**Name of Journal:** *World Journal of Gastroenterology*

**Manuscript NO:** 84785

**Manuscript Type:** MINIREVIEWS

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

Shoji Y *et al*. Multidisciplinary treatment for resectable EGJ cancer

Yoshiaki Shoji, Kazuo Koyanagi, Kohei Kanamori, Kohei Tajima, Mika Ogimi, Kentaro Yatabe, Miho Yamamoto, Akihito Kazuno, Kazuhito Nabeshima, Kenji Nakamura, Takayuki Nishi, Masaki Mori

**Yoshiaki Shoji, Kazuo Koyanagi, Kohei Kanamori, Kohei Tajima, Mika Ogimi, Kentaro Yatabe, Miho Yamamoto, Akihito Kazuno, Kazuhito Nabeshima, Kenji Nakamura, Takayuki Nishi, Masaki Mori,** Department of Gastroenterological Surgery, Tokai University School of Medicine, Isehara 259-1193, Japan

**Author contributions:** Shoji Y and Koyanagi K contributed to Conceptualization; Shoji Y contributed to writing and original draft preparation; Kanamori K, Tajima K, Ogimi M, Yatabe K, Yamamoto M, Kazuno A, Nabeshima K, Nakamura K and Nishi T contributed to investigation; Koyanagi K and Mori M contributed to supervision; All authors have read and agreed to the published version of the manuscript.

**Corresponding author: Kazuo Koyanagi, FACS, MD, PhD, Chairman, Professor,** Department of Gastroenterological Surgery, Tokai University School of Medicine, 143, Shimokasuya, Isehara 259-1193, Japan. kkoyanagi@tsc.u-tokai.ac.jp

**Received:** March 28, 2023

**Revised:** May 21, 2023

**Accepted:** June 2, 2023

**Published online:**

**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

Shoji Y, Koyanagi K, Kanamori K, Tajima K, Ogimi M, Yatabe K, Yamamoto M, Kazuno A, Nabeshima K, Nakamura K, Nishi T, Mori M. Current status and future perspectives for the treatment of resectable locally advanced esophagogastric junction cancer: A narrative review. *World J Gastroenterol* 2023; In press

**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.

**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 *H. 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.

***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.

***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 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], 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.

**REFERENCES**

1 **Sung H**, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, Bray F. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA Cancer J Clin* 2021; **71**: 209-249 [PMID: 33538338 DOI: 10.3322/caac.21660]

2 **Arnold M**, Laversanne M, Brown LM, Devesa SS, Bray F. Predicting the Future Burden of Esophageal Cancer by Histological Subtype: International Trends in Incidence up to 2030. *Am J Gastroenterol* 2017; **112**: 1247-1255 [PMID: 28585555 DOI: 10.1038/ajg.2017.155]

3 **Al-Batran SE**, Homann N, Pauligk C, Goetze TO, Meiler J, Kasper S, Kopp HG, Mayer F, Haag GM, Luley K, Lindig U, Schmiegel W, Pohl M, Stoehlmacher J, Folprecht G, Probst S, Prasnikar N, Fischbach W, Mahlberg R, Trojan J, Koenigsmann M, Martens UM, Thuss-Patience P, Egger M, Block A, Heinemann V, Illerhaus G, Moehler M, Schenk M, Kullmann F, Behringer DM, Heike M, Pink D, Teschendorf C, Löhr C, Bernhard H, Schuch G, Rethwisch V, von Weikersthal LF, Hartmann JT, Kneba M, Daum S, Schulmann K, Weniger J, Belle S, Gaiser T, Oduncu FS, Güntner M, Hozaeel W, Reichart A, Jäger E, Kraus T, Mönig S, Bechstein WO, Schuler M, Schmalenberg H, Hofheinz RD; FLOT4-AIO Investigators. Perioperative chemotherapy with fluorouracil plus leucovorin, oxaliplatin, and docetaxel versus fluorouracil or capecitabine plus cisplatin and epirubicin for locally advanced, resectable gastric or gastro-oesophageal junction adenocarcinoma (FLOT4): a randomised, phase 2/3 trial. *Lancet* 2019; **393**: 1948-1957 [PMID: 30982686 DOI: 10.1016/S0140-6736(18)32557-1]

