Intrathoracic Anastomosis or Cervical Anastomosis for Esophagogastric Junction Cancer Surgery: A Retrospective Cohort Study

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Aims: This study aimed to determine the degree of reflux esophagitis after either intrathoracic or cervical esophagogastrostomy in patients with esophagogastric junction carcinoma.

Patients and Methods: The study population consisted of 10 and 15 consecutive patients who underwent esophagectomy with gastric conduit reconstruction via intrathoracic (Ivor Lewis) or cervical (McKeown) esophagogastrostomy, respectively. Reflux esophagitis was evaluated annually after surgery and scored on a 0- to 4-point scale corresponding to grades N/M, A, B, C, and D, respectively. The reflux esophagitis score of each patient, defined as the average of scores at 1, 2, and 3 years after surgery, was compared between the groups.

Results: Of the 30 planned annual endoscopic follow-ups (3 years in 10 patients) in the Ivor Lewis group and 45 planned follow-ups (3 years in 15 patients) in the McKeown group, 24 and 29 such follow-ups were performed in the Ivor Lewis and McKeown groups, respectively. The reflux esophagitis score was significantly better in the McKeown group than in the Ivor Lewis group (0.51 ± 0.24 versus 1.46 ± 0.29, *P* = 0.019). Overall survival did not significantly differ between the Ivor Lewis and McKeown groups (respective 5-year survival rates, 64% versus 57%, *P* = 0.75).

Conclusions: The degree of reflux esophagitis may be greater in patients with esophagogastric junction cancer treated by Ivor Lewis esophagectomy than in those treated by McKeown esophagectomy. McKeown esophagectomy might be a more suitable method for the treatment of esophagogastric junction cancer with extended esophageal invasion.

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The incidence of adenocarcinoma of the esophagogastric junction (AEG) has increased substantially in the past few decades.[1–3] For AEG with esophageal invasion of 3 cm or less, a transhiatal approach is recommended because of its lower morbidity and comparable survival rates compared with the left thoracoabdominal approach.[4] However, in cases of bulky tumor or tumor with submucosal extension, a thoracic approach is sometimes necessary in order to establish a cancer-free proximal margin. In addition, mediastinal lymph node dissection via a right thoracic approach has been recommended for AEG with esophageal invasion of more than 3 cm.[5]

Surgical resection of esophagogastric junction cancer that requires a right thoracic approach is almost always followed by reconstruction with esophagogastrostomy. Because neck dissection is thought to be unnecessary for AEG, intrathoracic esophagogastrostomy is typically favored. However, esophagogastrostomy often leads to severe reflux esophagitis due to vigorous acid reflux, especially when intrathoracic esophagogastrostomy is performed. A few previous reports have compared the rate of reflux symptoms in patients after esophagectomy for esophageal cancer between intrathoracic esophagogastrostomy (Ivor-Lewis) and cervical esophagogastrostomy (McKeown),[6,7] but no studies have compared the rate of reflux esophagitis after Ivor-Lewis and McKeown esophagectomy for the surgical resection of AEG.

The aim of this study was to clarify the frequency and degree of reflux esophagitis, as well as other complications related to surgical procedures, after intrathoracic and cervical esophagogastrostomy in patients with esophagogastric junction carcinoma, in order to highlight the best practices.

Patients and Methods

This study was conducted in accordance with the 1995 Declaration of Helsinki (as revised in Edinburgh 2000) and approved by the Kitasato University School of Medicine Research Ethics Committee. The requirement for informed consent was waived because of the study's retrospective design.

Patients

From January 2000 through September 2012, there were 163 patients who underwent surgical resection for esophagogastric junction cancer at Kitasato University. Of these, 132 patients who were treated via a transhiatal or left thoracoabdominal approach were excluded from this study. Six patients who died within 1 year or who were unable to undergo endoscopic follow-up were also excluded.

The remaining 25 patients were included in this study; among these, 10 patients underwent Ivor Lewis esophagectomy with posterior mediastinal route reconstruction, and 15 underwent McKeown esophagectomy with retrosternal route reconstruction. We retrospectively reviewed the medical records of these patients. Ivor Lewis esophagectomy or McKeown esophagectomy was selected on the basis of the surgeon's preference. Median follow-up times for the 10 patients in the Ivor Lewis group and the 15 patients in the McKeown group were 52 months (range, 17–99 months) and 47 months (range, 16–167 months), respectively.

