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Review Article

Surgical and Perioperative Treatments for Esophagogastric Junction Cancer

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Esophagogastric junction cancer (EGJC) is a rare malignant disease that occurs in the gastroesophageal transition zone. In recent years, its incidence has been rapidly increasing not only in Western countries but also in East Asia, and it has been attracting the attention of both clinicians and researchers. EGJC has a worse prognosis than gastric cancer (GC) and is characterized by complex lymphatic drainage pathways in the mediastinal and abdominal regions. EGJC was previously treated in the same way as GC or esophageal cancer, but, in recent years, it has been treated as an independent malignant disease, and treatment focusing only on EGJC has been developed. A recent multicenter prospective study revealed the frequency of lymph node metastasis by station and established the optimal extent of lymph node dissection. In perioperative treatment, the combination of multi-drug chemotherapy, radiation therapy, molecular targeted therapy, and immunotherapy is expected to improve the prognosis. In this review, we summarize previous clinical trials and their important evidence on surgical and perioperative treatments for EGJC.

Keywords: esophagogastric junction cancer, lymphatic flow, surgery, perioperative treatment, minimally invasive surgery

Introduction

The incidence of esophagogastric junction cancer (EGJC) has been increasing rapidly in Western countries.[1–3] Its incidence in East Asia has also been increasing, which is associated with the decreasing prevalence of *Helicobacter pylori* infection.[4–7] EGJC is associated with several risk factors, including smoking, obesity, and gastroesophageal reflux disease. Barrett's epithelium is considered a premalignant lesion.[8–10] However, accurate statistical surveys are difficult because the definition of EGJC varies between countries and has evolved over time. EGJC in the West is defined as adenocarcinoma with the epicenter within 5 cm of the esophagogastric junction (EGJ).[1] The Siewert classification is used to classify EGJC into three categories based on the location of the epicenter.[11] Siewert type I tumors are located between 1 and 5 cm above the EGJ and are generally treated like esophageal cancer (EC). Siewert type II tumors are located 1 cm above to 2 cm below the EGJ and are recognized as "true EGJC." Siewert type III tumors represent subcardial gastric adenocarcinoma located 2–5 cm below the EGJ with invasion into the distal esophagus and are generally treated similarly to gastric cancer (GC). In Japan, when the epicenter of a tumor is located within 2 cm proximal or distal to the EGJ, it is

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designated as EGJC according to the Nishi classification, regardless of histological type.[12,13] Recently, an international consensus conference was held in Kyoto, Japan, and a new concept of EGJC has been proposed to define it as adenocarcinoma with a tumor epicenter within 1 cm from the EGJ.[14] Although surgery is currently the standard treatment for EGJC, there is no consensus on the optimal surgical approach, the extent of esophageal or gastric resection, or the range of lymph node dissection, the last of these due to the complex lymphatic flow and anatomical features of this region.[10] EGJC is recognized as a malignant disease with a poor prognosis that is a separate entity from both GC and EC.[15,16] However, since the incidence of EGJC is low, it is treated the same way as GC or EC. This narrative review focuses on clinical trials related to surgical and perioperative treatments for EGJC and introduces currently ongoing clinical trials for which details are available.

Surgical Treatment for EGJC

Frequency of lymph node metastasis

EGJC arises at the boundary between the esophagus and stomach, resulting in complex lymphatic flow in the mediastinal and abdominal regions.[17] Several studies examined lymphatic flow in EGJC but were retrospective in nature and were influenced by selection bias; the optimal lymph node dissection area for EGJC has not been clarified.[15,18–20] Total gastrectomy with lower esophagectomy was found to be preferred by gastric surgeons, while subtotal esophagectomy with upper gastrectomy was preferred by thoracic surgeons. This preference made it difficult to accurately assess the frequency of lymph node metastasis (**Tables 1** and **2**).

In a retrospective study by Siewert et al. regarding lymph node metastasis in 1002 patients with Siewert type I/II/III EGJC, extended total gastrectomy with transhiatal resection of the lower esophagus was performed for Siewert type II EGJC.[19] Among 271 Siewert type II EGJC patients, lymph node metastasis was observed in 186 patients, and the frequency of metastasis to the lower mediastinal lymph nodes was 15.6%. Pedrazzani et al. conducted a similar analysis on 143 patients with Siewert type I/II/III EGJC deeper than pT2. They showed that 44 of the 62 patients with Siewert type II EGJC had lymph node metastasis.[20] The frequency of lymph node metastasis in the lower mediastinum was 5.0%–12.9%, while that in the middle mediastinum was 1.6%–5.0%. The highest frequency of lymph node metastasis was 12.9% at station No. 110. According to a retrospective study in 315 patients with Siewert type II EGJC deeper than pT2, the frequencies of lymph node metastasis in the upper, middle, and lower mediastinal regions were 3.8%, 7.0%, and 11.4%, respectively.[15] A nationwide retrospective study in Japan was conducted in 2807 patients with EGJC defined by the Nishi classification (an epicenter within 2 cm proximal or distal to the EGJ), and in which the tumor diameter was less than 4 cm; the prevalence of adenocarcinoma was found to be 84.9%, while that of squamous cell carcinoma was 13.1%.[18] The frequencies of lymph node metastasis in the upper, middle, and lower mediastinal regions were at most 5.1%, 4.0%, and 11.9%, respectively, with the highest frequency at station No. 110. Similar retrospective studies were conducted, and its results suggested that the frequency of lymph node metastasis in EGJC was highest in the lower mediastinum.[21]

