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WJGO mainly publishes articles reporting research results and findings obtained in the field of gastrointestinal oncology and covering a wide range of topics including liver cell adenoma, gastric neoplasms, appendiceal neoplasms, biliary tract neoplasms, hepatocellular carcinoma, pancreatic carcinoma, cecal neoplasms, colonic neoplasms, colorectal neoplasms, duodenal neoplasms, esophageal neoplasms, gallbladder neoplasms, *etc.*

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Retrospective Study

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

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Abstract

BACKGROUND

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

AIM

To determine whether CRT was superior to chemotherapy (CT) 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 CRT and 259 patients received adjuvant CT. We followed patients for overall survival (OS), relapse-free survival, and recurrence pattern.

RESULTS

Five-year OS rates of the CRT group and the CT group for all patients were 66.7% and 41.9% ($P = 0.010$). Five-year OS 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 CRT were important prognostic factors for Siewert type III AGE.

CONCLUSION

For locally advanced Siewert type III AGE, adjuvant CRT may prolong OS 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 (CRT) in locally advanced Siewert type II/III adenocarcinoma of gastroesophageal junction. We identified 316 such patients and followed their overall survival (OS), relapse-free survival, and recurrence pattern. Our study found that for locally advanced Siewert type III gastroesophageal junction, adjuvant CRT may prolong OS 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 CRT + D2/R0 resection + adjuvant chemotherapy (CT) has been successful in the study of AGE. Long-term follow-up results from the POET study showed that preoperative CRT had the advantage of reducing local and regional recurrence and was prone to improving overall survival (OS) compared to preoperative CT[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 CRT was superior to CT alone after D2/R0 resection, comparing the OS, relapse-free survival (RFS), 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 CT 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 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 CT or radiotherapy, and those with less than 1 mo of postoperative survival were excluded from the study.

Adjuvant CRT and CT regimen

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 lymph nodes according to the Japanese Gastric Cancer Association (JGCA)[19] were included in the CTV. Based on the International Commission Radiological Units report No. 83[20], the planning target volume should consider not only the setup error but also the breath elements and tumor movement. Concurrent CT 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 CT, followed by CRT.

In the CT group, the main CT regimens included oxaliplatin + 5-FU (SOX, XELOX), cisplatin + 5-FU (PF, XP, SP), albumin-bound paclitaxel + S-1, and single-drug CT regimen (S-1, docetaxel, and irinotecan). Adjuvant CT 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 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.