Patient follow-up and esophagitis score

All patients underwent endoscopic examination annually after surgery, and reflux esophagitis was evaluated according to the Los Angeles classification by endoscopic specialists. Gastroesophageal acid reflux inhibitors, such as proton pump inhibitors or H2 receptor antagonists, were administered if patients had endoscopic reflux esophagitis or complained about reflux symptoms as determined by outpatient clinic doctors. The degree of reflux esophagitis was numerically converted as follows: 0 in grade N or M, 1 in grade A, 2 in grade B, 3 in grade C, and 4 in grade D. Representative endoscopy at each degree of reflux esophagitis is shown in Fig. 1. The reflux esophagitis score of each patient, defined as the average of scores at 1, 2, and 3 years after surgery, was compared between the groups.

Next, 9 patients with thoracic esophageal cancer who underwent esophagectomy with cervical anastomosis via posterior mediastinal route reconstruction during the study period were added as a control group, because no patients with esophagogastric junction cancer were treated with that type of reconstruction at our institution. In addition, 7 and 47 patients with thoracic esophageal cancer who
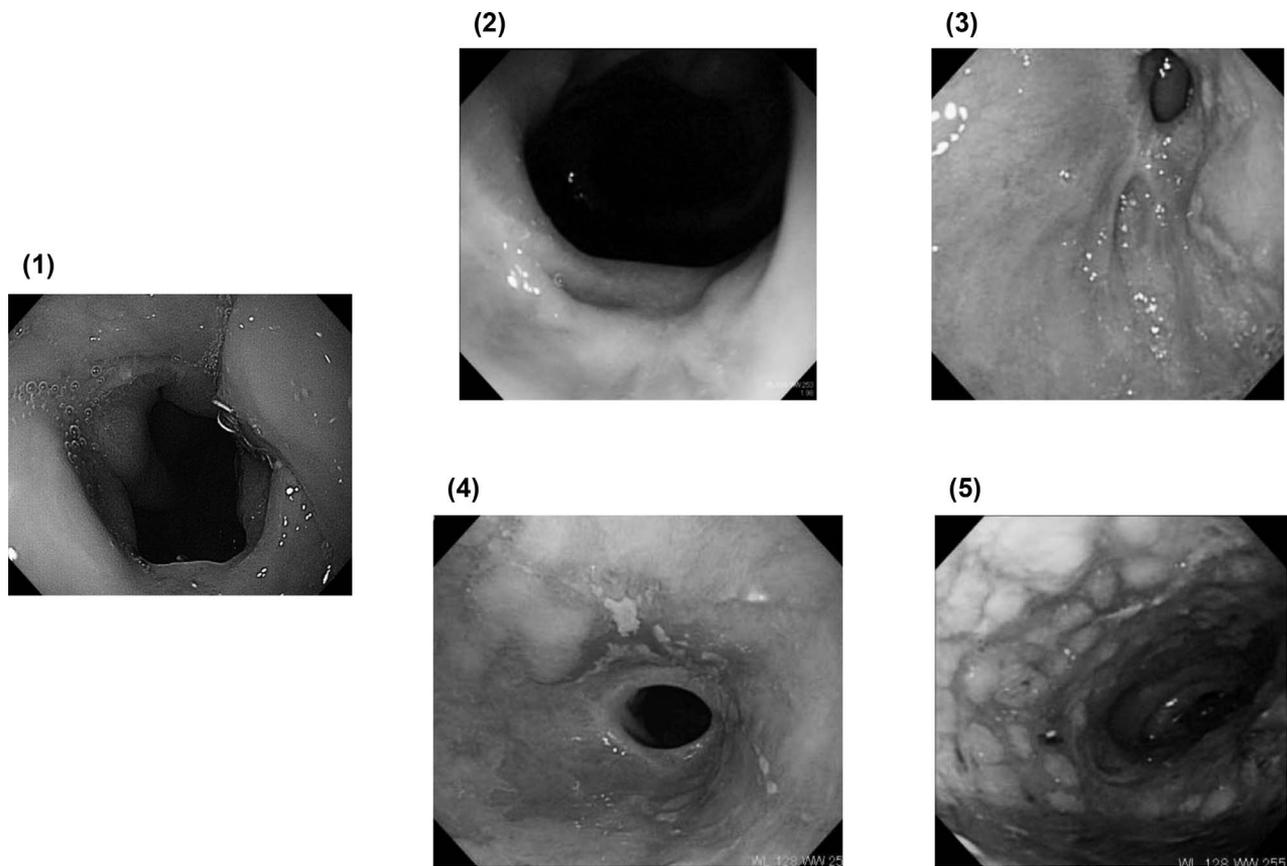
Fig. 1 Representative endoscopic images of each grade of reflux esophagitis are shown: (1) N, (2) A, (3) B, (4) C, and (5) D.

underwent Ivor Lewis esophagectomy and McKeown esophagectomy, respectively, during the study period were added to verify the findings of the small original study population.

