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Response to Letter to the Editor on "Impact of the Surgical Approach for Neoadjuvantly Treated Gastroesophageal Junction Type II Tumors: A Multinational, High-Volume Center Retrospective Cohort Analysis"

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We read the Comment to our publication "Impact of the Surgical Approach for Neoadjuvantly Treated Gastroesophageal Junction Type II Tumors: A Multinational, High-Volume Center Retrospective Cohort Analysis"[1] by Arnar B. Ingason and Mitchell C. Norotsky with interest.

The authors have discussed some limitations that are inherent to retrospective studies. While we share some of their concerns, the main conclusion remains unchanged.

First, regarding preoperative patient evaluation, it is true that patient comorbidities were accounted for mainly through the Anesthesiologists Physical Status (ASA) classification, and the majority of the cohort was ASA 2 or 3 patients, which is adequately reflecting the reality we see in our daily clinical practice.[2] Due to the advanced age of most of the patients of this cohort, diseases like arterial hypertension, diabetes, and coronary heart disease are frequent and are routinely preoperatively evaluated by anesthesiologists through the ASA score as it has been shown to be one of the strongest predictors for postoperative outcomes if applied alone and is generally used internationally to compare large patient cohorts due to its simplicity.[3]

The evaluation of frailty is discussed to improve preoperative scores but was not a standard in the last decades[3] and therefore not available for this high number of patients with Siewert type 2 tumors.

To account for the effects of patient frailty on long-term outcomes, subgroup analyses for overall survival were performed with exclusion of the 30- and 90-day mortality as frailty especially affects perioperative morbidity as well as mortality (Supplemental Figure 2A and B in the study by Wirsik et al[1]).

Furthermore, it is true that preoperative opioid or benzodiazepine use was not reported as it is not as frequently used in Europe as in the United States. It is believed to only play a marginal role in the patient cohort as in Europe only a prevalence of estimated 0.35% of high-risk opioid users aged 15 to 64 years exists in the whole population.[4]

The majority of the patients undergoing esophagectomy in the participating high-volume centers are discharged after 10 to 14 days postoperatively without prescriptions for any opioids or benzodiazepines despite undergoing thoracotomy.

Second, oncological pretreatment was not included as a factor in the propensity score model as a study published recently showed no survival differences between the mainly used pretreatments neoadjuvant radio chemotherapy CROSS[5] and perioperative chemotherapy FLOT[6] despite a higher rate of minor responder in the FLOT group.[7] The subgroup analysis for patients undergoing the same pretreatment was performed for patient solely undergoing chemotherapy, not chemoradiation (Figure 2C in the study by Wirsik et al[1]) as mentioned by Ingason and Norotsky as more of the patients received chemotherapy.

In addition, to address the issue of more distant metastasis in the gastrectomy group, a subgroup analysis with exclusion of all patients with distant metastasis was performed and shown in Figure 2D in the study by Wirsik et al.[1] Additionally, to address the higher number of full responders in the esophagectomy group as well as the higher number of distant metastasis in the gastrectomy group, a survival analysis after propensity score matching for pathological TNM[8] was performed, which showed an overall survival benefit for patients undergoing esophagectomy in Supplemental Figure 1A in the study by Wirsik et al.[1]

With these additional analyses, we tried to account for possible biases in this retrospective study influencing the long-term outcome.

Third, the study included different surgical techniques with open, minimal-invasive and robot-assisted approaches. Even though the authors cite a meta-analysis, there is so far no proven superiority of one of these techniques concerning the oncological survival outcome.[9–12] The differences the authors cite concern mainly transthoracic esophagectomies. To adequately account for potential, more postoperative morbidity after different surgical techniques, we (as mentioned above) performed survival analysis after exclusion of the 30- and 90-day mortality, which is shown in Supplemental Figure 2A and B in the study by Wirsik et al.[1]

All patients were treated in high-volume centers where the performing surgeons are trained in esophagectomies as well as gastrectomies, which is one of the main strengths of this study regarding the reliability and quality of intraoperative and postoperative treatment. The mean number of procedures per surgeon in a year is higher than in most other centers. The number of R0 resection and postoperative complications was comparable between the centers. Therefore, we did not include this factor in the propensity score model as there were no relevant differences to account for.

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In conclusion, this is and remains a retrospective cohort analysis of high-volume centers in Europe, but it reflects that the approach to adenocarcinoma Siewert type 2 changed in the last decades as supported by a questionnaire among upper gastrointestinal surgeons from 2022.[1,13] This study showed a long-term survival benefit for patients with Siewert type 2 adenocarcinomas in high-volume centers where esophagectomies have become a safe procedure with better oncological outcomes independent of the surgical techniques applied.[1] To finally answer the question of the surgical approach for Siewert type 2 tumors, we will have to wait for the results of the CARDIA trial.[14]

REFERENCES

1. Wirsik NM, Schmidt T, Nienhüser H, et al. Impact of the surgical approach for neoadjuvantly treated gastroesophageal junction type II tumors: a multinational, high-volume center retrospective cohort analysis. *Ann Surg*. 2023;278:683–691.
2. Davenport DL, Bowe EA, Henderson WG, et al. National Surgical Quality Improvement Program (NSQIP) risk factors can be used to validate American Society of Anesthesiologists Physical Status Classification (ASA PS) levels. *Ann Surg*. 2006;243:636–641; discussion 641.
3. Horvath B, Kloesel B, Todd MM, et al. The evolution, current value, and future of the american society of anesthesiologists physical status classification system. *Anesthesiology*. 2021;135:904–919.
4. Torrens M, Fonseca F. Opioid use and misuse in Europe: COVID-19 new challenges? *Eur Neuropsychopharmacol*. 2022;54:67–69.
5. Shapiro J, van Lanschot JJB, Hulshof M, et al. 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.
6. Al-Batran SE, Homann N, Pauligk C, et al. 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.
7. Donlon NE, Moran B, Kamilli A, et al. CROSS versus FLOT regimens in esophageal and esophagogastric junction adenocarcinoma: a propensity-matched comparison. *Ann Surg*. 2022;276:792–798.
8. Rice TW, Blackstone EH, Rusch VW. 7th edition of the AJCC Cancer Staging Manual: esophagus and esophagogastric junction. *Ann Surg Oncol*. 2010;17:1721–1724.
9. Esagian SM, Ziogas IA, Skarentzos K, et al. Robot-assisted minimally invasive esophagectomy versus open esophagectomy for esophageal cancer: a systematic review and meta-analysis. *Cancers (Basel)*. 2022;14.
10. van der Sluis PC, Babic B, Uzun E, et al. Robot-assisted and conventional minimally invasive esophagectomy are associated with better postoperative results compared to hybrid and open transthoracic esophagectomy. *Eur J Surg Oncol*. 2022;48:776–782.
11. van der Wielen N, Straatman J, Daams F, et al. Open versus minimally invasive total gastrectomy after neoadjuvant chemotherapy: results of a European randomized trial. *Gastric Cancer*. 2021;24:258–271.
12. ROMIO Study Group. Laparoscopic or open abdominal surgery with thoracotomy for patients with oesophageal cancer: ROMIO randomized clinical trial. *Br J Surg*. 2024;111.
13. de Groot EM, Goense L, Kingma BF, et al. Trends in surgical techniques for the treatment of esophageal and gastroesophageal junction cancer: the 2022 update. *Dis Esophagus*. 2023;36:doac099.
14. Leers JM, Knepper L, van der Veen A, et al. 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.