Changes of Esophagogastric Junctional Adenocarcinoma and Gastroesophageal Reflux Disease Among Surgical Patients During 1988–2012

A Single-institution, High-volume Experience in China

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Objective: To evaluate the changes of esophagogastric junctional adenocarcinoma (EGJA) and gastroesophageal reflux disease (GERD) among surgical patients from 1988 to 2012 in a Chinese high-volume hospital.

Background: The incidence of EGJA in Western countries has rapidly increased in recent decades. However, recent data from China remain sparse.

Methods: A retrospective analysis was performed on the basis of 5053 patients who underwent surgery for gastric and distal esophageal adenocarcinoma. Total of 1723 patients with EGJA who underwent surgery were included. Changes of the prevalence of GERD and the clinicopathological features and surgical treatment of EGJA were longitudinally analyzed by a 5-year interval.

Results: The proportion of EGJA was increased from 22.3% in period 1 (1988–1992) to 35.7% in period 5 (2008–2012) ($P < 0.001$). The proportion of Siewert type III (35.9% vs 47.0%) ($P < 0.001$) and type I (8.7% vs 15.8%) ($P = 0.002$) tumors of EGJA was also increased during the past 25 years. The prevalence of GERD had increased gradually from 6.5% in period 1 to 10.9% in period 5 for the 3 subgroups without significant difference ($P = 0.459$). There was an upward tendency with significant difference between the proportion of EGJA and the prevalence of GERD ($r = 0.946$, $P = 0.000$). Instead of type II and type III tumors, there was a positive correlation with change in GERD for type I tumors ($r = 0.438$, $P = 0.029$). Total gastrectomy was more preferred among patients with EGJA in period 5 than in period 1 (42.0% vs 19.6%) ($P < 0.001$).

Conclusions: An increasing trend of EGJA is observed during the past 25 years in West China Hospital. The prevalence of GERD among EGJA had showed a gradually increased trend. However, the causality between GERD and EGJA still needs to be researched further. Total gastrectomy is becoming more preferred procedure in patients with EGJA.

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Gastric and esophageal cancers are 2 of the most common malignancies in the world. More than 70% of gastric cancer cases and deaths occur in developing countries, and most occur in Eastern Asia.[1] There have been distinct changes in the incidences of cancer at different anatomical subsites of the stomach in Western countries.[2–4] Many population-based studies showed that the incidence rates of adenocarcinoma of the esophagus and esophagogastric junction (EGJ) were increased in Western countries and Asian countries, such as Japan and Korea.[2–8] Although squamous cell carcinoma of the esophagus is still predominant, more than half of newly diagnosed tumors are adenocarcinoma of distal esophagus and EGJ in Western countries and Japan.[2–4,6] Incidence of adenocarcinoma at the upper third of the stomach and EGJ has increased over the past 2 decades, with a rate which has exceeded that at any other site of stomach.[2,4] In contrast, incidence of adenocarcinoma at distal stomach has gradually declined over the past 50 years.[3] However, investigations on changes of esophagogastric junction adenocarcinoma (EGJA) in China remains sparse.

Gastroesophageal reflux disease (GERD) was one of the most common gastrointestinal diseases in Europe and the United States with prevalence rates of 10% to 25% in population-based studies.[9,10] Reports from many other regions have also demonstrated an increase in the prevalence of GERD.[11,12] Some of those with GERD may develop Barrett esophagus, which can lead to esophageal adenocarcinoma. In addition, the prevalence of GERD was also found to be closely associated with the risk of EGJA in some Asian countries.[13] Patients with Barrett esophagus need more intensive screening and surveillance for EGJA. Therefore, it is necessary to understand the changes of GERD and EGJA in China over time. However, there were rare reports that simultaneously assessed the trends of EGJA and GERD in China over time. A study by Zhou et al[14] showed that there was an increasing trend of gastric cardia cancer over a 12-year period in a northwest province of China.

With the increasing acceptance of Siewert's definition of EGJA, more and more researchers have studied this kind of clinicopathological entity.[15] However, there have been few investigations into the change over time of 3 subtypes of EGJA in China. The volume of surgeries done for gastric and esophageal cancers at our institution is large, and the sources of patients come from the Western China, which may serve as a reference for a large population-based study.

In this study, we aimed to evaluate the changes of clinicopathological features and surgical treatment of EGJA on the basis of the Siewert classification[16] and the prevalence of GERD among the surgical patients with EGJA in a high-volume Chinese hospital during 1988–2012.

MATERIALS AND METHODS

Patients

Based on the database of patients with gastric cancer in the Department of Gastrointestinal Surgery and patients with esophageal cancer in the Department of Thoracic Surgery of West China Hospital (between January 1988 and December 2012), 5053 patients underwent surgical resection of gastric and distal esophageal adenocarcinomas. Among the 5053 patients, 1723 (34.1%) were anatomically and pathologically classified as those with EGJA[15] (Siewert classification: type I, II, and III tumors) and analyzed in this study. The additional exclusion criteria included upper and middle thoracic esophageal cancer, synchronous multiple gastric and esophageal cancers, other types of malignancies of stomach and esophagus, and gastric stump cancer. Changing trends of EGJA and GERD were analyzed in 5 consecutive time periods: from 1988 to 1992 (period 1), from 1993 to 1997 (period 2), from 1998 to 2002 (period 3), from 2003 to 2007 (period 4), and from 2008 to 2012 (period 5).