RESULTS

Clinicopathological characteristics

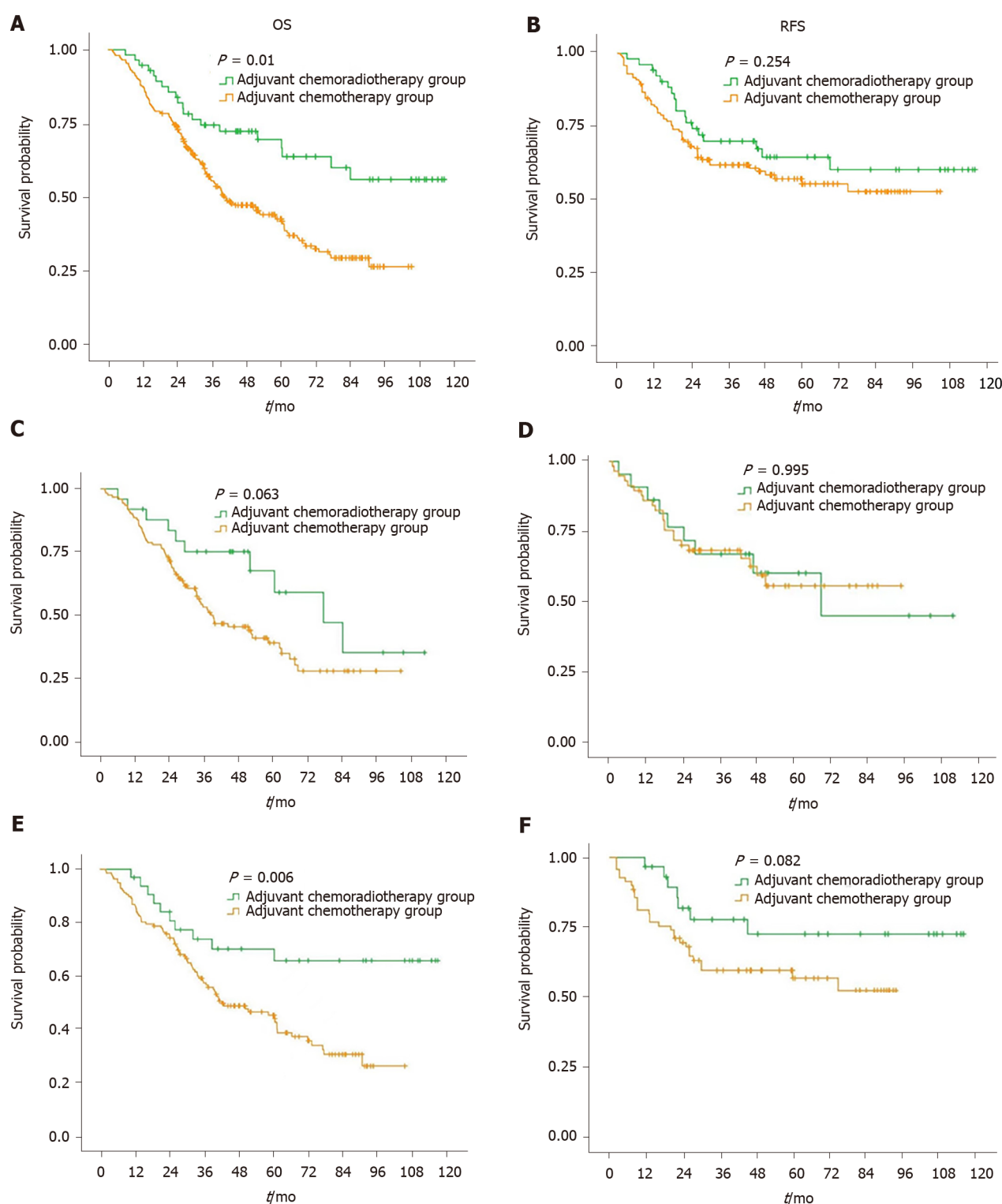
Table 1 summarizes the clinicopathological characteristics of the patients enrolled in this study. There were 57 patients in the CRT group and 295 patients in the CT group. The number and proportion of patients with Siewert type II and III AGE were 148 (46.8%) and 168 (53.2%), respectively.

Survival results

Figure 1A and B summarize the OS and RFS curves of the CRT and CT groups, respectively, for all patients. Figure 1C and D summarize the OS and RFS curves of the CRT and CT groups for patients with Siewert type II AGE, respectively. Figure 1E and F summarize the OS and RFS curves of the CRT and CT groups for patients with Siewert type III AGE, respectively.

Five-year OS rates of the CRT and CT groups for all patients were 66.7% and 41.9%, respectively ($P = 0.010$). Five-year OS 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 OS 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



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Figure 1 Kaplan-Meier curve for overall survival and relapse-free survival between patients in chemoradiotherapy group and chemotherapy group. A and B: summarizes the overall survival (OS) and relapse-free survival (RFS) survival curves of the chemoradiotherapy (CRT) group and chemotherapy (CT) group for all patients; C and D: summarizes the OS and RFS survival curves of the CRT group and CT group for Siewert type II gastroesophageal junction (AGE) patients; E and F: summarizes the OS and RFS survival curves of the CRT group and CT group for Siewert type III AGE patients).

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 and Figure 2).

