Author’s response to reviews

Title: Robotic versus laparoscopic distal pancreatectomy: an up-to-date meta-analysis

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Author’s response to reviews:

To Guangde Tu, editors in chief

BMC Surgery

Dear Professor,

Thank you for the opportunity of reviewing this manuscript. We have profoundly changed our article by taking into account all the reviewers' comments.

In particular, we have modified the conclusions, we have added a specific table on the oncological outcomes (as suggested by Kai Pun Wong), we have entered a new outcome (operative time), and finally we broadly enriched the discussion section.

We hope that this article could be of interest to the editorial board and readers of your prestigious journal.
Yours Faithfully,

Gian Piero Guerrini Md, PhD

Replies to reviewers' comments

All new changes to the manuscript were written in red to be traced

1 Reviewer: Dear Valeria Tonini Md-Phd

“this is an interesting and well-structured study on a controversial issue: there are still many doubts about what might be the most appropriate surgical technique in distal pancreatectomy. The selection criteria of the studies and the methodology adopted were impeccable. Perhaps it would have been worth widening the study by comparing the three techniques currently used for distal pancreatectomy: open, laparoscopic and robotic. Moreover it might be better to compare the different spleen preservation techniques (Kimura method versus Warsaw method) and the type of laparoscopic technique (conventional multi-laparoscopy versus single-incision laparoscopy). The results of this study should be interpreted with caution due to some limitations. While all the studies included in this meta-analysis were found to be high-quality studies, none of them were randomized trials, because there are none on this subject. Therefore, the authors could only analyze retrospective studies with the well-known limitations of this approach. RDP is a relatively new technique and there are still many issues related to costs, organization and learning curve. The main risk of non-randomized studies investigating new techniques is obviously patient selection: it is possible that more challenging cases might be treated more readily with an established technique (such as LDP in this case), while the newer technique (in this case RDP) is employed in less difficult cases. In this meta-analysis the results of the two techniques were substantially overlapping, as reported in other studies. The morbidity and mortality were similar. Conversely, RDP procedures have a lower conversion rate, a higher spleen preservation rate, a shorter length of hospital stay but higher costs compared to LDPs. Another limitation of this study is not differentiating between the various indications for DP. In my opinion, it does not make much sense to compare the results of two surgical techniques applied to completely different pathologies, ranging from small IPMNs to big cancers. Spleen preservation must be taken into great consideration when comparing of the two techniques: preserving the spleen is a must in benign or borderline pathology, whereas splenectomy is almost always necessary in malignant disease for oncological reasons. Since the RDP technique offers significantly better spleen conservation rates, it could become the technique of choice in benign pathologies, regardless of the higher costs of the procedure. It is also worth noting that, on top of all the expenses already accounted for by the various authors, I think it would be important to consider a cost that is difficult to estimate: the cost of an unnecessary splenectomy and the loss of its function, with subsequent immunodeficiency and increased risk of infection. Although the radicality and the adequacy of lymphadenectomy after RDP appear encouraging, oncologic results cannot be evaluated at this time, since a longer follow-up is needed to validate them. In conclusion I would say that the study is valid, well-conducted, sparks interest in a hot surgical
topic, encourages operators to improve their expertise in a new technique that seems to offer substantial advantages. Moreover it is possible that the costs of this techniques will decrease over time once its learning curve will be completed. I think that an increased surgical volume and experience with RDP and a longer follow-up period are necessary to establish its most appropriate use and its potential superiority over the laparoscopic technique and to support its widespread adoption in current surgical practice. Obviously, large, multicenter, prospective randomized controlled trials are needed to prove these results.”

Answer:

Thank you very much for your very detailed and accurate comments. We're glad you liked this article. We agree with your observations. We have tried to summarize your comments in three key points:

1) This meta-analysis is based on retrospective studies so the risk of bias is potentially high. Therefore, we have reformulated the conclusions about the oncological outcomes. In fact, we have no longer written that robotic distal pancreatectomy is superior to laparoscopic one in terms of oncological results because statistically adequate comparison is not possible from the data available. We highlighted that both techniques are comparable in terms of surgical outcome. In addition, the discussion highlights the risk of bias related to the retrospective nature of the studies.

2) We introduced in the section discussion a paragraph discussing Kimura's technique and Warshaw's technique, clearly saying that the authors did not describe the method used to preserve the spleen.

3) We reported in the discussion section how the cost of the operation is highly variable between the various centers, even in the same country. Therefore cost comparison between the RDP and LDP can therefore lead to interpretative errors.