Other clinical analyses

Patients' medical records were reviewed, and their age, sex, intraoperative findings, and length of postoperative hospital stay were recorded. Esophageal invasion was evaluated by the barium swallow test. Postoperative complications were assessed according to the Clavien-Dindo classification.[8,9] Resected specimens were histopathologically examined to determine histologic type, depth of tumor invasion, extent of lymph node metastasis, and pathologic tumor stage according to the Union for International Cancer Control TNM classification of malignant tumors, 7th edition.[10] Overall survival was calculated from the date of surgery or the date of starting chemotherapy in patients who received preoperative chemotherapy to the date of death by

any cause. Patients who survived up to the time of the last visit were regarded as censored.

Statistical analysis

Mann-Whitney U test was used to analyze continuous variables. Chi-square test or Fisher exact test was used to analyze categoric variables as appropriate. Survival was calculated by the Kaplan-Meier method. All calculations were performed using JMP 11.2.0 (SAS Institute Inc, Cary, North Carolina), and P values less than 0.05 were considered to indicate statistical significance.

Results

Patient characteristics

Patient characteristics are detailed in Table 1. Age, sex, histologic characteristics, and pathologic stage were similar between the Ivor Lewis and McKeown groups. More than 80% of patients were male in both groups. The median length of esophageal invasion was 43 mm in the Ivor Lewis group and

Table 1   Patient characteristics

	Ivor Lewis (n = 10)	McKeown (n = 15)	P value
Age, y, median (range)	71 (35−75)	66 (48−81)	0.62
Sex, n			0.80
Male	9	13	
Female	1	2	
Length of esophageal invasion, mm, median (range)	43 (1−60)	40 (5−55)	1.00
pT, n			0.88
0	1	0	
1a	0	1	
1b	2	4	
2	1	1	
3	6	9	
pN, n			0.60
0	5	7	
1	3	3	
2	2	1	
3	0	4	
pStage, n			0.49
0	1	0	
IA	1	4	
IB	1	1	
IIA	2	2	
IIIA	4	4	
IIIB	1	0	
IIIC	0	3	
IV	0	1	
Histology			0.40
Adeno	5	10	
SCC	5	5	

Adeno, adenocarcinoma; SCC, squamous cell carcinoma.

40 mm in the McKeown group, with no statistical difference.

Surgical outcomes

The surgical outcomes of patients undergoing Ivor Lewis and McKeown esophagectomy are detailed in Table 2. Video-assisted thoracic surgery was performed for 2 patients in the Ivor Lewis group and 3 in the McKeown group. Cervical paraesophageal lymph nodes were dissected in 8 patients in the McKeown group. No significant differences in operation time, estimated blood loss, number of dissected lymph nodes, or days of postoperative hospital stay were observed between the groups.

Surgical complications, classified as Clavien-Dindo grade IIIa or higher, are detailed in Supplementary Table 1. Anastomotic leakage was more frequently observed in the Ivor Lewis group than in the McKeown group [4 (40%) versus 2 (13%), $P = 0.18$]. However, no significant differences in total number of complications were observed between the groups. No mortality occurred in either group.

Reflux esophagitis

Of the 3 planned annual endoscopic follow-ups for each patient, for a total of 30 planned follow-ups (3 visits by 10 patients) in the Ivor Lewis group and 45 planned follow-ups (3 visits by 15 patients) in the McKeown group, esophagogastroduodenoscopy was performed at 24 and 29 follow-up visits in the Ivor Lewis and McKeown groups, respectively. Of the 24 and 29 esophagogastroduodenoscopy procedures performed as part of annual follow-ups, acid inhibitors, such as proton pump inhibitors and H2 receptor antagonists, were administered at the time of esophagogastroduodenoscopy to 17 patients and 15 patients in the Ivor Lewis and McKeown groups, respectively (71% versus 52%, $P = 0.17$). As shown in Table 3, the reflux esophagitis score was significantly lower (better) in the McKeown group than in the Ivor Lewis group (0.41 ± 0.13 versus 1.54 ± 0.31, $P = 0.019$).

