# ANSWERS TO COMMENTS OF THE REVIEWERS

**Reviewer #1 (Reviewer's code:** 03033812):

1. The topic is interesting and important; however the manuscript needs a great deal of rewriting in order to have significant results. The manuscript in the current from is no more than the description of the results of a pool of operated patients. Overall survival and comparison between adjuvant or surgery only are examples. The idea based on the title should be to focus on the adjuvant group only and assess better the fate of patients based on tumor response and consequent staging change.

   *We thank the reviewer for this valid comment. With this retrospective cohort study on patients that underwent surgery in our department, we aimed in the first place to address the question whether postoperative TNM stages indicate the same prognostic relevance for patients that underwent either neoadjuvant treatment or not. Therefore, the main focus of our manuscript lies on the comparison of these two groups of patients. However, we agree that a more detailed analysis of tumor response and changes in TNM stages with potential subsequent effects on outcome might be worthwhile. Therefore, we included an analysis on patients with unchanged or upstaged T stages. Please see as well our answer to question 8 of reviewer #3.*

2. Do not exclude in hospital deaths since an intention to treat design is better.

   *We aimed with our current study to analyze <u>longterm outcome</u> after surgery with or without neoadjuvant pretreatment addressing the question of prognostic relevance of postoperative TNM stages. An inclusion of in hospital deaths in an "intention to treat design" in this context might impact on longterm results as perioperative morbidity and mortality does not necessarily depend on TNM stage. Therefore, elimination of in hospital deaths allows a comparison of the relevance of postoperative TNM stages on longterm outcome in patients that were not affected by perioperative complications. This method is well described and often used by many other authors who specifically investigated longterm outcome. However, if requested, we are happy to provide supplemental analysis including in hospital deaths.*

**Reviewer #2 (Reviewer's code:** 01221925)

1. How do the authors explain the fact that the location of the tumor, according to the classification, did not impact survival? There was the argument that the location implied different "disease types"; is that not the case anymore?

   *We thank the reviewer for this valid comment. In fact, a number of studies reported that prognosis and tumor biology differs between AEG tumors at different locations according to the Siewert classification (type I to III), supporting for example the concept that Siewert type III carcinoma represent true gastric adenocarcinoma with a worse prognosis compared to Siewert type I and II carcinoma (Kulig et al. 2016; PMID: 27241921; Curtis et al. 2014; PMID: 24243140). Interestingly, however, the seventh AJCC/UICC TNM classification did not include Siewert classification for prognostication and classified all tumors within 5 cm of the gastroesophageal junction as esophageal carcinoma. Based on the discrepancy of available data, we performed subgroup analyses with regards to outcome of tumors in different locations according to the Siewert classification. Our data showed that, in general, location of the tumor classified by Siewert classification did not impact on outcome of patients with or without neoadjuvant pretreatment. Only patients with pT1 tumors in Siewert type 2 AEG tumors showed a better survival after neoadjuvant therapy (p=0.017), but this analysis based on only 7 versus 3 patients, questioning the final significance of these findings. We can only hypothesize that our study might be underpowered to finally answer the question as to whether location of tumors impacts on outcome. Further studies are needed to elucidate this specific and highly relevant question in more detail.*
   *We added a brief section to the discussion to address this comment of the reviewer.*

2. The authors show that tumor downstaging makes no difference as opposed to LN downstaging. How do they explain this?

   *This is an interesting fact pointed out by the reviewer. We found in our study that tumor downstaging does not affect longterm outcome, whereas nodal downstaging seems to improve survival (borderline significance: p=0.052). This observation is supported by the fact that nodal involvement is one of the most important and strongest prognostic factors of AEG tumors. Data showed that lymph node involvement is more important for prognosis compared to regional anatomic location (Mariette et al. 2008; PMID: 18216546). However, we have to acknowledge that the assessment of tumor and nodal downstaging as conducted in the current study might be affected by a certain examiner-dependent inaccuracy in the preoperative assessment via endoscopic ultrasound (Puli et al. 2008; PMID: 18330935; DaVee et al. 2017; PMID: 28223720). We added a brief section to the discussion to address this comment of the reviewer.*

**Reviewer #3 (Reviewer's code:** 00001114)

1. Please clarify the criteria to enroll in this study. The authors described that they selected eligible patients and excluded patients with preoperative tumor stages that preclude neoadjuvant treatment. However, I feel this criterion is not specific because neoadjuvant treatment indication depends on each hospital.

*We thank the reviewer for this comment and apologize for inadequate description of inclusion/exclusion criteria. Between 1996 and 2014, a total of 254 consecutive patients underwent curative surgery for adenocarcinoma of the gastroesophageal junction (AEG) at the University Medical Center Schleswig-Holstein, Campus Lübeck. Data of all patients were identified from institutional database and assessed for inclusion into the current study. Inclusion criteria were: age > 18 years, histological confirmation of adenocarcinoma of the gastroesophageal junction (Siewert type I to III) on the basis of postoperative resection specimen, curative intent of surgery/treatment, formal eligibility for neoadjuvant / perioperative treatment based on preoperative clinical tumor stages (cTNM stages according to AJCC Classification 8th edition; please see for details below in the section "Neoadjuvant / perioperative treatment"). Exclusion criteria were: in hospital deaths (as we aimed to analyze long-term outcome), early stage cancers cT1 cN0 cM0 and cT2 cN0 cM0.*
*After identification of eligible patients, we applied exact matching techniques in order to finally select patients for both groups "neoadjuvant treatment " and "no neoadjuvant treatment", and analyzed the data of the respective patients retrospectively. Local ethics board approval for the study was obtained.*