Results of recurrence

Among the 195 patients for whom recurrence information could be obtained, 18 (34.6%) and 61 (42.7%)

Table 1 Clinicopathological features of all patients

Variable	Overall	Adjuvant chemoradiotherapy group	Adjuvant chemotherapy group
	316	57	259
Age, <i>n</i> (%)			
< 40 yr	6 (1.9)	2 (3.5)	4 (1.5)
≥ 40 yr	310 (98.1)	55 (96.5)	255 (98.5)
Sex, <i>n</i> (%)			
Male	268 (84.8)	46 (80.7)	222 (85.7)
Female	48 (15.2)	11 (19.3)	37 (14.3)
BMI, <i>n</i> (%)			
< 18.5 or > 23.9	169 (53.5)	27 (47.4)	142 (54.8)
18.5-23.9	147 (46.5)	30 (52.6)	117 (45.2)
The degree of differentiation, <i>n</i> (%)			
Poorly differentiated	233 (73.7)	45 (78.9)	188 (72.6)
Moderately-highly differentiated	83 (26.3)	12 (21.1)	71 (27.4)
Nerve invasion, <i>n</i> (%)			
Yes	269 (85.1)	43 (75.4)	226 (87.3)
No	47 (14.9)	14 (24.6)	33 (12.7)
Vascular invasion, <i>n</i> (%)			
Yes	263 (83.2)	40 (70.2)	223 (86.1)
No	53 (16.8)	17 (29.8)	36 (13.9)
Pathologic T stage, <i>n</i> (%)			
pT1-3	179 (56.6)	34 (59.6)	145 (56.0)
pT4a-4b	137 (43.4)	23 (40.4)	114 (44.0)
Pathologic N stage, <i>n</i> (%)			
pN1-2	73 (23.1)	10 (17.5)	63 (24.3)
PN3	243 (76.9)	47 (82.5)	196 (75.7)
Pathological stage, Siewert type II	148 (46.8)	25 (43.9)	123 (47.5)
IIIB stage	30 (9.5)	6 (10.5)	24 (9.3)
IVA stage	118 (37.3)	19 (33.3)	99 (38.2)
Pathological stage, Siewert type III	168 (53.2)	32 (56.1)	136 (52.5)
IIIA	32 (10.1)	1 (1.8)	31 (12.0)
IIIB	80 (25.3)	22 (38.6)	58 (22.4)
IIIC	56 (17.7)	9 (15.8)	47 (18.1)

BMI: Body mass index.

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 4). For Siewert type III AGE, multivariate Cox regression analysis showed that vascular invasion, nerve invasion, and adjuvant CRT were important prognostic factors (Table 5).

Table 2 5-year survival rate in adjuvant chemoradiotherapy group and adjuvant chemotherapy group

	Group	N	5-yr survival rate (%)	Log rank test
OS	All patients			$P = 0.010$
	Adjuvant chemoradiotherapy group	57	66.7	
	Adjuvant chemotherapy group	295	41.9	
RFS	All patients			$P = 0.254$
	Adjuvant chemoradiotherapy group	52	64.5	
	Adjuvant chemotherapy group	128	55.3	
OS	Siewert type II			$P = 0.063$
	Adjuvant chemoradiotherapy group	25	59.3	
	Adjuvant chemotherapy group	123	39.4	
RFS	Siewert type II			$P = 0.995$
	Adjuvant chemoradiotherapy group	22	60.5	
	Adjuvant chemotherapy group	58	55.9	
OS	Siewert type III			$P = 0.006$
	Adjuvant chemoradiotherapy group	32	65.7	
	Adjuvant chemotherapy group	136	43.9	
RFS	Siewert type III			$P = 0.082$
	Adjuvant chemoradiotherapy group	30	72.6	
	Adjuvant chemotherapy group	70	56.8	

OS: Overall survival; RFS: Relapse-free survival.

