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ORIGINAL ARTICLE

Postoperative complications after a transthoracic esophagectomy or a transhiatal gastrectomy in patients with esophagogastric junctional cancers: a prospective nationwide multicenter study

Shinji Mine[1,10] · Yukinori Kurokawa[2] · Hiroya Takeuchi[3] · Masanori Terashima[4] · Takushi Yasuda[5] · Kazuhiro Yoshida[6] · Hiroshi Yabusaki[7] · Yasuhiro Shirakawa[8] · Kazumasa Fujitani[9] · Takeshi Sano[10] · Yuichiro Doki[2] · Yuko Kitagawa[11]

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Abstract

Background Esophagogastric junction (EGJ) cancers are resected thorough esophagectomy or gastrectomy, with the incidence of postoperative complications influenced by the chosen procedure.

Methods In this prospective nationwide multicenter study, patients with cT2–T4 EGJ cancers were enrolled before surgery. Based on the protocol, surgeons performed a transthoracic esophagectomy (TTE) or a transhiatal gastrectomy (THG) and dissected all lymph nodes prespecified as the standardized procedure. Postoperative complications were correlated with the clinical factors in each procedure.

Results A total of 345 patients were eligible for this study. TTE and THG were performed in 120 and 225 patients, respectively. Complications of Clavien-Dindo ≥ Grade II were found in 115/345 (33.3%) patients. Recurrent laryngeal nerve palsy was found only in the TTE group ($p < 0.001$). The incidence of other complications was not significantly different between the two groups. High body mass index (BMI) in the TTE group, male sex, and longer esophageal invasion in the THG group were significantly correlated with complications ≥ Grade II ($p = 0.049$, 0.037, and 0.019, respectively). Anastomotic leakage was most frequently observed (12.2%). Tumor size in the THG group ($p = 0.02$) was significantly associated with leakage. All six patients with ≥ Grade IV leakage underwent THG, whereas, none of the patients in the TTE group had leakage ≥ Grade IV (2.7% vs. 0%, $p = 0.096$).

Conclusions Surgical resection should be performed with utmost care, particularly in patients with a high BMI undergoing TTE, and in patients with larger tumors, longer esophageal invasion, or male patients undergoing THG.

Keywords Esophagogastric junction · Adenocarcinoma · Squamous cell carcinoma · Postoperative complications · Anastomotic leakage

✉ Shinji Mine
mineshinji921@gmail.com

[1] Department of Esophageal and Gastroenterological Surgery, Juntendo University Hospital, 3-1-3, Hongo, Bunkyo-ku, Tokyo 113-8431, Japan

[2] Department of Gastroenterological Surgery, Osaka University Graduate School of Medicine, Osaka, Japan

[3] Department of Surgery, Hamamatsu University School of Medicine, Hamamatsu, Japan

[4] Division of Gastric Surgery, Shizuoka Cancer Center, Nagaizumi, Japan

[5] Department of Surgery, Faculty of Medicine, Kindai University, Osaka, Japan

[6] Department of Gastroenterological and Pediatric Surgery, Gifu University School of Medicine, Gifu, Japan

[7] Department of Gastroenterological Surgery, Niigata Cancer Center Hospital, Niigata, Japan

[8] Department of Gastroenterological Surgery, Graduate School of Medicine, Dentistry and Pharmaceutical Science, Okayama University, Okayama, Japan

[9] Department of Surgery, Osaka General Medical Center, Osaka, Japan

[10] Department of Gastroenterological Surgery, Cancer Institute Hospital, Tokyo, Japan

[11] Department of Surgery, Keio University School of Medicine, Tokyo, Japan

Introduction

The incidence of esophagogastric junction (EGJ) cancers, especially adenocarcinoma, has dramatically increased in the last two decades [1]. This trend is remarkable in Western countries, and the same trend is expected in Japan in the near future owing to the spread of obesity and rapid decrease of *Helicobacter pylori* stomach infection.