The above retrospective studies also examined abdominal lymphatic flow. The regions with a high frequency of lymph node metastasis were the paracardial (Nos. 1, 2), lesser curvature (No. 3), and left gastric artery and supra-pancreas (Nos. 7, 8a, 9, 11p).[18–21] On the other hand, there was a low frequency of metastasis to the greater curvature or pyloric lymph nodes (Nos. 4sa, 4sb, 4d, 5, 6).

A multicenter prospective study conducted in collaboration with the Japanese Gastric Cancer Association (JGCA) and the Japan Esophageal Society (JES) investigated the frequency of lymph node metastasis in 371 cases of cT2–4 EGJC defined by the Nishi classification.[22] The frequencies of metastasis in the lower, middle, and upper mediastinal lymph nodes were 13.3%, 7.1%, and 6.1%, respectively. When the length of esophageal involvement exceeds 2.0 cm or 4.0 cm, the metastasis rate in lower mediastinal station No. 110 or upper mediastinal station No. 106recR, respectively, is above 10%; in such cases, the frequency of lymph node metastasis in the mediastinal lymph nodes increases with the length of esophageal involvement. Based on these results, a treatment algorithm for EGJC was published in the latest Japanese Gastric Cancer Treatment Guidelines and the Esophageal Cancer Practice guidelines from JGCA and JES.[23,24] The algorithm recommends either the right transthoracic or transhiatal surgical approach based on the length of esophageal involvement and also specifies the minimum stations of lymph node dissection required. This prospective study also analyzed lymph node metastasis in the abdominal region and showed

Table 1 Frequency of mediastinal and abdominal lymph node metastasis in patients with EGJC

	Siewert[19]	Pedrazzani[20]	Kurokawa[15]	Yoshikawa[21]	Yamashita[18]
Year	2000	2007	2015	2016	2017
Number of patients	271	62	315	381	2807
Definition of EGJC	Siewert type II	Siewert type II	Siewert type II	Siewert type II	Nishi
Eligibility	pT1–4	pT2–4	pT2–4	pT1–4	pT1–4 & tumor size ≤4 cm
Histological type					
SCC	0	0	0	0	13.2
AC	100	100	100	100	84.9
Other	0	0	0	0	1.9
Tumor size, mm	NA	NA	55 (8–100)	50 (10–180)	25 (16,39)
Preoperative treatment	22.6	0	14.0	10.8	0
T status					
T1	14.0	0	0	20.7	56.6
T2	57.2	51.6	18.1	14.7	19.2
T3	20.3	46.8	45.1	36.0	24.1
T4	8.5	1.6	36.8	28.6	
N status					
N0	31.4	29.0	23.8	35.7	69.5
N1	29.5		21.6	20.7	16.7
N2	22.5	71.0	27.6	22.6	9.0
N3	16.6		27.0	21.0	4.8
M status					
M0	83.8	100	100	93.2	100
M1	16.2	0	0	6.8	0
Esophagectomy					
Total/subtotal	NA	NA	7.0	7.1	NA
Lower/abdominal	Predominated	NA	93.0	92.9	NA
Gastrectomy					
Total	NA	NA	77.1	69.3	NA
Proximal/upper	NA	NA	22.9	30.7	NA
Upper mediastinal nodes	NA	NA	3.8		0–5.1
No. 105					0–1.1
No. 106recL					
No. 106recR					0–5.1
No. 106tb					0
Middle mediastinal nodes	NA		7.0		0–4.0
No. 107		1.6			0–1.7
No. 108		<5.0			0.8–4.0
No. 109					0–2.8
N0. 109L					
No. 109R					
Lower mediastinal nodes	15.6		11.4		0.3–11.9
No. 110		12.9			0.5–11.9
No. 111		5.0–10.0			0.3–3.4
No. 112		5.0–10.0			0–2.3
Abdominal nodes					
No. 1	56.9	~50		39.8	35.2
No. 2	67.8	≥30		30.8	27.1
No. 3	67.8	≥50		41.5	38
No. 4	16.1				

(Continued)

Table 1 (Continued)

	Siewert[19]	Pedrazzani[20]	Kurokawa[15]	Yoshikawa[21]	Yamashita[18]
No. 4sa		<5.0		4.3	4.2
No. 4sb				2.7	0.8
No. 4d		5.0–10.0		2.9	2.2
No. 5	1.4	<5.0		1.7	1.1
No. 6		<5.0		0.8	1.7
No. 7	15.1	30.6		26.7	23.5
No. 8a		15.0–20.0		4.9	7.1
No. 9	7	15.0–20.0		11.7	12.4
No. 10		~5		9.5	
No. 11	4.8	5.0–10.0			
No. 11p				17.2	13.6
No. 11d				6.3	4.3
No. 12	4.8	0.0		1.4	
No. 16a1		<5.0			
No. 16a2				14.4	4.7
No. 19				6.3	5.4
No. 20				0.0	4.8