Siewert Classification and GERD

Siewert and Stein[16] proposed a widely approved classification of EGJA in 1998 that divided EGJA into 3 subgroups on the basis of the distance from epicenter to EGJ. A lesion was considered to be a tumor of the EGJ if its center was within 5 cm proximal or distal to the anatomical EGJ, as defined by Siewert et al.[15] Tumors with the center located from 5 to 1 cm above the EGJ were designated type I, defined as adenocarcinoma of the distal esophagus. Tumors with the center located 1 cm above to 2 cm below the EGJ were designated type II, representing true carcinoma of the cardia. Tumors centered 2 to 5 cm below the EGJ were designated type III, representing subcardial gastric carcinoma. We recorded the margin of the tumor, the EGJ, and the tumor center. The diagnoses of GERD were referred to the standard reported from America.[17]

Clinicopathological Data

Clinicopathological data including demographic parameters, maximal diameter of tumor (cm), Borrmann types, pT stage, pN stage, Tumor-Nodes-Metastasis (TNM), and degree of tumor differentiation (well differentiated, moderate, undifferentiated: poor and signet-ring cell type) were reviewed. For type II and type III tumors, the macroscopic type, pathologic degree, T-stage, N-stage, and TNM stages were classified on the basis of Japanese classification of gastric carcinoma: 3rd English edition.[18] The TNM stages of type I tumors were classified according to AJCC cancer staging system for esophageal and esophagogastric junction.[19] Surgery-related parameters included resection pattern, surgical radicality, number of lymph nodes dissection, combined organ resection, and the short-term surgical outcomes. The major postoperative complications were defined as disease or disorder occurring as a result of gastric cancer or its resection that required reoperation or other intervention. Operative mortality was any death, regardless of reasons, occurring less than 30 days after surgery in or out of the hospital and more than 30 days after the operation during the same hospitalization.[20,21]

Surgical Approaches

Before surgery, all patients in our study had obtained chest radiographs, an abdominal ultrasonogram, or a computed tomographic scan for tumor staging. The Siewert type of cancer was diagnosed preoperatively by upper gastrointestinal barium meal or endoscopic findings, which also provided a reference for the surgical approach. Patients in the study mainly underwent abdominal or thoracic incision with total or subtotal gastrectomy or esophagectomy. For type I tumors, a left transthoracic proximal (PG) or total gastrectomy (TG) and esophagectomy was routinely performed in our department of thoracic surgery. The Ivor Lewis thoracoabdominal approach was selectively used for tumor locating at higher level that required anastomosis in the region of the aortic arch. For type II adenocarcinomas invading the distal of esophagus, transhiatal TG or PG combined with mediastinal lymphadenectomy was preferred.[22] Thoracoabdominal incision might be performed for subtotal esophagectomy to guarantee curability, if the frozen section of proximal esophageal cutting edge was positive even after repeating resection of distal esophagus. For type III tumors, transabdominal PG or TG was performed in our department of gastrointestinal surgery. D2 lymphadenectomy was routinely performed, whereas D1/D1+ lymphadenectomy was selectively used. The inferior mediastinal or extended (en bloc) lymph node dissection was performed for patients with esophageal involvement. Intraoperative frozen section was a routine procedure aiming to secure the tumor cells free from the resection margins. For the reconstruction, Roux-en-Y anastomosis was mainly adopted for TG and esophagogastric anastomosis after PG. Combined organ resection was selectively performed to achieve a possible curative resection.

Statistical Analysis

Continuous variables were shown as mean ± standard deviation and compared by 1-way analysis of variance test. Changes of EGJA subgroup and the categorical variables were analyzed by χ^2 tests. The correlation between the proportion of EGJA and the prevalence of GERD for patients was investigated by linear regression. All statistical analyses were 2-sided and performed at less than 0.05 level of significance using software SPSS (SPSS version 19.0 for Windows, IBM Corp., Armonk, NY).

RESULTS

Anatomical Distribution

From 1988 to 2012, a total of 6612 cases of gastric and distal esophageal cancer were included in our gastric and esophageal database; among them, 1559 patients were excluded because of remnant gastric cancer ($n = 132$), other malignancy of stomach ($n = 223$), distal esophageal squamous carcinoma ($n = 1075$), and multicentric gastric or esophageal malignancy ($n = 129$), leaving a final study cases of 5053. Among all these patients, 413 were treated in period 1, 518 in period 2, 1104 in period 3, 1038 in period 4, and 1980 in period 5 (Table 1).

The proportion of distal esophageal adenocarcinoma was 18.7% among all distal esophageal cancers. Among the 5053 cases, 1723 (34.1%) cases were classified as EGJA, whereas the other 3330 cases were not: tumors of 523 cases were located at the body of the stomach (10.4%), 2605 at the antrum (51.6%), and 202 cases invaded the entire stomach (4.0%). There were just 92 patients with EGJA undergoing surgical resection in the period 1, whereas this number had increased to 707 in the period 5. A gradual increasing in proportion of EGJA was seen: from 22.3% in period 1 to 35.7% in period 5 ($P < 0.001$).

