

Dear Editors and Reviewers:

Thanks for your careful and detail review for our manuscript entitled “**Is total laparoscopic pancreaticoduodenectomy superior to the open procedure? A meta-analysis**” (Manuscript NO. 48303). We have read the comments carefully and talked with our team members, corrections have been made in the revised manuscript, explanations and additional data to address the reviews comments have been provided accordingly. The comments are valuable and meaningful, we respond then point by point. All revisions are displayed or marked in the revised manuscript. Now, the quality of our revised is improved and we hope that it is now be acceptable for publication in World Journal of Gastroenterology.

All revisions are listed as follows:

Responds to the Editor:

1. Please provide point to point answer to all reviewers. Please revise your manuscript according to the “guideline” and “format”.

Author’s response: We have provided point to point answer to all reviewers later in the text. The manuscript has been revised according to the “guideline” and “format” and all revisions have been marked in red.

2. A short running title of no more than 6 words should be provided. It should state the topic of the paper. e.g. Losurdo G et al. Two-year follow-up of duodenal lymphocytosis.

Author’s response: The short running title has been provided as:
Laparoscopic *vs* open pancreaticoduodenectomy: A meta-analysis.

3. ORCID provides a persistent digital identifier that distinguishes you from every other researcher and, through integration in key research workflows such as manuscript and grant submissions, supports automated linkages between you and your professional activities, thereby ensuring that your work is recognized. Please visit the ORCID website at <https://orcid.org/> for more information. All authors must provide their personal ORCID registration number. For example, Marcos Pasarín

(0000-0002-4122-1235); Juan G Abraldes (0000-0002-4392-660X); Eleonora Liguori (0000-0002-0244-927X); Beverley Kok (0000-0002-1727-5030); Vincenzo La Mura (0000-0003-4685-7184).

Author's response: The ORCID registration number of the authors have been added as: Hua Zhang (0000-0002-8002-7603); Xiang Lan (0000-0003-2109-5312); Bing Peng (0000-0002-2952-1083); Bo Li (0000-0002-3260-6221).

4. The format of this section will be as follows: Author contributions: Wang CL, Liang L, Fu JF, Zou CC, Hong F and Wu XM designed the research; Wang CL, Zou CC, Hong F and Wu XM performed the research; Xue JZ and Lu JR contributed new reagents/analytic tools; Wang CL, Liang L and Fu JF analyzed the data; Wang CL, Liang L and Fu JF wrote the paper.

Author's response: We have modified the format of this section and marked in red in page 1, line 24-27.

5. Please download the Conflict of Interest (PDF), fill it in, and then upload the completed PDF version to the system. Note: The Corresponding Author is responsible for filling out a Conflict-of-Interest Form. Please add Conflict-of-interest statement. e.g. There is no conflict of interest associated with any of the senior author or other coauthors contributed their efforts in this manuscript.

Author's response: We have filled in the Conflict of Interest, and will upload it as a file.

6. In order to improve the quality of Systemic Review manuscripts, authors should download and complete the 'PRISMA 2009 Checklist' to ensure that the manuscript meets the requirements of the PRISMA 2009 Statement. Authors must state on the title page of the manuscript that the guidelines of the PRISMA 2009 Statement have been adopted (see below). Authors must upload the PDF version of the completed checklist to the system. Sample wording: The authors have read the PRISMA 2009 Checklist, and the manuscript was prepared and revised according to the PRISMA 2009

Checklist.

Author's response: We have complete the 'PRISMA 2009 Checklist' and will upload it as a file, the state has been added in page 2, line 34-35.

7. Only one corresponding author is allowed. Designation of co-corresponding authors is not permitted. The corresponding author's contact information should be provided in the following format: Author names (unabbreviated) should be followed by the author's title in bold, and the affiliation, complete name of institution, present address, city, province/state, postcode, country, and E-mail. The corresponding author's E-mail address must be issued by his/her institution. All the letters in the E-mail address should be typed in lowercase, and separated from the country by a period and a space. For example, Andrzej S Tarnawski, MD, PhD, DSc (Med), Professor of Medicine, Chief, Gastroenterology, VA Long Beach Health Care System, University of California, Irvine, 5901 E Seventh St, Long Beach, CA 90822, United States.
astarnaw@uci.edu

Author's response: We have modified the format of this section in page 2, line 45-47.

8. Telephone and fax numbers should consist of +, country number, district number and telephone or fax number; for example, +86-10-85381892

Author's response: Telephone and fax numbers have been added in our revised manuscript in page 2, line 48-49.