4 **van Hagen P**, Hulshof MC, van Lanschot JJ, Steyerberg EW, van Berge Henegouwen MI, Wijnhoven BP, Richel DJ, Nieuwenhuijzen GA, Hospers GA, Bonenkamp JJ, Cuesta MA, Blaisse RJ, Busch OR, ten Kate FJ, Creemers GJ, Punt CJ, Plukker JT, Verheul HM, Spillenaar Bilgen EJ, van Dekken H, van der Sangen MJ, Rozema T, Biermann K, Beukema JC, Piet AH, van Rij CM, Reinders JG, Tilanus HW, van der Gaast A; CROSS Group. Preoperative chemoradiotherapy for esophageal or junctional cancer. *N Engl J Med* 2012; **366**: 2074-2084 [PMID: 22646630 DOI: 10.1056/NEJMoa1112088]

5 **Kitagawa Y**, Uno T, Oyama T, Kato K, Kato H, Kawakubo H, Kawamura O, Kusano M, Kuwano H, Takeuchi H, Toh Y, Doki Y, Naomoto Y, Nemoto K, Booka E, Matsubara H, Miyazaki T, Muto M, Yanagisawa A, Yoshida M. Esophageal cancer practice guidelines 2017 edited by the Japan Esophageal Society: part 1. *Esophagus* 2019; **16**: 1-24 [PMID: 30171413 DOI: 10.1007/s10388-018-0641-9]

6 **Yamashita H**, Seto Y, Sano T, Makuuchi H, Ando N, Sasako M; Japanese Gastric Cancer Association and the Japan Esophageal Society. Results of a nation-wide retrospective study of lymphadenectomy for esophagogastric junction carcinoma. *Gastric Cancer* 2017; **20**: 69-83 [PMID: 27796514 DOI: 10.1007/s10120-016-0663-8]

7 **Kurokawa Y**, Takeuchi H, Doki Y, Mine S, Terashima M, Yasuda T, Yoshida K, Daiko H, Sakuramoto S, Yoshikawa T, Kunisaki C, Seto Y, Tamura S, Shimokawa T, Sano T, Kitagawa Y. Mapping of Lymph Node Metastasis From Esophagogastric Junction Tumors: A Prospective Nationwide Multicenter Study. *Ann Surg* 2021; **274**: 120-127 [PMID: 31404008 DOI: 10.1097/SLA.0000000000003499]

8 **Mine S**, Kurokawa Y, Takeuchi H, Terashima M, Yasuda T, Yoshida K, Yabusaki H, Shirakawa Y, Fujitani K, Sano T, Doki Y, Kitagawa Y. Postoperative complications after a transthoracic esophagectomy or a transhiatal gastrectomy in patients with esophagogastric junctional cancers: a prospective nationwide multicenter study. *Gastric Cancer* 2022; **25**: 430-437 [PMID: 34590178 DOI: 10.1007/s10120-021-01255-9]

9 **Yamashita Y**, Tatsubayashi T, Okumura K, Miyamoto T, Ueno K. Modified side overlap esophagogastrostomy after laparoscopic proximal gastrectomy. *Ann Gastroenterol Surg* 2022; **6**: 594-599 [PMID: 35847432 DOI: 10.1002/ags3.12549]

10 **Yamashita Y**, Yamamoto A, Tamamori Y, Yoshii M, Nishiguchi Y. Side overlap esophagogastrostomy to prevent reflux after proximal gastrectomy. *Gastric Cancer* 2017; **20**: 728-735 [PMID: 27942874 DOI: 10.1007/s10120-016-0674-5]

11 **Shoji Y**, Nunobe S, Ida S, Kumagai K, Ohashi M, Sano T, Hiki N. Surgical outcomes and risk assessment for anastomotic complications after laparoscopic proximal gastrectomy with double-flap technique for upper-third gastric cancer. *Gastric Cancer* 2019; **22**: 1036-1043 [PMID: 30838469 DOI: 10.1007/s10120-019-00940-0]