By contrast, a significant decrease was observed in gastric adenocarcinoma of antrum, from 63.7% in period 1 to 50.5% in period 5 ($P < 0.001$). The proportion of adenocarcinoma in the entire stomach remained relatively stable during the past 25 years ($P = 0.324$) (Table 1 and Fig. 1)

Proportion Changes of EGJA According to Siewert's Classification

The changing trends in subtypes of EGJA according to Siewert's classification were shown in Figure 2. Among all the 1723 patients with EGJA (all periods), 679 (39.4%) had type III

TABLE 1. Anatomical Distribution of Gastric Adenocarcinoma in the 25-Year Period Between 1988 and 2012

Tumor Location*	Period 1, 1988–1992 (n = 413)	Period 2, 1993–1997 (n = 518)	Period 3, 1998–2002 (n = 1104)	Period 4, 2003–2007 (n = 1038)	Period 5, 2008–2012 (n = 1980)	P†
Esophagogastric junction	92 (22.3%)	175 (33.8%)	388 (35.1%)	361 (34.8%)	707 (35.7%)	<0.001
Body	35 (8.5%)	60 (11.6%)	106 (9.6%)	127 (12.2%)	195 (9.9%)	0.108
Antrum	263 (63.7%)	259 (50.0%)	567 (51.4%)	516 (49.7%)	1000 (50.5%)	<0.001
Entire stomach	23 (5.6%)	24 (4.6%)	43 (3.9%)	34 (3.3%)	78 (3.9%)	0.324

*The definition of tumor location was according to Japanese classification of gastric carcinoma: 3rd English edition.
†Comparisons were performed with χ^2 test for categorical variables.

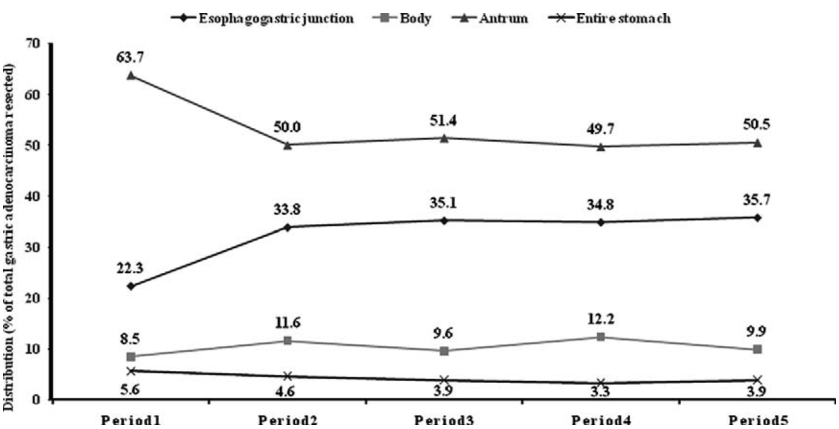

FIGURE 1. Time trends of gastric adenocarcinoma at different anatomical locations over the 25-year period from 1988 to 2012.

tumors, 797 (46.3%) had type II tumors, and 247 (14.3%) had type I tumors. The proportion of type II tumors had declined from 55.4% in period 1 to 37.2% in period 5, whereas the proportion of type III tumors rose from 35.9% in period 1 to 47.0% in period 5 ($P < 0.001$). And the proportion of type I tumors also rose from 8.7% in period 1 to 15.8% in period 5 ($P = 0.012$). The proportion of type III tumors had increased rapidly during the past 25 years and had exceeded the proportion of type II tumors in the last period (47.0% vs 37.2%).

Changes of Prevalence of GERD in Patients With EGJA

The changing trends of prevalence of GERD in patients with EGJA are shown in Figure 3. The prevalence of GERD was 6.5% in period 1 and had increased gradually to 10.9% in period 5 for the 3 subgroups without significant difference ($P = 0.459$) (Table 2). In patients with Siewert I tumors, the prevalence of GERD fluctuated from 41.3% to 57.1% ($P = 0.456$). The prevalences of GERD were

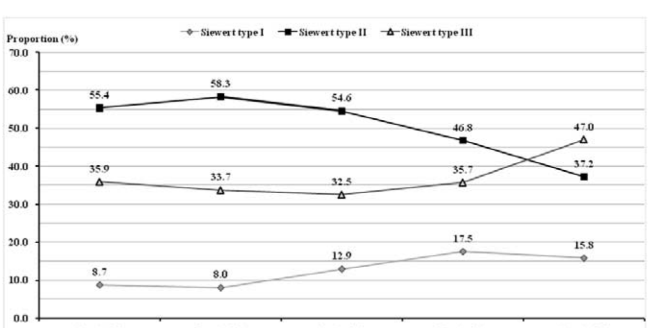

FIGURE 2. Trend in subtype of esophagogastric junctional adenocarcinoma according to Siewert's classification.

nearly stable for Siewert II (ranged from 2.4 to 5.9, $P = 0.768$) and III tumors (ranged from 1.5 to 3.4, $P = 0.846$), respectively. As regard to the correlation analyses, we analyzed the linear correlation between the proportion of EGJA and the prevalence of GERD for all the patients with EGJA. The results demonstrated that there was an upward tendency with significant difference ($r = 0.946$, $P = 0.000$). And there was also a positive correlations with change in GERD for type I tumors ($r = 0.438$, $P = 0.029$). However, no such tendencies were observed in type II tumors ($r = 0.158$, $P = 0.449$) and type III tumors ($r = -0.153$, $P = 0.466$).