The mainstay of EGJ cancer treatment is surgical resection, even in the era of multidisciplinary treatments [2]. However, the appropriate extent of or the proper approach to resection remain unclear, especially for true cardiac tumors or Siewert type II tumors [3–7]. Thus, various approaches and extents of resections have been applied for EGJ cancers, and these differences could lead to differences in the incidence of postoperative morbidities. A previous randomized clinical trial that compared transthoracic esophagectomy with transhiatal esophagectomy in the Netherlands showed that transthoracic esophagectomy was significantly associated with a higher incidence of pulmonary complications, as well as longer durations of ventilation and ICU, and hospital stays [8]. Another randomized clinical trial that compared left thoracoabdominal total gastrectomy with transhiatal total gastrectomy in Japan demonstrated that bronchoscopic tracheal toileting was performed more frequently among the patients who undergone the left thoracoabdominal approach [7]. Nevertheless, no prospective study has compared transthoracic esophagectomy with transhiatal gastrectomy for EGJ cancer to date.

Recently, we performed a nationwide multicenter prospective study by standardizing a surgical protocol to evaluate the incidence of nodal metastasis in each nodal station of EGJ cancers in Japan [9]. Using data from this prospective study, we aimed to analyze the postoperative morbidity correlated with the types of surgical approaches or clinical factors.

Methods

This study was performed using data from our previous multicenter prospective study [9], in which the primary endpoint was the incidence of nodal metastasis in each nodal station for EGJ cancers. The secondary endpoints were R0 resection rate, survival, and postoperative complications.

Ethics

This prospective study was approved by the review boards of each participating institution. Written informed consent was obtained from all the patients enrolled in this study. This study was registered with UMIN-CTR (number UMIN000013205).

Eligibility criteria

The eligibility criteria were as follows: (1) tumor epicenter located within 2.0 cm of the EGJ; (2) histologically proven adenocarcinoma, squamous cell carcinoma (SCC), or adenosquamous carcinoma; (3) cT2–T4; (4) tumor deemed to be resectable; (5) patient age ≥ 20 years; (6) Eastern Cooperative Oncology Group performance status of 0, 1, or 2; (7) no prior history of gastrectomy; (8) adequate organ function; and (9) provision of written informed consent. The location of the EGJ was defined as the lower margin of palisading small vessels on endoscopy according to the Japanese Classification of Esophageal Cancer (11th edition) [10]. In addition, the patients who could not undergo the surgical treatment specified in the protocol were excluded from this study regarding postoperative complications.

Neo-adjuvant and adjuvant treatments were not specified, and all treatment regimens were acceptable in this study.

Surgical protocols

The surgical protocols used in this study are shown in Fig. 1. If EGJ cancer was adenocarcinoma with esophageal invasion ≤ 3 cm and there was no clinical upper or middle mediastinal nodal metastasis, the patient underwent an gastrectomy via a transhiatal approach (transhiatal gastrectomy group). In this group, a proximal gastrectomy with a lower esophagectomy was acceptable, and D2 abdominal lymphadenectomy and lower mediastinal lymphadenectomy were performed in all patients. If EGJ cancer was adenocarcinoma with esophageal invasion > 3 cm, or if a clinical upper or middle mediastinal nodal metastasis was detected,

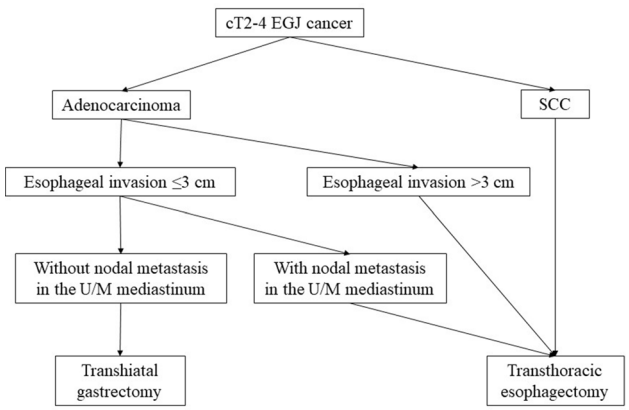

Fig. 1 Schema of the surgical protocol. *EGJ* esophagogastric junction, *SCC* squamous cell carcinoma, *U* upper, *M* middle

the patient underwent an esophagectomy via a transthoracic approach (transthoracic esophagectomy group). If the patient had SCC located at the EGJ, esophagectomy was also performed (transthoracic esophagectomy group). A transthoracic esophagectomy had to accompany lymphadenectomy of the upper, middle, lower mediastinal, and abdominal areas, but neck dissection was not indispensable. Both the McKeown procedure and the Ivor-Lewis procedures were acceptable. In addition, all patients in either the transthoracic esophagectomy or transhiatal gastrectomy groups underwent para-aortic lymphadenectomy above the left renal vein [11, 12]. In all cases, minimally invasive surgery (MIS) was chosen based on the surgeon's preference.