9. The 5 sections of the structured abstract are: Background, Aims, Methods, Results, and Conclusion.

Author's response: The format and structure of abstract have been modified in revised manuscript in page 2-4.

10. The purpose of the study should be stated clearly, with no or minimal background information, following the format of: "To investigate/study/determine..."

Author's response: This section has been modified and added in revised

manuscript in page 3, line 67-68.

11. Please list 5-10 key words for each paper, which reflect the content of the study.

Author's response: This section has been modified as : total laparoscopic pancreaticoduodenectomy; open pancreaticoduodenectomy; safety; feasibility; meta-analysis.

12. Please write a summary of no more than 100 words to present the core content of your manuscript, highlighting the most innovative and important findings and/or arguments. The purpose of the Core Tip is to attract readers' interest for reading the full version of your article and increasing the impact of your article in your field of study.

70~100 words, please supplement.

Author's response: The core tips has been added in page 4, line 113-120.

13. Please offer the audio core tip, the requirement are as follows: In order to attract readers to read your full-text article, we request that the first author make an audio file describing your final core tip. This audio file will be published online, along with your article. Please submit audio files according to the following specifications:

Acceptable file formats: .mp3, .wav, or .aiff

Maximum file size: 10 MB

To achieve the best quality, when saving audio files as an mp3, use a setting of 256 kbps or higher for stereo or 128 kbps or higher for mono. Sampling rate should be either 44.1 kHz or 48 kHz. Bit rate should be either 16 or 24 bit. To avoid audible clipping noise, please make sure that audio levels do not exceed 0 dBFS.

Author's response: The audio core tips has been completed following the guidelines and will upload as a file.

14. Please distinguish between the title of the article series. Three levels of subtitles are allowed: (1) First subtitle: All in bold and capital; (2) Second subtitle: All in bold and italic; and (3) Third subtitle: All in bold.

Main text. The main text contains INTRODUCTION, MATERIALS AND

METHODS, RESULTS, DISCUSSION, and ARTICLE HIGHLIGHTS (Research background, Research motivation, Research objectives, Research methods, Research results, Research conclusions, and Research perspectives),

Author's response: The format and structure of the article have been modified in the revised manuscript following the instruction.

15. The guidelines for writing and formatting Article Highlights are as follows:

(1) Research background

The background, present status and significance of the study should be described in detail.

(2) Research motivation

The main topics, the key problems to be solved, and the significance of solving these problems for future research in this field should be described in detail.

(3) Research objectives

The main objectives, the objectives that were realized, and the significance of realizing these objectives for future research in this field should be described in detail.

(4) Research methods

The research methods (e.g., experiments, data analysis, surveys, and clinical trials) that were adopted to realize the objectives, as well as the characteristics and novelty of these research methods, should be described in detail.

(5) Research results

The research findings, their contributions to the research in this field, and the problems that remain to be solved should be described in detail.

(6) Research conclusions

The following questions should be briefly answered:

What are the new findings of this study?

What are the new theories that this study proposes?

What are the appropriate summarizations of the current knowledge that this study provided?

What are the original insights into the current knowledge that this study offered?

What are the new hypotheses that this study proposed?

What are the new methods that this study proposed?

What are the new phenomena that were found through experiments in this study?

What are the hypotheses that were confirmed through experiments in this study?

What are the implications of this study for clinical practice in the future?

(7) Research perspectives

What experiences and lessons can be learnt from this study?

What is the direction of the future research?

What is/are the best method/s for the future research?

Please write this section.

Author's response: The section has been added in revised manuscript in page 19-20, line 563-602.

16. Please check and confirm that there are no repeated references!

Please add PubMed citation numbers (PMID NOT PMCID) and DOI citation to the reference list and list all authors. Please revise throughout. The author should provide the first page of the paper without PMID and DOI.

PMID (<http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=PubMed>)

(Please begin with PMID:) DOI

(<http://www.crossref.org/SimpleTextQuery/>) (Please begin with DOI: 10.**)

Author's response: We have checked the references and confirmed that there were no repeated references. PMID and DOI have been added in revised manuscript.

17. Please don't include abbreviations in the title of the figure/table.

Author's response: The title has been modified as: Results of the sensitivity-analysis of total laparoscopic pancreaticoduodenectomy (TLPD) vs open pancreaticoduodenectomy (OPD).

18. Regarding the figures: Please provide the decomposable figure of figures, whose parts are all movable and editable, organize them into a PowerPoint file, and submit as "Manuscript No. -Figures.ppt" on the system, we need to edit the words in the figures. All submitted figures, including the text contained within the figures, must be editable. Please provide the text in your figure(s) in text boxes.