Values are median (range) or [25%, 75% quartile]
EGJC: esophagogastric junction cancer; AC: adenocarcinoma; SCC: squamous cell carcinoma; NA: not available

metastasis frequencies at station Nos. 4sa, 4sb, 4d, 5, and 6 were less than 5%. This suggests that dissection of these lymph nodes can be omitted for EGJC; therefore, proximal gastrectomy is sufficient, and total gastrectomy is unnecessary. However, when the tumor size exceeded 6.0 cm, the lymph node metastasis rates were found to be above 10% for perigastric station Nos. 4d, 5, and 6. Therefore, total gastrectomy might be considered for large EGJC tumor sizes. A prospective study examined the risk of para-aortic lymph node metastasis in 344 patients who underwent lymphadenectomy at station No. 16a2lat.[25] Lymph node metastases at station Nos. 2 and 7 were independent risk factors for renal vein periphery lymph node (No. 16a2lat) metastasis. Furthermore, when there were metastases at both station Nos. 2 and 7, the metastasis rate at station No. 16a2lat was 23.7%. In this study, neoadjuvant treatment, which may have influenced the lymph node status, was administered to approximately one-third of the patients. Moreover, the lymph node dissection area was tentatively recommended based on the frequency of lymph node metastasis; however, long-term prognostic results were unavailable and the prognostic contribution of dissecting these lymph nodes remains unclear. In the future, it is necessary to evaluate the therapeutic index, including long-term prognosis. Recently, the TIGER study, an international observational cohort study, is ongoing to evaluate the distribution of lymph node metastases in patients with resectable (cT1-4a, N0–3, M0) squamous cell or adenocarcinoma of EC or EGJC. These results are expected to strengthen the evidence related to lymphatic flow in EGJC and contribute to developing consensus between the East and West countries.[26]

Surgical approach

Two important randomized controlled trials (RCTs) from the Netherlands and Japan examined the surgical approach for EGJC (**Table 3**). The Dutch trial compared the right transthoracic approach with the transhiatal approach for Siewert type I or II EGJC.[27–29] Postoperative respiratory complications were significantly higher with the right transthoracic approach than the transhiatal approach (57% vs. 27%, respectively, P <0.001), and the in-hospital mortality was also higher, although non-significantly, with the right transthoracic approach (4% vs. 2%, respectively, P = 0.45). The 5-year survival rate was comparable in both groups (34% vs. 36%, respectively, P = 0.71). In Siewert type I EGJC, the 5-year survival rate was higher with the right transthoracic approach than with the transhiatal approach, but the difference was not significant (51% vs. 37%, respectively). On the other hand, in Siewert type II, EGJC, there was no difference between the two approaches (27% vs. 31%, respectively).

The JCOG9502 trial compared the left thoracoabdominal approach and the abdominal transhiatal approach for

Table 2 Correspondence between JES, JGCA, and AJCC classification system

JGCA and JES[23,24]		AJCC 8th edition for esophagus and esophagogastric junction[57]	
Number of LN station	Definitions of LN station	Number of LN station	Definitions of LN station
Cervical LNs			
100	Superficial LNs of the neck		
100spf	Superficial cervical LNs		
100sm	Submandibular LNs		
100tr	Cervical pretracheal LNs		
100ac	Accessory nerve LNs		
101	Cervical paraesophageal LNs	1R/1L	Right and left lower cervical paratracheal LNs
102	Deep cervical LNs		
102up	Upper deep cervical LNs		
102mid	Middle deep cervical LNs		
103	Peripharyngeal LNs		
104	Supraclavicular LNs		
Mediastinal LNs			
Upper mediastinal			
105	Upper thoracic paraesophageal LNs	8U	Upper thoracic paraesophageal LNs
106	Thoracic paratracheal LNs		
106rec	Recurrent nerve LNs		
106recL	Left recurrent nerve LNs	2L	Left upper paratracheal LNs
106recR	Right recurrent nerve LNs	2R	Right upper paratracheal LNs
106pre	Pretracheal LNs	4R	Right lower paratracheal LNs
106tb	Tracheobronchial LNs		
106tbL	Left tracheobronchial LNs	4L	Left lower paratracheal LNs
106tbR	Right tracheobronchial LNs	4R	Right lower paratracheal LNs
Middle mediastinal			
107	Subcarinal LNs	7	Subcarinal LNs
108	Middle thoracic paraesophageal LNs	8M	Middle thoracic paraesophageal LNs
109	Main bronchus LNs	7	Subcarinal LNs
Lower mediastinal			
110	Lower thoracic paraesophageal LNs	8Lo	Lower thoracic paraesophageal LNs
111	Supradiaphragmatic LNs	15	Diaphragmatic LNs
112	Posterior mediastinal LNs		
112aoA	Anterior thoracic para-aortic LNs	8M/8Lo	Middle thoracic paraesophageal LNs and Lower thoracic paraesophageal LNs
112aoP	Posterior thoracic para-aortic LNs	8M/8Lo	Middle thoracic paraesophageal LNs and Lower thoracic paraesophageal LNs
112pul	Pulmonary ligament LNs	9R/9L	Pulmonary ligament LNs
113	Ligamentum arteriosum LNs (Botallo's LNs)		
114	Anterior mediastinal LNs		
Abdominal LNs			
1	Right paracardial LNs	16	Paracardial LNs
2	Left paracardial LNs	16	Paracardial LNs
3a	Lesser curvature LNs along the branches of the left gastric artery	17	Left gastric LNs
3b	Lesser curvature LNs along the 2nd branches and distal part of the right gastric artery		
4sa	LNs along the short gastric vessels		

