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MINIREVIEWS

Current status and future perspectives for the treatment of resectable locally advanced esophagogastric junction cancer: A narrative review

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Abstract

Incidence rates for esophagogastric junction cancer are rising rapidly worldwide possibly due to the economic development and demographic changes. Therefore, increased attention has been paid to the prevention, diagnosis, and the treatment of esophagogastric junction cancer. Although there are discrepancies in the treatment strategy between Asian and Western countries, surgery remains the mainstay of treatment for esophagogastric junction cancer. Recent developments of perioperative multidisciplinary treatment may lead to better therapeutic effect, higher complete resection rate, and better control of the residual diseases, thus result in prolonged prognosis. In this review, we will focus on the treatment of locally advanced resectable esophagogastric junction cancer, and discuss the current status and future perspectives of the perioperative treatment including chemotherapy, radiation therapy, and immunotherapy, as well as the surgical strategy. Better understanding of the latest treatment strategy and future overlook may enable to standardize and individualize the treatment for esophagogastric junction cancer, thus leading to better prognosis for those patients.

Key Words: Esophagogastric junction cancer; Perioperative therapy; Neoadjuvant therapy; Surgery; Multidisciplinary treatment

Core Tip: In recent years, increased attention has been paid to the prevention, diagnosis, and the treatment of esophagogastric junction cancer. Recent developments of perioperative multidisciplinary treatment led to increased patient outcomes. In this review, we will focus on the current status and future perspectives of the perioperative treatment including chemotherapy, radiation therapy, targeted therapy, and immunotherapy, as well as the surgical strategy for locally advanced esophagogastric adenocarcinoma. Better understanding of the latest treatment strategy and future overlook may lead to better prognosis for the patients.

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INTRODUCTION

Incidence rates for esophagogastric junction (EGJ) cancer, especially EGJ adenocarcinoma (EGJAC) are rising rapidly worldwide possibly due to increased excess body weight, increasing gastroesophageal reflux disease, and decreasing levels of chronic infection with *Helicobacter pylori*[1,2]. These trends are predicted to continue, thus leading to increased incidence of EGJAC[1]. Treatment strategy for resectable locally advanced EGJAC differ from country to country, where perioperative therapy combined with surgery has been the standard of care for locally advanced EGJAC in the western countries[3,4], whereas surgery with or without adjuvant chemotherapy has been widely accepted in Japan since the significance of preoperative therapy has not yet been established[5]. Nevertheless, surgery remain the mainstay of treatment for locally advanced EGJAC, and therefore, there is an emerging need for the development of surgical approach, as well as other treatment modalities including chemotherapy, radiation therapy, and immunotherapy in order to improve patient outcomes.

Due to its unique anatomical location, optimal surgical strategy for EGJAC have long been questioned, and different opinions have been proposed between gastrointestinal and thoracic surgeons. Siewert type I tumors, which the tumor epicenter is located between 1cm to 5 cm above the EGJ, have usually been treated as esophageal cancer, whereas Siewert type III tumors, which is located between 2 cm to 5 cm below the EGJ, have generally been treated as gastric cardia cancer. Surgical procedure for Siewert type II tumors (1 cm above to 2 cm below EGJ) have been selected by individual surgeons or institutional preferences. Recent retrospective and prospective studies have unveiled the lymphatic flow for EGJ cancers[6,7], and thereby a standardized surgical strategy have been proposed. Another critical surgical issue during EGJ cancer treatment is the reconstruction method, which have long been related to high anastomotic complication rates[8]. Recent inventions and improvement of anastomotic methods [9-11] have enabled a safe esophagogastric anastomosis with less incidence of anastomotic leakage and gastroesophageal reflux.

Researchers have focused on the development of more intensive perioperative therapy to overcome the poor prognosis of advanced EGJ cancers. Preoperative chemotherapy or chemoradiotherapy have been utilized in the western countries[3,4], however, question remains whether which is the best treatment option. In recent years, immunotherapy has received particular attention in the treatment of EGJ cancers. Adjuvant checkpoint inhibitor immunotherapy is now the standard of care for EGJ cancer patients who received neoadjuvant chemoradiotherapy and had residual pathological disease after curative resection[12]. Recent studies have unveiled the efficacy of immunochemotherapy in neoadjuvant settings[13,14].

In this review, we will focus on locally advanced resectable EGJAC, and discuss the current clinical practice, ongoing clinical trials, and future perspectives of multidisciplinary treatment options for EGJAC.