Changes of Clinicopathological Features for EGJA

The general information of patients with EGJA is shown in Table 2. In the 1723 cases with EGJA, the ratio of male to female was 4.4:1, which was much higher than that of overall patients with gastric cancer (2.6:1, data were not shown in the tables). The mean age that was significantly increased from period 1 (55.2 ± 10.0) to period 5 (61.0 ± 9.8) ($P < 0.001$) for all EGJA cases was (59.5 ± 10.2) years.

The clinicopathological features of patients with EGJA are also listed in Table 2. A decreased trend was seen in the maximal tumor size of EGJA from period 1 (6.4 ± 3.0) cm to period 4 (5.3 ± 2.7) cm ($P = 0.001$). Comparing with period 1, the proportion of Borrmann 2 was increased from 32.6% to 53.3%, whereas the proportion of Borrmann 3 was decreased from 46.7% to 26.6% in period 5 ($P < 0.001$). The proportion of differentiated tumors decreased from 45.7% in period 1 to 29.8% in period 5, whereas the proportion of undifferentiated tumors increased from 54.3% to 70.2% ($P < 0.001$). Among the 1723 cases with EGJA, the overall proportion of pT1 tumors was 5.9%. The proportion of pT1 tumors increased gradually with time, from 1.1% in period 1 to 7.5% in period 5 ($P = 0.023$). Constituent ratios for pTNM stage were shown in Figure 4. The proportion of patients with stage I increased from

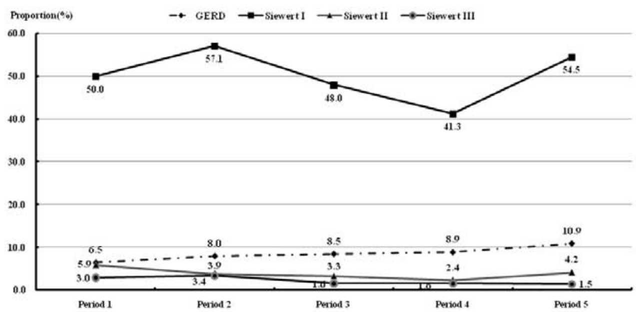

FIGURE 3. Time trend of GERD among esophagogastric junctional adenocarcinoma (EGJA) and the proportion trend of GERD among subtype of EGJA according to Siewert's classification. GERD indicates gastroesophageal reflux disease.

4.4% in period 1 to 13.6% in period 5 ($P = 0.028$), whereas patients with stage III was gradually decreased from 69.6% to 56.0% in period 5 ($P = 0.005$). The rate of lymph node metastasis was also decreased from 84.8% to 75.1% in period 5 ($P = 0.046$).

Changes of Surgical Treatment and the Postoperative Complications for EGJA

Surgery-related information is described in Table 3. Among 1723 patients, the rate of transabdominal TG had increased from 19.6% in period 1 to 42.0% in period 5 ($P < 0.001$), whereas the rate of PG had declined to 42.7% in period 5 ($P < 0.001$). Corresponding with these changes, the Roux-en-Y reconstructions had gradually become a dominating mode with the rate increasing to 41.2% in period 5 ($P < 0.001$). The proportion of R0 resection was also gradually increased from 71.7% to 85.3% during the past 25 years ($P = 0.004$). The mean number of harvested lymph nodes was significantly increased to 25.2 ± 11.6 in period 5 ($P < 0.001$). The rate of combined organ resection has dropped from 22.8% to 6.4% in

TABLE 2. Demographics and Clinicopathological Features of 1723 Patients With Esophagogastric Junctional Adenocarcinoma

