Author’s response to reviews

Title: Different prognostic implication of ypTNM stage and pTNM stage for gastric cancer: A Propensity Score-matched Analysis

Authors:
Ziyu Li (ziyu_li@hsc.pku.edu.cn)
Yinkui Wang (wykchangfeng@163.com)
Xiangji Ying (yingxjii@163.com)
Fei Shan (shanfei@hsc.pku.edu.cn)
Zhouqiao Wu (wuzhouqiao@gmail.com)
Lianhai Zhang (zlhzlh@hotmail.com)
Shuangxi Li (lishx@hsc.pku.edu.cn)
Yongning Jia (yongningjia@bjmu.edu.cn)
Hui Ren (renhui88@sina.com)
Jiafu Ji (jijiafu@hsc.pku.edu.cn)

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Author’s response to reviews:

Dear editors,

Thank you for considering our paper. We are grateful to the reviewers for their constructive comments. We have addressed all the points raised by the reviewers. Please see the point-to-point response below.

Reviewer reports:

Mikito Inokuchi (Reviewer 1): You showed patients after neoadjuvant chemotherapy had significantly worse survival as compared with patients after surgery alone in same pathological stage. This study is large-scale, and this manuscript is well-written. However, this study has
several critical problems to be revised. In principle, pretreatment factors should be matched in a study using propensity score, but not posttreatment factors (e.g. pathological stage) authors used.

Major revision

1. What was the indication of NAC?

As recommended by the NCCN guideline, the indication for NAC was gastric cancer staging cT2-4NanyM0. We believe the prospective readers of the paper may wonder this as well so have added the following sentence to the Methods part of the manuscript: “In accordance with the NCCN guideline, NACT was recommended to gastric cancer patients of stage cT2-4NanyM0.” We thank the reviewer for bringing this up.

In principle, pretreatment factors should be matched in a study using propensity score, but not posttreatment factors (e.g. pathological stage) you used.

We totally agree with the reviewer that posttreatment factors should not be used to calculate the propensity score. However, the two “treatments” being compared in current study are not NAC and non-NAC, but ypTNM and pTNM. As we have carefully explained in the manuscript, the estimated hazard ratio of 1.34 does not implicate that patients with NAC had worse overall survival compared to those in the non-NAC group. Therefore, factors before the pathological report came out were considered pre-treatment.

We did, however, take this advice of the reviewer into account and re-examined the factors that were included in the propensity score model, to make sure the factors used were indeed pretreatment. As listed in the previous Table 2 (now appendix Table 1), the factors included in the propensity score model are age, gender, family history of cancer, BMI, ECOG, tumor location, tumor size (both short and long diameter), pathological type, differentiation grade, T stage, N stage, vascular cancer embolus status, hospital stay, operative time, blood loss, gastrectomy type, resection range, multiorgan excision status, reconstruction approach, ASA, number of lymph nodes dissected, and number of metastatic lymph nodes.
For the majority of the factors listed above, whether or not they were pre- or post-treatment could be easily determined. However, making this classification appeared to be tricky for three factors. One is hospital stay. This factor is considered pre-treatment because the pathological report normally became available around the discharge day in our center. However, we understand that hospital stay may be considered as post-treatment under the circumstances of other hospitals, and are open to further suggestions from the reviewer regarding this factor.

The other two variables that may be questionable are T and N stages. However, as we have explained in the manuscript, the inclusion of T and N stages in the propensity model was to balance the distribution of T and N stages between ypTNM and pTNM, so to achieve the goal of comparing the overall survival for patients with certain ypTNM stage to those with the same pTNM stage: “In this study, we used propensity score matching for the purpose of minimizing confounding as well as another: making the distribution of T stage and N stage comparable between the ypTNM and pTNM group, so to compare the prognostic implication of ypTNM and pTNM staging when the absolute number of the stage was the same. That is, for instance, whether a patient at stage of ypT1a, ypN3a, and M0 had the same overall survival as a patient of pT1a, pN3a, and M0.” (original Page 7 Line 53)

We apologize for this lengthy response and would like again to show our gratitude for this comment. We are certainly open to reviewer’s further suggestions regarding the construction of the propensity score model.

2. In same pathological stage, several factors (such as macroscopic type, or poorly differentiated adenocarcinoma) are well-known factors to impact on survival.

