Author’s response to reviews

Title: Indications for adjuvant chemotherapy in patients with AJCC stage IIa T3N0M0 and T1N2M0 gastric cancer—an east and west multicenter study

Authors:
Ze-Ning Huang (958464601@qq.com)
Jacopo Desiderio (djdesi85@hotmail.it)
Qi-Yue Chen (690934662@qq.com)
Chao-Hui Zheng (wwkzch@163.com)
Ping Li (pingli811002@163.com)
Jian-Wei Xie (364531721@qq.com)
Jia-Bin Wang (847044493@qq.com)
Jian-Xian Lin (linjian379@163.com)
Jun Lu (78379048@qq.com)
Long-Long Cao (1291821982@qq.com)
Mi Lin (170894572@qq.com)
Ru-Hong Tu (794561137@qq.com)
Ju-Li Lin (632366024@qq.com)
Hua-Long Zheng (291167038@qq.com)
Chang-Ming Huang (hcmlr2002@163.com)

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Indications for adjuvant chemotherapy in patients with AJCC (7th ed.) stage IIa T3N0M0 and T1N2M0 gastric cancer – an east and west, multicenter study
Reviewer reports:

Jianxian Lin (Reviewer 1): The manuscript BMGE-D-19-00501 "Indications for adjuvant chemotherapy in patients with AJCC (7th ed.) stage IIa T3N0M0 and T1N2M0 gastric cancer - an east and west, multicenter study" analyzed 1593 patients from SEER database and validation using FJUUH and IMIGASTRIC patients. They found that T3N0M0 and T1N2M0 gastric cancer patients should be treated with adjuvant chemotherapy, especially for high-benefit patients. This is an interesting study. In Japanese guideline, the T3N0M0 and T1N2M0 patients were not recommended for AC. So the authors investigated these patients and found the effect of AC in these patients. It is a well written manuscript. There were some minor comments:

1. The 7th and newest 8th edition of AJCC TNM stage system is the same in stage IIa, so in the title, the 7th ed. should be delete.

Response: We have deleted this description from the title. The new title is “Indications for adjuvant chemotherapy in patients with AJCC stage IIa (T3N0M0 and T1N2M0) gastric cancer—an east and west multicenter study.”

2. There were several limitation in this study, the authors need to recommend in the discussion.

Response: Although this study contained a large and global sample population with long-term follow-up data, and the results obtained were further verified and validated. However, some limitations of the study should be mentioned. First, there is inevitable bias in retrospective studies. Second, the SEER database does not include data regarding some outcomes, such as the cutting edge-positive rate and postoperative complications. Third, the number of cases and the available pathological data differed among the three centers, which may have influenced the results. Therefore, global multicenter prospective studies are needed. (Discussion section, line 15-24, page 9)

3. The figure 2 and 3 should change to white background.

Response: According to the reviewer’s comment, the backgrounds of Figure 2 and 3 have been changed to white.

Yanqing Li (Reviewer 2): This study used multicenter data from eastern and western datasets to explore that whether T3N0M0 and T1N2M0 gastric cancer patients need AC and what kind of patients will receive a benefit from AC. This is a well-designed study which would provide useful information for doctors and patients. The English expression is excellent. We recommend "Accept after minor essential revisions" for this manuscript. We listed some minor comments below and hope these comments could help to improve this manuscript.

1. This study listed several elimination criteria. It is better to also list the number of patients that were excluded from the analysis of this study for each elimination criterion. These detailed information could help the readers understand the real value of the results and the bias in this retrospective studies.

