

Dear Ying Dou, dear reviewers,

thank you for your efforts about the revision of our manuscript No. 52824 entitled "Perioperative Chemotherapy for Advanced Gastric Cancer. Results from a Tertiary-Care Hospital in Germany". It will be a pleasure for us to revise the manuscript.

First of all we address the number of patients and the statistical power of the results:

We completely agree with the fact that power could be not high enough to detect a difference between patients treated with and without chemotherapy and consequently that a Beta error could be present. By the way, a sample size of 158 patients is not extremely small, considering the large amount of studies, also randomized, offering smaller sample sizes (references number 5,14,15 and 16). Pilot studies are performed often with 30 patients and the results are used as basis for future studies. This study should be considered a basis to investigate the role of chemotherapy in a setting of randomized controlled trial in the future. For sure, a limitation of this study, is the design itself as retrospective. For this reason we could not perform a precise sample size calculation as in case of a RCT. Thank you again for stressing this point, we made it clearer throughout the limitations part of the discussion of the manuscript.

In case of a comparison of the survival of two groups of patients regarding one variable (chemotherapy yes or no) it makes from a statistical point of view no difference if a COX proportional hazard model is used or a Kaplan Mayer method with Log Rank Test. The obtained result is comparable. Regarding the multivariate analysis: the aim of our study was the investigation of the role of chemotherapy on survival. As this variable was not significant in an univariate analysis (Kaplan Meyer) we didn't perform a multivariate analysis, as generally only variable which are significant in the univariate analysis should be included in a multivariate analysis. Additionally, as generally known, retrospective studies are high risk of bias studies, so we feel that the results of a multi variate analysis could not be trusted.

In the following we process the comments of each reviewer point by point:

1) Editing the comments of the first reviewer:

Please see our comment above about sample size and statistical power.

2) Editing the comments of the second reviewer:

To prove if elderly patients would benefit as well as younger patients from the perioperative chemotherapy it was recommended to make comparisons including aspects of quality of life: As the analysis is retrospective and about 70 % of the analysed patients are already dead it is not possible to examine the quality of life. Regarding the number of analysed patients and the statistical significance for p-values: Please see our above listed arguments.

3) Editing the comments of the third reviewer:

Again the small number of patients was suspected to cause a type 2 error "ß". We discussed this in the limitations part of the discussion.

The German S3-guidelines report a prevalence of a *Helicobacter pylori* infection in Germany about 3% in children, 48% in adults and between 70 and 90% in elder persons (> 65 years). On the base of the chronic gastritis caused by *Helicobacter pylori* it is estimated that about actually 89,0% of the Non-Cardia-Carcinomas are referred to the influence of a *Helicobacter pylori*-infection. In Germany investigation of *Helicobacter pylori* status in tumour tissue is not a standard practice.

The two recent studies were added in the discussion part and to the references.

Language polishing was done (e.g. slightly better) for the whole manuscript.

4) Editing the comments of the forth reviewer:

The patients of the chemotherapy group underwent a perioperative chemotherapy with three cycles of chemotherapy before and three cycles after surgery. So in the whole manuscript the term perioperative chemotherapy is used.

The small number of patients was criticized: Please see our arguments above.

The desired data of patients' number and results were added into the abstract part.

The criteria to select the patients between upfront surgery or perioperative chemotherapy was the tumour stage. Therefore only patients with an expected tumour > T2 and/or nodal positive stadium were analysed in order not to falsify the results of the analysis with T1 N0 or T2 N0 patients. This was explained in the methods part. The decision of the interdisciplinary tumor conference was done also dependent of the general condition of the patient. Upfront surgery was preferred in case of patients with poor PS or comorbidity independent of patient's age. This could

lead to a selection bias which was discussed in the limitations' part of the discussion. If perioperative chemotherapy for patients with advanced gastric cancer would have a significant effect on the overall survival, this effect would be even bigger if two slightly different groups of patients are compared: a younger group of patients who received chemotherapy more often and a group of elderly patients who received chemotherapy less often based on comorbidity and bad performance status. But our analysis presents converse results.

This analysis was carried out in accordance to the standard procedures of the German Federal Medical Association which confirmed that a decision by the Ethics Commission for the retrospective analysis of our internal hospital data is not necessary.

The whole manuscript was polished regarding the English once again.

