Author’s response to reviews

Title: Meta-analysis comparing laparoscopic versus open resection for gastric gastrointestinal stromal tumors larger than 5 cm

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Author’s response to reviews:

Reviewer #1

The authors present both a single institution retrospective cohort study of laparoscopic versus open resection of large gastric GISTs AND a systematic review and meta-analysis. The combination of these two study designs makes the manuscript difficult to review and limits the overall quality and depth of presentation of the methods and data for either design. I recommend the authors split the two study designs into separate manuscripts.
Review comments:

1. The abstract states the patients were "matched" but there is no detail in the methods/statistical analysis of how they were matched.

Answer: Thank you for your comments. I am sorry for ignorance the description of the match method. In this study, we matched the 81 patients who underwent open resection to the 13 patients who received laparoscopic resection with a 1:1 matched ratio. The matching condition we set was that the gap of the tumor size between the two groups was not greater than one centimeter, and the gmatch macro of SAS 9.2 (SAS institute, Cary, NC, USA) written by Erik Bergstralh & Jon Kosanke (http://www.mayo.edu/research/departments-divisions/department-health-sciences-research/division-biomedical-statistics-informatics/software/locally-written-sas-macros) was used to execute this pair matching process. The principle of this macro is computerized matching of cases to controls using the greedy matching algorithm with a fixed number of controls per case. Controls may be matched to cases using one or more factors (X's). In this study, we set patients underwent laparoscopic resection group as cases, and patients underwent open resection as controls. The only matching factor is the size of the tumor. We have supplemented the detail in Methods (paragraph 1, line 3 and paragraph 6, line 4).

2. The meta-analysis should follow the PRISMA checklist. The flow diagram is lacking detail.

Answer: Based on the valuable advice you have made, in order to get a more clear description of the literature screening process, we strictly followed the PRISMA checklist to improve the flow chart and supplement the details (Fig 1).

3. I find it hard to believe that a comprehensive search of the listed keywords yielded only 129 titles. How many titles were reviewed and how many from each database?

Answer: Thank you for your comments. We did not really pay attention to the description of the search strategies before, just a simple list of a few keywords, which may mislead you. In order to
eliminate your doubts, we re-search the literature according to our set of search strategies ranged from 2005 to 2016. We initially identified 167 potential articles from PubMed, EMBASE and the Cochrane Library databases. Although the number of potential articles has a little discrepancy with the previous (129), the total amount is still small. Then we screened these articles follow the previous inclusion criteria, the same six titles were included in the study as before. The detailed search strategies of the three databases are presented as follows (Appendix 1). The revised flow chart also been presented (Fig 1), and a small change was made to the Results section (paragraph 3, line 1).

“Details of the search strategy:

Two authors (LX and GM) utilize the search strategies for each online database defined by (FF) to independently screened potentially eligible studies.

Pubmed

Performed:12/11/2016


N=66

EMBASE

Performed:12/11/2016

‘gastric’:ti AND (‘gastrointestinal stromal tumor’:ti OR ‘gastrointestinal stromal tumors’:ti OR ‘GISTs’:ti OR ‘GIST’:ti) AND (‘open’:ti OR ‘laparoscopic’:ti OR ‘laparoscopy’:ti) AND (‘resection’:ti OR ‘surgery’:ti)

N=100
Cochrane:

Performed: 12/12/2016

gastric AND ("gastrointestinal stromal tumor" OR "gastrointestinal stromal tumors" OR "GISTs" OR "GIST") AND (open OR laparoscopic OR laparoscopy) AND (resection OR surgery)

N=1”

4. Figure 2 for the systematic review portion has poor resolution and cannot be interpreted.

Answer: We apology for the poor resolution figure submitted before, we have adjusted the resolution of the Figure 2, and re-submitted it online for a better interpretation of the systematic review.

5. Why was the Takahashi article included when tumor size and follow was not available?

Answer: Thank you for your comments. I think you want to know why the Piessen article was included when tumor size and follow was not available. This article first compared the postoperative outcomes and oncologic results of laparoscopic versus open surgery for gGISTs in a large multicenter European database. Then the author divided the overall patients into <5cm and > 5cm according to tumor size, and focus on the analysis of subgroup with tumors larger than 5cm after matching. However, the author did not provide the specific data about the mean tumor size and mean follow-up time, only describe the baseline data about the overall patients. We have tried to contact the author via email to get the relevant data, but he has not yet responded. There is no doubt that this article met the inclusion criteria of our study.