(Continued)

Table 2 (Continued)

JGCA and JES[23,24]		AJCC 8th edition for esophagus and esophagogastric junction[57]	
Number of LN station	Definitions of LN station	Number of LN station	Definitions of LN station
4sb	LNs along the left gastroepiploic artery		
4d	LNs along the right gastroepiploic artery		
5	Suprapyloric LNs		
6	Infrapyloric LNs		
7	LNs along the left gastric artery	17	Left gastric LNs
8a	LNs along the common hepatic artery (Anterosuperior group)	18	Common hepatic LNs
8p	LNs along the common hepatic artery (Posterior group)	18	Common hepatic LNs
9	LNs along the celiac artery	20	Celiac LNs
10	LNs at the splenic hilum		
11p	LNs along the proximal splenic artery	19	Splenic LNs
11d	LNs along the distal splenic artery		
12	LNs in the hepatoduodenal ligament		
13	LNs on the posterior surface of the pancreatic head		
14a	LNs along the superior mesenteric artery		
14v	LNs along the superior mesenteric vein		
15	LNs along the middle colic artery		
16a1	LNs in the aortic hiatus		
16a2	LNs around the abdominal aorta (from the upper margin of the celiac trunk to the lower margin of the left renal vein)		
16b1	LNs around the abdominal aorta (from the lower margin of the left renal vein to the upper margin of the inferior mesenteric artery)		
16b2	LNs around the abdominal aorta (from the upper margin of the inferior mesenteric artery to the aortic bifurcation)		
17	LNs on the anterior surface of the pancreatic head		
18	LNs along the inferior margin of the pancreas		
19	Infradiaphragmatic LNs	16	Paracardial LNs
20	LNs in the esophageal hiatus of the diaphragm	16	Paracardial LNs

JGCA: the Japanese Gastric Cancer Association; JES: the Japan Esophageal Society; AJCC: American Joint Committee on Cancer; LN: lymph node

adenocarcinoma of the EGJ or gastric cardia in both cases with esophageal invasion of 3 cm or less.[30] In two other RCTs, the left thoracoabdominal approach was associated with a higher incidence of postoperative respiratory complications, worse quality of life, and worse 5-year overall survival (OS) rate (51% vs. 37%, respectively, P = 0.060) than the abdominal approach.[31,32] The 5-year OS rate for Siewert type II EGJC was similar between the left thoracoabdominal approach and the transhiatal approach (42% vs. 50%, respectively, hazard ratio [HR] 1.19, 95% confidence interval (CI) 0.72–1.95, P = 0.50), but for Siewert type III EGJC, the left thoracoabdominal approach was associated with a lower 5-year OS rate (36% vs. 59%, respectively, HR 1.67, 95% CI 0.90–3.11, P = 0.10). Based on the results of these two RCTs, the right transthoracic approach is recommended for Siewert type I EGJC, while the transhiatal approach is recommended for Siewert II/III type EGJC with esophageal invasion less than 3 cm.

Table 3 Randomized controlled trials regarding the surgical approach for EGJC

	Dutch trial[27–29]	JCOG9502[30–32]
Country	Netherlands	Japan
Eligibility	Siewert type I/II EGJC	Siewert type II/III EGJC with esophageal involvement ≤3 cm
Number of patients	220	167
Surgical approach	Transhiatal vs. right transthoracic	Abdominal-transhiatal vs. left thoracoabdominal
Tumor location		
Siewert type I	43.9%	0
Siewert type II	56.1%	57.6%
Siewert type III	0	38.2%
Stomach	0	4.2%
Histological type		
AC	96.1%	100%
Other	3.9%	0
Type of gastrectomy		
Proximal	92.2%	3.6%
Total gastrectomy	1.4%	95.2%
Unresected	6.4%	1.2%
R0 resection	71.6% vs. 71.8%	92.7% vs. 88.2%
Complication	NA	34.1% vs. 49.4%
Anastomotic leakage	14.1% vs. 15.8%	6.1% vs. 8.2%
Pneumonia	27.3% vs. 57.0%[a]	3.7% vs. 12.9%
Cardiac	16.0% vs. 26.3%	NA
Vocal cord paralysis	13.2% vs. 21.1%	NA
Chylous leakage	1.9% vs. 9.6%	NA
Pancreatic fistula	NA	12.1% vs. 16.5%
Abdominal abscess	NA	8.5% vs. 14.1%
Pyothorax	NA	1.2% vs. 4.7%
Mediastinitis	NA	0 vs. 4.7%
Mortality	1.9% vs. 4.4%	0% vs. 5.9%
5-year survival	34% vs. 36%	51% vs. 37%
Siewert type I	37% vs. 51%	–
Siewert type II	31% vs. 27%	50% vs. 42%
Siewert type III	–	59% vs. 36%
10-year survival	NA	37% vs. 24%
Siewert type I	NA	–
Siewert type II	NA	35% vs. 29%
Siewert type III	–	44% vs. 22%

[a]Data including pneumonia and atelectasis.