We further calculated the esophagitis scores of 9 patients with thoracic esophageal cancer who underwent esophagectomy with cervical anastomosis via posterior mediastinal route reconstruction, because we had not performed this surgery for esophagogastric junction cancer during the study period. These 9 patients also had a significantly lower (better) mean reflux esophagitis score than those in the Ivor Lewis group (0.25 ± 0.11 versus 1.54 ± 0.31, $P < 0.001$). They also had a slightly

Table 2   Surgical outcomes

	Ivor Lewis (n = 10)	McKeown (n = 15)	P value
Operation time, min, median (range)	405 (360–1040)	478 (320–735)	0.64
Estimated blood loss, mL, median (range)	1050 (820–1370)	760 (450–1380)	0.20
No. of dissected lymph nodes, median (range)	48 (24–87)	43 (17–69)	0.54
Days of postoperative hospital stay, median (range)	39 (17–142)	36 (18–309)	0.68
VATS	2	3	1.00
Dissection of cervical paraesophageal LNs	N/A	8	

LN, lymph node; N/A, not applicable; VATS, video-assisted thoracic surgery.

Table 3 Distribution of endoscopic findings 1, 2, and 3 years after surgery, and esophagitis score

	Ivor Lewis, n				McKeown, n				
	1 y	2 y	3 y	Total	1 y	2 y	3 y	Total	P value
Endoscopic findings									
N	4	2	3	9	10	6	3	19	
A	0	2	2	4	3	3	3	9	
B	1	1	1	3	0	0	0	0	
C	1	3	1	5	1	0	0	1	
D	2	0	1	3	0	0	0	0	
N/A	2	2	2	6	1	6	9	16	
Esophagitis score, mean ± SE				1.54 ± 0.31				0.41 ± 0.13	0.019

N/A, not applicable.

better mean reflux esophagitis score than in those in the McKeown group (0.25 ± 0.11 versus 0.41 ± 0.13, $P = 0.31$; Fig. 2).

Finally, we included 7 and 47 patients with thoracic esophageal cancer who underwent Ivor Lewis esophagectomy and McKeown esophagectomy, respectively, during the study period, who were newly added to each group so as to yield an Ivor Lewis group with 17 patients and a McKeown group with 62 patients. The esophagitis score was again significantly lower (better) in the enlarged McKeown group than that in the enlarged Ivor Lewis group (0.35 ± 0.06 versus 1.34 ± 0.22, $P < 0.001$).

Survival analysis

As shown in Fig. 3, overall survival did not significantly differ between the Ivor Lewis and McKeown groups (respective 5-year overall survival rates, 64% versus 57%, $P = 0.75$).

Discussion

Although Ivor Lewis esophagectomy is favored for the treatment of esophagogastric junction cancer, reflux esophagitis frequently occurs after this surgery. By contrast, after McKeown esophagectomy, reflux esophagitis may be less severe, but surgical stress is considered to be greater than that of Ivor Lewis esophagectomy. Because no studies have investigated the rate of reflux esophagitis after surgical resection of AEG by comparing Ivor-Lewis and McKeown esophagectomy, we aimed to clarify the frequency and degree of reflux esophagitis, as well as other complications related to surgical procedures, after intrathoracic and cervical esophagogastrostomy in patients with esophagogastric junction carcinoma.

This study had two major findings. The first is that esophagitis score was significantly worse in the Ivor Lewis group than in the McKeown group. The second is that the rate of anastomotic leakage was slightly higher in the Ivor Lewis group than in the McKeown group.

Esophagitis score was significantly worse in the Ivor Lewis group than in the McKeown group. The JCOG9502 study found no benefit in a left thoracoabdominal approach for the treatment of AEG with esophageal invasion of 3 cm or less. For patients with esophagogastric junction cancer with esophageal invasion exceeding 3 cm, surgery with a left thoracoabdominal approach may be unable to ensure a negative proximal margin; therefore, a right thoracic approach is preferred for these patients. However, if the remnant esophagus is sufficiently long enough for the site of the esophagogastric anastomosis to lie caudal to the azygos arch, despite there being no oncologic need for this extra length in esophagogastric junction cancer, the risk of reflux esophagitis is increased. Moreover, if a low anastomosis is performed in the Ivor Lewis operation, a redundant intrathoracic stomach causes the patient to experience severe symptoms of prominent regurgitation.[11] Therefore, in esophagogastrostomy with Ivor Lewis esophagectomy, the intrathoracic remnant esophagus should be as short as possible.