Yours sincerely,

Katrin Bauer

Dear Ying Dou, dear reviewers,

thank you very much for your efforts about the revision of our manuscript No. 52824 entitled "Perioperative Chemotherapy for Advanced Gastric Cancer. Results from a Tertiary-Care Hospital in Germany".

All reviewers agreed on the importance of this topic. According to the comments it will be a pleasure for us to revise the manuscript.

First of all we will discuss the number of patients and the statistical power of the results because all reviewers addressed this topic:

We completely agree with the fact that power could be not high enough to detect a difference between patients treated with and without chemotherapy and consequently that a Beta error could be present. By the way, a sample size of 158 patients is not extremely small, considering the large amount of studies, also randomized, offering smaller sample sizes (references number 5,14,15 and 16). Pilot studies are performed often with 30 patients and the results are used as basis for future studies. This study should be considered a basis to investigate the role of chemotherapy in a setting of randomized controlled trial in the future. For sure, a limitation of this study, is the design itself as retrospective. For this reason we could not perform a precise sample size calculation as in case of a RCT. Thank you again for stressing this point, we made it clearer throughout the limitations part of the discussion of the manuscript.

Please find our point-by-point response below:

**1) Comment of Reviewer 03270441:**

*This is an innovative article. Based on a retrospective analysis, the authors questioned the application of neoadjuvant / perioperative chemotherapy recommended by the guidelines in gastric cancer. A large number of data analyses have been done and it is concluded that neoadjuvant / perioperative chemotherapy does not benefit the overall survival of patients with locally advanced stage gastric cancer, despite the recommendations of the guidelines. However, the article has major defects: First, the sample size of this retrospective analysis is very small. The OS curves of the combined chemotherapy group and the pure operation group is obviously separated, and there is no overlap between the two curves. The lack of statistical significance of p value may be caused by the insufficient statistical power. Second, the sample size is too small for subgroup analysis, which may*

*directly affect the results. Thirdly, although the authors have carried out a lot of subgroup analysis in subgroups, the focus is not prominent enough.*

*Finally, the influence of each factor on OS may interact to each other, for example: age, location of tumors, and implementation of chemotherapy et al. Multivariate analysis methods may be needed, such as Cox proportional hazards model (this is needed to be confirmed by statisticians) to further determine or exclude the role of neoadjuvant / perioperative chemotherapy in local advanced gastric cancer. In summarize, I personally think that the data provided by the authors is not enough to draw the conclusions proposed by the authors.*

#### **Response to the Reviewer:**

About the sample size and statistical power please see our common statement above. In case of a comparison of the survival of two groups of patients regarding one variable (chemotherapy yes or no) it makes from a statistical point of view no difference if a COX proportional hazard model is used or a Kaplan Mayer method with Log Rank Test. The obtained result is comparable. Regarding the multivariate analysis: the aim of our study was the investigation of the role of chemotherapy on survival. As this variable was not significant in an univariate analysis (Kaplan Meyer) we didn't perform a multivariate analysis, as generally only variable which are significant in the univariate analysis should be included in a multivariate analysis. Additionally, as generally known, retrospective studies are high risk of bias studies, so we feel that the results of a multi variate analysis could not be trusted.

#### **2) Comment of Reviewer 03478911:**

*The authors raised doubts about the suitability to older patients in the use of neoadjuvant/perioperative chemotherapy, which is recommended for the treatment of advanced gastric cancer (>T2, N +) before tumor resection according to the European guidelines. Indeed, refusing the need for chemotherapy after surgery is expected to receive clinically negative feedback even when treating elderly patients. Therefore, it would be much better to support the author's claim by making comparisons, including aspects of quality of life. In addition to that, there are also issues that are important for analysis. The sample size (the number of patients) of this retrospective analysis is very small. Therefore, there is a lack of statistical significance for p values can be caused by insufficient statistical meaning. If the authors can give a clear confidence in the analysis, this reviewer ready to strongly agree with the author's argue.*

#### **Response to the Reviewer:**

To prove if elderly patients would benefit as well as younger patients from the perioperative chemotherapy it was recommended to make comparisons including aspects of quality of life: As the analysis is retrospective and about 70 % of the analysed patients are already dead it is not possible to examine the quality of life. Regarding the number of analysed patients and the statistical significance for p-values: Please see our above listed arguments.

