



## Comment on: “Phase II study of S-1 and oxaliplatin as neoadjuvant chemotherapy for locally advanced adenocarcinoma of the gastric or esophagogastric junction: KSCC1601. Gastric cancer, 2021 Aug 11” by Iwatsuki et al

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Dear Editor,

We have read with interest a recent paper entitled “Phase II study of S-1 and oxaliplatin as neoadjuvant chemotherapy for locally advanced adenocarcinoma of the gastric or esophagogastric junction: KSCC1601” [1]. In this study, Iwatsuki et al. highlighted a phase II study that investigated the efficacy and safety of S-1 and oxaliplatin (SOX) as neoadjuvant chemotherapy (NAC) for locally advanced gastric cancer (LAGC) and esophagogastric junction cancer (EGJC). We congratulate the authors for this pioneering study that potentially adds new insights of the perioperative chemotherapy for LAGC and EGJC patients. However, there are several issues in this study that are worthy of attention and discussion.

As reported by Iwatsuki et al., the pathological response rate (pRR) of preoperative-SOX was 59.5%. Forty-two patients (42 in 47, 89.4%) underwent surgery, and R0 resection rate was 93% (41 in 42). The 3 year OS and RFS rate were 62.9 and 53.2%, respectively. Despite a high 3 year OS and RFS rate for LAGC and EGJC observed in this single-arm phase II study, it is still unknown whether those patients benefit more from perioperative SOX regimen or standard postoperative chemotherapy. Most recently, a large phase III

RCT study (RESOLVE) from China with more than 1000 patients has provided some insights to answer this question [2]. Zhang et al. found that perioperative-SOX showed a survival benefit compared with adjuvant-CapOx (intravenous oxaliplatin plus oral capecitabine) in patients with locally advanced adenocarcinoma of the gastric or esophagogastric junction who had D2 gastrectomy (3 year disease-free survival was 59.4 versus 51.1%).

From the perspective of security, we noticed that the rate of severe anastomotic leakage (Clavien–Dindo classification grade III or higher) in 20 EGJC was 25.0% in this study. The authors hold the view that laparoscopic procedure might explain the high rates of severe anastomotic leakage. The CLASS-01 study evaluated the surgical safety of laparoscopic gastrectomy with D2 lymphadenectomy when compared with conventional open gastrectomy for patients with advanced gastric adenocarcinoma. There was no statistically significant difference in anastomotic leakage rates between the two groups (1.9 versus 0.6%) [3]. In addition, for patients with advanced Siewert type II and type III EGJC, a propensity score-matched case–control study presented that the anastomotic leakage rates for the laparoscopic total gastrectomy and open total gastrectomy groups were 4.5 and 3.7%, respectively [4]. Therefore, these results indicate that the laparoscopic approach can be safely performed in patients with EGJC by experienced surgeons. There is another consideration (preoperative SOX regimen) for the high anastomotic leakage that should be pointed out. One phase II RCT from Sah et al. evaluated the safety of neoadjuvant SOX in patients with advanced gastric cancer (including esophagogastric junction) [5], and 1 (4.2%) anastomotic leakage was observed. Furthermore, in the neoadjuvant SOX group of RESOLVE study (EGJC constitutes 35%), the anastomotic leakage rate was only 0.34% (1 in 295) [2]. These

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results suggest that preoperative SOX regimen itself does not increase the risk of anastomotic leakage.

In summary, the clarification and discussion of these issues by the authors would provide further insights and a better understanding of the efficacy and safety of preoperative-SOX as neoadjuvant chemotherapy for LAGC and EGJC. In all, SOX could be a promising option in neoadjuvant settings for LAGC and EGJC.

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