Table 3 Distributions of recurrence in Adjuvant chemoradiotherapy group and adjuvant chemotherapy group

Recurrence site	Adjuvant chemoradiotherapy group		Adjuvant chemotherapy group	
	No. of patients	% of recurrence patients ($n = 18$)	No. of patients	% of recurrence patients ($n = 61$)
Local recurrence, n (%)				
Remnant stomach	1	5.6	1	1.6
Anastomosis site	3	16.7	14	23.0
Regional recurrence	5	27.8	24	39.3
Distant metastasis, n (%)				
One site				
Peritoneum	5	27.8	8	13.1
Pleura	2	11.1	4	6.6
Solid organ	4	22.2	16	26.2
Distant LNs	2	11.1	5	8.2
Bone metastases	2	11.1	3	4.9
≥ 2 sites				
Peritoneum + solid organ	2	11.1	3	4.9
Solid organs	1	5.6	2	3.3
Peritoneum + distant LNs	0	0	1	1.6
Solid organs + distant LNs	0	0	1	1.6

LNs: Lymph nodes.

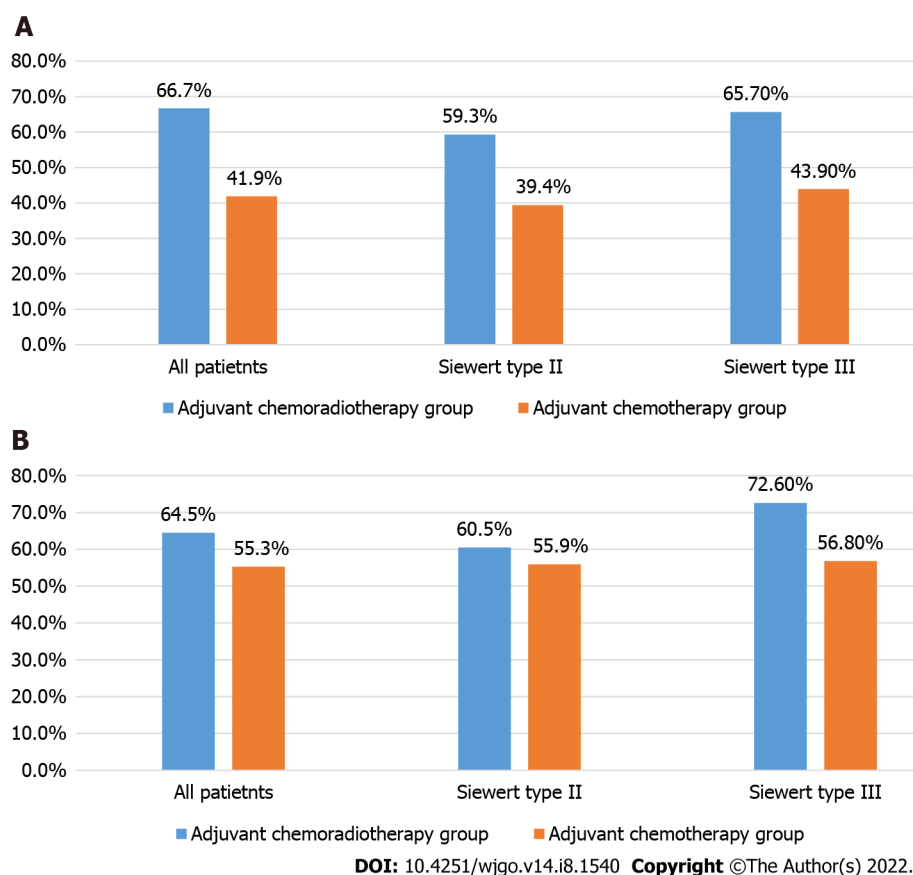


Figure 2 Five-year overall survival rate and recurrence free survival rate of all patients, Siewert type II gastroesophageal junction patients, and Siewert type III gastroesophageal junction patients in chemoradiotherapy group and chemotherapy group. A: Five-year overall survival rate in chemoradiotherapy (CRT) group and chemotherapy (CT) group; B: Five-year recurrence free survival rate in CRT group and CT group.