STANDARDIZING THE SURGICAL PROCEDURE FOR EGJAC

Mediastinal lymph node dissection

The initial study to demonstrate the frequency of lymph node (LN) metastasis for EGJAC was reported by Rüdiger Siewert *et al*[15] in 2000. In this retrospective single-center study, 1002 patients with EGJAC underwent either transthoracic esophagectomy or transhiatal extended gastrectomy depending on the tumor location. Among the 271 patients with carcinoma of the cardia arising immediately at the esophagogastric junction (defined as Type II in the literature), 29 (15.6%) patients had lower mediastinal

lymph node metastasis. In another single center study by Pedrazzani *et al*[16], nodal involvement of 143 patients with locally advanced EGJAC were analyzed. In this study, middle/Lower mediastinal LN dissection was performed in 70%-85% of the patients with Siewert type I tumor, whereas the dissection rate was only 3.3%-35.5% for the patients with Siewert type III tumor. Middle and/or lower mediastinal LN metastasis was observed in 46.2%, 29.5%, and 9.3% for Siewert type I, II, and III tumors, respectively.

In 2017, Yamashita *et al*[6] conducted a questionnaire-based national retrospective study in Japan to define the optimal extent of LN dissection for EGJ cancers[6]. In this study, EGJ cancer was defined as having its tumor epicenter within 2 cm above or below EGJ according to the definition promulgated by the Japanese Gastric Cancer Association[17] and the Japanese Esophageal Society[18], and patients with tumors ≤ 4 cm were considered eligible. In total, 1560 patients with Siewert Type I/II EGJAC were enrolled. The estimated survival benefit by LN dissection was high for the abdominal LN along the lesser curvature, right and left cardia, and the left gastric artery, however, optimal extent of the mediastinal LN dissection could not be determined due to the low rate of upper/middle mediastinal LN dissection, which was below 20%. To further determine the value of mediastinal LN dissection in EGJ cancers, Kurokawa *et al*[7] reported the results of a prospective multicenter study in 2021[7], in which cT2-T4 cancers located within 2 cm of the EGJ were enrolled. Upper mediastinal LN dissection was performed for patients with esophageal invasion > 3 cm, whereas patients with esophageal invasion ≤ 3 cm underwent lower mediastinal LN dissection only. Within the 98 patients who had esophageal invasion > 3 cm (67 EGJAC and 31 esophageal squamous cell carcinomas, ESCC), rate of right recurrent laryngeal nerve LN metastasis was 10.7% (3/28) when the length of esophageal invasion exceeded 4 cm. As a result, surgical algorithm for EGJ cancers was proposed, and upper mediastinal LN dissection was recommended for advanced EGJ cancer patients with esophageal invasion > 4 cm and clinically positive LN in the upper/middle mediastinal field[19].

One of the unique features of these Japanese studies is that squamous cell carcinomas located within 2 cm of the EGJ are included, and are analyzed along with EGJAC. In Japan, regardless of histological type, tumors within 2 cm of the EGJ are classified as "EGJ cancers" according to the Nishi classification [17], possibly due to the high incidence of ESCC, whereas only adenocarcinomas have been regarded as EGJ cancers in the western countries. The difference in the definition of EGJ cancer have caused the difference in the treatment, including surgery and chemo (radio)therapy for tumors of the EGJ between countries. In the former study[7], rate of upper-mediastinal LN metastasis was similar between adenocarcinomas and squamous cell carcinomas for tumors within 2 cm of the EGJ, suggesting that similar surgical strategy may be applied regardless of histological type. Although further studies are needed to determine the optimal extent of LN dissection for tumors with greater esophageal invasion.

Some issues remain unsolved. First, is the difficulty to accurately measure the distance from the EGJ to the tumor proximal margin in patients with large tumors, circumferential tumors, and hiatal hernia. Therefore, extent of mediastinal LN dissection may not be determined preoperatively for such patients. Second, as mentioned above, EGJ tumors with long esophageal invasion, usually classified as Siewert type I, were excluded in recent studies. In our institute, 35 patients with Siewert type I EGJAC underwent curative resection including upper-mediastinal LN dissection between 2007 to 2022 (Tables 1 and 2). The rate for upper/middle/Lower mediastinal LN metastasis for the patients were 31.4%/29.4%/34.4%, respectively, suggesting the high incidence of mediastinal LN metastasis, and the importance of mediastinal LN dissection for those patients. However, survival benefit for mediastinal LN dissection for EGJAC remain unclear. In 2020, CARDIA-trial, a multinational, multicenter, randomized clinical trial which aimed to show the superiority of transthoracic esophagectomy with mediastinal LN dissection against transhiatal extended gastrectomy regarding overall survival (OS) was proposed, and is now undergoing[20]. To determine the value of mediastinal LN dissection, the results of this study and the survival analysis of the recent prospective study[7] is awaited.

