^[7,8]. For locally advanced AGE, the local and regional recurrence and distant metastasis rates remain high after D2/R0 resection, leading to poor prognosis^[9-11]. As an important local treatment, radiotherapy can reduce the local recurrence rate and prolong survival time^[12]. Phase III clinical studies of adjuvant

chemoradiotherapy after D2/R0 resection For resectable gastric cancer in the East and West have reached different conclusions [13,14]. Postoperative radiotherapy may be beneficial for patients who fail to achieve D2/R0 resection for various reasons, as well as in those with high-risk factors for local recurrence (high rate of lymph node metastasis, insufficient safe resection distance, etc.) [15]. Although the INT-0116 trial confirmed the survival benefit of postoperative radiotherapy in patients with resectable gastric cancer, the majority of patients in this study underwent D0 or D1 gastrectomy[16]. The efficacy of adjuvant radiotherapy in patients with gastric cancer undergoing D2/R0 resection is controversial[17]. Neoadjuvant chemoradiotherapy + D2/R0 resection + adjuvant chemotherapy has been successful in the study of AGE. Long-term follow-up results from the POET study showed that preoperative chemoradiotherapy had the advantage of reducing local and regional recurrence and was prone to improving overall survival compared to preoperative chemotherapy[18]. However, the significance of postoperative adjuvant radiotherapy for locally advanced Siewert type II/III AGE is unclear. In this study, we reviewed 316 patients with locally advanced Siewert type II/III AGE patients to determine whether chemoradiotherapy was superior to chemotherapy alone after D2/R0 resection, comparing the overall survival, relapse-free survival, and recurrence modes between the CRT and CT groups.

MATERIALS AND METHODS

Patient Selection and Data collection

We identified 316 patients with locally advanced Siewert type II/III AGE who were admitted to the Department of Pancreatic and Gastric Surgery, National Cancer Center, between January 2011 and May 2018. All patients underwent D2/R0 resection and did not receive neoadjuvant chemotherapy or radiotherapy. Patients were divided into a CT group and a CRT group according to whether they received postoperative adjuvant radiotherapy. Patients were followed-up by telephone, which was completed on April 30, 2020. The median follow-up time was 62.7 mo. Pathologists determined the classification of the Siewert type. The pathological staging

(pTNM) criteria were based on the 8th edition of the American Joint Committee on Cancer (AJCC) guidelines for esophageal adenocarcinoma (all Siewert type II adenocarcinomas invade the dentate line) and gastric cancer (Siewert type III). Patients who were lost to follow-up or were unwilling to cooperate were excluded. Patients with Siewert type I AGE were not included in this study. Patients younger than 18 years or older than 80 years, those who received neoadjuvant chemotherapy or radiotherapy, and those with less than 1 mo of postoperative survival were excluded from the study.

Adjuvant chemoradiotherapy and chemotherapy regimens
Patients in the CRT group received a total dose of 45–50.4 Gy in 25–28 fractions. Intensity-modulated radiation therapy or volumetric modulated arc therapy were used. For tumor margins ≤ 3 cm, the anastomosis site was included in the clinical target volume (CTV). For the T4b stage, the tumor bed should also be included. Regional draining LNs according to the Japanese Gastric Cancer Association (JGCA)^[19] were included in the CTV. Based on the International Commission Radiological Units (ICRU) report No. 83^[20], the planning target volume should consider not only the setup error but also the breath elements and tumor movement. Concurrent chemotherapy regimens included FU-based drugs such as 5-FU, capecitabine, or tegafur (S-1) on radiotherapy days. Patients in the CRT group received 4–6 cycles of chemotherapy, followed by CRT. In the CT group, the main chemotherapy regimens included oxaliplatin + 5-FU (SOX, XELOX), cisplatin + 5-FU (PF, XP, SP), albumin-bound paclitaxel + S-1, and single-drug chemotherapy regimen (S-1, docetaxel, and irinotecan). Adjuvant chemotherapy is usually performed for 4–6 cycles.