Accumulation of data

The TNM 7th edition was used for tumor classification [13]. Data on postoperative complications, which were determined in the protocol, were collected from the case report form. Postoperative complications were classified based on the Clavien-Dindo classifications [14].

Statistical analyses

All statistical analyses were performed using EZR version 1.54 (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R software (The R Foundation for Statistical Computing, Vienna, Austria) that incorporates frequently used biostatistical functions [15]. Differences in clinical factors between the groups were analyzed using Fisher's exact test for categorical variables or the Mann–Whitney *U* test for continuous variables. Differences were considered statistically significant at two-tailed p-values < 0.05.

Results

From April 2014 to September 2017, 363 eligible patients from 42 institutions, were enrolled in this trial. Five patients for whom surgical resection of tumors was considered intraoperatively unfeasible were excluded from this study. Moreover, one patient who underwent transhiatal esophagectomy, three patients who underwent gastrectomy via a left thoracoabdominal approach, and nine patients who underwent gastrectomy or proximal gastrectomy via a right thoracotomy were excluded. These 18 patients did not complete the treatment specified in the protocol; thus, they were excluded from this analysis. Finally, data on postoperative complications in 345 patients were analyzed (Fig. 2).

The patient characteristics are shown in Table 1. As this trial was not a randomized controlled trial, there were significant differences in characteristics between the transthoracic

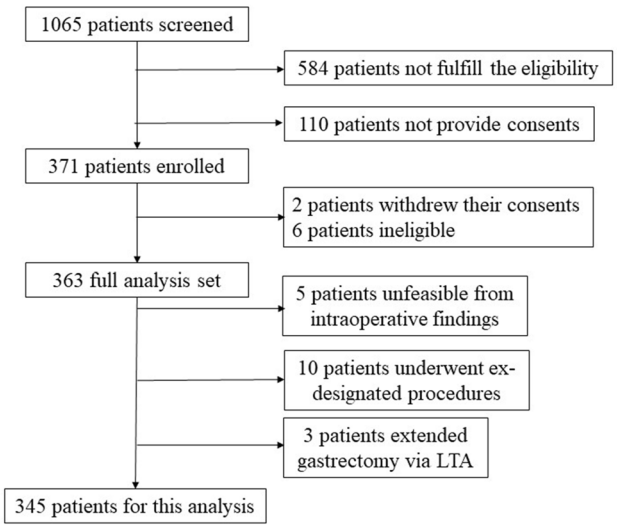

Fig. 2 Flow diagram of patients in this study. *LTA* left thoracoabdominal approach

esophagectomy and transhiatal gastrectomy groups. Patients in the transthoracic esophagectomy group were likely to be younger, with a high incidence of SCC, larger tumor sizes, longer esophageal invasions, and more neoadjuvant treatments. In addition, patients in the transthoracic esophagectomy group tended to have cStage III–IV, although these differences were not statistically significant.

Regarding surgical procedures, patients in the transthoraic esophagectomy group were likely to have longer operations. In the transhiatal gastrectomy group, more than 70% of the patients underwent total gastrectomy; whereas, the remaining 59 (26.2%) underwent proximal gastrectomy. In the transthoracic esophagectomy group, 44.1% of the patients underwent hybrid minimally invasive esophagectomy (thoracoscopic and open abdominal procedures), whereas, only 9.3% of the patients in the transhiatal gastrectomy group underwent laparoscopic procedures, probably because lymphadenectomy around the left renal vein [11] area required advanced skills if performed laparoscopically (Table 1).