Minimal-required proximal margin length

Negative surgical margin, as well as an adequate LN dissection, is essential to achieve curative resection in the surgical treatment for EGJAC. Although, especially during transhiatal approach, excessive proximal margin may lead to severe difficulty in anastomosis, thus result in higher complication rate. In 2013, Mine *et al*[21] reported the results of a single-center retrospective study which analyzed the proximal margin length of the 140 patients who underwent surgery for Siewert type II and III EGJAC. Patients with gross proximal margins greater than 20 mm had better survival outcomes than those shorter than 20 mm, and further, gross proximal margin ≤ 20 mm (hazard ratio (HR), 3.56; 95%CI: 1.39-9.14; P = 0.008) as well as pathological node status (HR, 1.76; 95%CI: 1.08-2.86; P = 0.024) were independent prognostic factors by multivariable analysis. Another recent study[22] retrospectively analyzed the proximal margin length in resected specimens for 289 EGJ/gastric cancer with gross esophageal invasion. Maximum length of discrepancy between the gross and pathological proximal boundary of the tumor was 15 mm for superficial growth type and 20 mm for expansive growth type tumors, respectively. These two studies indicate that 20 mm may be a sufficient proximal margin for advanced EGJAC, however, since proximal margins were measured in resected specimens in both studies, preoperative measures to decide the resection line remain unclear. Further, optima proximal margin for cases after preoperative therapy needs to be further studied.

Table 1 Patients with Siewert type I esophagogastric junction adenocarcinoma who underwent surgery at our institute

n	35
Male	34 (97.1%)
Age (yr)	67 (42-79)
Field of LN dissection 2/3	2/33
Open/MIE/Robot assisted	6/24/5
Preoperative chemotherapy	4 (11.4%)
Tumor size (mm)	35.3 (9-110)
Esophageal invasion length (mm)	30 (18-110)
pT 1a/1b/2/3/4a/4b[1]	4/10/3/18/0/0
pN 0/1/2/3[1]	15/4/4/12
pM 0/1[1]	30/5
pStage IA/IB/IIA/IIB/IIIA/IIIB/IVA/IVB[1]	3/7/2/6/0/4/8/5
Upper mediastinal LN metastasis	11/35 (31.4%)
Middle mediastinal LN metastasis	10/34 (29.4%)
Lower mediastinal LN metastasis	11/32 (34.4%)
Recurrence	14 (40.0%)
Site of recurrence[2]	
Liver	5
Adrenal gland	5
Distant LN	3
Peritoneum	2
Bone	2
Pleura	1
Pancreas	1

[1]Classified by the 8th edition of the Union for International Cancer Control (UICC)-Tumor Node Metastasis (TNM) classification.
[2]Including overlapped cases.
EGJAC: Esophagogastric adenocarcinoma; LN: Lymph node; MIE: Minimally invasive esophagectomy.

Reconstruction to prevent anastomotic complications

As a result of Japanese nationwide retrospective and prospective studies[6,7], LN along the distal portion of the stomach were much less often metastatic compared to LN along the right and left cardia, lesser curvature, and the left gastric artery for Siewert type II EGJAC. Therefore, the distal portion of the stomach does not need to be necessarily removed for Siewert type II EGJAC smaller than 4 cm, and proximal gastrectomy or total gastrectomy combined with distal esophagectomy is selected according to oncological status, patient condition, or institutional preference. According to a meta-analysis which compared proximal *vs* total gastrectomy for proximal early gastric cancer[23], proximal gastrectomy was superior to total gastrectomy in terms of operation time, intraoperative blood loss, and long-term nutritional status. Although, proximal gastrectomy followed by esophagogastrostomy was associated with a higher incidence of anastomotic complications such as stenosis and reflux esophagitis, as have been reported elsewhere[24,25]. In a prospective nationwide multicenter study in Japan[8], anastomotic leakage was observed in 12.2% of the 225 patients after transhiatal esophagectomy, and further, six patients suffered Clavien-Dindo (CD) grade IV or above anastomotic leakage where none of the patients after transthoracic esophagectomy hade leakage ≥ CD grade IV. Recently, novel surgical techniques, such as double-flap technique[11,26] and side overlap esophagogastrostomy[9,10] have been developed during gastric cancer surgery, and been introduced to EGJ cancers in order to overcome these anastomotic complications. Researchers have reported favorable results regarding anastomotic complications; however, these techniques require a more complex intracorporeal suturing technique and longer duration of surgery especially when performed for EGJ cancers which often requires intrathoracic anastomosis. Further investigation may be required for a higher level of evidence.