Recurrence pattern
Specific imaging or pathological diagnosis is needed when defining tumor recurrence. In this study, we divided recurrence into local recurrence, regional recurrence, and metastatic recurrence according to the first site of recurrence during the follow-up period.

Recurrence in the anastomotic stoma, tumor bed, and remnant stomach was defined as a local recurrence. Recurrence in the lymphatic drainage area, according to the JGCA

guidelines^[19] for gastric cancer and the Japan Esophageal Cancer Research Association (JEOG) guidelines^[21] for the esophagus, was defined as a regional recurrence. The diagnosis of recurrent lymph nodes on imaging should satisfy one of the following criteria: (1) short diameter of lymph nodes > 8 mm; (2) ratio of the long diameter to the short diameter of lymph nodes is close to one; (3) central lymph nodes are necrotic; (4) multiple lymph nodes are aggregated; and (5) lymph nodes are significantly enhanced on computed tomography. Distant recurrence was defined as distant lymph node, bone, peritoneal or pleural, and solid organ metastases such as liver, lung, and ovarian metastases.

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RESULTS

Clinicopathological characteristics

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Table 1 summarizes the clinicopathological characteristics of the patients enrolled in this study. There were 57 patients in the CRT group and 295 patients in the CT group. The number and proportion of patients with Siewert type II and III AGE were 148 (46.8%) and 168 (53.2%), respectively.

Survival results

Figures 1A and 1B summarize the OS and RFS curves of the CRT and CT groups, respectively, for all patients. Figures 1C and 1D summarize the OS and RFS curves of the CRT and CT groups for patients with Siewert type II AGE, respectively. Figures 1E and 1F summarize the OS and RFS curves of the CRT and CT groups for patients with Siewert type III AGE, respectively. Five-year overall survival rates of the CRT and CT groups for all patients were 66.7% and 41.9%, respectively ($P = 0.010$). Five-year overall survival rates of the CRT and CT groups for Siewert type II AGE patients were 59.3% and 39.4%, respectively ($P = 0.063$). Five-year overall survival rates of the CRT and CT groups for Siewert type III AGE patients were 65.7% and 43.9%, respectively ($P = 0.006$). Five-year recurrence-free survival rates of the CRT and CT groups for all patients were 64.5% and 55.3%, respectively ($P = 0.254$). Five-year recurrence-free survival rates of the

CRT and CT groups for Siewert type II AGE patients were 60.5% and 55.9%, respectively ($P = 0.995$). Five-year recurrence-free survival rates of the CRT and CT groups for Siewert type III AGE patients were 72.6% and 56.8%, respectively ($P = 0.082$) (Table 2, Figure 2).

Results of recurrence

Among the 195 patients for whom recurrence information could be obtained, 18 (34.6%) and 61 (42.7%) were diagnosed with recurrence in the CRT and CT groups, respectively. The local and regional recurrence rates were lower in the CRT group than in the CT group (22.2% vs. 24.6% and 27.8% vs. 39.3%, respectively). The distant recurrence rate was higher in the CRT group than in the CT group (100% vs. 68.9%) (Table 3 and Figure 3).

Multivariable Cox regression analysis

For Siewert type II AGE, multivariate Cox regression analysis showed that vascular invasion was an important prognostic factor (Table 4A). For Siewert type III AGE, multivariate Cox regression analysis showed that vascular invasion, nerve invasion, and adjuvant chemoradiotherapy were important prognostic factors (Table 4B).

DISCUSSION

In the past, adjuvant treatment for AGE was based on the experience of esophageal adenocarcinoma or gastric adenocarcinoma. However, a growing number of researchers believe that AGE is a separate tumor^[22]. There have been very few randomized controlled studies on the significance of adjuvant chemoradiotherapy for AGE^[23]. In this study, we found that postoperative adjuvant chemotherapy combined with regional radiotherapy could prolong the overall survival of patients with locally advanced Siewert type III AGE. The local and regional recurrence rates in the CRT group were lower than those in the CT group. These results provide evidence supporting the use of postoperative adjuvant radiotherapy for AGE. The role of adjuvant radiotherapy after D2/R0 resection in gastric cancer remains controversial. The Korean ARTIST 1 study^[17] suggested that patients with lymph node