We thank the reviewer for this thoughtful comment. The differentiation grade of the patients was reported in Table 1 and was included in the propensity score model. The three categories of differentiation were previously marked as “low, middle, high”, which was not accurate (as mentioned by the second reviewer) and have been changed into “poor, moderate, well”.

We understand that in Japan, macroscopic type is considered as a very important factor when making decisions on whether or not the patient should receive NAC. In particular, Borrmann IV, large Borrmann III, or bulky lymph nodes are the indications of NAC in Japan. These are normally the patients with late stage. These are different from the indications of NAC in China,
which is cT2-4NanyM0 as recommended by the NCCN guideline. Therefore, whether or not the patient in our dataset received NAC did not depend on his/her macroscopic type. As such, omitting Borrmann type in the propensity score model will not introduce bias to our estimation. However, from the point of view that Borrmann type is associated with patient survival, it is worthwhile to have this factor in the model. Unfortunately, as the current study is in retrospective nature, we do not have the information of Borrmann type in the dataset. We have therefore added this to the limitations of our study, as follows:

“Thirdly, Borrmann type has been considered as an important prognostic factor of gastric cancer and is one of the indications of NACT in countries such as Japan. Due to the lack of information, this factor was not included in the propensity score or the conventional multivariate analysis. However, given that NACT indications in China do not contain patient Borrmann type, omitting this factor will not introduce bias to the HR estimation.”

Your study did not mean ypTNM staging was different from pTNM staging, although neoadjuvant chemotherapy (NAC) had worse survival than patients without neoadjuvant chemotherapy in same pathological stage. Therefore, your title may mislead readers. Two groups should be named as NAC group and non-NAC group.

We have to politely decline reviewer’s suggestion here because there seems to be some misunderstanding. As mentioned above, the current study aims to compare ypTNM with pTNM, not NAC with non-NAC. It is true that there is a connection between yp-/p-TNM staging and NAC/non-NACT: patients with NAC are those who have ypTNM staging. However, difference exists between the research question of “the effect of NAC vs non-NAC on patient survival” and the question of “whether patients with specific ypTNM have the same survival as those with the corresponding pTNM”. This is why several post-NAC variables were included in the propensity score model, such as vascular cancer embolus status and operative time. Without controlling for these factors, the research question would become the former one, which would lead to a misleading results.

We do think that our title is vague, in a way that the phrase “prognosis implication” is not very self-exploratory. However, we are not able to come up with a better title at this point and would really appreciate if the reviewer has better suggestion.
3. As described above, macroscopic type is very important factor to impact survival in same pathological stage. More patients underwent NAC might have type 4 with the poorest survival. Would you show clinical macroscopic type (type 1, 2, 3, and 4) between two groups?

We again thank the reviewer for this suggestion. As mentioned in the response to Comment #2, we do not have the information on macroscopic type. However, this will not introduce bias to our estimation as macroscopic type was not associated with the use of NAC. Regardless, we do agree with the reviewer that this is an important factor in terms of survival and have added this lack of information as a limitation to our study.

4. Patients underwent NAC might have more poorly differentiated adenocarcinoma. Would you show the detailed pathological type of adenocarcinoma (well, moderate, and poorly differentiated type) between two groups?

As mentioned in the response to Comment #2, the information on differentiation grade was given in Table 1. There was indeed a significant association between differentiation grade and the two groups (previous Table 2, now Appendix Table 1).

5. Patients underwent NAC must have more advanced clinical (preoperative) stage. Would you show clinical stage between two groups?

The reviewer has brought up a splendid point here. The addition of cstage to current analysis would definitely increase the significance of our study. However, the information on cstage is incomplete in our dataset and we therefore took this variable out of the equation. We have mentioned this as a limitation of our study in the manuscript, as following: “Secondly, as previously mentioned, because information on cTNM was in lack for this study, we cannot backup the explanations of our results. However, this does not affect the conclusion of current study, as we only considered the prognostic value of pTNM and ypTNM stage.”

6. Would you show the detailed pathological stage, such as IA, IB, IIA…, and IIIC between two groups?
We have added stage information to the tables. Please refer to the tables for detailed information.

Would you show the survival curve in the detailed stage? Survival rate is very different between pathological stage IIIA and IIIC.