	Period 1 (n = 92)	Period 2 (n = 175)	Period 3 (n = 388)	Period 4 (n = 361)	Period 5 (n = 707)	P^*
Sex						0.085
Male	78 (84.8%)	154 (88.0%)	321 (82.7%)	286 (79.2%)	566 (80.1%)	
Female	14 (145.2%)	21 (12.0%)	67 (17.3%)	75 (20.8)	141 (19.9%)	
Age, yr						<0.001
<40	6 (6.5%)	9 (5.1%)	17 (4.4%)	12 (3.3%)	18 (2.5%)	
40–60	56 (60.9%)	82 (46.9%)	180 (46.4%)	164 (45.4%)	281 (39.8%)	
>60	30 (32.6%)	84 (48.0%)	191 (49.2%)	185 (51.2%)	408 (57.7%)	
Age, yr	55.2 ± 10.0	57.5 ± 9.9	59.1 ± 10.8	59.4 ± 9.9	61.0 ± 9.8	<0.001
GERD*	6 (6.5%)	14 (8.0%)	33 (8.5%)	32 (8.9%)	77 (10.9%)	0.459
Siewert's classification†						<0.001
Type I	8 (8.7%)	14 (8.0%)	50 (12.9%)	63 (17.5%)	112 (15.8%)	0.012
Type II	51 (55.4%)	102 (58.3%)	212 (54.6%)	169 (46.8%)	263 (37.2%)	<0.001
Type III	33 (35.9%)	59 (33.7%)	126 (32.5%)	129 (35.7%)	332 (47.0%)	<0.001
Maximal tumor size (cm)	6.4 ± 3.0	5.9 ± 2.8	5.5 ± 2.3	5.3 ± 2.7	5.9 ± 3.3	0.001
Macroscopic type						
Superficial	3 (3.3%)	3 (1.7%)	14 (3.6%)	20 (5.5%)	46 (6.5%)	0.027
Borrmann classification‡						<0.001
Type 1	5 (5.4%)	15 (8.6%)	24 (6.2%)	21 (5.8%)	29 (4.1%)	0.178
Type 2	30 (32.6%)	58 (33.1%)	161 (41.5%)	176 (48.8%)	377 (53.3%)	<0.001
Type 3	43 (46.7%)	83 (47.4%)	155 (40.0%)	113 (31.3%)	188 (26.6%)	<0.001
Type 4	11 (12.0%)	16 (11.1%)	34 (8.8%)	31 (8.6%)	67 (9.5%)	0.887
Histological grade§						<0.001
Differentiated	42 (45.7%)	75 (42.9%)	147 (37.9%)	99 (27.4%)	211 (29.8%)	
Undifferentiated	50 (54.3%)	100 (57.1%)	241 (62.1%)	262 (72.6%)	496 (70.2%)	
Depth of invasion§						0.010
T1	1 (1.1%)	4 (2.3%)	22 (5.7%)	21 (5.8%)	53 (7.5%)	0.023
T2	9 (9.8%)	17 (9.7%)	36 (9.3%)	33 (9.1%)	70 (9.9%)	0.995
T3	10 (10.9%)	20 (11.4%)	31 (8.0%)	41 (11.4%)	107 (15.1%)	0.013
T4	72 (78.3%)	134 (76.6%)	299 (77.1%)	266 (73.7%)	477 (67.5%)	0.003
Lymph node metastasis						0.046
Negative	14 (15.2%)	31 (17.7%)	76 (19.6%)	86 (23.8%)	176 (24.9%)	
Positive	78 (84.8%)	144 (82.3%)	312 (80.4%)	275 (76.2%)	531 (75.1%)	
TNM stage§						0.002
I	4 (4.4%)	13 (7.4%)	41 (10.6%)	43 (11.9%)	96 (13.6%)	0.028
II	9 (9.8%)	21 (12.0%)	62 (16.0%)	68 (18.8%)	147 (20.8%)	0.009
III	64 (69.6%)	119 (68.0%)	246 (63.4%)	215 (59.6%)	396 (56.0%)	0.005
IV	15 (16.3%)	22 (12.6%)	39 (10.1%)	35 (9.7%)	68 (9.6%)	0.283

*Continuous variables are reported as mean ± standard deviation. Comparisons were performed with 1-way analysis of variance test for continuous variables and χ^2 test for categorical variables.

†Type of esophagogastric junctional adenocarcinoma was according to Siewert's classification.

‡Borrmann classification suits only for advanced gastric cancer (type II and type III tumors).

§Histologic grade and TNM stage are based on the Japanese classification of gastric carcinoma: 3rd English edition.

GERD indicates gastroesophageal reflux disease.

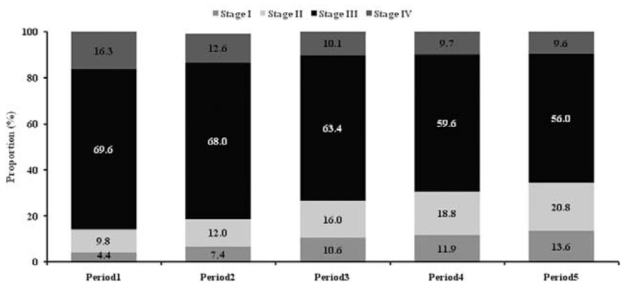

FIGURE 4. Time trends of esophagogastric junctional adenocarcinoma in distribution of TNM stage during the past 25 years in West China Hospital. TNM stage is based on the Japanese classification of gastric carcinoma: 3rd English edition.

period 5 ($P < 0.001$). The postoperative complications and postoperative morbidity are presented in Table 4. The rate of patients with postoperative major complications was gradually decreased from 34.8% in period 1 to 17.1% in period 5 ($P < 0.001$). The overall 30-day mortality rate after resection was 1.0% and did not change with time.