Table 2 Details of the mediastinal lymph node metastasis for the patients in Table 1

LN location		Metastasis rate (%)	
Upper mediastinum	Upper thoracic paraesophageal LN	8.5	(3/35)
	Left recurrent nerve LN	15.2	(5/33)
	Right recurrent nerve LN	20.6	(7/34)
	Left trachebronchial LN	17.4	(4/23)
Meddle mediastinum	Subcranial LN	18.2	(6/33)
	Middle thoracic paraesophageal LN	20.0	(7/35)
	Left main bronchus LN	12.9	(4/31)
	Right main bronchus LN	16.2	(5/31)
Lower mediastinum	Lower thoracic paraesophageal LN	17.1	(6/35)
	Supradiaphragmatic LN	13.3	(4/30)
	Posterior mediastinal LN	17.2	(5/29)

Number of patients with metastasis/number of patients who underwent lymph node dissection is indicated in each parenthesis. LN: Lymph node.

Minimally invasive surgery for EGJ cancers

Although none of the clinical trials specifically focusing on EGJ cancers have been conducted, several studies have demonstrated the safety and efficacy of minimally invasive surgery for esophageal/gastric cancer, which may also be applied to EGJ cancers. In 2012, Biere *et al*[27] reported the results of a multicenter, open-label, randomized control trial which aimed to demonstrate the safety of minimally invasive esophagectomy (MIE) verses open esophagectomy (OE) for patients with esophageal/EGJ cancers[27]. Patients in the study received preoperative therapy consisting of paclitaxel plus carboplatin plus concurrent radiotherapy of 41.4 Gy, followed by esophagectomy with two-field LN dissection, 6-8 wk after preoperative therapy. Within the 56 and 59 patients who were assigned to OE and MIE, respectively, OE group had more in-hospital pulmonary infection compared to MIE group (relative risk, 0.35; 95%CI: 0.16-0.78, P = 0.005), demonstrating the short-term benefits of MIE. Favorable short-term results regarding cardiopulmonary complications, postoperative pain, quality of life, and postoperative functional recovery were also reported in a single-center randomized trial comparing robot-assisted minimally invasive esophagectomy (MIE) *vs* OE for intrathoracic esophageal cancer (ROBOT trial)[28]. In the follow up study of ROBOT trial[29], long-term outcomes of the 112 patients including 40 EGJ cancer patients were analyzed. Comparable 5-year OS (41% *vs* 40%, P = 0.827) and disease-free survival (DFS, 42% *vs* 43%, P = 0.749) rates were observed for patients after RAMIE *vs* OE, respectively.

Regarding gastrectomy, the short-term surgical outcomes of a single-center non-inferiority randomized trial for laparoscopic *vs* open gastrectomy was reported in 2018[30]. In this study, 328 patients with cT2-3N0-3M0 gastric cancer, including 70 upper-third gastric cancer underwent open or laparoscopic total (33.5%), proximal (5.6%), and distal (60.9%) gastrectomy with D2 LN dissection depending on the tumor location. Overall complication rate was similar (laparoscopic, 11.7%; open, 14.4%; P = 0.512) between the groups, suggesting the feasibility of laparoscopic gastrectomy for advanced cancers.

Although evidence is lacking, especially for the oncological safety of minimally invasive transhiatal lower esophagectomy, minimally invasive surgery for EGJ cancer have been performed worldwide and is expanding rapidly. Surgeons must carefully decide the indication of minimally invasive surgery according to each patients general and oncological condition. In order to determine the superiority of robot-assisted over laparoscopic/thoracoscopic surgeries, results of ongoing studies[31] are awaited.

OPTIMAL PERIOPERATIVE TREATMENT FOR EGJAC

Neoadjuvant chemotherapy or chemoradiotherapy, which is the best choice?