Yours Faithfully,

Gian Piero Guerrini Md, PhD

2 Reviewer: Dear Daniel Vargo Md-Phd

This is a meta-analysis comparing laparoscopic to robotic distal pancreatectomy. It is well researched, analyzed, and written. I have some suggestions for the authors: Line 27 on page 5 should be "latest" or "most recent", not "last". The figures have different colors marking the means. When speaking of the oncologic result, that is a broad statement that can be taken to mean needing chemotherapy, recurrence rate, survival, etc. State what you mean, which is achieving an R0 resection. When you speak of cost, you need to stress direct hospital cost. There was no overall assessment of cost, including time off work, loss of salary, etc.
Answer: We thank you for your very important comments and we are happy that you liked our article.

We did all the modifications that you have suggested. In particular we replaced "last" with "most recent". In the discussion we have added an oncological statement saying that there are no data available about chemo-radiotherapy treatments with adjuvant or neoadjuvant intent, disease free survival and tumour recurrence. Therefore it is not possible to determine whether robotic distal pancreatectomy is superior to LDP in terms of oncological outcomes. Even with regard costs, we have explained how the cost of the operation is highly variable between the various centers, even in those of the same nation. Cost comparison can therefore lead to interpretative errors.

Yours Faithfully,

Gian Piero Guerrini MD, PhD

3 Reviewer: Dear Kai Pung Wong MD

The meta-analysis compared with oncological outcome and surgical outcome between laparoscopic and robotic distal pancreatectomy. The study design is appropriate and the clinical question is important. However, meta-analysis of retrospective studies are prone to bias and level of evidence is inferior. Methodology and study design needed further elaboration for better interpretation and understandings. 1. Criteria of selection of article should be clearly stated, including date of data search, human studies, language of articles and minimal number of objects in the study. 2. In 2nd paragraph under heading of "inclusion criteria, intra-abdominal abscess was one of the outcome measures while no analysis on that was found. Please state clearly what morbidity are included in this studies 3. According to funnel plots, publications bias was present in numbers of analysis including conversion rate and hospital stay. The author should better state its presence and describe in their manuscript. Quantitative analysis will be more appropriate. 4. What is use of classification of heterogeneity into low, moderate and high level? If not indicated, please delete it. 5. For pancreatic fistula, it is appropriate to perform the analysis only if they follow the same definitions, i.e. ISGPF. And it is important to show which 6 article are using this classifications. 6. In "result", is there any difference in demographics in any of the articles? if no analysis was performed, it cannot be stated that "....... two groups were similar...." 7. For oncological parameters, further elaboration and clarification of results is recommended. Though results on oncological outcome was diverse, table showing the result of different article is recommended.

Answer: We thank you for your very accurate comments because they have allowed us to make this article stronger. We will reply point by point to your observations

11. Criteria of selection of article should be clearly stated, including date of data search, human studies, language of articles and minimal number of objects in the study.
We have included this statement in the article: “We included studies with more than five patients in each arm for comparison of clinical outcomes. Narrative reviews, case series or studies without matched groups and surveys were excluded.”.

2. In 2nd paragraph under heading of "inclusion criteria, intra-abdominal abscess was one of the outcome measures while no analysis on that was found. Please state clearly what morbidity are included in this studies

This was our mistake because we did not consider the intra-abdominal abscess as outcome in the study. We have corrected the paragraph

3. According to funnel plots, publications bias was present in numbers of analysis including conversion rate and hospital stay. The author should better state its presence and describe in their manuscript. Quantitative analysis will be more appropriate

For these two specific outcomes, random-effects model was applied

4. What is use of classification of heterogeneity into low, moderate and high level? If not indicated, please delete it.

This classification has been removed.

5. For pancreatic fistula, it is appropriate to perform the analysis only if they follow the same definitions, i.e. ISGPF. And it is important to show which 6 article are using this classifications.

For this specific outcome we first performed meta-analysis on all studies, then we made a subgroup of analysis on the studies that used the classification of Pancreatic fistula according to ISGPF but in both groups there was no statistically significant difference.

6. In "result", is there any difference in demographics in any of the articles? if no analysis was performed, it cannot be stated that "....... two groups were similar...."

We have added this statement in the results section as you suggested us: “The two groups were similar as regards demographics (age, body mass index (BMI), gender), comorbidities (American Society of Anesthesiologist score) and pathological characteristics.”

7. For oncological parameters, further elaboration and clarification of results is recommended. Though results on oncological outcome was diverse, table showing the result of different article is recommended.

We have created a table to summarize the oncological outcomes. We have reformulated the conclusions on this specific point and introduce a paragraph in the discussion section.

Yours Faithfully,
Gian Piero Guerrini Md, PhD