Survival curves by detailed pathological stage have been added to the files as Appendix Figure 1. Please refer to the Appendix Figure 1 for detailed information. Probably because of the decreased sample size and lack of statistical power, a significant difference of survival rate is only observed in Stage IIIb, and hazard ratio as well as p-value were not estimable for Stage Ia, Ib, and Iia as the Cox model could not converge.

7. Table 2 is unnecessary, because aim of this study is to compare two groups.

We have moved this table to the Appendix Table 1.

Reviewer 2:

OBJECTIVE - Full research articles: is there a clear objective that addresses a testable research question(s) (brief or other article types: is there a clear objective)?

Yes - there is a clear objective

DESIGN - Is the current approach (including controls and analysis protocols) appropriate for the objective?

Yes - the approach is appropriate

EXECUTION - Are the experiments and analyses performed with technical rigor to allow confidence in the results?

Yes - experiments and analyses were performed appropriately
INTERPRETATION - Is the current interpretation/discussion of the results reasonable and not overstated?

Yes - the author's interpretation is reasonable

OVERALL MANUSCRIPT POTENTIAL - Could an appropriately REVISED version of this work represent a technically sound contribution?

Maybe - with major revisions

PEER REVIEWER COMMENTS:

GENERAL COMMENTS: The manuscript describes the analysis of whether, in gastric cancer, the new neoadjuvant staging system (ypTNM) yields similar patient survival outcomes as the conventional pTNM staging system. One of their findings is that patients with specific ypTNM stages were more likely to die than patients corresponding to the same pTNM stage. This is not surprising since these patients were down-staged, and direct comparison to a non-NACT treated patient is what is being done. Regardless, the study appears to be the first direct comparison of both staging systems using a fairly large cohort that is well balanced. For the most part, it is well done, and the results are clearly presented. The manuscript itself, however, needs improvement.

REQUESTED REVISIONS:

1. Page 2, Line 6: Pathological stage is considered as the best prognosis indicator. This sentence should include that this relates specifically to gastric cancer.

The sentence has been changed to “Pathological stage is considered as the best prognosis indicator for gastric cancer”.

2. Page 2, Line 12: However, no study has investigated if ypTNM stage has the same prognostic implication as pTNM stage for gastric cancer.
We have added “for gastric cancer” to the end of the sentence as suggested.

3. Page 2, Line 47: certain ypTNM stage. Certain is not clear, please define this exactly. Which stage? This is repeated many times in the manuscript. Please change this throughout.

We checked the whole manuscript. The same phrase is repeated twice in the abstract and four times in the main body. In all of these sentences, we were not trying to refer to a specific stage, but were stating a general conclusion that is applicable to all stages. However, we do concern the word “certain” is somewhat informal and have therefore changed the it into “specific” in all sentences. We are open to reviewer’s further suggestion on this matter.

4. Page 2, Line 53: Multivariate Cox regression yielded a similar hazard ratio (HR) of 1.35 (95%CI=1.09-1.67, P=0.006). This statement could be more specific. What is the comparison that yielded a similar HR?

The comparison was between the results of PS methods and that of the conventional multivariate Cox regression. This sentence has therefore been changed into the following for the clarification: “Similar to the results of PS matching, multivariate Cox regression yielded a hazard ratio (HR) of 1.35 (95%CI=1.09-1.67, P=0.006).”

5. Page 2, Line 54: Subgroup analysis indicated this survival difference varied by TNM stage. Again, this could be rewritten to be more clearly.

This sentence has been changed into the following for further clarification: “Subgroup analysis indicated this survival difference between ypTNM and pTNM stage varied by the specific TNM stage of patients”.

6. Page 3, Line 6: certain ypTNM stage. Certain is not clear, please define this exactly.
As responded in Comment #3, we were not trying to refer to a specific stage, but were stating a general conclusion that is applicable to all stages. Nonetheless, the word “certain” has been changed to “specific” in all sentences for better wording.

7. Page 4, Line 3: Gastric cancer is one of the most common cancers worldwide.

The word “cancer” has been changed to “cancers” as suggested.

8. Page 4, Line 23: It has been adopted as the base of guideline by the NCCN since its first edition published in 1976 and has been widely implemented to clinical practice ever since while being revised and updated for several times. This is an awkwardly written sentence.