AC: adenocarcinoma; EGJC: esophagogastric junction cancer; NA: not available

However, these results are based on clinical trials conducted in the 1990s, when thoracotomy and laparotomy were the standard procedures. In recent years, surgical devices, techniques, and perioperative management have improved, as have the outcomes of esophagectomy for EC, a procedure characterized by a high risk of morbidity and mortality. In particular, there have been marked advances in minimally invasive surgery; thus, it may be worth re-examining the surgical approaches for EGJC.

Minimally invasive surgery

Clinical trials comparing open and laparoscopic gastrectomy have mostly involved GC, and few have included EGJC. Minimally invasive surgery for EGJC has the advantage of allowing both the surgeon and the assistant to perform manipulations with a clear, magnified surgical view, even in the narrow, deep surgical field of the lower mediastinum.[33] Some studies on Siewert type II EGJC showed that the laparoscopic transhiatal

approach resulted in a better prognosis and the harvesting of a significantly larger number of lymph nodes compared with the open approach[34,35]; however, no RCTs have compared the minimally invasive and open transhiatal approaches for EGJC, and the usefulness of the former is not clear. In particular, a subgroup analysis of a Japanese multicenter prospective study showed a relatively high anastomotic leakage rate (19.0%) with the laparoscopic transhiatal approach for EGJC, indicating that reconstructive procedures with a narrow surgical view in the lower mediastinum remain technically difficult (**Table 4**).[36]

In contrast to the transhiatal approach, there is evidence that the minimally invasive transthoracic approach is beneficial for EGJC.[10] In the TIME trial, thoracoscopic and open surgery were compared for EC and EGJC.[37,38] Thoracoscopic surgery was associated with a significantly lower frequency of postoperative pneumonia than open surgery (12% vs. 34%, respectively) (relative risk (RR) 0.35, 95% CI 0.16–0.78, P = 0.005); however, there was no significant difference in long-term outcomes between the two groups in terms of 3-year survival rate (50.5% vs. 40.4%, respectively, P = 0.207). In the MIRO trial, a hybrid procedure (laparoscopic gastric mobilization with open right thoracotomy) was compared with an open procedure (open gastric mobilization and open right thoracotomy) in patients who were scheduled to undergo Ivor–Lewis surgery for middle and lower third EC or Siewert type I EGJC.[39] The primary endpoint, specifically the incidence of intraoperative or postoperative complications of grade II or higher according to the Clavien–Dindo classification, occurred in 36% vs. 64% of patients in the hybrid and open groups, respectively, and the hybrid group had a significantly lower incidence of complications (odds ratio, 0.31, 95% CI 0.18–0.55, P <0.001). In particular, the incidence of pulmonary complications was lower in the hybrid group (18% vs. 30%, respectively). The 3-year survival rate was 67% in the hybrid group and 55% in the open group, indicating no significant difference. In the ROBOT trial, a single-center RCT in the Netherlands comparing robot-assisted esophagectomy and open esophagectomy in patients with EC or Siewert type I/II EGJC, the robot-assisted esophagectomy group had a significantly lower incidence of pulmonary complications (RR 0.54, 95% CI 0.34–0.85, P = 0.005) and cardiac complications (RR 0.47, 95% CI 0.27–0.83, P = 0.006), with a comparable survival rate (P = 0.427).[40] Recently, the ROBOT-2 trial is going to compare robotic vs. laparoscopic surgery of both abdominal and thoracic procedures in patients with esophageal adenocarcinoma or EGJC, and the primary endpoint is the total number of dissected lymph nodes.[41]

Perioperative Treatment for EGJC

Neoadjuvant chemotherapy

The perioperative treatment strategy for EGJC differs between East Asia and Western countries. In East Asia, the main treatments are surgery plus adjuvant chemotherapy, similar to GC; however, most previous trials demonstrating the survival benefit of adjuvant chemotherapy for GC included few EGJC patients. In the CLASSIC trial, which demonstrated the superiority of surgery plus postoperative CAPEOX compared to surgery, and the RESOLVE trial, which proved the non-inferiority of postoperative SOX therapy for postoperative CAPEOX, the proportion of patients with EGJC were available and were 2.3% and 36.5%, respectively.[42] The proportion of EGJC patients included in these trials was limited, resulting in insufficient evidence for postoperative adjuvant chemotherapy. On the other hand, in Western countries, perioperative chemotherapy or chemoradiotherapy with multi-drug regimens is preferred, and there is some evidence specific to EGJC (**Table 5**).