Response: According to the reviewer’s comment, we have listed the number of patients that were excluded from the analyses in the methods section. (Method section, line 8-11, page 4)

2. The patients are from very different periods for the three different database (SEER database from January 1988 to December 2012, FMUUH from October 2008 to December 2014, Italy IMIGASTRIC Center from January 2000 to December 2014). Could this factor have some influence on the results of
this study?
Response: It is true that the time periods of the patient data differ extensively among the three different databases, contributing to database differences the number of cases; furthermore, the available pathological data differed among the three centers. These factors may have influenced the results of this study. However, more rigorous results must be obtained in clinical trials containing multi-center, prospective and large samples. We have added this information to the discussion of the limitations of the study. (Discussion section, line 22-24, page 9)

3. In the IMIGASTRIC center data, no significant difference between high-benefit and low-benefit patients was found. Is there any other reason for this except for the sample size?
Response: Although there was no significant difference between the high-benefit and low-benefit patients in the IMIGASTRIC center data, $P = 0.060$, which is close to the threshold of statistical significance. We believe with a larger sample size, a significant difference would have been detected. We have added this information to the discussion section. (Discussion section, line 27-28, page 8)

Emanuele Lo Menzo (Reviewer 3): I congratulate the authors for the manuscript entitled: "Indications for adjuvant chemotherapy in patients with AJCC (7th ed.) stage IIa T3N0M0 and T1N2M0 gastric cancer - an east and west, multicenter study"
In the manuscript the authors compare patients from the Surveillance, Epidemiology, and End Results(SEER) database and the databases from Fujian Medical University Union Hospital(FJUUH) and the Italian IMIGASTRIC center to determine the ideal role of adjuvant chemotherapy.
Major Compulsory Revisions
1- Your objective was to determine the ideal indications of adjuvant chemotherapy (AC) in patients with stage IIa gastric cancer (T3N0M0 and T1N2M0). However, I have concerns that this objective can be accomplished using epidemiological databases with several missing data points.
Response: This study used multicenter data to research the indications of adjuvant chemotherapy (AC) in patients with stage IIa gastric cancer. Although the SEER database does include information on outcomes such as positive margins and postoperative complications, we also analyzed the data from China and Italy. The results show the indications for chemotherapy suggested by ours can be well validated; however, data from clinical trials and multicenter, prospective studies with large sample sizes are needed. We have this information to the discussion section of the article. (Discussion section, line 19-20, page 9)

2- There is a big disparity between the AC group (Group C) (n = 287) and the non-AC group (Group N) (n = 1306). Can you please comment on the potential impact on your results?
Response: Compared with the non-AC group, the AC group had more male patients, more patients aged ≤ 65 years, fewer lymph node dissections ≤ 15, more tumors ≥ 20 mm, and more nonadenocarcinoma. Although the AC group had more tumors ≥ 20 mm, more nonadenocarcinoma and other risk factors affecting patient survival, the OS group of the AC group was significantly higher than that of the non-AC group ($P = 0.042$). We believe this latter finding is due to the greater numbers of patients ≥ 65 years old and with lymph node dissections ≤ 15 in the non-AC group; these risk factors have greater impacts on patient survival than does tumor size or pathological type. Therefore, data from clinical trials and multicenter, prospective studies with large sample sizes are needed. We have added this information to the discussion section of the article. (Discussion section, line 21-24, page 9)

3- Since in the Eastern countries AC is not recommended in T3N0M0 and T1N2M0, these patients treated with AC in the FJUUH database (198) might have had other reasons for having AC. Can you offer some potential explanations?
Response: Because there is controversy about whether or not adjuvant chemotherapy is appropriate for patients with stage IIa gastric cancer, at FJUHH, doctors inform their patients of the possible advantages and disadvantages of chemotherapy vs. no chemotherapy, and the patients choose whether to undergo postoperative adjuvant chemotherapy. Therefore, 198 patients at FJUHH received chemotherapy.

4- I believe it is necessary to mention as a limitation the fact that the variables not mentioned in the SEER database were not included in the analysis.
Response: The SEER database does not include data regarding some outcomes, such as the cutting edge-positive rate and postoperative complications. This is a limitation of the study. We have added this information to the discussion section of the article. (Discussion section, line 19-20, page 9)

5- Do you have any information on the type of resection these patients had? That is a major variable missing in your study. Without this data, your conclusions might be skewed.
Response: According to the reviewer's request, we have added information on the type of patient surgery in Table 1.