12 **Kelly RJ**, Ajani JA, Kuzdzal J, Zander T, Van Cutsem E, Piessen G, Mendez G, Feliciano J, Motoyama S, Lièvre A, Uronis H, Elimova E, Grootscholten C, Geboes K, Zafar S, Snow S, Ko AH, Feeney K, Schenker M, Kocon P, Zhang J, Zhu L, Lei M, Singh P, Kondo K, Cleary JM, Moehler M; CheckMate 577 Investigators. Adjuvant Nivolumab in Resected Esophageal or Gastroesophageal Junction Cancer. *N Engl J Med* 2021; **384**: 1191-1203 [PMID: 33789008 DOI: 10.1056/NEJMoa2032125]

13 **Tang Z**, Wang Y, Liu D, Wang X, Xu C, Yu Y, Cui Y, Tang C, Li Q, Sun J, Zhang Q, Ji Y, Ma G, Li H, Shen Z, Shen K, Zheng R, Hou Z, Liu T, Wang J, Sun Y. The Neo-PLANET phase II trial of neoadjuvant camrelizumab plus concurrent chemoradiotherapy in locally advanced adenocarcinoma of stomach or gastroesophageal junction. *Nat Commun* 2022; **13**: 6807 [PMID: 36357415 DOI: 10.1038/s41467-022-34403-5]

14 **André T**, Tougeron D, Piessen G, de la Fouchardière C, Louvet C, Adenis A, Jary M, Tournigand C, Aparicio T, Desrame J, Lièvre A, Garcia-Larnicol ML, Pudlarz T, Cohen R, Memmi S, Vernerey D, Henriques J, Lefevre JH, Svrcek M. Neoadjuvant Nivolumab Plus Ipilimumab and Adjuvant Nivolumab in Localized Deficient Mismatch Repair/Microsatellite Instability-High Gastric or Esophagogastric Junction Adenocarcinoma: The GERCOR NEONIPIGA Phase II Study. *J Clin Oncol* 2023; **41**: 255-265 [PMID: 35969830 DOI: 10.1200/JCO.22.00686]

15 **Rüdiger Siewert J**, Feith M, Werner M, Stein HJ. Adenocarcinoma of the esophagogastric junction: results of surgical therapy based on anatomical/topographic classification in 1,002 consecutive patients. *Ann Surg* 2000; **232**: 353-361 [PMID: 10973385 DOI: 10.1097/00000658-200009000-00007]

16 **Pedrazzani C**, de Manzoni G, Marrelli D, Giacopuzzi S, Corso G, Minicozzi AM, Rampone B, Roviello F. Lymph node involvement in advanced gastroesophageal junction adenocarcinoma. *J Thorac Cardiovasc Surg* 2007; **134**: 378-385 [PMID: 17662776 DOI: 10.1016/j.jtcvs.2007.03.034]

17 **Japanese Gastric Cancer Association**. Japanese classification of gastric carcinoma: 3rd English edition. *Gastric Cancer* 2011; **14**: 101-112 [PMID: 21573743 DOI: 10.1007/s10120-011-0041-5]

18 **Japan Esophageal Society**. Japanese Classification of Esophageal Cancer, 11th Edition: part I. *Esophagus* 2017; **14**: 1-36 [PMID: 28111535 DOI: 10.1007/s10388-016-0551-7]

19 **Japanese Gastric Cancer Association**. Japanese Gastric Cancer Treatment Guidelines 2021 (6th edition). *Gastric Cancer* 2023; **26**: 1-25 [PMID: 36342574 DOI: 10.1007/s10120-022-01331-8]

20 **Leers JM**, Knepper L, van der Veen A, Schröder W, Fuchs H, Schiller P, Hellmich M, Zettelmeyer U, Brosens LAA, Quaas A, Ruurda JP, van Hillegersberg R, Bruns CJ. The CARDIA-trial protocol: a multinational, prospective, randomized, clinical trial comparing transthoracic esophagectomy with transhiatal extended gastrectomy in adenocarcinoma of the gastroesophageal junction (GEJ) type II. *BMC Cancer* 2020; **20**: 781 [PMID: 32819399 DOI: 10.1186/s12885-020-07152-1]

21 **Mine S**, Sano T, Hiki N, Yamada K, Kosuga T, Nunobe S, Yamaguchi T. Proximal margin length with transhiatal gastrectomy for Siewert type II and III adenocarcinomas of the oesophagogastric junction. *Br J Surg* 2013; **100**: 1050-1054 [PMID: 23754647 DOI: 10.1002/bjs.9170]