The FLOT4 trial was conducted in Germany as a randomized phase II/III trial for resectable cT2–4 or cN(+) GC or EGJC.[43] In a total of 716 patients, three preoperative and three postoperative 3-week cycles of ECX/ECF were compared with four preoperative and four postoperative 2-week cycles of FLOT (docetaxel, oxaliplatin, leucovorin, and fluorouracil). The percentage of patients who achieved pathological complete regression was higher in the FLOT group than in the ECX/ECF group in the phase II portion of the trial (16% vs. 6%, respectively, P = 0.02).[44] The FLOT group demonstrated a longer median OS than the ECF/ECX group (50 vs. 35 months, respectively, HR 0.77, 95% CI 0.63–0.94, P = 0.012). In this trial, 56% of patients had EGJC, and FLOT showed a similar effect in them as in the GC patients (HR 0.76). Based on these results, the standard perioperative treatment for GC and EGJC in Europe changed from ECX/EXCF to FLOT.

The PRODIGY study was conducted in South Korea as a randomized phase III trial for resectable T2–3 N(+) or T4 Nany GC or EGJC.[45] A total of 416 patients were assigned to D2 surgery followed by adjuvant S-1 with three preoperative 3-week cycles or DOS (docetaxel,

Table 4 Randomized controlled trials regarding transthoracic esophagectomy for EC and EGJC

	TIME trial[37,38]	MIRO trial[39]	ROBOT trial[40]
Countries	Netherlands	French	Netherlands
Institutions	5	13	1
Eligibility	cT1–3 N0–1 M0	cT1–3 N0–2 M0	cT1–4a N0–3 M0
Number of patients	115	207	112
Surgical approach			
Thoracic	Thoracoscopy vs. thoracotomy	Thoracotomy	Robotic vs. thoracotomy
Abdominal	Laparoscopy vs. laparotomy	Laparoscopy vs. laparotomy	Laparoscopy vs. laparotomy
Histological type			
AC	61.7%	59.4%	77.1%
SCC	37.4%	40.6%	22.9%
Other	0.9%	0	0
Tumor location			
Upper third	3.5%	0.5%	0.9%
Middle third	41.7%	30.4%	11.9%
Lower third or EGJ	54.8%	69.1%	87.2%
Neoadjuvant treatment			
Chemoradiotherapy	92.2%	31.9%	79.5%
Chemotherapy	7.8%	41.5%	8.9%
None	0	26.6%	11.6%
Esophagectomy			
McKeown	64.4% vs. 66.1%	0	92.9% vs. 98.2%
Ivor-Lewis	28.8% vs. 26.8%	99.0% vs. 99.0%	0
No resection	6.8% vs. 7.1%	1.0% vs. 1.0%	7.1% vs. 1.8%
Operation time	329 vs. 299 min	327 vs. 330 min	349 vs. 296 min
Blood loss	200 vs. 475 ml	NA	400 vs. 569 ml
Open conversion rate	13.6%	2.9%	5.40%
Complications	NA	35.9% vs. 64.4%[a]	57.1% vs. 78.6%[a]
Pulmonary complications	8.5% vs. 28.6%[b] 11.9% vs. 33.9%[c]	17.4% vs. 29.8%[d]	30.3% vs. 57.1%[e]
Anastomotic leakage	11.9% vs. 7.1%	10.7% vs. 6.7%	23.2% vs. 19.6%[f]
Reoperation	13.6% vs. 10.7%	NA	23.2% vs. 32.1%
Mortality			
30-day mortality	1.7% vs. 0	1.0% vs. 1.9%	1.8% vs. 0
90-day mortality	NA	3.9% vs. 5.8%	8.9% vs. 1.8%
R0 resection	91.5% vs. 83.9%	94.1% vs. 97.1%	89.2% vs. 94.6%
DFS	3-year: 42.9% vs. 37.3% log-rank, P = 0.602	3-year: 57% vs. 48% HR: 0.76 (95% CI, 0.52–1.11)	median: 26 vs. 28 months log-rank, P = 0.983
OS	3-year: 42.9% vs. 41.2% log-rank, P = 0.633	3-year: 67% vs. 55% HR: 0.67 (95% CI, 0.44–1.01)	log-rank, P = 0.427

Data show minimally invasive surgery vs. open surgery.
[a]Clavien–Dindo classification grade ≥2
[b]Within 2 weeks
[c]In-hospital
[d]Within 30 days
[e]Including pneumonia, pneumothorax, pulmonary embolism, ARDS
[f]Type II/III using the classification of the Esophagectomy Complications Consensus Group
AC: adenocarcinoma; SCC: squamous cell carcinoma; NA: not available; DFS: disease-free survival; OS: overall survival; HR: hazard ratio; CI: confidence interval

oxaliplatin, and S-1) before D2 surgery followed by adjuvant S-1. Patients in the preoperative DOS group achieved a pathological complete response (pCR) rate of 10%. The preoperative DOS group had a higher 3-year progression-free survival (PFS) rate than the upfront surgery group (66.3% vs. 60.2%, respectively,