DISCUSSION

In the past 2 decades, we have noticed significant changes in epidemiological characteristics and treatment approaches for EGJA.[5–8] However, the incidence of EGJA was rarely reported in China. In our retrospective cohort study, we analyzed the clinicopathological features derived from 5053 cases who underwent surgical resection for gastric and distal esophageal adenocarcinomas during a period of 25 years. In line with previous studies,[3–8] we find a significant increasing trend of incidence of EGJA, and the operative method for EGJA has also significantly changed during the past 25 years. Total gastrectomy is becoming a mainstay of surgical treatment of patients with EGJA. The subtype of EGJA had also changed significantly during the past 25 years according to Siewert classification that the proportions of type I and type III tumors were significantly increased whereas type II tumors decreased during the past 25 years. The rate of postoperative complications among patients with EGJA was also significantly decreased during the past 25 years.

In this single-institution series, EGJA accounted for 34.1% of all gastric and esophageal adenocarcinomas after surgical resection. Our study showed a significant higher prevalence of EGJA in China than in Western countries.[3,4] In consistent with a previous report that indicated a rising trend of gastric cardia cancer in Gansu province of China from 1993 to 2004 by Zhou et al,[14] the proportion of EGJA indicated a dramatic rising trend during the past 25 years in our institution. The proportion of EGJA in our institution was substantially higher than available reports from the United States,[3,4] Japan,[5,6] and Korea.[7,8] From our analysis, most of this increase occurred between the first period and the second period. The increasing trend of EGJA may have direct association with the raised detection rate of gastric and esophageal cancers in recent years in China because of the increased applications of various diagnostic modalities such as endoscopy in symptomatic patients. Furthermore, with the strengthened examination by endoscopy in our country, the proportion of early-stage tumors among patients with EGJA was also significantly increased.

The proportion of EGJA was increased in recent years; this might be related to changes in risk factors such as alcohol abuse and the increased incidence of GERD.[22,23] The prevalence of GERD has been reported to range from 10% to 48% in Asia, which is slightly lower than that in Western countries and increasing year by year.[24–27]

TABLE 3. Surgical Information of 1723 Patients With Esophagogastric Junctional Adenocarcinoma

	Period 1 (n = 92)	Period 2 (n = 175)	Period 3 (n = 388)	Period 4 (n = 361)	Period 5 (n = 707)	P*
Method of operation						<0.001
Transhiatal total gastrectomy	18 (19.6%)	36 (20.6%)	87 (22.4%)	106 (29.4%)	297 (42.0%)	<0.001
Transhiatal proximal gastrectomy	67 (72.8%)	99 (56.6%)	193 (49.7%)	155 (42.9%)	302 (42.7%)	<0.001
Proximal gastrectomy with distal esophagectomy via left thoracotomy	5 (5.4%)	38 (21.7%)	104 (25.8%)	97 (26.9%)	88 (12.4%)	<0.001
Total gastrectomy with distal esophagectomy via left thoracotomy	1 (1.1%)	2 (1.1%)	1 (0.3%)	1 (0.3%)	0 (0%)	
Ivor-Lewis operation	0 (0%)	0 (0%)	2 (0.5%)	2 (0.6%)	20 (2.8%)	
Thoracoabdominal esophagectomy and gastrectomy	1 (1.1%)	0 (0%)	1 (0.3%)	0 (0%)	0 (0%)	
Mode of reconstruction						<0.001
EGA	72 (78.3%)	137 (78.3%)	297 (76.5%)	252 (69.8%)	390 (55.2%)	
Roux-en-Y	19 (20.7%)	37 (21.1%)	82 (21.1%)	101 (28.0%)	291 (41.2%)	
Roux-en-Y + Pouch	0 (0.0%)	0 (0.0%)	2 (0.5%)	4 (1.1%)	19 (2.7%)	
JIPA†	1 (1.1%)	1 (0.6%)	7 (1.8%)	4 (1.1%)	7 (1.0%)	
Mean number of harvested lymph nodes	6.1 ± 2.9	8.1 ± 3.6	10.3 ± 4.6	16.6 ± 9.1	25.2 ± 11.6	<0.001
Combined organ resection‡	21 (22.8%)	19 (10.9%)	36 (9.3%)	26 (7.2%)	45 (6.4%)	<0.001
Radicality						0.004
R0	66 (71.7%)	136 (77.7%)	309 (79.6%)	292 (80.9%)	603 (85.3%)	
R1/R2	26 (28.3%)	39 (22.3%)	79 (20.4%)	69 (19.1%)	104 (14.7%)	

*Continuous variables are reported as mean ± standard deviation. Comparisons were performed with analysis of variance for continuous variables and χ^2 test for categorical variables.

†JIPA: Jejunal interposition anastomosis—includes esophagojejunal anastomosis and gastrojejunal anastomosis.

‡Combined organs include esophagus, lung, pericardium, pancreas, spleen, colon, small intestine, gallbladder, and diaphragm.

EGA indicates esophagus-gastric anastomosis.