22 **Koterazawa Y**, Ohashi M, Hayami M, Makuuchi R, Ida S, Kumagai K, Sano T, Nunobe S. Required esophageal resection length beyond the tumor boundary to ensure a negative proximal margin for gastric cancer with gross esophageal invasion or esophagogastric junction cancer. *Gastric Cancer* 2023; **26**: 451-459 [PMID: 36725762 DOI: 10.1007/s10120-023-01369-2]

23 **Xu Y**, Tan Y, Wang Y, Xi C, Ye N, Xu X. Proximal versus total gastrectomy for proximal early gastric cancer: A systematic review and meta-analysis. *Medicine (Baltimore)* 2019; **98**: e15663 [PMID: 31083268 DOI: 10.1097/MD.0000000000015663]

24 **An JY**, Youn HG, Choi MG, Noh JH, Sohn TS, Kim S. The difficult choice between total and proximal gastrectomy in proximal early gastric cancer. *Am J Surg* 2008; **196**: 587-591 [PMID: 18519129 DOI: 10.1016/j.amjsurg.2007.09.040]

25 **Ronellenfitsch U**, Najmeh S, Andalib A, Perera RM, Rousseau MC, Mulder DS, Ferri LE. Functional outcomes and quality of life after proximal gastrectomy with esophagogastrostomy using a narrow gastric conduit. *Ann Surg Oncol* 2015; **22**: 772-779 [PMID: 25212836 DOI: 10.1245/s10434-014-4078-7]

26 **Hayami M**, Hiki N, Nunobe S, Mine S, Ohashi M, Kumagai K, Ida S, Watanabe M, Sano T, Yamaguchi T. Clinical Outcomes and Evaluation of Laparoscopic Proximal Gastrectomy with Double-Flap Technique for Early Gastric Cancer in the Upper Third of the Stomach. *Ann Surg Oncol* 2017; **24**: 1635-1642 [PMID: 28130623 DOI: 10.1245/s10434-017-5782-x]

27 **Biere SS**, van Berge Henegouwen MI, Maas KW, Bonavina L, Rosman C, Garcia JR, Gisbertz SS, Klinkenbijl JH, Hollmann MW, de Lange ES, Bonjer HJ, van der Peet DL, Cuesta MA. Minimally invasive versus open oesophagectomy for patients with oesophageal cancer: a multicentre, open-label, randomised controlled trial. *Lancet* 2012; **379**: 1887-1892 [PMID: 22552194 DOI: 10.1016/S0140-6736(12)60516-9]

28 **van der Sluis PC**, van der Horst S, May AM, Schippers C, Brosens LAA, Joore HCA, Kroese CC, Haj Mohammad N, Mook S, Vleggaar FP, Borel Rinkes IHM, Ruurda JP, van Hillegersberg R. Robot-assisted Minimally Invasive Thoracolaparoscopic Esophagectomy Versus Open Transthoracic Esophagectomy for Resectable Esophageal Cancer: A Randomized Controlled Trial. *Ann Surg* 2019; **269**: 621-630 [PMID: 30308612 DOI: 10.1097/SLA.0000000000003031]

29 **de Groot EM**, van der Horst S, Kingma BF, Goense L, van der Sluis PC, Ruurda JP, van Hillegersberg R. Robot-assisted minimally invasive thoracolaparoscopic esophagectomy versus open esophagectomy: long-term follow-up of a randomized clinical trial. *Dis Esophagus* 2020; **33** [PMID: 33241302 DOI: 10.1093/dote/doaa079]

30 **Shi Y**, Xu X, Zhao Y, Qian F, Tang B, Hao Y, Luo H, Chen J, Yu P. Short-term surgical outcomes of a randomized controlled trial comparing laparoscopic versus open gastrectomy with D2 lymph node dissection for advanced gastric cancer. *Surg Endosc* 2018; **32**: 2427-2433 [PMID: 29234941 DOI: 10.1007/s00464-017-5942-x]