Details regarding post-operative complications are presented in Table 2. Postoperative complications with Clavien-Dindo $\geq$ Grade II were observed in 44/120 (36.7%) and in 71/225 (31.6%) patients in the transthoracic esophagectomy and transhiatal gastrectomy groups, respectively. Mortality rates were 2/120 (1.7%) and 1/225 (0.4%) in the transthoracic esophagectomy and transhiatal gastrectomy groups, respectively. Of all postoperative complications, anastomotic leakage occurred most frequently, observed in 15/120 (12.5%) and in 27/225 (12.0%) in the transthoracic esophagectomy and the transhiatal gastrectomy groups, respectively. Moreover, of all complications, recurrent laryngeal nerve palsy was significantly related to the type of procedure ($p < 0.001$), and the patients with this complication were found only in

Table 1 Patients' characteristics

	Transthoracic esophagectomy group $n=120$	Transhiatal gastrectomy group $n=225$	p value
Age (median, range)	64 (27–79)	67 (30–90)	0.0016
Sex (male/female)	97/23	180/45	0.89
BMI	23.7 (14.5–34.5)	22.5 (14.8–33.1)	0.27
Histology (adenocarcinoma/SCC)	89/31	225/0	< 0.001
Tumor size (mm, median, range)	50 (20–150)	40 (10–100)	< 0.001
Length of esophageal invasion (mm, median, range)	40 (5–100)	13 (− 8 to 30)	< 0.001
cTNM7th (I/II/III–IV)	12/28/80	44/46/135	0.069
Neoadjuvant (with/without)	78/42	38/187	< 0.001
Operation time (min, median, range)	539 (320–883)	323 (155–662)	< 0.001
Bleeding (ml, median, range)	355 (30–2168)	379 (10–3820)	0.37
Blood transfusion	8	22	0.42
Esophagectomy/extended TG/extended PG	120/0/0	0/166/59	< 0.001
Thoracic part (open/MIS)	47/73	–	–
Abdominal part (open/MIS)	96/24	204/21	0.007

BMI body mass index, *SCC* squamous cell carcinoma, *TG* total gastrectomy, *PG* proximal gastrectomy, *MIS* minimally invasive surgery

Table 2 Grading of postoperative complications*

Clavien-Dindo classification	Transthoracic esophagectomy group $n=120$	Transhiatal gastrectomy group $n=225$	p value
≥ Grade I	48 (40.0%)	75 (33.3%)	0.24
≥ Grade II	44 (36.7%)	71 (31.6%)	0.34
≥ Grade III	26 (21.7%)	42 (18.7%)	0.57
≥ Grade IV	8 (6.7%)	12 (5.3%)	0.63
Grade V	2 (1.7%)	1 (0.4%)	0.28
Any (≥ Grade I)			
Leak	15 (12.5%)	27 (12.0%)	0.87
Pneumonia	7 (5.8%)	8 (3.6%)	0.41
Abdominal abscess	2 (1.7%)	12 (5.3%)	0.15
Wound infection	5 (4.2%)	3 (1.3%)	0.13
Recurrent laryngeal nerve palsy	8 (6.7%)	0	< 0.001
Pancreatic fistula	0	6 (2.7%)	0.096
Respiratory failure	3 (2.5%)	2 (0.9%)	0.35
Pyothorax	0	4 (1.8%)	0.30

*Data are presented as *n* (%)

the transthoracic esophagectomy group. Pancreatic fistula occurred more frequently in the transhiatal gastrectomy group, although the difference with the esophagectomy group was not statistically significant ($p=0.096$). By contrast, pulmonary complications, including pneumonia, respiratory failure, and pyothorax, were not associated with the type of procedure ($p=0.41$, 0.35, and 0.3, respectively).

Next, we analyzed the correlation between clinical factors and the incidence of postoperative complications with Clavien-Dindo ≥ Grade II in both groups (Table 3). In this analysis, a patient having any complications (anastomotic leakage, pneumonia, abdominal abscess, wound infection, recurrent laryngeal nerve palsy, pancreatic fistula, respiratory failure, pyothorax, or other complications) with Clavien-Dindo ≥ Grade II was classified as having postoperative complications. In the transthoracic esophagectomy group, patients with complications of Clavien-Dindo ≥ Grade II were likely to have a high BMI ($p=0.049$). In the transhiatal gastrectomy group, male sex and a longer esophageal invasion were significantly associated with

Table 3 Relationships between any complications (≥Grade II) and clinical factors based on surgical approach*