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 CRT for AGE[23]. In this study, we found that postoperative adjuvant CT combined with regional radiotherapy could prolong the OS 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 CT 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 CRT 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 RFS in all patients or OS in patients with Siewert type II AGE. However, we observed a significant extension of OS in patients with Siewert type III AGE after adjuvant CRT. A possible explanation is that adjuvant radiotherapy reduces

Table 4 Univariate and multivariable cox proportional hazards modeling for overall survival in Siewert type II gastroesophageal junction

Clinicopathological features	Univariate analysis		Multivariable analysis	
	HR (95%CI)	P value	HR (95%CI)	P value
Sex				
Male	Ref.			
Female	0.683 (0.389-1.199)	<i>P</i> = 0.185		
BMI				
18.5-23.9	Ref.			
< 18.5 or > 23.9	1.019 (0.657-1.581)	<i>P</i> = 0.931		
The degree of differentiation				
Poorly differentiated	Ref.			
Moderately-highly differentiated	0.733 (0.437-1.227)	<i>P</i> = 0.237		
Nerve invasion				
Yes	Ref.		Ref.	
No	0.083 (0.020-0.339)	<i>P</i> = 0.001	0.117 (0.028-0.500)	<i>P</i> = 0.004
Vascular invasion				
Yes	Ref.		Ref.	
No	0.215 (0.093-0.496)	<i>P</i> < 0.001	0.425 (0.178-1.014)	<i>P</i> = 0.054
Pathologic T stage				
Group 1-3	Ref.		Ref.	
Group 4a-4b	1.404 (0.899-2.194)	<i>P</i> = 0.136	1.271 (0.777-2.080)	<i>P</i> = 0.340
Pathologic N stage				
Group 1-2	Ref.		Ref.	
Group 3a-b	2.089 (1.137-3.721)	<i>P</i> = 0.012	1.027 (0.385-2.739)	<i>P</i> = 0.958
Pathologic TNM stage				
IIIB stage	Ref.		Ref.	
IVA stage	2.540 (1.267-5.091)	<i>P</i> = 0.009	2.081 (0.629-6.885)	<i>P</i> = 0.230
Adjuvant chemoradiotherapy				
Yes	Ref.		Ref.	
No	1.859 (0.956-3.614)	<i>P</i> = 0.068	1.877 (0.943-3.738)	<i>P</i> = 0.073

BMI: Body mass index; HR: Hazard ratio; CI: Confidence interval.

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 CRT requires further study. Multivariable Cox regression analysis showed that adjuvant CRT was an important factor affecting the prognosis of patients with Siewert type III AGE, further verifying the necessity of adjuvant CRT.

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 CRT following D2/R0 resection may prolong OS

Table 5 Univariate and multivariable cox proportional hazards modeling for overall survival in Siewert type III gastroesophageal junction

Clinicopathological features	Univariate analysis		Multivariable analysis	
	HR (95%CI)	P value	HR (95%CI)	P value
Sex				
Male	Ref.			
Female	0.573 (0.277-1.186)	<i>P</i> = 0.134		
BMI				
18.5-23.9	Ref.			
< 18.5 or > 23.9	1.142 (0.755-1.728)	<i>P</i> = 0.530		
The degree of differentiation				
Poorly differentiated	Ref.			
Moderately-highly differentiated	0.945 (0.592-1.509)	<i>P</i> = 0.813		
Nerve invasion				
Yes	Ref.		Ref.	
No	0.086 (0.021-0.349)	<i>P</i> = 0.001	0.169 (0.037-0.774)	<i>P</i> = 0.022
Vascular invasion				
Yes	Ref.		Ref.	
No	0.041 (0.006-0.295)	<i>P</i> = 0.002	0.092 (0.012-0.689)	<i>P</i> = 0.020
Pathologic T stage				
Group 1-3	Ref.		Ref.	
Group 4a-4b	1.479 (0.975-2.242)	<i>P</i> = 0.065	1.151 (0.751-1.763)	<i>P</i> = 0.518
Pathologic N stage				
Group 1-2	Ref.		Ref.	
Group 3	1.983 (1.099-3.580)	<i>P</i> = 0.023	3.621 (0.380-34.469)	<i>P</i> = 0.263
Pathologic TNM stage				
IIIA stage	Ref.		Ref.	
IIIB stage	1.420 (0.759-2.656)	<i>P</i> = 0.273	1.801 (0.180-18.037)	<i>P</i> = 0.617
IIIC stage	2.783 (1.472-5.261)	<i>P</i> = 0.002	0.681 (0.434-1.069)	<i>P</i> = 0.095
Adjuvant chemoradiotherapy				
Yes	Ref.		Ref.	
No	2.465 (1.270-4.782)	<i>P</i> = 0.008	2.258 (1.145-4.453)	<i>P</i> = 0.019