Due to the poor survival outcome, researchers have focused on the development of more intensive preoperative treatment for advanced EGJAC. However, development and research for new therapeutic strategy has yet to be unified between Western and Asian countries. In addition, since EGJAC has been recognized as esophageal or gastric cancer until recently, various theories abound, and the optimal treatment option remain unclear.

In the Western countries, pre- and postoperative combination of docetaxel, oxaliplatin, leucovorin, and fluorouracil (FLOT) is now regarded as the standard treatment for locally advanced gastric cancer and EGJAC as a result of the FLOT4 trial[3]. For the 716 patients with cT2-4 cN+ gastric or EGJ cancer, median OS was 50 mo (95%CI: 38.33 to not reached), and pathological complete response (pCR) rate was 16% (95%CI: 10%-23%) after FLOT therapy[32], which were both significantly increased compared to conventional ECF/ECX therapy in this study. Subgroup analysis revealed that the effect of FLOT was similar between gastric and EGJ cancers. Another standard preoperative therapy for EGJ cancers in the Western countries is chemoradiotherapy as a result of the CROSS trial[4,33]. In this study, 368 patients with cT1N1 or cT2-3N0-1 esophageal or EGJ caner were either enrolled to surgery alone or neoadjuvant chemoradiotherapy followed by surgery. The chemoradiotherapy consisted of carboplatin, paclitaxel, and concurrent radiotherapy of 41.4 Gy. Within the 368 patients, results of the 366 patients were analyzed, and 88 (24%) of those patients had EGJAC. Median OS for the neoadjuvant therapy group was 48.6 (95%CI: 32.1-65.1) months, which was significantly longer than the surgery alone group. A pCR was achieved in 47 of the 161 patients (29%) who underwent resection after chemoradiotherapy.

In Korea, a phase III PRODIGY study[34] was designed to demonstrate the superiority of neoadjuvant docetaxel, oxaliplatin, and S-1 triplet therapy (DOS) followed by surgery and adjuvant S-1, *vs* conventional adjuvant S-1 after surgery in patients with gastric cancer and EGJAC. Neoadjuvant therapy was administered for 238 patients with cT2-3N+ and cT4 patients. Three-year progression-free survival (PFS) rate was 66.3% *vs* 60.2% (HR, 0.70; 95%CI: 0.52–0.95; P = 0.023) in the neoadjuvant group compared to surgery-first group. Neoadjuvant therapy led to pCR rate of 10.4%. As a result, preoperative DOS therapy is now considered as one of the standard treatment options in selected countries, however, OS was not significantly different between the two groups possibly because of the study setting, and the standard therapy for EGJAC is still questioned due to the relatively small population of EGJAC in this study (Table 3).

Thus far, several trials compared the therapeutic effect of preoperative chemoradiotherapy *vs* chemotherapy for EGJ cancers. In the NeoRes trial[35,36], patients with cT1N+ or cT2-3 esophageal or EGJ cancer were either randomized to neoadjuvant chemotherapy consisting of cisplatin plus fluorouracil, or the same chemotherapeutic regimen plus concurrent radiation therapy of 40 Gy. In this study, neoadjuvant chemoradiotherapy have achieved higher pCR rate (24% *vs* 8%) and R0 resection rate (76% *vs* 64%) when compared to neoadjuvant chemotherapy, however, three-year OS rates were equivalent between the groups (HR, 1.09; 95%CI: 0.73–1.64; P = 0.77). In another prospective randomized phase III trial[37], patients with cT3-4 EGJAC received either three courses of neoadjuvant triplet therapy (cisplatin, fluorouracil, and leucovorin, PLF) or two courses of PLF plus combined chemoradiotherapy consisting of cisplatin, etoposide, and concurrent radiation of 30 Gy. Within the evaluated 119 patients, high in-hospital mortality rate after neoadjuvant chemoradiotherapy (10.2%) compared to chemotherapy (3.8%) was observed, however, three-year OS rates were relatively higher in the neoadjuvant chemoradiotherapy group (47.4% *vs* 27.7%, HR, 0.67; 95%CI: 0.41–1.07; P = 0.07, Table 4). In 2021, preliminary results of a phase III study, which aimed to compare CROSS *vs* FLOT or MAGIC (epirubicin, cisplatin/oxaliplatin, and 5-fuluorouracil/capecitabine) regimen in terms of OS for esophagus and EGJ cancer were reported (Neo-AEGIS trial)[38]. Within the 362 evaluable patients, at a median follow up of 24.5 (1-92) mo, the 3-year estimated survival probability was equivalent between CROSS and MAGIC/FLOT arm (HR, 1.02; 95%CI: 0.74-1.42).