6. There is no data on the use of neoadjuvant or adjuvant therapy, making the conclusion on OS and recurrence difficult to interpret.
Answer: We understand that you had a concern about the influence of the adjuvant therapy on the OS or recurrence. We did not show these data in our manuscript before considering the difficult in effect (OS/DFS) merge due to the unavailable survival information of the included studies. We list the available relevant data in the table below (Appendix 4). In detail, Kim et al [25] and Chun et al [29] did not mention the adjuvant therapy at all. Hsiao et al [26] used adjuvant target therapy for patients with large or high-risk GISTs, but did not provide the specific data. 16% of overall patients (included tumor size ≤5cm) benefited from adjuvant tyrosine kinase inhibitor therapy in the study of Piessen [28]. We can see that there is no significant difference in neoadjuvant or adjuvant therapy between the laparoscopic and open resection of Lin [17], Takahashi [27] and our study, so the baseline of neoadjuvant or adjuvant could be consider as comparable. For our center, patients with intermediate or high risk of recurrence was demanded to take the imatinib (400mg daily) after surgery for at least 1 year according to the NCCN guideline, and adjusted the treatment plan according to the result of postoperative reexamination. However, some patients had poor treatment compliance, may be due to economic factor, after all, imatinib is not entirely covered by the insurance in China at present. We had added the relevant content in resubmitted manuscript. (Methods section, paragraph 1, line 6, Results section, paragraph 1, line 3 and Table 1.)

Reviewer #2

1. The written English in your revised manuscript is much improved with the assistance of the American Journal Experts. There are still some sentences and words that need to be edited. I advise against using "etc." in any sentence.

In Methods section, I recommend revising your last sentence under Patients: "after considering the comprehensive conditions, such as growth pattern, tumor location, etc." Please state the conditions that were used to make the decision and not use "etc".

Answer: Thank you for your comments and understanding English is not my native language. We did ignore the written language specification before, follow your advice, we have revised the sentence more specific:

“Although the choice of surgical approach was the discretion of the surgeon, as a rule. Laparoscopic resection was performed on tumors > 5 cm only if this surgery was evaluated as beneficial and safe for patients after considering the tumor size, growth pattern, tumor location and other factors.” (Methods section, paragraph 1, line 5)
2. In your study, you have 94 patients that were eligible and of these 13 were laparoscopic. You did not describe in your methods how you chose the matched 13 open patients out of the 81 remaining. I think this is important for the reader to know in order to understand the amount of bias.

Answer: Thank you for your comments. I am sorry for ignorance the description of the match method. In this study, we matched the 81 patients who underwent open resection to the 13 patients who received laparoscopic resection with a 1:1 matched ratio. The matching condition we set was that the gap of the tumor size between the two groups was not greater than one centimeter, and the gmatch macro of SAS 9.2 (SAS institute, Cary, NC, USA) written by Erik Bergstralh & Jon Kosanke (http://www.mayo.edu/research/departments-divisions/department-health-sciences-research/division-biomedical-statistics-informatics/software/locally-written-sas-macros) was used to execute this pair matching process. The principle of this macro is computerized matching of cases to controls using the greedy matching algorithm with a fixed number of controls per case. Controls may be matched to cases using one or more factors (X's). In this study, we set patients underwent laparoscopic resection group as cases, and patients underwent open resection as controls. The only matching factor is the size of the tumor. We have supplemented the detail in Methods (paragraph 1, line 3 and paragraph 6, line 4).

3. In Table 1, you are missing a patient in risk classification LAP group: 6 intermediate/6 high, yet you have 13 patients in this group.

Answer: We apology for the missing information of the patient in risk classification. It was really the missing data in pathological report previous. This patient was in an intermediate risk classification after the reexamination of pathology department in our center. The data information in manuscript and Table 1 had been revised and resubmitted.
Additional comments

While several recent meta-analyses on the same topic are referenced, there is no mention of their results in the text. It would be appropriate to do so in the Introduction and Discussion sections for comparison reasons.

Reporting on methods undertaken for the systematic review and meta-analysis need to be revised; a formal statistical review may be needed but details are lacking at this time (including the requested PRISMA checklist) to inform this.

Answer: Thank you for your comments. Indeed, several large scale meta-analyses had investigated the feasibility and safety of a laparoscopic versus open approach for general size or small tumors as mentioned in the background part of the manuscript, however, so far there is no systematic review of the comparative resection treatment for tumor size greater than 5 cm. We think that the results of the study for different grade of sizes of gastric stromal tumors are not comparable, so we had not discussed more about recent published systems reviews. Hope for your understanding.

We have improved the report quality of methods for the systematic review to some extent (Methods section, paragraph 3, line 1). Furthermore, the PRISMA checklist has been submitted to inform the detail of our meta-analysis (Appendix 3).