McKeown esophagectomy is more invasive than Ivor Lewis esophagectomy. However, patients with cervical anastomosis have been reported to experience significantly fewer reflux symptoms.[12] To our knowledge, no study has directly compared Ivor Lewis esophagectomy and McKeown esophagectomy in esophagogastric junction cancer patients. This study, although retrospective, compared the degree of reflux esophagitis between patients who underwent Ivor Lewis esophagectomy and McKeown
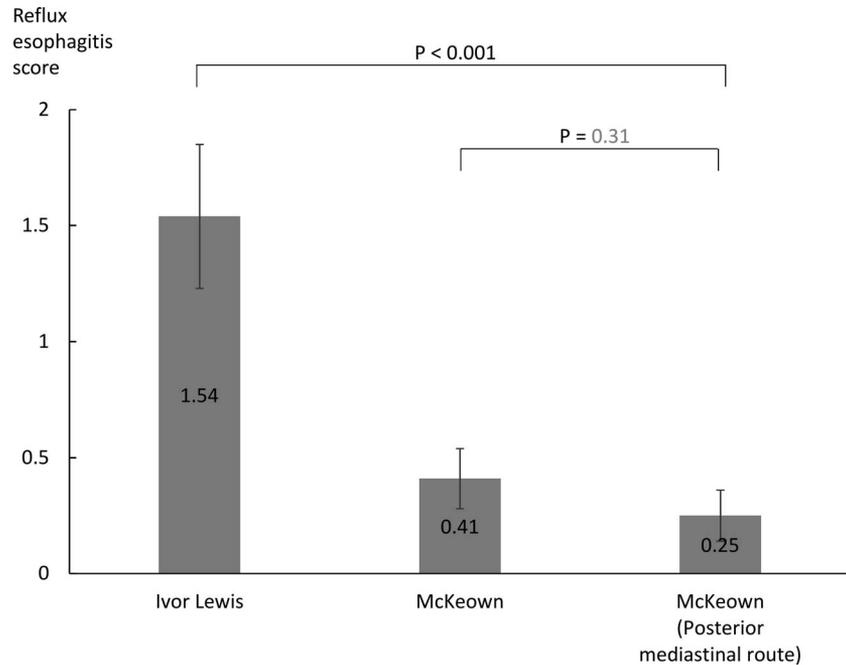
Fig. 2 Comparison of the reflux esophagitis scores of patients in the Ivor Lewis group, the McKeown group, and the McKeown (posterior mediastinal route) group.

esophagectomy. Although comprehensive quality of life evaluation is necessary, an endoscopic finding of reflux esophagitis is one of the most important factors affecting the quality of life of patients who have undergone esophagectomy. Therefore, although it is less invasive than McKeown esophagectomy, Ivor Lewis esophagectomy may not be preferable.

The inclusion of additional patients with thoracic esophageal cancer for the expanded Ivor Lewis and McKeown groups, with 17 and 62 patients, respectively, supported the original findings. The esophagitis score was again significantly lower (better) in

the McKeown group than that in the Ivor Lewis group (0.35 ± 0.06 versus 1.34 ± 0.22, $P < 0.001$).

Because this study compared not only intrathoracic and cervical anastomosis but also posterior mediastinal route reconstruction and retrosternal route reconstruction, we further compared intrathoracic anastomosis (Ivor Lewis) and cervical anastomosis with posterior mediastinal route reconstruction (Fig. 2). Patients who underwent cervical anastomosis via posterior mediastinal route also had a significantly lower (better) esophagitis score than those who underwent Ivor Lewis reconstruction. By contrast, the reflux esophagitis
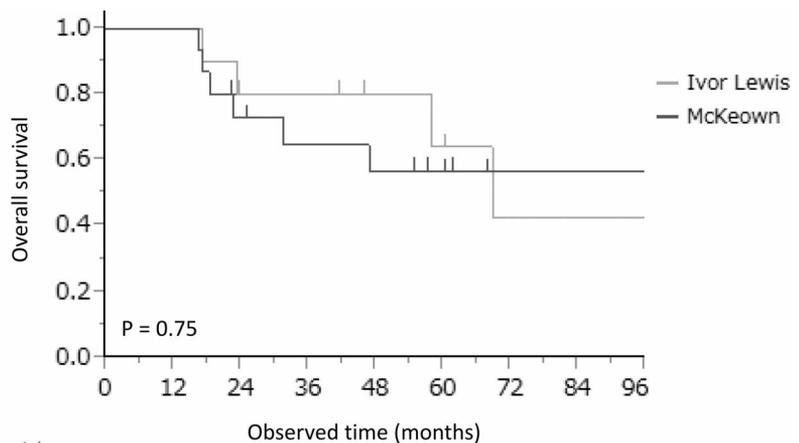