Table 5 Randomized controlled trials regarding perioperative treatment for EGJC

	Perioperative chemotherapy		Perioperative immunotherapy		Perioperative chemoradiotherapy		
	FLOT4[43,44]	PRODIGY[45,46]	RESOLVE[48]	Checkmate577[56]	CROSS[51,52]	POET[53]	NeoRes I[54,55]
Phase	II/III	III	III	III	III	III	II
Eligibility	cT2–4 or cN(+)	cT2–3 cN(+) or cT4	cT4a cN(+) or cT4b	ypStage II–III after pre-CRT plus surgery	cT1 N1 M0 or cT2–3 N0–1 M0	cT3-4 NX M0	cT1 N(+) M0 or cT2–3 NX M0
Treatment arm	Pre-FLOT and post-FLOT vs. pre-ECF/ECX and post-ECF/ECX	Pre-DOS and post-S-1 vs. post-S-1	Pre-SOX and post-SOX + S-1 (Arm-C) vs. post-CAPEOX	Post-nivolumab vs. (none)	Pre-PTX + CBDCA + RT vs. (surgery alone)	pre-PLF + CRT (EP) vs. pre-PLF	Pre-FP + RT vs. pre-FP
Number of patients	716	484	1022	794	368	119	181
Proportion of EGJC	56%	6%	36%	40%	24%	100%	17%
Primary endpoint	Median OS: 50 vs. 35 months log-rank, P = 0.012	3-year PFS: 66.3% vs. 60.2% log-rank, P = 0.023	3-year DFS: 59.4% vs. 51.1% log-rank, P = 0.028	Median DFS: 22.4 vs. 11.0 months log-rank, P <0.001	Median OS: 49.4 vs. 24.0 months log-rank, P = 0.003	3-year OS: 47.4% vs. 27.7% log-rank, P = 0.07	pCR rate: 28% vs. 9% P = 0.002

Post: postoperative; Pre: preoperative; ECF: epirubicin + cisplatin + 5-fluorouracil; ECX: epirubicin + cisplatin + capecitabine; FLOT: 5-FU + leucovorin + oxaliplatin + docetaxel; DOS: docetaxel + oxaliplatin + S-1; SOX: S-1 + oxaliplatin; CAPEOX: capecitabine + oxaliplatin; PTX: paclitaxel; CBDCA: carboplatin; RT: radiotherapy; PLF: fluorouracil + leucovorin + cisplatin; CRT: chemoradiotherapy; EP: cisplatin + etoposide; FP: platin + 5-fluorouracil; OS: overall survival; PFS: progression-free survival; DFS: disease-free survival

HR 0.70, 95% CI 0.52–0.95, P = 0.023). Furthermore, the OS rate after long-term follow-up was higher in the preoperative DOS group than in the upfront surgery group (HR 0.72, 95% CI 0.54–0.96, P = 0.027).[46] In this study, 5.6% of patients had EGJC, and the HR for death in these patients was higher than that in GC patients (0.62 vs. 0.80, respectively). Another phase II study conducted in Japan evaluated the efficacy and safety of preoperative DOS in patients with cStage III GC or EGJC.[47] Patients received two or three cycles of neoadjuvant DOS before surgery, followed by adjuvant S-1 monotherapy. The pathologic response rate of grade 1b or higher was 63%. The 3-year PFS, OS, and disease-specific survival rates were 54.2%, 68.7%, and 75.8%, respectively.

The RESOLVE study was conducted in China as a randomized phase III trial for resectable T4a N(+) or T4b Nany GC or EGJC.[48] A total of 1022 patients were assigned to D2 surgery followed by adjuvant CAPEOX, D2 surgery followed by adjuvant SOX, or three preoperative 3-week cycles of SOX before D2 surgery followed by five cycles postoperatively followed by three cycles of S-1 monotherapy. Patients in the preoperative SOX group achieved a pCR rate of 5.6%. The 3-year disease-free survival (DFS) rates were 51.1%, 56.5%, and 59.4% in the adjuvant CAPEOX, adjuvant SOX, and perioperative SOX groups. Perioperative SOX resulted in higher 3-year DFS rates than adjuvant CAPEOX (56.5% vs. 59.4%, respectively, HR 0.77, 95% CI 0.61–0.97, P = 0.027). In this trial, 37% of patients had EGJC, and the HR for DFS was similar in EGJC and GC patients (0.83 vs. 0.74, respectively).

These RCTs included both EGJC and GC patients, and few clinical trials have focused on perioperative treatment for EGJC alone. It is necessary to develop perioperative treatments specific to EGJC. A retrospective study of patients with cStage IIB–IV Siewert type I–III EGJC demonstrated the high efficacy of three preoperative 3-week cycles of DOS before surgery followed by S-1 monotherapy, with a pCR rate of 31%.[49] The pCR rate of EGJC was also better than that of GC in the subgroup analysis of the PRODIGY trial, suggesting that DOS may be effective for EGJC. JCOG2203 (NEOJPEG study) is now ongoing as a randomized phase II/III trial for cStage III or IVA (UICC-TNM 8th edition) Siewert type I or II EGJC.[50] In the phase II portion of the trial, either three preoperative cycles of DOS or four preoperative cycles of FLOT will be selected depending on which is more promising, and in the phase III portion, the treatment will be compared with surgery followed by postoperative adjuvant S-1 or DS. The primary endpoint is the pCR rate for the phase II portion and OS for the phase III portion, and the aim is to enroll a total of 460 patients.