BMI: Body mass index; HR: Hazard ratio; CI: Confidence interval.

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 CRT in AGE.

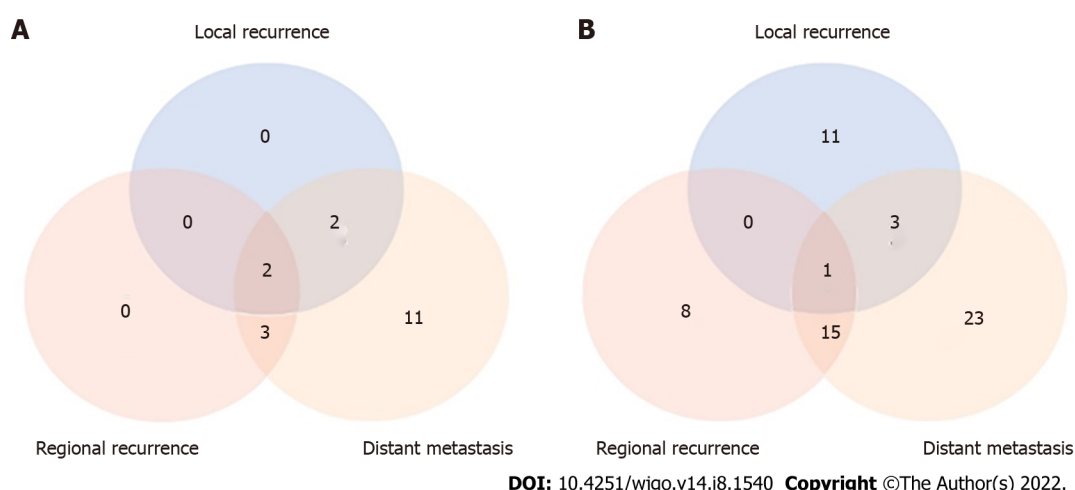


Figure 3 Distributions of recurrence in chemoradiotherapy group and chemotherapy group. A: Chemoradiotherapy group; B: Chemotherapy group.

ARTICLE HIGHLIGHTS

Research background

The role of adjuvant chemoradiotherapy (CRT) in adenocarcinoma of gastroesophageal junction (AGE) is unclear.

Research motivation

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

Research objectives

To evaluate the effect of adjuvant CRT *vs* adjuvant chemotherapy (CT) on overall survival (OS), relapse-free survival (RFS), and recurrence pattern in locally advanced Siewert II/III type adenocarcinoma of AGE patients undergoing D2/R0 resection.

Research methods

We compared the OS, RFS, and recurrence modes between the adjuvant CRT and adjuvant CT groups.

Research results

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

Research conclusions

Adjuvant CRT may be appropriate for adenocarcinoma of AGE, especially for Siewert type III adenocarcinoma of AGE.

Research perspectives

Multicenter prospective clinical trials should be conducted to investigate the significance of adjuvant CRT in adenocarcinoma of AGE.

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FOOTNOTES

Author contributions: Tian YT and Jin J designed the research; Kang WZ, Shi JM, Wang BZ, Xiong JP and Shao XX analyzed the data and wrote the paper; Hu HT collected the patient's clinical data; Kang WZ and Shi JM contributed equally to this work.

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Informed consent statement: Patients were not required to give informed consent to the study because the analysis used anonymous data that were obtained after each patient agreed to treatment by written consent.

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Data sharing statement: Dataset available from the first author at kwz@whu.edu.cn.

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