As shown, accumulated evidence has shown that neoadjuvant therapy may improve survival for patients with EGJAC, however, various issues remain unclear. First, is the ideal chemotherapeutic regimen for neoadjuvant treatment. The Japan Clinical Oncology Group (JCOG) is now planning a nationwide prospective study directly comparing DOS *vs* FLOT regimen as neoadjuvant treatment in EGJAC. Second, is the efficacy by the addition of radiotherapy to chemotherapy, since none of the previous studies used the current standard chemotherapeutic regimen for the chemoradiotherapy arm. Although the superiority of chemoradiotherapy have not yet been demonstrated, neoadjuvant chemoradiotherapy may be of utility in cases such as borderline resectable EGJAC because of the relatively high pCR rate. Finally, the safety of radiation therapy is a critical issue, and needs to be further discussed. Currently, a randomized phase III RACE[39] trial, which aimed to compare perioperative chemotherapy *vs* chemoradiotherapy (FLOT *vs* FLOT based chemoradiotherapy including concurrent radiation of 45 Gy) in terms of PFS in undergoing, and the results are awaited.

Immune checkpoint inhibitor immunotherapy, a paradigm shift in cancer treatment

Recent advances of immunotherapeutic agents, especially immune checkpoint inhibitors (ICI), have dramatically improved the treatment outcomes in several cancer types. In esophageal, gastric, and EGJ cancers, anti-PD-1 antibody (nivolumab/pembrolizumab) and anti-CTLA-4 antibody (ipilimumab) have already been regarded as one of the standard treatment options for unresectable/recurrent tumors[40-43]. In a recent phase II trial[13], the neoadjuvant combination of ICI and chemotherapy was investigated in locally advanced gastric and EGJ cancers. Thirty-six patients with cT3-4N+ diseases including 19 patients with EGJAC received capecitabine and simultaneous radiotherapy for 5 wk, sandwiched by a 21-d cycle of oxaliplatin plus capecitabine twice daily (days 1-14) followed by surgery. Anti-PD-1 antibody camrelizumab (day 1) was given for 5 cycles since initiating chemotherapy. The primary endpoint pCR rate was 33.3% (95%CI: 18.6-51.0), and patients with < 10% residual tumor cells/R0

Table 3 Clinical trials of neoadjuvant therapy for esophagogastric junction cancer included in this review

Study name	FLOT4[3,32]	CROSS[4,33]	PRODIGY[34]
Ref.	Al-Batran *et al*[3,32]	Shapiro *et al*[33], van Hagen *et al*[4]	Kang *et al*[34]
Year	2016/2019	2012/2015	2021
Study design	Phase II/III	Phase III	Phase III
Eligible patients	cT2-4 and/or cN+, cM0	cT1N+ or cT2-3, cM0	cT2-3N+ or cT4, cM0
	Gastric or EGJ cancer	Esophageal or EGJ cancer	Gastric or EGJ cancer
Experimental arm	FLOT	CBDCA + PTX + RT	DOS + adjuvant S1
Control arm	ECF/ECX	Surgery alone	Adjuvant S1
Total number of patients	716	366	484
EGJ cancer patients	56%	24%	6%
Primary outcome	OS	OS	Progression free survival
OS	50 *vs* 35 mo	48.6 *vs* 24.0 mo	NA
pCR rate	16% *vs* 6%	29%	10.40%
R0 resection rate	85% *vs* 78%	92% *vs* 69%	89% *vs* 84%
Special notes	Effective for EGJ cancer		Progression free survival, 66.3 months *vs* 60.2 months. Equivalent OS. Small population of EGJ cancer patients (27 patients)

EGJ: Esophagogastric junction; pCR: Pathological complete response; FLOT: 5-fluorouracil + leucovorin + oxaliplatin + docetaxel; ECF: Epirubicin + cisplatin + 5-fluorouracil; ECX: Epirubicin + cisplatin + capecitabine; CBDCA: Carboplatin; PTX: Paclitaxel; RT: Radiation therapy; DOS: Docetaxel + oxaliplatin + S-1; NA: Not available; OS: Overall survival.

