Author's response to reviews

Title: Which is the Best Postoperative Chemotherapy Regimen in Patients with Rectal Cancer after Neoadjuvant Therapy?: Analysis of Surveillance, Epidemiology, and End Results-Medicare Data

Authors:

Peng Gao (gaokaji16@163.com)
Yong-xi Song (songyongxi840309@126.com)
Jing-xu Sun (sun2003999@163.com)
Xiao-wan Chen (chenxiaowan516@gmail.com)
Ying-ying Xu (lovecmustar@163.com)
Jun-hua Zhao (zjh900521@163.com)
Xuan-zhang Huang (qq_347310502@126.com)
Hui-mian Xu (xuhiufan@126.com)
Zhen-ning Wang (josieon826@sina.cn)

Version: 3
Date: 4 October 2014

Author's response to reviews: see over
Dear Sir,

Thank you very much for your comments and suggestions on improving our manuscript “Which is the Best Postoperative Chemotherapy Regimen in Patients with Rectal Cancer after Neoadjuvant Therapy?: Analysis of Surveillance Epidemiology and End Results-Medicare Data” (1605246167129326). Those comments are all valuable and very helpful for revising and improving our paper, as well as the important guiding significance to our research. We have revised our manuscript according to the suggestions of reviewers.

Following Reviewer#1 Ruihua Shi’s comments and suggestions:

1. Following Reviewer#1 “there is a lack of explanation of statistical methods used in the study” We appreciate this kind suggestion very much. Following your suggestion, we changed the words “Continuous data were presented as the mean±standard deviation. The OS was analyzed by Kaplan-Meier survival curves, and comparisons were made by the log-rank test” into “In the univariable analysis, the cancer-specific (CSS) was analyzed by Kaplan-Meier survival curves, and comparisons were made by the log-rank test stratified by the ypTNM stage.” And then, we added “The CSS was then compared in these PS-matched cohorts using the log-rank test stratified by the ypTNM stage” in the Statistical Analysis section of MATERIAL AND METHODS part. Meanwhile, we added “The covariates included all variables that were identified to be significantly related to survival in the univariable analysis and the tests were made stratified by the ypTNM stage” in the Statistical Analysis section of MATERIAL AND METHODS part.

2. Following Reviewer#1 “there are few explanations of the rationale for the study design” Thank you for your excellent comments. We revised the DISSCUSSION
part and added following words about the study design: “Considering the importance of ypTNM stage in determining the need for adjuvant chemotherapy, all tests were made stratified by ypTNM stage. We compared the prognosis among patients in no-chemo, 5-FU, and oxaliplatin group in the unmatched univariable survival analysis. We found that postoperative 5-FU-based chemotherapy did not prolong the CSS in ypStage I (ypT1-2N0) (Figure 1A) and ypStage II (ypT3-4N0) (Figure 1B), which was similar to the study by Govindarajan et al. On the contrary, adding postoperative 5-FU-based chemotherapy significantly improved survival of patients in ypStage III (ypN1-2) (Figure 1C). To the best of our knowledge, the outcome of postoperative 5-FU-based chemotherapy in ypStage III patients was never reported previously, although researchers stressed the need for a randomized clinical trial. To confirm our results, both the PS-matched analysis and the Cox proportional hazards model were used to make adjusted analysis and the results were in accordance with the univariable survival analysis (Figure 2, Table 2).”

3. Following Reviewer#1 “The manuscript needs further carefully polished concerning English grammar, spelling and sentence structure” This is a fairly good recommendation. According to your suggestion, we invited an English specialist to improve the style of written English in the paper and we examined the English grammar, spelling and sentence structure carefully.

Following Reviewer#2 Vicente Alonso’s comments and suggestions:

1. Following Reviewer#2 “Patients with pCR were excluded from analysis (bias selection). No data of patients achieving pCR are presented; since those patients represent 10-20%, may suppose the same percentage of patients receiving Oxaliplatin” We appreciate this kind suggestion very much. This study was based on the SEER-medicare database, in which the pCR status was not well supported. We re-analyzed our data and found that 203 cases which followed inclusion rules were staged as pathological TxNxMx. Maybe these cases were with pCR, but we could not confirm that because there was significantly heterogeneous in the
prognosis of them. Since that, we had to exclude patients with pCR in this study. We added the following words in the Patient Selection section of MATERIAL AND METHODS part: “Patients were excluded from this study if they … (7) had complete pathologic response because it was unable to identify accurately in the SEER-Medicare database”. Meanwhile, we added the following words in the Limitations section of DISCUSSION part: “Patients with pCR were excluded from analysis because the pCR status was not well supported by the SEER-medicare database.”