	Any complications ≥ Grade II			
	Transthoracic esophagectomy	*p*	Transhiatal gastrectomy	*p*
	44/120 (36.7%)		71/225 (31.6%)	
Age (years)				
<65	20/61 (32.8%)	0.45	33/92 (35.9%)	0.31
≥65	24/59 (40.7%)		38/133 (28.6%)	
Sex				
Male	39/97 (40.2%)	0.15	65/180 (36.1%)	0.0037
Female	5/23 (21.7%)		6/45 (13.3%)	
BMI				
<18.5	2/12 (16.7%)	0.049	3/13 (23.1%)	0.83
18.5–25	23/71 (32.4%)		50/153 (32.7%)	
≥25	19/37 (51.4%)		18/59 (30.5%)	
Tumor size (mm)				
<45	16/42 (38.1%)	0.84	38/127 (29.9%)	0.57
≥45	28/78 (35.9%)		33/98 (33.7%)	
Length of esophageal invasion (mm)				
<20	2/10 (20.0%)	0.32	35/137 (25.5%)	0.019
≥20	42/110 (38.2%)		36/88 (40.9%)	
cStage				
I, II	11/40 (27.5%)	0.16	30/90 (30.0%)	0.66
III, IV	33/80 (41.3%)		41/135 (30.4%)	
Neo-adjuvant				
With	28/78 (35.9%)	0.84	12/38 (31.6%)	1
Without	16/42 (38.1%)		58/187 (31.6%)	
Any MIS				
With	26/77 (33.8%)	0.43	8/21 (38.1%)	0.62
Without	18/43 (41.9%)		63/204 (30.9%)	

BMI body mass index, *MIS* minimally invasive surgery

*Data are presented as *n* (%)

Table 4 Relationships between anastomotic leakage and clinical factors based on surgical approach*

	Anastomotic leakage ≥ Grade II			
	Transthoracic esophagectomy	*p*	Transhiatal gastrectomy	*p*
	15/120 (12.5%)		27/225 (12.0%)	
Age (years)				
<65	8/61 (13.1%)	1	11/92 (12.0%)	1
≥65	7/59 (11.9%)		16/133 (12.0%)	
Sex				
Male	15/97 (15.5%)	0.072	25/180 (13.9%)	0.12
Female	0/23 (0%)		2/45 (4.4%)	
BMI				
<18.5	0/12 (0%)	0.11	2/13 (15.4%)	0.72
18.5–25	7/71 (9.9%)		17/153 (11.1%)	
≥25	8/37 (21.6%)		8/59 (13.6%)	
Tumor size (mm)				
<45	5/42 (11.9%)	1	10/127 (7.9%)	0.038
≥45	10/78 (12.8%)		17/98 (17.3%)	
Length of esophageal invasion (mm)				
<20	0/10 (0%)	0.36	12/137 (8.8%)	0.091
≥20	15/110 (13.6%)		15/88 (17.0%)	
cStage				
I, II	2/40 (5.0%)	0.14	12/90 (13.3%)	0.68
III, IV	13/80 (16.3%)		15/135 (11.1%)	
Neo-adjuvant				
With	9/78 (11.5%)	0.77	3/38 (7.9%)	0.58
Without	6/42 (14.3%)		24/187 (12.8%)	
Any MIS				
With	10/77 (13.0%)	1	4/21 (19%)	0.29
Without	5/43 (11.6%)		23/204 (11.3%)	

BMI body mass index, *MIS* minimally invasive surgery

*Data are presented as *n* (%)

postoperative complications ≥ Grade II ($p = 0.0037$ and 0.019, respectively).

Finally, we examined anastomotic leakage because this was the most frequently observed among all complications. We focused on the associations between anastomotic leakage (≥Grade II) and clinical factors in both groups (Table 4). In the transhiatal gastrectomy group, larger tumors were correlated with more anastomotic leakage ($p = 0.038$). In addition, longer esophageal invasion was more likely to be related to leakage, although this finding was not statistically significant ($p = 0.091$). In the transthoracic esophagectomy group, a high BMI was likely to be associated with more anastomotic leakage (0% in low BMI, 9.9% in normal BMI, 21.6% in high BMI group); however, this trend was not statistically significant ($p = 0.11$). In addition, it is surprising that all six patients with leakage of Clavien-Dindo ≥ Grade IV underwent transhiatal gastrectomy, and none of the patients in the transthoracic esophagectomy group had anastomotic leakage ≥ Grade IV (2.7% vs. 0%, $p = 0.096$). Furthermore, it is noteworthy that patients in the transhiatal gastrectomy group who underwent MIS had a high incidence of anastomotic leakage (4/21, 19.0%), although this correlation was not statistically significant and was based on very limited data.