31 **Tagkalos E**, van der Sluis PC, Berlth F, Poplawski A, Hadzijusufovic E, Lang H, van Berge Henegouwen MI, Gisbertz SS, Müller-Stich BP, Ruurda JP, Schiesser M, Schneider PM, van Hillegersberg R, Grimminger PP. Robot-assisted minimally invasive thoraco-laparoscopic esophagectomy versus minimally invasive esophagectomy for resectable esophageal adenocarcinoma, a randomized controlled trial (ROBOT-2 trial). *BMC Cancer* 2021; **21**: 1060 [PMID: 34565343 DOI: 10.1186/s12885-021-08780-x]

32 **Al-Batran SE**, Hofheinz RD, Pauligk C, Kopp HG, Haag GM, Luley KB, Meiler J, Homann N, Lorenzen S, Schmalenberg H, Probst S, Koenigsmann M, Egger M, Prasnikar N, Caca K, Trojan J, Martens UM, Block A, Fischbach W, Mahlberg R, Clemens M, Illerhaus G, Zirlik K, Behringer DM, Schmiegel W, Pohl M, Heike M, Ronellenfitsch U, Schuler M, Bechstein WO, Königsrainer A, Gaiser T, Schirmacher P, Hozaeel W, Reichart A, Goetze TO, Sievert M, Jäger E, Mönig S, Tannapfel A. Histopathological regression after neoadjuvant docetaxel, oxaliplatin, fluorouracil, and leucovorin versus epirubicin, cisplatin, and fluorouracil or capecitabine in patients with resectable gastric or gastro-oesophageal junction adenocarcinoma (FLOT4-AIO): results from the phase 2 part of a multicentre, open-label, randomised phase 2/3 trial. *Lancet Oncol* 2016; **17**: 1697-1708 [PMID: 27776843 DOI: 10.1016/S1470-2045(16)30531-9]

33 **Shapiro J**, van Lanschot JJB, Hulshof MCCM, van Hagen P, van Berge Henegouwen MI, Wijnhoven BPL, van Laarhoven HWM, Nieuwenhuijzen GAP, Hospers GAP, Bonenkamp JJ, Cuesta MA, Blaisse RJB, Busch ORC, Ten Kate FJW, Creemers GM, Punt CJA, Plukker JTM, Verheul HMW, Bilgen EJS, van Dekken H, van der Sangen MJC, Rozema T, Biermann K, Beukema JC, Piet AHM, van Rij CM, Reinders JG, Tilanus HW, Steyerberg EW, van der Gaast A; CROSS study group. Neoadjuvant chemoradiotherapy plus surgery versus surgery alone for oesophageal or junctional cancer (CROSS): long-term results of a randomised controlled trial. *Lancet Oncol* 2015; **16**: 1090-1098 [PMID: 26254683 DOI: 10.1016/S1470-2045(15)00040-6]

34 **Kang YK**, Yook JH, Park YK, Lee JS, Kim YW, Kim JY, Ryu MH, Rha SY, Chung IJ, Kim IH, Oh SC, Park YS, Son T, Jung MR, Heo MH, Kim HK, Park C, Yoo CH, Choi JH, Zang DY, Jang YJ, Sul JY, Kim JG, Kim BS, Beom SH, Cho SH, Ryu SW, Kook MC, Ryoo BY, Kim HK, Yoo MW, Lee NS, Lee SH, Kim G, Lee Y, Lee JH, Noh SH. PRODIGY: A Phase III Study of Neoadjuvant Docetaxel, Oxaliplatin, and S-1 Plus Surgery and Adjuvant S-1 Versus Surgery and Adjuvant S-1 for Resectable Advanced Gastric Cancer. *J Clin Oncol* 2021; **39**: 2903-2913 [PMID: 34133211 DOI: 10.1200/JCO.20.02914]

35 **Klevebro F**, Alexandersson von Döbeln G, Wang N, Johnsen G, Jacobsen AB, Friesland S, Hatlevoll I, Glenjen NI, Lind P, Tsai JA, Lundell L, Nilsson M. A randomized clinical trial of neoadjuvant chemotherapy versus neoadjuvant chemoradiotherapy for cancer of the oesophagus or gastro-oesophageal junction. *Ann Oncol* 2016; **27**: 660-667 [PMID: 26782957 DOI: 10.1093/annonc/mdw010]