TABLE 4. Postoperative Complications of 1723 Patients With Esophagogastric Junctional Adenocarcinoma

	Period 1 (n = 92)	Period 2 (n = 175)	Period 3 (n = 388)	Period 4 (n = 361)	Period 5 (n = 707)	P^*
Postoperative complications	32 (34.8%)	47 (26.9%)	88 (22.7%)	69 (19.1%)	121 (17.1%)	<0.001
Postoperative pulmonary complications	8 (8.7%)	13 (7.4%)	28 (7.2%)	18 (5.0%)	29 (4.1%)	
Pancreatic fistula	1 (1.1%)	2 (1.1%)	3 (0.8%)	1 (0.3%)	4 (0.6%)	
Pneumothorax	2 (2.2%)	4 (2.3%)	4 (1.0%)	6 (1.7%)	8 (1.1%)	
Chest infection	1 (1.1%)	1 (0.6%)	2 (0.5%)	5 (1.4%)	4 (0.6%)	
Pleural effusion	2 (2.2%)	1 (0.6%)	4 (1.0%)	4 (1.1%)	4 (0.6%)	
Chylothorax	0 (0%)	1 (0.6%)	2 (0.5%)	1 (0.3%)	3 (0.4%)	
Intra-abdominal infection	3 (3.3%)	4 (2.3%)	9 (2.3%)	5 (1.4%)	17 (2.4%)	
Intra-abdominal hemorrhage	0 (0%)	0 (0%)	2 (0.5%)	1 (0.3%)	2 (0.3%)	
Leakage	6 (6.5%)	8 (4.6%)	11 (2.8%)	7 (1.9%)	14 (2.0%)	
Gastroplegia	1 (1.1%)	0 (0%)	4 (1.0%)	2 (0.6%)	5 (0.7%)	
Wound infection	7 (7.6%)	9 (5.1%)	18 (4.6%)	14 (3.9%)	27 (3.8%)	
Others†	1 (1.1%)	4 (2.3%)	1 (0.3%)	5 (1.4%)	4 (0.6%)	
Operative mortality‡	1 (1.1%)	1 (0.6%)	3 (0.8%)	5 (1.4%)	8 (1.1%)	0.892

*Comparisons were performed with $\chi 2$ test for categorical variables.
†Others include pyothorax, chest hemorrhage, chylous leakage, pancreatitis, cholecystitis, cardiocerebral events, anesthetic mishap, and venous thrombosis.
‡Operative mortality was any death, regardless of cause, occurring less than 30 days after surgery in or out of the hospital and more than 30 days, during the same hospitalization, after the operation.

Although our results had showed no significant difference, the prevalence of GERD had increased gradually from 6.5% in period 1 to 10.9% in period 5 for the 3 subgroups. Epidemiological studies have consistently suggested that symptom of GERD is the main risk factor for Barrett esophagus and esophageal adenocarcinoma.[13] Obesity has also been reported to be associated with development of EGJA at an early age,[28] and it is suspected that increased reflux may account for the association.[29] It has been reported that the increasing prevalence of GERD among population of Asia might be closely associated with the increasing trend of EGJA in Eastern countries.[30,31] And our results also demonstrated that there was a tendency between the proportion of EGJA and the prevalence of GERD for all the patients with EGJA with significant differences. However, cohort studies demonstrated that symptoms of GERD were found monthly in almost 50% of US adults and weekly in nearly 20%, but EGJA is not popular in these patients.[32] Therefore, the causality between GERD and EGJA still needs to be researched further.[32]

It should be noted that the prevalences of GERD in patients with Siewert type I tumors in each period accounted nearly 50%, which indicated that there might be closed relationships between GERD and type I tumors. Actually, Lagergren et al[33] reported that there was a strong and probably causal relation between gastroesophageal reflux and esophageal adenocarcinoma, including type I EGJA. Wang et al[34] also found that the annual detection rate of type I EGJA seemed to be positively correlated with reflux esophagitis in time trend. Although our results found the positive correlations with change in GERD for type I tumors, the correlation was not very strong (correlation coefficient = 0.438). Hence, we consider that evidence is inadequate to show the causality between GERD and type I tumors. Wang et al[34] also consider that the similarities in change over time in the rate of detection of EGJA and reflux esophagitis could not easily account for causal relationship.

The widespread application of upper gastrointestinal endoscopy in hospitals of China has made the detection rate of gastric and esophageal cancer increasing. Because of the improvement of our upper gastrointestinal endoscopic technology, the detection rate of tumors located in cardia and fundus has also distinctly increased during the past 25 years. On the contrary, the healthy consciousness of Chinese people has greatly shifted during the past 2 decades. The upper gastrointestinal endoscopic examination is becoming more and more acceptable in our country. We also advocated the cancer-screening propaganda to promote the early diagnosis of upper gastrointestinal tumors in recent years. In accordance with these changes, the rate of pT1 or pN0 tumors and stage I disease among patients with EGJA was also significantly increased, whereas the maximal diameter of tumor and the proportion of stage III tumors showed a decreased trend during the past 25 years.

The Siewert's classification for EGJA is now widely accepted. We classified EGJA into 3 subtypes according to Siewert's classification. We found significant higher prevalence of type II and type III tumors and lower rate of type I tumors in China when compared with data from Western countries.[35–37] Among all the EGJAs in our series, 14.3% were type I, 46.3% were type II, and 39.4% were type III by reviewing the database of gastric and esophageal cancer of our hospital. These findings are similar to reports from Hasegawa et al[38] in Japan and Bai et al[39] in China. The increased trend of type I tumors could be explained by the improvement on the rate of detection and changed etiological factors over time. The proportion of Siewert type II tumors was significantly decreased whereas type III increased during the past 25 years in our study. This trend was similar to report from Siewert et al[35] in Germany and Chung et al[40] in Korea. However, Wang et al[34] had indicated that type II and type III tumors just exhibited a fluctuated trend from 2000 to 2009 in China. There are still some controversies on the changing trend of type II and III tumors in China. Therefore, the epidemiological survey for large population is necessary to conduct in the future. From our analysis, type III tumors are gradually becoming a dominant type of EGJA in recent decades.