Discussion

In this study, we evaluated postoperative complications using data from a prospective multicenter study on EGJ cancers. We showed that transthoracic esophagectomy or transhiatal gastrectomy for EGJ cancers could be performed safely, with the in-hospital mortality rate only being 0.9% even when lymphadenectomy around the left renal vein area was performed. However, postoperative complications with

Clavien-Dindo ≥ Grade II were observed in 115 (33.3%) patients in this cohort, which was relatively high. Thus, we aimed to define clinical factors related to postoperative complications.

Because this was a prospective study and not a randomized controlled trial, the transthoracic esophagectomy and transhiatal gastrectomy groups had a significant difference in terms of patient backgrounds. The influences of these different backgrounds are complicated. The transhiatal gastrectomy group tended to be older and undergo less minimally invasive surgery, factors that might increase the incidence of postoperative complications. On the other hand, that group tended to have smaller tumors, less neoadjuvant treatment, and a shorter operation time, factors that might decrease the incidence of postoperative complications. Despite these differences however, the incidence of each complication was mostly comparable, except for recurrent laryngeal nerve palsy and pancreatic fistula. Recurrent laryngeal nerve palsy is thought to be strongly related to lymphadenectomy around the recurrent laryngeal nerve, and all patients with this complication underwent transthoracic esophagectomy. Pancreatic fistula is one of the most frequent complications in gastrectomy [16]. In addition, when complications were stratified based on grade, the incidence of complications according to each grade was also comparable between both groups in this cohort. Postoperative complications are considered more common with transthoracic esophagectomy than transhiatal gastrectomy. However, according to previous randomized controlled studies of the Japanese Clinical Oncology Group (JCOG), the incidence of the postoperative complications was 34% in both transthoracic esophagectomy (JCOG 9907) [17] and transhiatal gastrectomy (JCOG 9502) [7]. Although these two studies had different aims, patients, periods, and perioperative treatments, the incidence of postoperative complications in esophagectomy and transhiatal gastrectomy might be similar in Japan. Our study also showed that high BMI was related to postoperative complications only in the esophagectomy group and not in the gastrectomy group. The actual incidence of postoperative complications in the high BMI group that underwent esophagectomy was 51.4%, which was relatively high. However, relatively few Japanese patients have high BMI; therefore, we considered that BMI did not affect the results significantly and the incidences of complications in both groups might be comparable.

Based on the analyses of correlations between clinical factors and postoperative complications (≥ Grade II), male sex, longer esophageal invasion in the transhiatal gastrectomy group, and high BMI in the transthoracic esophagectomy group were related to postoperative complications. Previous studies have demonstrated that male sex is significantly associated with postoperative complications [18, 19]. Regarding the length of esophageal invasion, a significant correlation with complications was found only in the transhiatal gastrectomy group ($p = 0.002$) but not in the transthoracic esophagectomy group ($p = 0.68$). It is suggested that a longer esophageal invasion could cause technical difficulties in the transhiatal procedure, which were found only in the transhiatal gastrectomy group. Additionally, previous studies have shown that patients with a high BMI are likely to have a higher incidence of postoperative complications after esophagectomy [20, 21]. On the other hand, a high BMI was not related to a higher incidence of postoperative complications in gastrectomy according to several previous studies [22, 23].