2. Following Reviewer#2 “While in adjuvant treatment of stage II colon cancer the analysis of less than 12 lymph nodes is an adverse prognostic factor, this has not been demonstrated in rectal cancer after preoperative treatment. In fact, retrieval of less than 12 nodes in the specimen of rectal cancer patients treated with neoadjuvant chemoradiation seems not to affect overall survival and has been described as a possible marker of higher tumor response.” This is a fairly good recommendation. We made additional analysis and found that the retrieval of less than 12 nodes was not significantly related with prognosis of the rectal cancer after preoperative treatment. The Kaplan-Meier survival curves were listed here:

Therefore, we removed the “retrieval of less than 12 nodes” from the risk features and we deleted all contents about the “poor prognostic features in ypStage II” considering that this part was not quilt suitable in this paper. And then, the variables “the number of lymph nodes examined”, “tumor grade”, “preoperative intestinal obstruction”, and “preoperative intestinal perforation” were still included in the PS-matched cohorts and Cox proportional hazards model.
3. Following Reviewer#2 “The number of patients treated with oxaliplatin-based chemotherapy is small which implies a bias in patient’s selection” Thank you for your excellent comments. This was a retrospective study based on the SEER-medicare and about 35% patients were diagnosed before the oxaliplatin came into the market, so bias in patient’s selection existed. Considering that, we have used a PS-matched method to adjust the result, and we added following words in the Limitations section of DISCUSSION part: “as it was a retrospective exploratory study, the potential for confounding based on patient selection could not be eliminated”

4. Following Reviewer#2 “Adjuvant treatment schedules are not described. Moreover, by their influence on survival would be desirable to present data from dose-intensity and compliance.” We appreciate this kind suggestion very much. Following your suggestion, we analyzed the influence of adjuvant treatment schedule on survival. We compared the prognosis between the patients with different treatment schedule. Both the “Days between the surgery and the first claim of chemotherapy” and the “Weeks having 5-FU/oxaliplatin” were analyzed stratified by ypStage and chemotherapy regimen. We found no significant differences in survival in all tests except in oxaliplatin group with ypStage I (the survival patients with ≤8 weeks having 5-FU claims was worse than that with >8 weeks having 5-FU claims, p=0.024, may be caused by the small sample counts of 36). To avoid making the paper tediously long, we did not add these results by now. The detail of the results was listed here:
5. Following Reviewer#2 “In this analysis more than 50% of patients do not receive adjuvant treatment, which does not reflect the usual clinical practice in western countries (where 60-70% of the patients receive adjuvant treatment)” Thank you for your excellent comments. We re-examined our data carefully and confirmed the previous results. The reason for the low percentage of patients receiving adjuvant treatment may be: 1) all patients in this study was >65 years old; 2) the chemotherapy group only included patients with record for chemotherapy within 120 days of surgery [a].

6. Following Reviewer#2 “The analysis of patients >65 years reflects a subgroup the patients, although the most numerous in rectal cancer, does not allow to extract conclusions for younger patients.” We appreciate this kind suggestion very much. The SEER-medicare database only include patients >65 years, which may limit the applicability of the findings to younger patients with rectal cancer. We added following words in the Limitations section of DISCUSSION part: “only patients aged ≥66 years at the time of diagnosis were included in this study, which may limit the applicability of the findings to younger patients with rectal cancer”.

7. Following Reviewer#2 “Some of the more important prognostic factors that influence in the decision of adjuvant treatment are not considered (such as tumoral regression grade).” Thank you for your excellent comments. We added following words in the Limitations section of DISCUSSION part: “the role of several known prognostic features such as tumor regression grade, preoperative carcinoembryonic antigen, microsatellite instability, perineural invasion, and lymphovascular invasion could not be investigated, as these characteristics were not available within the SEER-Medicare database.”

8. Following Reviewer#2 “Extended time of analysis, that could influence in the diagnosis methods (with or without MRI), surgery type (Total Mesorectal Excision) and different chemotherapy schedules” This is a fairly good recommendation. We tried to remove the cases diagnosed before 1997 and found that that did not influent the result of this study. Meanwhile, “Year of diagnosis” was included in the PS-matched cohorts and Cox proportional hazards model, which may less the influence of “Extended time of analysis” on the test.

9. Following Reviewer#2 “Background First paragraph – preoperative chemotherapy and preoperative radiotetrapy should be changed by chemoradiotherapy” Thank you for your excellent suggestion. We have revised
our paper following your suggestion.

10. Following Reviewer#2 “Background First paragraph.- penetration more the muscularis propia (T3 T4), Penetration of the muscularis propia is T2” This is a fairly good recommendation. We have changed the previous words into “invading through the muscularis propria into the pericolorectal tissues (cT3), penetrating to the surface of the visceral peritoneum (cT4a), invading or being adherent to other organs or structures (cT4b)”.

Sincerely yours,

Zhen-ning Wang, M.D., Ph.D.
Professor and Associate Director
Department of Surgical Oncology and General Surgery,
First Hospital of China Medical University
Shenyang 110001, China
E-mail: josieon826@sina.cn