resection rates were 44.4%/91.7%, respectively. Two-year PFS and OS rates were 66.9% and 76.1%, respectively in this study. In another phase II study[14], neoadjuvant nivolumab once every two weeks, 6 cycles, and ipilimumab once every six weeks, 2 cycles, followed by surgery and adjuvant nivolumab once every four weeks (nine injections) were administered in 32 patients with locally advanced resectable, deficient mismatch repair (dMMR)/microsatellite instability-high (MSI-H), cT2-4 gastric (16 patients) and GEJ cancer (16 patients). Twenty-nine patients who received surgery all had an R0 resection, and 17 (58.6%; 90%CI, 41.8-74.1) had pCR. Of those 29 patients with surgery, 23 received adjuvant nivolumab. At database lock (median follow-up, 14.9 mo), no patient had relapse and one died without relapse. Combination of ICI and chemotherapy with or without concurrent radiotherapy may exhibit promising pathological response with tolerable toxicity in patients with locally advanced EGJAC, and future phase III trials to demonstrate the safety and efficacy are awaited (Table 5).

Future of targeted therapy

In 2022, the results of the NRG Oncology/RTOG 1010 study[44], a multicenter randomized phase III trial which aimed to demonstrate the impact of monoclonal anti-HER2 (ERBB2) antibody trastuzumab with trimodality treatment for esophageal adenocarcinoma with HER2 expression was reported. In this study, patients with HER2 positive cT1N1-2 or cT2-3N0-2 diseases were either assigned to weekly intravenous paclitaxel and carboplatin for 6 wk with radiotherapy of 50.4 Gy followed by surgery, with or without intravenous trastuzumab for 5 wk during chemoradiotherapy, once preoperatively, and every 3 wk for 13 treatments starting 21-56 d after surgery. In total, 203 patients were included, and the median DFS (primary endpoint) was 19.6 mo and 14.2 mo for chemoradiotherapy with trastuzumab and chemoradiotherapy alone, respectively (HR, 0·99; 95%CI: 0.71-1.39; P = 0.97) (Table 5). Although addition of trastuzumab did not lead to increased toxicities, the study failed to demonstrate survival benefits, suggesting that combination with other chemotherapeutic agents or other drugs targeting HER2 may be necessary for the treatment of HER2 positive EGJAC. Currently, the treatment effect of an antibody-drug conjugate trastuzumab deruxtecan (T-DXd) against HER2 positive gastric and EGJ adenocarcinoma is tested under a phase II study in Japan (EPOC2003 study)[45]. In a recent analysis utilizing the Cancer Genome Atlas (TGCA)[46], EGJAC was classified into esophageal adenocarcinoma like and gastric adenocarcinoma like EGJAC according to the 400-gene classifier. Esophageal adenocarcinoma like EGJAC have shown significantly higher copy number amplification of ERBB2, as well as an increased protein expression of ERBB2 and EGFR, suggesting that the molecular characterization of EGJAC may enable to select patients who will benefit by ERBB2/EGFR blockade. Agents targeting vascular endothelial growth factor (VEGF) might also be future candidates for neoadjuvant therapy[47],

Table 4 Clinical trials comparing neoadjuvant chemotherapy versus chemoradiotherapy for esophagogastric junction cancer included in this review

Study name	NeoRes[35,36]	POET[37]	Neo-AEGIS[38]
Ref.	Klevebro *et al*[35,36]	Stahl *et al*[37]	John *et al*[38]
Year	2015/2016	2009	2021
Study design	Randomized phase II	Phase III	Phase III
Eligible patients	cT1N+ or cT2-3, M0	cT3-4, M0	cT2-3N0-3M0
	Esophageal or EGJ cancer	EGJ cancer	Esophageal or EGJ cancer
Experimental arm	CF + RT	PLF + RT	CROSS
Control arm	CF	PLF	MAGIC/FLOT
Total number of patients	181	119	377
EGJ cancer patients	17%	100%	NA
Primary outcome	pCR	OS	OS
OS	NA	33 *vs* 21 mo	NA
pCR rate	24% *vs* 8%	15.6% *vs* 2.0%	NA
R0 resection rate	76% *vs* 64%	69.5% *vs* 71.5%	NA
Special notes	Equivalent 3-year OS	Study closed early due to low accrual, high in-hospital mortality after chemoradiotherapy	Equivalent 3-year estimated survival probability

EGJ: Esophagogastric junction; pCR: Pathological complete response; CF: Cisplatin + 5-fluorouracil; RT: Radiation therapy; PLF: Paclitaxel + leucovorin + 5-fluorouracil; CROSS: Carboplatin + paclitaxel + radiation therapy; MAGIC: Epirubicin + cisplatin (oxaliplatin) + 5-fluorouracil; FLOT: 5-fluorouracil + leucovorin + oxaliplatin + docetaxel; NA: Not available; OS: Overall survival.