According to our analyses of anastomotic leakage, a high BMI was likely to be associated with leakage in the transthoracic esophagectomy group (however, this is of no statistical significance; $p = 0.11$). A high BMI is thought to be a risk factor for postoperative complications, as described above [20, 21]. Larger tumors among patients in the transhiatal gastrectomy group were significantly related to leakage, and longer esophageal invasion was likely to be associated with anastomotic leakage (however, this finding is of no statistical significance; $p = 0.056$). In cases of transhiatal gastrectomy, anastomotic procedures are speculated to become technically more difficult if esophagojejunostomy is performed at a higher site. Tumor size was also significantly associated with the length of esophageal invasion ($r = 0.647$, $p < 0.001$; data not shown), and larger tumors might cause technically challenging anastomoses. In addition, we note the relatively high incidence of leakage among patients who have undergone minimally invasive transhiatal gastrectomy (4/21, 19.0%). We speculated that this could also be attributed to technical difficulties associated with anastomoses under MIS. In this study, since lymphadenectomy around the left renal vein area was necessary, less than 10% of the patients underwent transhiatal gastrectomy under MIS. In other words, only experts who had high confidence in their own MIS skills have performed this anastomosis. Although data are very limited, this incidence is particularly high and more improvements in anastomotic procedure are inevitable.

It is worth noting that all six patients with anastomotic leakage of Clavien-Dindo ≥ Grade IV underwent transhiatal gastrectomy, whereas no patient in the transthoracic esophagectomy group had anastomotic leakage ≥ Grade IV. One reason for the low number of severe complications from leakage in the transthoracic esophagectomy group is that cervical anastomosis was more common than Ivor-Lewis esophagogastrostomy in Japan (cervical anastomosis: 57.9% vs. intrathoracic anastomosis: 38.0%, from the Japanese national database) [24]. Unfortunately, we do not have data on the anastomotic site (cervical vs. intrathoracic anastomosis) in this study because this specific information was lacking in the protocol. Nevertheless, when anastomotic leakage occurs in the thorax, it is not clear whether esophagogastrostomy

or esophagojejunostomy could lead to more critical conditions among the patients, and there are few reports comparing intrathoracic esophagogastric leakage with intrathoracic esophagojejunal leakage. Hoeppner et al. reported that all six patients in their study who had intrathoracic esophagogastric anastomotic leakage survived, whereas, two out of 10 patients who had intrathoracic esophagojejunal anastomotic leakage did not survive with a self-expanding stent treatment [25].

In the present study, the rate of anastomotic leakage in the transhiatal gastrectomy group (11.8%) was higher than that reported in a previous Japanese randomized controlled trial (8%, JCOG9502) [7]. Because approximately 20 years passed between the former and present studies, the rates of postoperative complications for the same operation should naturally be reduced. We speculate that the high rate of leakage could be attributed to the difference in patient selection between these two studies. Since the former JCOG9502 study was a randomized controlled trial, the eligibility criteria were stricter than those of the present study; for instance, patients aged > 75 years, poor pulmonary function, past history of myocardial infarction, and other cancer treatment for 10 years were excluded from the former study. As a result, we believe that our current study included a wider range of patients, and our results would be more similar to those in the real world [26]. Moreover, the patients in the transhiatal gastrectomy group in the current study were likely to have a longer esophageal invasion (median 15 mm vs. 12 mm) and a higher tendency to be men (80.3% vs. 74.1%), in contrast to those in the former study.

This study has several limitations. First, this was a prospective, and not a randomized controlled study. Second, the information available to us in the case report forms was limited. For instance, data including the site or route of anastomosis or patients' preoperative comorbidities were not available.

In conclusion, for patients with EGJ cancers, both transhiatal gastrectomy and transthoracic esophagectomy could be performed safely even when lymphadenectomy around the left renal vein area was performed. However, over 30% of the patients in our cohort had postoperative but non-fatal complications (≥ Grade II). Male sex and a longer esophageal invasion in the transhiatal gastrectomy group, as well as a high BMI in the transthoracic esophagectomy group were significantly correlated with postoperative complications. Of all complications, anastomotic leakages were the most common and were observed more frequently than expected. Therefore, we should perform anastomoses with utmost care in obese patients undergoing transthoracic esophagectomy, and in patients with larger tumors undergoing transhiatal gastrectomy. In addition, a transhiatal esophagojejunostomy should be performed very carefully because leakage from the anastomosis can lead to a critical condition.

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Declarations

Conflict of interest The authors declare no conflict of interest regarding this study.

Ethical approval This prospective study was approved by the review boards of each participating institution. Written informed consent was obtained from all the patients enrolled in this study.

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