metastases may benefit from postoperative irradiation. However, the ARTIST 2 study^[24] showed that SOX chemotherapy combined with radiotherapy did not improve outcomes in patients with lymph node metastasis after D2/R0 resection. In addition, the majority of patients enrolled in these clinical trials had distal gastric cancer, while fewer had proximal gastric cancer. Owing to the specificity of the anatomic site, the benefits of adjuvant radiotherapy in AGE may not be consistent with those in gastric cancer. Therefore, we designed this retrospective clinical study to evaluate the value of adjuvant chemoradiotherapy in locally advanced AGE. Because of the special location of AGE, cancer cells can metastasize to the mediastinum and abdominal cavity along the lymphatic vessels. However, for Siewert type II/III AGE, abdominal lymph node metastasis is the main direction of metastasis^[25]. The JCOG9502 study showed that for Siewert type II/III AGE that underwent D2/R0 Lymph node dissection, the positive rate of lymph nodes at station 16 was 15.2%, and the postoperative lymph node recurrence rate was 17.4%^[26]. These results provide evidence for the delineation of radiotherapy targets for locally advanced AGE. Our study found that adjuvant radiotherapy did not significantly improve relapse-free survival in all patients or overall survival in patients with Siewert type II AGE. However, we observed a significant extension of overall survival in patients with Siewert type III AGE after adjuvant CRT. A possible explanation is that adjuvant radiotherapy reduces local and regional recurrence rates. The overall recurrence rate in the CRT group was lower than that in the CT group. Compared with the CT group, more attention should be paid to distant metastasis during postoperative reexamination in the CRT group. We found that patients with Siewert type III AGE were more sensitive to adjuvant radiotherapy. The difference between Siewert type II and III AGE in adjuvant chemoradiotherapy requires further study. Multivariable Cox regression analysis showed that adjuvant chemoradiotherapy was an important factor affecting the prognosis of patients with Siewert type III AGE, further verifying the necessity of adjuvant chemoradiotherapy. Our study has several limitations. First, this was a single-center retrospective study, and

thus inherently has a lower level of evidence than a multicenter prospective clinical trial. Furthermore, did not compare surgical approaches for different types of AGE. In addition, the toxic effects of radiotherapy were not investigated in this study.

CONCLUSION

For locally advanced Siewert type III AGE, adjuvant chemoradiotherapy following D2/R0 resection may prolong overall survival and reduce the local and regional recurrence rate. Postoperative radiotherapy may be feasible for Siewert type III AGE patients. Multicenter prospective clinical trials should be conducted to investigate the significance of adjuvant chemoradiotherapy in AGE.

ARTICLE HIGHLIGHTS

Research perspectives

Multicenter prospective clinical trials should be conducted to investigate the significance of adjuvant chemoradiotherapy in adenocarcinoma of gastroesophageal junction.

Research conclusions

Adjuvant chemoradiotherapy may be appropriate for adenocarcinoma of gastroesophageal junction, especially for Siewert type III adenocarcinoma of gastroesophageal junction.

Research results

Adjuvant Chemoradiotherapy improves the 5-year survival rate of adenocarcinoma of gastroesophageal junction, especially Siewert type III adenocarcinoma of gastroesophageal junction, and reduces local and regional recurrence rates.

Research methods

We compared the overall survival, relapse-free survival, and recurrence modes between the adjuvant chemoradiotherapy and adjuvant chemotherapy groups.

Research objectives

To evaluate the effect of adjuvant chemoradiotherapy *vs* adjuvant chemotherapy on overall survival, relapse-free survival, and recurrence pattern in locally advanced Siewert II/III type adenocarcinoma of gastroesophageal junction patients undergoing D2/R0 resection.

Research motivation

Radiotherapy may reduce the local recurrence rate and prolong survival time for locally advanced Siewert II/III type adenocarcinoma of gastroesophageal junction.

Research background

The role of adjuvant chemoradiotherapy in adenocarcinoma of gastroesophageal junction is unclear.

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