Table 5 Clinical trials of neoadjuvant immunotherapy/targeted therapy for esophagogastric junction cancer included in this review

Study name	Neo-PLANET[13]	NEONIPIGA[14]	NRG Oncology/RTOG 1010[44]
Ref.	Tang *et al*[13]	Andre *et al*[14]	Safran *et al*[44]
Yr	2022	2023	2022
Study design	Phase II	Phase II	Phase III
Eligible patients	cT3-4N+, M0	cT2-4, M0, dMMR/MSI-H	cT1N1-2 or cT2-3N0-2 HER2 positive
	Gastric or EGJ cancer	Gastric or EGJ cancer	Esophageal adenocarcinoma
Experimental arm	Camrelizumab plus chemoradiotherapy	Nivolumab plus ipilimumab	Trastuzumab plus chemoradiotherapy
Control arm	NA	NA	Chemoradiotherapy
Total number of patients	36	29	203
EGJ cancer patients	53.80%	50.00%	NA
Primary endpoint	pCR	pCR	Disease-free survival
OS	NA	NA	38.5 *vs* 38.9 mo
pCR rate	33.30%	58.60%	27% *vs* 29%
R0 resection rate	91.70%	100%	98% *vs* 100%
Special notes	Two-year OS, 76.2%		Disease-free survival, 19.6 *vs* 14.2 mo

EGJ: Esophagogastric junction; pCR: Pathological complete response; NA: Not available; OS: Overall survival.

and should be further discussed.

Is adjuvant therapy needed?

In Japan, EGJAC has usually been treated as gastric cancer, and the same agents have been administered

as adjuvant therapy for both cancer types. In the CLASSIC trial[48,49] which investigated the effect of adjuvant capecitabine plus oxaliplatin for pStage II-III gastric or EGJ adenocarcinoma, a trend toward improving OS was shown in the small subset of patients with EGJAC (24 patients, HR, 0.63; 95%CI: 0.09–4.45). In another randomized controlled phase III trial JACCRO CG-07[50,51], the effect of S-1 plus DOS over S-1 alone was demonstrated for pStage III gastric cancer, however, the study included only eight EGJAC patients. Although sufficient analysis for EGJAC alone could not be performed due to the small sample size, with the results against gastric adenocarcinomas, capecitabine plus oxaliplatin, S-1 plus DOS, or S-1 monotherapy[52] have been regarded as the standard adjuvant therapy for EGJAC.

In the recent CheckMate 577 study[12], the value of adjuvant ICI (nivolumab) was evaluated in patients with ypStage II-III esophageal or EGJ cancers after neoadjuvant chemoradiotherapy. A total of 794 patients, which included 319 (40.2%) EGJAC, after curative resection were either postoperatively randomized to receive nivolumab adjuvant therapy or placebo. Median DFS was 22.4 and 11.0 mo for nivolumab group and placebo group, respectively (HR, 0.69; 95%CI: 0.56–0.86; $P < 0.001$), which demonstrated the impact of adjuvant ICI. However, in the subgroup analysis, adjuvant nivolumab could not show prognostic advantages during EGJAC (HR, 0.87; 95%CI: 0.63–1.21). Value of adjuvant therapy for EGJAC, especially for patients after neoadjuvant chemotherapy, remain unclear. The ideal regimen, and further, whether adjuvant treatment is needed, should be further investigated.

CONCLUSION

Recent development of the perioperative treatment has improved therapeutic effect for EGJAC, and further, novel immunochemotherapeutic strategies have high expectations to further improve survival outcomes for the patients. Previous studies have enabled to standardize the surgical procedure for EGJAC, and novel surgical techniques have improved the safety of operation. Since the incidence of EGJAC are rising rapidly worldwide, there is an urgent need to accumulate new evidence and to unify the treatment strategy globally. Although multiple issues remain unclear, ongoing clinical trials included in this review may further contribute to improving outcomes for patients with EGJAC.

FOOTNOTES

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