36 **Klevebro F**, Johnsen G, Johnson E, Viste A, Myrnäs T, Szabo E, Jacobsen AB, Friesland S, Tsai JA, Persson S, Lindblad M, Lundell L, Nilsson M. Morbidity and mortality after surgery for cancer of the oesophagus and gastro-oesophageal junction: A randomized clinical trial of neoadjuvant chemotherapy vs. neoadjuvant chemoradiation. *Eur J Surg Oncol* 2015; **41**: 920-926 [PMID: 25908010 DOI: 10.1016/j.ejso.2015.03.226]

37 **Stahl M**, Walz MK, Stuschke M, Lehmann N, Meyer HJ, Riera-Knorrenschild J, Langer P, Engenhart-Cabillic R, Bitzer M, Königsrainer A, Budach W, Wilke H. Phase III comparison of preoperative chemotherapy compared with chemoradiotherapy in patients with locally advanced adenocarcinoma of the esophagogastric junction. *J Clin Oncol* 2009; **27**: 851-856 [PMID: 19139439 DOI: 10.1200/JCO.2008.17.0506]

38 **Reynolds JV,** Preston SR, O'Neill B, Lowery MA, Baeksgaard L, Crosby T, Cunningham M, Cuffe S, Griffiths GO, Roy R, Falk S, Hanna G, Bartlett FR, Parker I, Alvarez-Iglesias A, Nilsson M, Piessen G, Risum S, Ravi N, McDermott RS. Neo-AEGIS (Neoadjuvant trial in Adenocarcinoma of the Esophagus and Esophago-Gastric Junction International Study): Preliminary results of phase III RCT of CROSS vs perioperative chemotherapy (Modified MAGIC or FLOT protocol). (NCT01726452). *Journal of Clinical Oncology*. 2021;**39** (15\_suppl):4004- [DOI:10.1200/JCO.2021.39.15\_suppl.4004]

39 **Lorenzen S**, Biederstädt A, Ronellenfitsch U, Reißfelder C, Mönig S, Wenz F, Pauligk C, Walker M, Al-Batran SE, Haller B, Hofheinz RD. RACE-trial: neoadjuvant radiochemotherapy versus chemotherapy for patients with locally advanced, potentially resectable adenocarcinoma of the gastroesophageal junction - a randomized phase III joint study of the AIO, ARO and DGAV. *BMC Cancer* 2020; **20**: 886 [PMID: 32933498 DOI: 10.1186/s12885-020-07388-x]

40 **Doki Y**, Ajani JA, Kato K, Xu J, Wyrwicz L, Motoyama S, Ogata T, Kawakami H, Hsu CH, Adenis A, El Hajbi F, Di Bartolomeo M, Braghiroli MI, Holtved E, Ostoich SA, Kim HR, Ueno M, Mansoor W, Yang WC, Liu T, Bridgewater J, Makino T, Xynos I, Liu X, Lei M, Kondo K, Patel A, Gricar J, Chau I, Kitagawa Y; CheckMate 648 Trial Investigators. Nivolumab Combination Therapy in Advanced Esophageal Squamous-Cell Carcinoma. *N Engl J Med* 2022; **386**: 449-462 [PMID: 35108470 DOI: 10.1056/NEJMoa2111380]

41 **Sun JM**, Shen L, Shah MA, Enzinger P, Adenis A, Doi T, Kojima T, Metges JP, Li Z, Kim SB, Cho BC, Mansoor W, Li SH, Sunpaweravong P, Maqueda MA, Goekkurt E, Hara H, Antunes L, Fountzilas C, Tsuji A, Oliden VC, Liu Q, Shah S, Bhagia P, Kato K; KEYNOTE-590 Investigators. Pembrolizumab plus chemotherapy versus chemotherapy alone for first-line treatment of advanced oesophageal cancer (KEYNOTE-590): a randomised, placebo-controlled, phase 3 study. *Lancet* 2021; **398**: 759-771 [PMID: 34454674 DOI: 10.1016/S0140-6736(21)01234-4]