We have changed the sentence into the following: “Several revisions have been made to this staging system since its first edition in 1976.”


We meant to say that “this conclusion was drawn before ypTNM was proposed”. We have changed the word “proposition” to “introduction”.

10. Page 5, Line 23: Patient clinicopathological information was restored in this database since their first-time treatment at the hospital. What does “restored” mean?

We meant to say the information was saved in the database. We have changed the word “restored” to “stored”.

11. Page 6, Line 17: distinguished might be reworded as determined.
We agree with the reviewer that the word “determined” is more appropriate. The change has been made accordingly.

12. Page 6, Line 45: All patients had either ypTNM stage or pTNM stage as they would either receive preoperative NACT or not. This is not clearly written and is confusing.

We apologize for this confusion which may be due to the inappropriate use of tense or the redundant use of the word “preoperative” before the acronym “NACT”. What we meant is the following. If the patient had preoperative chemotherapy, ypTNM staging was used. If the patient did not receive preoperative chemotherapy, pTNM staging was used instead. Therefore, a patient could either have an ypTNM stage or pTNM stage. He/she could not have both. Nonetheless, we believe that this sentence may not be that informative and have removed it from the manuscript to avoid confusion.

13. Page 9, line 14: why were the 36 patients excluded?

We excluded these patients for the following reasons: ASA score equals to 4, adenosquamous carcinoma, adenocarcinoma with NET, ECOG score equals to 3, missing tumor size, and T0 stage. These reasons are listed in Figure 1, which is noted at the end of the sentence.

Additionally, we noticed that there had been a typo in this number, which should be 46 rather than 36. We have therefore modified the sentence into the following: “1487 eligible patients were included in this study, of which 46 were excluded for reasons listed in Figure 1, leaving a sample of 1441 for analysis.”

14. Page 9, line 26: Most tumors were at middle differentiation grade. Is middle actually moderate differentiation?

Yes. We have changed the word middle to moderate in this sentence. Additionally, we checked the whole manuscript if the same expression was used. We changed the “middle” category under the variable “differentiation grade” to “moderate” in the tables as well.
15. Page 9, line 45: To better control for the confounding and make the two groups comparable in terms of …This sentence is awkwardly written.

We have changed the wording into the following: “To better control for confounding and achieve comparable distribution of T and N stage between the two groups…” Please let us know if this is still poorly written and we will make further modifications.

16. Page 9, line 53: score-matched samples were comprised…. 

A word “were” has been added to the sentence accordingly.

17. Page 10, line 23: We calculated Harrell's c-index when pathological staging used was ypTNM and when otherwise, to compare the prognostic prediction ability of ypTNM and pTNM. This sentence is awkwardly written.

The sentence has been changed to “We calculated Harrell's c-index to compare the prognostic prediction ability of ypTNM staging and pTNM staging.”, which we believe is better worded. However, we are open to make further modifications.

18. Page 12, line 25: counterfactual is not clear to its meaning.

We understand the word counterfactual is not self-explanatory and have changed the wording of the sentence, as follows: “These patients would therefore have much worse prognosis than those in pTNM stage I because they would have a worse pTNM stage have they had one.”

19. There should be a period after all references and not before unless this is the journal style.

We have checked the whole manuscript and moved the punctuation marks after the references when applicable.
20. Table 1: differentiation is usually poor, moderate and well not high, middle and low.

As responded in Comment #14, “High, middle, low” have been changed to “Well, moderate, poor” in all tables according to reviewer’s suggestion.

Note: This reviewer report can be downloaded - see attached pdf file.

If improvements to the English language within your manuscript have been requested, you should have your manuscript reviewed by someone who is fluent in English. If you would like professional help in revising this manuscript, you can use any reputable English language editing service. We can recommend our affiliates Nature Research Editing Service (http://bit.ly/NRES_BS) and American Journal Experts (http://bit.ly/AJE_BS) for help with English usage. Please note that use of an editing service is neither a requirement nor a guarantee of publication. Free assistance is available from our English language tutorial (https://www.springer.com/gb/authors-editors/authorandreviewertutorials/writinginenglish) and our Writing resources (BMC_WRITING_RESOURCES_URL http://www.biomedcentral.com/getpublished/writing-resources). These cover common mistakes that occur when writing in English.

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