### **3) Comment of Reviewer 00058340:**

*In many European guidelines neoadjuvant/perioperative chemotherapy is recommended for the treatment of advanced gastric cancer before tumor resection. However, it is not certain whether perioperative chemotherapy is as effective in distal as in proximal tumors, and in elderly patients. The authors explored these questions in a retrospective study of their patient population – 158 patients in a tertiary-care hospital in the clinic of Kempten certified by the German Cancer Society for the treatment of gastric cancers. They concluded that administration of perioperative chemotherapy for advanced gastric cancer did not lead to a significant 5-year survival advantage and that their data are not sufficient to justify perioperative chemotherapy in patients with advanced gastric cancer independent of tumor localization, or patient age. Comments: 1. The topic is important for a proper management of patients with advanced gastric cancer. 2. While the study is well conceived, designed and executed the conclusions are weakened by relatively small number of patients with a possibility of type 2 error “ $\beta$ ”. Beta depends on the power of the test (i.e. the probability of not committing a type 2 error, which is equal to  $1-\beta$ ). The authors should clearly spell out and discussed this. 3. How many patients were *H. pylori* positive? If possible, please provide this information. 4. The authors may wish to add 2 references listed below. 5. Some minor typos e.g. “similar, lightly better five-year survival time”. Should be “slightly” Bang Wool Eom et al. Survival Benefit of Perioperative Chemotherapy in Patients with Locally Advanced Gastric Cancer: A Propensity Score Matched Analysis. J Gastric Cancer. 2018 Mar; 18(1): 69–81; doi: 10.5230/jgc.2018.18. e9; PMCID: PMC5881012 PMID: 29629222 Shingo Kanaji et al. Recent updates in perioperative chemotherapy and recurrence pattern of gastric cancer Ann Gastroenterol Surg. 2018 Nov; 2(6): 400–405; doi: 10.1002/ags3.12199; PMCID: PMC6236108; PMID: 30460342*

### **Response to the Reviewer:**

Again the small number of patients was suspected to cause a type 2 error “ $\beta$ ”. We discussed this in the limitations part of the discussion.

The German S3-guidelines report a prevalence of a *Helicobacter pylori* infection in Germany about 3% in children, 48% in adults and between 70 and 90% in elder persons (> 65 years). On the base of the chronic gastritis caused by *Helicobacter pylori* it is estimated that about actually 89,0% of the Non-Cardia-Carcinomas are referred to the influence of a *Helicobacter pylori*-infection. In Germany investigation of *Helicobacter pylori* status in tumour tissue is not a standard practice.

The two recent studies were added in the discussion part and to the references.

Language polishing was done (e.g. slightly better) for the whole manuscript.

#### **4) Comment of Reviewer 00001114:**

*Thank you for allowing me to review the manuscript: "Perioperative Chemotherapy for Advanced Gastric Cancer Results from a Tertiary-care Hospital in Germany " by Katrin Bauer et al. I have the following comments. 1. Perioperative chemotherapy includes neoadjuvant and adjuvant chemotherapy. The authors had better use the terminology of neoadjuvant chemotherapy instead of perioperative chemotherapy. 2. The authors concluded that there was no significant advantage of perioperative chemotherapy for advanced gastric cancer in the German population from a tertiary-care hospital. 5- year survival rate was 40% in the perioperative chemotherapy and 29% in the upfront surgery group (difference 11%), respectively. However, as the authors mentioned in the Discussion, they are similar to the following RCT data, that Ychou et al. published in the JCO (38% vs. 24%, difference 14%) and Cunningham et al. published in the NEJM (36% vs. 23%, difference 14%). This study simply seemed the lack of patients' number. This study is a retrospective study with a small patient number. Therefore, I would feel the authors' discussion was too subjective. 3. There was no specific data in the Abstract, such as patient number, survival time in this study, and so on. Most of the readers need those data to evaluate this study. The authors should revise the abstract, including the results with data. 4. There were no specific criteria to select upfront surgery or neoadjuvant chemotherapy in the methods regarding treatment strategy. I think this caused a selection bias although it was described that the interdisciplinary tumor board determined it. Conversely, I think this selection bias can lead this result showed there was no advantage of perioperative chemotherapy. The authors had better add a more concrete explanation, for example, upfront surgery was preferred in case of patients with poor PS or comorbidity. 5. I feel this study needs to obtain a decision by the Ethics Commission for this study, but informed consent can be waived via the opt-out method.*

Response to the Reviewer:

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Yours sincerely,

Katrin Bauer