42 **Janjigian YY**, Shitara K, Moehler M, Garrido M, Salman P, Shen L, Wyrwicz L, Yamaguchi K, Skoczylas T, Campos Bragagnoli A, Liu T, Schenker M, Yanez P, Tehfe M, Kowalyszyn R, Karamouzis MV, Bruges R, Zander T, Pazo-Cid R, Hitre E, Feeney K, Cleary JM, Poulart V, Cullen D, Lei M, Xiao H, Kondo K, Li M, Ajani JA. First-line nivolumab plus chemotherapy versus chemotherapy alone for advanced gastric, gastro-oesophageal junction, and oesophageal adenocarcinoma (CheckMate 649): a randomised, open-label, phase 3 trial. *Lancet* 2021; **398**: 27-40 [PMID: 34102137 DOI: 10.1016/S0140-6736(21)00797-2]

43 **Kang YK**, Chen LT, Ryu MH, Oh DY, Oh SC, Chung HC, Lee KW, Omori T, Shitara K, Sakuramoto S, Chung IJ, Yamaguchi K, Kato K, Sym SJ, Kadowaki S, Tsuji K, Chen JS, Bai LY, Oh SY, Choda Y, Yasui H, Takeuchi K, Hirashima Y, Hagihara S, Boku N. Nivolumab plus chemotherapy versus placebo plus chemotherapy in patients with HER2-negative, untreated, unresectable advanced or recurrent gastric or gastro-oesophageal junction cancer (ATTRACTION-4): a randomised, multicentre, double-blind, placebo-controlled, phase 3 trial. *Lancet Oncol* 2022; **23**: 234-247 [PMID: 35030335 DOI: 10.1016/S1470-2045(21)00692-6]

44 **Safran HP**, Winter K, Ilson DH, Wigle D, DiPetrillo T, Haddock MG, Hong TS, Leichman LP, Rajdev L, Resnick M, Kachnic LA, Seaward S, Mamon H, Diaz Pardo DA, Anderson CM, Shen X, Sharma AK, Katz AW, Salo J, Leonard KL, Moughan J, Crane CH. Trastuzumab with trimodality treatment for oesophageal adenocarcinoma with HER2 overexpression (NRG Oncology/RTOG 1010): a multicentre, randomised, phase 3 trial. *Lancet Oncol* 2022; **23**: 259-269 [PMID: 35038433 DOI: 10.1016/S1470-2045(21)00718-X]

45 **Takahari D,** Kawazoe A, Machida N, Minashi K, Yamagata Y, Hara H, Wakabayashi M, Komura Y, Sato A, Kuwata T, Kojima M, Shitara K. Phase 2 study of trastuzumab deruxtecan in the neoadjuvant treatment for patients with HER2-positive gastric and gastroesophageal junction adenocarcinoma (EPOC2003). *Journal of Clinical Oncology*. 2022;**40** (16\_suppl):TPS4161-TPS [DOI:10.1200/JCO.2022.40.16\_suppl.TPS4161]

46 **Suh YS**, Na D, Lee JS, Chae J, Kim E, Jang G, Lee J, Min J, Ock CY, Kong SH, George J, Zhang C, Lee HJ, Kim JI, Kim SJ, Kim WH, Lee C, Yang HK. Comprehensive Molecular Characterization of Adenocarcinoma of the Gastroesophageal Junction Between Esophageal and Gastric Adenocarcinomas. *Ann Surg* 2022; **275**: 706-717 [PMID: 33086305 DOI: 10.1097/SLA.0000000000004303]

47 **Yang YM**, Hong P, Xu WW, He QY, Li B. Advances in targeted therapy for esophageal cancer. *Signal Transduct Target Ther* 2020; **5**: 229 [PMID: 33028804 DOI: 10.1038/s41392-020-00323-3]

48 **Bang YJ**, Kim YW, Yang HK, Chung HC, Park YK, Lee KH, Lee KW, Kim YH, Noh SI, Cho JY, Mok YJ, Kim YH, Ji J, Yeh TS, Button P, Sirzén F, Noh SH; CLASSIC trial investigators. Adjuvant capecitabine and oxaliplatin for gastric cancer after D2 gastrectomy (CLASSIC): a phase 3 open-label, randomised controlled trial. *Lancet* 2012; **379**: 315-321 [PMID: 22226517 DOI: 10.1016/S0140-6736(11)61873-4]

