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Professor Andrzej S Tarnawski, DSc, MD, PhD, Gastroenterology Research Department,
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Editor-in-Chief

World Journal of Gastroenterology

Dear Prof. Andrzej S Tarnawski,

We thank for your kind review for the article entitled “Current Status and Future Perspectives for the Treatment of Resectable Locally Advanced Esophagogastric Junction Cancer; A Narrative Review”, which has been submitted to ***World Journal of Gastroenterology***. We have improved our manuscript according to the reviewers’ comments. Below are the point-by-point responses to the reviewer’s suggestions. All the changes are highlighted within the manuscript.

Reviewer #1:

First, the definition is inconsistent across regions and countries, including studies cited by this review, which may also determined the differences in treatment of EGJ cancer

We thank you for your valuable comment. As the reviewer mentioned, the difference in the definition for EGJ cancer has caused differences in the treatment of EGJ cancer, especially for the surgical treatment. We have added a paragraph in the **Standardizing the surgical procedure for EGJAC, Mediastinal lymph node dissection** section as below,

One of the unique features of these Japanese studies is that squamous cell carcinomas located within 2cm of the EGJ are included, and are analyzed along with EGJAC. In Japan, regardless of histological type, tumors within 2cm 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 2cm 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.

Second, along with the popularization of laparoscopic and robotic technology, minimally invasive surgery has also been investigated in treatment for EGJ cancer, however, the evidence support its widely generalization is limited

We thank you again for your important comment. As the reviewer commented, safety and efficacy of minimally invasive surgery is an important topic for EGJ cancer treatment, however, evidence is still lacking. We have added a new section *Minimally invasive surgery for EGJ cancer* under **Standardizing the surgical procedure for EGJAC** section as follows,

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, Surya et al. 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 weeks 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) versus 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% versus 40%, $p=0.827$) and disease-free survival (DFS, 42% versus 43%, $p=0.749$) rates were observed for patients after RAMIE versus OE, respectively.

Regarding gastrectomy, the short-term surgical outcomes of a single-center non-inferiority randomized trial for laparoscopic versus 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.

Third, there has debate on the extent to which the stomach should be cut for EGJ cancer, some centers adopt total gastrectomy to avoid gastroesophageal reflux, while others may prefer proximal gastrectomy to retain some functions of stomach.

Thank you again for your comment. Functional aspects are also important to determine the optimal reconstruction method for EGJ cancers. We have reorganized **Standardizing the surgical procedure for EGJAC**, *Reconstruction to prevent anastomotic complications* section along with new references as follows,

Therefore, the distal portion of the stomach does not need to be necessarily removed for Siewert type II EGJAC smaller than 4cm, 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 versus 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).

Reviewer #2:

Introduction “have possibly been treated” what does this mean? Consider clarification or

language review.

Thank you for your comment. We have corrected the **Introduction** section as follows, Surgical procedure for Siewert type II tumors (1cm above to 2cm below EGJ) have been selected by individual surgeons or institutional preferences.

“Further, resent studies” change to recent.

Thank you for your correction. We have removed “Further” and corrected to “recent studies” in the **Introduction** section.

Minimal-required prox margin length “Proximal margins larger” change larger to greater

Thank you again for your correction. We have corrected “larger” to “greater” in the **Standardizing the surgical procedure for EGJAC, Minimal-required proximal margin length** section.

Optimal perioperative treatment for EGJAC CROSS study, is it really correct that survival benefit was limited in adenocarcinomas? As I recall survival benefit was shown in both SCCsa and adenocarcinomas?

Thank you for your important comment. According to the subgroup analysis according to histologic subtype in the CROSS trial, As the reviewer mentioned, although hazard ratios for death was relatively larger for adenocarcinomas compared to SCC (0.741 (0.536-1.024) vs 0.422 (0.226-0.788)), no significant difference was observed. Therefore, we have removed the sentence shown below, and corrected related comments in the **Optimal perioperative treatment for EGJAC, Neoadjuvant chemotherapy or chemoradiotherapy, which is the best choice?** Section. Subgroup analysis revealed that although effective, the survival benefit of neoadjuvant chemoradiotherapy was limited in adenocarcinomas when compared to squamous cell carcinomas.

Stahl study, you state that the mortality was high after CRT but still the 3 year survival was better in the group treated w CRT compared to the CT group. Any mortality from the CRT will be taken into account in the survival analysis.

Thank you again for your important comment. As the reviewer pointed out, the writing about POET study may have caused confusion. We have corrected **Optimal perioperative treatment**

for EGJAC, Neoadjuvant chemotherapy or chemoradiotherapy, which is the best choice? section as follows,

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% versus 27.7%, HR, 0.67; 95% CI, 0.41–1.07; P=0.07, Table 4).

Should NEO-aegis be mentioned here as well?

Thank you again for your important comment. The preliminary result of the Neo-AEGIS trial have been reported in 2021, and should have been included in the manuscript. We have included new reference and sentences in the **Optimal perioperative treatment for EGJAC, Neoadjuvant chemotherapy or chemoradiotherapy, which is the best choice?** section as follows, and added Neo-AEGIS trial in Table 4.

In 2021, preliminary results of a phase III study, which aimed to compare CROSS versus FLOT or MAGIC (epirubicin, cisplatin/oxaliplatin, and 5-fluorouracil/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) months, the 3-year estimated survival probability was equivalent between CROSS and MAGIC/FLOT arm (HR, 1.02; 95%CI, 0.74-1.42).

GERCOR NEONIPIGA study, “at database lock” for how long were the patients studied at database lock?

Thank you for your comment. As the reviewer mentioned, follow-up term should have been clarified in the manuscript. We have corrected **Optimal perioperative treatment for EGJAC, Neoadjuvant chemotherapy or chemoradiotherapy, which is the best choice?** section as follows, At database lock (median follow-up, 14.9 months)

“Checkmate 577 study the prognostic”, consider removing prognostic

Thank you for your correction. We have removed “prognostic” in the **Optimal perioperative treatment for EGJAC, Is adjuvant therapy needed?** Section.

Reviewer #3:

I think it is a good paper, but adding some considerations on the molecular characterization could be of interest. It has been shown that different molecular phenotypes of esophagogastric junction cancers exist. Thus, the evaluation and implementation of molecular biomarkers, rather than tumor location, plays an important role in future clinical trial designs and could impact on the therapeutic choice of such a patients. I suggest authors to add some comments on that.

Thank you for your valuable comment. Indeed, molecular characterization would play an important role in defining individual treatment option for EGJ cancer patients in the near future. We have corrected **Optimal perioperative treatment for EGJAC**, *Future of targeted therapy* section along with new references as follows,

In a recent analysis utilizing the Cancer Genome Atlas (TCGA) (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.

We thank you again for the opportunity to revise the manuscript according to the reviewer's comments. I sincerely hope that you will find this manuscript acceptable for publication in the *World Journal of Gastroenterology* and that you will give favorable consideration to the article.

Best regards,

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