*Neoadjuvant / perioperative treatment*
*Neoadjuvant chemotherapy was used as standard treatment in the context of a multidisciplinary approach for locally advanced cancers from 2005 on. Our local standard protocol for neoadjuvant / perioperative treatment is based in the German National Guidelines for Diagnostics and Treatment of Adenocarcinomas of the Stomach and the Gastroesophageal Junction (http://www.awmf.org/uploads/tx_szleitlinien/032-009l_S3_Magenkarzinom_Diagnostik_Therapie_Adenokarzinome_oesophagogastraler_Uebergang_2012-abgelaufen.pdf). Briefly, patients were deemed eligible for neoadjuvant treatment / perioperative treatment if tumor was locally advanced. In detail, we recommend neoadjuvant / perioperative treatment for patients with locally advanced tumor stages (cT2 Npositive disease as well as cT3/4), and patients with cT1 cN0 cM0, cT2 cN0 cM0 were not recommended for pretreatment. Patients prior to 2005 received neoadjuvant / perioperative treatment on an individual basis based on recommendations of the local interdisciplinary tumorboard.*

*We adjusted the methods section accordingly and hope that this description of inclusion / exclusion criteria is sufficient for interpretation of our results.*

2. About surgical procedures, I would recommend that the authors described the detail of lymphoidectomy.

   *Surgical standard procedure in our hospital included two-field lymphadenectomy in case of esophagectomy and D2-lymphadenectomy in case of gastrectomy. We added this information in the method section.*

3. How many patients were followed up by telephone but not visit? Because I feel this affects the study quality.

   *This is a valid comment. The Department of Surgery includes an outpatient cancer clinic for follow up of cancer patients. Most of our cancer patients are being followed up in this outpatient clinic, including follow up investigations etc. However, if patients requested follow up with their GP (for example based on the location of their residence), we obtained follow up information via telephone and entered the respective information into our database.*
   *We added this information to the manuscript. Unfortunately, we are not able at this stage to provide the exact number of patients that underwent telephone follow up, but the majority of patients was followed up in our unit.*

4. The authors should insert tables or figures in the middle of the main text.

   *We adjusted the manuscript accordingly.*

5. In "Result" section, the authors described that patients who underwent neoadjuvant treatment were slightly younger than their not-treated counterparts (58 versus 64 years; p=0.043). However, this p-value is less than 0.05 as the authors described a p-value of p<0.050 was considered significant. So I sure this difference is significant. Please revised it. The other results were also applied.

   *According to the reviewer´s comment, we changed this in the revised version and described that patients who underwent neoadjuvant treatment were significantly younger.*

6. Please show breakdown of cTNM Stage in both group and ypTNM Stage in neoadjuvant Tx.

   *We added the information on postoperative pTNM stages for both groups in table 1.*

7. The authors described nodal downstaging after neoadjuvant tx resulted in significantly improved long-term survival. However, p-value was 0.053 that was over 0.05. I think this is not significant.

*We thank the reviewer for this comment. Initially, we considered a p-value of p≤0.050 as significant, that is why we argued that these findings are significant. However, based on the comment of the reviewer, we changed our manuscript and described the respective results as only "borderline significant".*

8. I am interested in how about the long-term survival of unchanged or upstaged patients. I think it is clinically more important. Similarly, when stage change for the worse after neoadjuvant chemotherapy, his or her prognosis depends on yp TNM stage or worse.

*We agree with the reviewer that this aspect is very interesting. Unfortunately, our data are somewhat limited as we have only 34 patients in total with longterm follow up data that presented unchanged or upstaged T stages after neoadjuvant treatment We now performed additional analysis on these patients and prepared a supplement figure. In this analysis, patients with upstaging presented a trend towards worse survival compared to patients with unchanged disease, but comparison did not reach significance (p=0.628). However, this analysis includes 30 patients with unchanged versus only 4(!) patients with upstaged disease. We therefore added a brief paragraph in the results section and mentioned these results but did not discuss these data further.*
*If requested by the reviewer, however, we are happy to include these results into the discussion despite the limited relevance due to extreme low numbers.*

9. Limitation in discussion section is redundant in particular about restrospective study. Please shorten them

*We shortened this part of the discussion according to the reviewer´s comment.*

10. I was wondering if the duration of neoadjuvant chemotherapy affected this result. Please show the duration of neoadjuvant chemotherapy and discuss about it. In other words, I was wondering if we have to continue the chemotherapy until achieving the maximum response, in particular, nodal downstaging.

*We agree with the reviewer, that the question of optimal / maximal response to neoadjuvant / perioperative treatment is a highly relevant clinical question. In fact, a very recently published meta-analysis in "Diseases of the Esophagus" addressed this question in the context of an analysis of the impact of the time interval between neoadjuvant treatment and surgery, and found that a longer interval (more than the standard 7–8 weeks) from the end of preoperative nCRT to surgery did not increase the rate of pCR in esophageal cancer (Lin et al. 2016; PMID:* 26542065). *Moreover, recently published data from the UK MRC OE05 trial (open-label, randomised phase 3 trial) showed that four cycles of neoadjuvant ECX compared with two cycles of CF did not increase survival (Alderson et al. 2017;*

*PMID: 28784312). Shortening neoadjuvant therapy might prevent unnecessarily delayed surgery, especially in case of an absence of a response following neoadjuvant treatment.*

*In our current study, however, neoadjuvant / perioperative treatment protocols somewhat changed over time and included a number of different cisplatin and 5-FU based regimens such as cisplatin/5-FU, ECX, FLOT or ECF, as outlined in the methods section. The use of different protocols however results in different durations / numbers of cycles of neoadjuvant therapy. Therefore, our data do not allow a proper analysis of this highly interesting question.*