49 **Noh SH**, Park SR, Yang HK, Chung HC, Chung IJ, Kim SW, Kim HH, Choi JH, Kim HK, Yu W, Lee JI, Shin DB, Ji J, Chen JS, Lim Y, Ha S, Bang YJ; CLASSIC trial investigators. Adjuvant capecitabine plus oxaliplatin for gastric cancer after D2 gastrectomy (CLASSIC): 5-year follow-up of an open-label, randomised phase 3 trial. *Lancet Oncol* 2014; **15**: 1389-1396 [PMID: 25439693 DOI: 10.1016/S1470-2045(14)70473-5]

50 **Yoshida K**, Kodera Y, Kochi M, Ichikawa W, Kakeji Y, Sano T, Nagao N, Takahashi M, Takagane A, Watanabe T, Kaji M, Okitsu H, Nomura T, Matsui T, Yoshikawa T, Matsuyama J, Yamada M, Ito S, Takeuchi M, Fujii M. Addition of Docetaxel to Oral Fluoropyrimidine Improves Efficacy in Patients With Stage III Gastric Cancer: Interim Analysis of JACCRO GC-07, a Randomized Controlled Trial. *J Clin Oncol* 2019; **37**: 1296-1304 [PMID: 30925125 DOI: 10.1200/JCO.18.01138]

51 **Kakeji Y**, Yoshida K, Kodera Y, Kochi M, Sano T, Ichikawa W, Lee SW, Shibahara K, Shikano T, Kataoka M, Ishiguro A, Ojima H, Sakai Y, Musha N, Takase T, Kimura T, Takeuchi M, Fujii M. Three-year outcomes of a randomized phase III trial comparing adjuvant chemotherapy with S-1 plus docetaxel versus S-1 alone in stage III gastric cancer: JACCRO GC-07. *Gastric Cancer* 2022; **25**: 188-196 [PMID: 34351555 DOI: 10.1007/s10120-021-01224-2]

52 **Sasako M**, Sakuramoto S, Katai H, Kinoshita T, Furukawa H, Yamaguchi T, Nashimoto A, Fujii M, Nakajima T, Ohashi Y. Five-year outcomes of a randomized phase III trial comparing adjuvant chemotherapy with S-1 versus surgery alone in stage II or III gastric cancer. *J Clin Oncol* 2011; **29**: 4387-4393 [PMID: 22010012 DOI: 10.1200/JCO.2011.36.5908]

**Footnotes**

**Conflict-of-interest statement:** All the authors report no relevant conflicts of interest for this article.

**Open-Access:** This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: https://creativecommons.org/Licenses/by-nc/4.0/

**Provenance and peer review:** Invited article; Externally peer reviewed.

**Peer-review model:** Single blind

**Corresponding Author's Membership in Professional Societies:** The Japanese Society of Gastroenterology.

**Peer-review started:** March 28, 2023

**First decision:** May 12, 2023

**Article in press:**

**Specialty type:** Gastroenterology and hepatology

**Country/Territory of origin:** Japan

**Peer-review report’s scientific quality classification**

Grade A (Excellent): 0

Grade B (Very good): B

Grade C (Good): C, C

Grade D (Fair): 0

Grade E (Poor): 0

**P-Reviewer:** Edholm D, Sweden; Li J, China; Molinari C, Italy **S-Editor:** Li L **L-Editor:** A **P-Editor:**

**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/4b1 | 4/10/3/18/0/0 |
| pN 0/1/2/31 | 15/4/4/12 |
| pM 0/11 | 30/5 |
| pStage IA/IB/IIA/IIB/IIIA/IIIB/IVA/IVB1 | 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 recurrence2 |  |
| Liver | 5 |
| Adrenal gland | 5 |
| Distant LN | 3 |
| Peritoneum | 2 |
| Bone | 2 |
| Pleura | 1 |
| Pancreas | 1 |

1Classified by the 8th edition of the Union for International Cancer Control (UICC)-Tumor Node Metastasis (TNM) classification.

2Including overlapped cases.

EGJAC: Esophagogastric adenocarcinoma; LN: Lymph node; MIE: Minimally invasive esophagectomy.

**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.

**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]** |
| Author | Al-Batran *et al*[3,32] | Shapiro *et al*[33], van Hagen *et al*[4] | Kang *et al*[34] |
| Yr | 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.

**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]** |
| Author | 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]** |
| Author | 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.