For the operative procedures, we found that transabdominal TG was gradually becoming more and more common for EGJA in our institution. In Western countries, PG is a traditional procedure to preserve a gastric stump as much as possible for upper-third cancer.[41] Proximal gastrectomy has also been generally accepted by most gastrointestinal surgeons for tumors in an early stage providing that a sufficient distal resection margin can be ensured.[42] However, Yoo et al[43] had found that the recurrence rate of TG group was lower than PG group, because it might have been associated with more radical resection extent. In addition, the rate of postoperative complications was higher in patients who underwent PG since the higher incidence of reflux esophagitis and anastomotic stenosis after PG.[44] Proximal gastrectomy with distal esophagectomy via transthoracic esophagectomy approach was common for EGJA for a time in our institution. However, Sasako et al[22] reported that an abdominal-transhiatal approach for Siewert II/III tumors achieved a better survival. Therefore, EGJA could be removed safely by TG from an abdominal approach. Transhiatal with mediastinal lymphadenectomy plus TG comprises a more radical resection margin that prevents residual disease at the esophageal margin and allows removal of all the perigastric and peridiaphragmatic hiatus lymph nodes.[42] Nowadays, for patients with advanced diseases, many surgeons recommend abdominal-transhiatal approach with TG to be the standard procedure to achieve a more radical effect for Siewert II/III tumors of advanced EGJA.[43] These may partly explain the decreased rate of left thoracotomy approach that was selected for type I tumors, and a significant decreased trend was observed in our study.

Surgical resection plus D2 lymph nodes resection is becoming a standard treatment of gastric cancer. With these changes, the mean number of harvested lymph nodes has significantly increased from 6.1 ± 2.9 in period 1 to 25.2 ± 11.6 in the last period in our institution. The dissection and checkout of lymph nodes had become more and more standard during the past 2 decades. The increase of harvested nodes may be due to the improvements in surgical technique and the improvement in examining lymph nodes. Accompanying these aforementioned changes, our radical degree has also significantly increased during the past 25 years. Although lymph nodal dissection has been reported to increase morbidity,[45] the rate of postoperative complications in our institution has fallen from 34.8% in period 1 to 17.1% in period 5. This change may be related to the improvement in surgical skills and postoperative care. Improvements in surgical skills include the surgeon's accumulated experience with large volume of patients, the use of monopolar electrocautery and ultrasound scalpel throughout the procedure, and the adoption of standardized lymph nodes dissection techniques. The advancements in perioperative nutritional support may also be associated with the decrease of postoperative complications. The application of total parenteral nutrition after operation can reduce the risk of postoperative complications among patients with poor nutritional status.[46]

One limitation of this study is that it comes from a single institution, so the results may not represent the Chinese population well. However, the volume of surgeries done for gastric and esophageal cancers at our institution is large and the sources of patients come from the area of Western China, which may serve as a reference for a large population-based study. This study strove to describe the changing trend of clinicopathological features, surgical treatment, and proportion of EGJA with the data of patients who underwent resection. Another limitation of our study is that it was confined to operated cases, and patients who underwent nonresection surgery (bypass or biopsy only) were excluded.

CONCLUSIONS

There seems to be a similar increased trend in the incidence of EGJA in China compared with other regions. The Siewert type I and type III had indicated an increased trend, whereas type II had decreased among past 25 years. The prevalence of GERD among EGJA had also shown a gradually increasing trend. However, the causality between GERD and EGJA still needs further research. Total gastrectomy is becoming a more common procedure for EGJA.

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Kai Liu and Kun Yang contributed equally to this study.

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The author contributions are as follows:

Jiankun Hu and Xinzu Chen made substantial contributions to conception and design for this study. Kai Liu and Weihan Zhang acquired and analyzed data and Kai Liu drafted the article. Because this a large sample research in our institution, nearly 5000 cases included in our study. Bo Zhang, Zhixin Chen, Jiaping Chen, Yongfan Zhao, and Zongguang Zhou provided large number of cases and gave many important suggestions for this study. Kun Yang, Xiaolong Chen, Jiankun Hu, and Longqi Chen participated in interpreting critically for important intellectual results. Jiankun Hu and Longqi Chen gave final approval of the version to be published. Kun Yang collected the data of Siewert I tumors and GERD and performed the reanalyses in the process of revision. So Kun Yang completed the revision of important contents and was listed as the co–first author. Professor Longqi Chen kindly provided the data from the database of esophageal cancers in the Department of Thoracic Surgery of West China Hospital and interpreted the results and Professor Longqi Chen gave final approval of the version to be published. Hence, Professor Longqi Chen was also listed as the corresponding author with Professor Jiankun Hu.

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