Fig. 3 Kaplan-Meier curves for overall survival in the Ivor Lewis group and the McKeown group. There was no significant difference between the groups.

score was not significantly worse but was slightly better in patients who underwent esophagectomy with cervical anastomosis via posterior mediastinal route compared with the patients in the McKeown group. These findings suggest that reflux esophagitis may be due to the level of anastomosis rather than the difference of reconstruction route.

The rate of anastomotic leakage was slightly higher in the Ivor Lewis group than in the McKeown group. Anastomotic leakage is the most feared complication in Ivor Lewis esophagectomy because if anastomotic leakage occurs, the resultant empyema can be fatal. The prevalence of this complication in Ivor Lewis esophagectomy has been reported to range from 5% to 8%, with mortality between 8.5% and 35.7%.[13–15] Patients experiencing anastomotic leakage after Ivor Lewis esophagectomy were reported to have a significantly shorter long-term survival, even following full recovery after the leakage.[16] At our institution, almost all operations for esophageal and esophagogastric junction cancer that required right thoracotomy involved McKeown esophagectomy; thus, we were less experienced in Ivor Lewis esophagectomy. Therefore, the rate of anastomotic leakage in the Ivor Lewis group reached 40%. Fortunately, no mortality occurred in either group. This high rate of anastomotic leakage could be reduced through greater experience with this type of surgery.

In contrast, although McKeown esophagectomy requires subtotal esophagectomy and cervical incision, anastomotic leakage in McKeown esophagectomy results only in cervical abscess, which can be cured by drainage from the cervical incision site. Cases of anastomotic leakage after McKeown esophagectomy typically result in minor problems. In-hospital death during surgery should be avoided as much as possible. In light of this aspect, McKeown esophagectomy might be more favorable for surgery to treat esophagogastric junction cancer with esophageal invasion of more than 3 cm when the surgical team is not well experienced in Ivor Lewis esophagectomy.

The current study has the following limitations. First, the analysis was based on retrospective data from a single institution during a long time period. Because of the small number of patients included, we were obliged to add patients with thoracic esophageal cancer who underwent Ivor Lewis esophagectomy or McKeown esophagectomy to confirm our results. In addition, because no patients with esophagogastric junction cancer underwent esophagectomy with cervical anastomosis via posterior mediastinal route reconstruction, we were obliged to add patients with thoracic esophageal cancer who underwent this reconstruction to establish a control group to clarify whether the difference in reflux esophagitis score was due to the level of anastomosis or the difference in reconstruction route. Therefore, the finding of this study that reflux esophagitis was more severe in patients with esophagogastric junction cancer who underwent Ivor Lewis esophagectomy compared with those who underwent McKeown esophagectomy because of the level of anastomosis rather than the difference of reconstruction route, is not conclusive. Second, whether patients took a gastric acid secretion inhibitor, such as a proton pump inhibitor or H2 receptor antagonist, depended on the discretion of doctors in the outpatient clinic. Third, not all patients underwent annual endoscopic follow-up every year because some patients died within 3 years after surgery. Fourth, *Helicobacter* infection was not investigated in this study. Well-designed, multicenter randomized controlled trials comparing Ivor Lewis esophagectomy and McKeown esophagectomy via retrosternal route for esophagogastric junction cancer should be performed to overcome these limitations.

In conclusion, the degree of reflux esophagitis may be greater in patients with esophagogastric junction cancer treated by Ivor Lewis esophagectomy compared with those treated by McKeown esophagectomy. McKeown esophagectomy might be a more suitable procedure for esophagogastric junction cancer with extended esophageal invasion. A prospective randomized trial is needed to confirm the superior surgery in terms of comprehensive quality of life indicators, including reflux esophagitis.

Acknowledgments

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