Neoadjuvant chemoradiotherapy

Neoadjuvant chemoradiotherapy is a perioperative treatment option that was established in the West, and several important clinical trials have been reported. The CROSS trial was conducted in Europe as a randomized phase III trial for patients with potentially curable EC or EGJC, both of stage T1 N1 or T2–3 N0–1.[51,52] A total of 368 patients were randomized either to neoadjuvant chemoradiotherapy followed by surgery or to surgery alone. Of the cases in this study, 75% were adenocarcinoma, and 24% were EGJC. The median OS duration was 49.4 months in the neoadjuvant chemoradiotherapy group and 24.0 months in the surgery alone group (HR 0.657, 95% CI 0.495–0.871, P = 0.003). However, in a subgroup analysis, the survival benefit of neoadjuvant chemoradiotherapy was lower in adenocarcinoma (adjusted HR 0.741, 95% CI 0.536–1.024, P = 0.07) than in squamous cell carcinoma (adjusted HR 0.422, 95% CI 0.226–0.788, P = 0.007). The phase III POET trial was conducted in Germany with a focus on cT3–4 EGJC.[53] Although this trial was expected to register 354 patients, it was discontinued midway after only 126 patients were registered, and 119 eligible patients were evaluated. The 3-year OS rate was 47.4% in the neoadjuvant chemoradiotherapy group and 27.7% in the neoadjuvant chemotherapy group (HR 0.67, 95% CI 0.41–1.07, P = 0.07). Although the chemoradiation group had a non-significantly better prognosis than the chemotherapy group, the perioperative mortality rate in the neoadjuvant chemoradiotherapy group was 10.2%, which was higher than the 3.8% in the chemotherapy group. The NeoRes I trial was conducted in Sweden and Norway as a randomized phase II trial comparing neoadjuvant chemotherapy with neoadjuvant chemoradiotherapy followed by surgery in patients with adenocarcinoma or squamous cell carcinoma of cT1–3, excluding T1N0 EC or EGJC.[54,55] Of the 181 patients enrolled in the trial, 131 (72%) had AC, and 31 (17%) were located in EGJ. There was a higher pCR rate (28% vs. 9%) and R0 resection rate (87% vs. 74%) in the neoadjuvant chemoradiotherapy group compared with the neoadjuvant chemotherapy group. Despite these differences, the 5-year OS rates were statistically similar, with 42.2% in the

chemoradiotherapy group and 36.9% in the chemotherapy group (P = 0.60).

Perioperative immunotherapy

Perioperative chemotherapy or chemoradiotherapy for GC or EGJC has been performed using a multidrug regimen with cytotoxic anticancer agents. Treatment with immunotherapy and concurrent perioperative chemotherapy or chemoradiotherapy has recently been developed; it is expected to improve the prognosis of EGJC. CheckMate 577 was a global phase III RCT.[56] Patients with ypStageII–III EC or EGJC who received neoadjuvant chemoradiotherapy and underwent R0 resection were assigned in a 2:1 ratio to receive either placebo or the PD-1 immune checkpoint inhibitor antibody nivolumab for up to 1 year after surgery. Overall, 70.9% of patients had adenocarcinoma, which was located in the EGJ in 40.2%. The median DFS was 22.4 months in the nivolumab group and 11.0 months in the placebo group (HR 0.69, 95% CI 0.56–0.86, P <0.001). In a subgroup analysis, the nivolumab group had a better prognosis than the placebo group regardless of histological type, but no superiority was observed for EGJC (HR 0.87, 95% CI 0.63–1.21). Therefore, nivolumab has uncertain effectiveness for EGJC in patients who have undergone preoperative chemoradiotherapy followed by surgery.

Conclusion

This review summarized important clinical trials of surgical and perioperative treatments for EGJC. EGJC is an independent malignant disease with a poor prognosis and complex lymphatic flow, and there is no standard treatment. However, a recent multicenter prospective study revealed the frequency of lymph node metastasis by station and established the optimal extent of lymph node dissection. Although no standard perioperative treatment has been established specifically for EGJC, some clinical trials targeting EGJC are currently ongoing. It is expected that new standard treatments for EGJC will be determined based on the results. The development of immune checkpoint inhibitors and molecular targeted drugs for unresectable upper gastrointestinal cancers has been significant, and adapting for the development of perioperative treatments for EGJC may further improve outcomes. Furthermore, conversion surgery for tumors with distant metastasis has been reported to have favorable results in limited cases. As for minimally invasive surgery, it is interesting whether robotic surgery will become the mainstream of minimally invasive surgery or whether it will be applied only to more difficult surgeries. To resolve these questions, further research is necessary, and an evaluation from a medical-economic perspective is also required for robotic surgery.

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