Author's response: The figures has been modified and organized into a Powerpoint file entitled "Manuscript No. 48303-Figures", the Powerpoint will uploaded as a file.

19. Regarding the figures: Please provide the decomposable figure of figures, whose parts are all movable and editable, organize them into a PowerPoint file, and submit as "Manuscript No. -Figures.ppt" on the system, we need to edit the words in the figures. All submitted figures, including the text contained within the figures, must be editable. Please provide the text in your figure(s) in text boxes.

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Author’s response: The figures has been modified and organized into a Powerpoint file entitled “Manuscript No. 48303-Figures”, the Powerpoint will uploaded as a file.

24. Please don’t include abbreviations in the title of the figure/table.

Author’s response: The “POPF” has been replaced by “postoperative pancreatic fistula (POPF)” in the revised manuscript.

25. Regarding the figures: Please provide the decomposable figure of figures, whose parts are all movable and editable, organize them into a

PowerPoint file, and submit as “Manuscript No. -Figures.ppt” on the system, we need to edit the words in the figures. All submitted figures, including the text contained within the figures, must be editable. Please provide the text in your figure(s) in text boxes.

Author’s response: The figures has been modified and organized into a Powerpoint file entitled “Manuscript No. 48303-Figures”, the Powerpoint will uploaded as a file.

26. Please don’t include abbreviations in the title of the figure/table.

Author’s response: The “DGE” has been replaced by “delayed gastric emptying (DGE)” in the revised manuscript.

27. Regarding the figures: Please provide the decomposable figure of figures, whose parts are all movable and editable, organize them into a PowerPoint file, and submit as “Manuscript No. -Figures.ppt” on the system, we need to edit the words in the figures. All submitted figures, including the text contained within the figures, must be editable. Please provide the text in your figure(s) in text boxes.

Author’s response: The figures has been modified and organized into a Powerpoint file entitled “Manuscript No. 48303-Figures”, the Powerpoint will uploaded as a file.

28. Please don’t include abbreviations in the title of the figure/table.

Author’s response: The “DGE(Grade B/C)” has been replaced by “delayed gastric emptying (DGE) (Grade B/C)” in the revised manuscript.

29. Regarding the figures: Please provide the decomposable figure of figures, whose parts are all movable and editable, organize them into a PowerPoint file, and submit as “Manuscript No. -Figures.ppt” on the system, we need to edit the words in the figures. All submitted figures, including the text contained within the figures, must be editable. Please provide the text in your figure(s) in text boxes.

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Author's response: The figures has been modified and organized into a Powerpoint file entitled "Manuscript No. 48303-Figures", the Powerpoint will uploaded as a file.

31. Please don't include abbreviations in the title of the figure/table.

Author's response: The "PPH" has been replaced by "postpancreatectomy hemorrhage (PPH)" in the revised manuscript.

32. Regarding the figures: Please provide the decomposable figure of figures, whose parts are all movable and editable, organize them into a PowerPoint file, and submit as "Manuscript No. -Figures.ppt" on the system, we need to edit the words in the figures. All submitted figures, including the text contained within the figures, must be editable. Please provide the text in your figure(s) in text boxes.

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Author's response: The figures has been modified and organized into a Powerpoint file entitled "Manuscript No. 48303-Figures", the Powerpoint will uploaded as a file.

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Author’s response: The figures has been modified and organized into a Powerpoint file entitled “Manuscript No. 48303-Figures”, the Powerpoint will uploaded as a file.

35. Please don’t include abbreviations in the title of the figure/table.

Author’s response: The “ICU” has been replaced by “intensive care unit (ICU)” in the revised manuscript.

36. Regarding the figures: Please provide the decomposable figure of figures, whose parts are all movable and editable, organize them into a PowerPoint file, and submit as “Manuscript No. -Figures.ppt” on the system, we need to edit the words in the figures. All submitted figures, including the text contained within the figures, must be editable. Please provide the text in your figure(s) in text boxes.

Author’s response: The figures has been modified and organized into a Powerpoint file entitled “Manuscript No. 48303-Figures”, the Powerpoint will uploaded as a file.

37. Please don’t include abbreviations in the title of the figure/table.

Author’s response: The “LOS” has been replaced by “length of hospital stay (LOS)” in the revised manuscript.

38. Regarding the figures: Please provide the decomposable figure of figures, whose parts are all movable and editable, organize them into a PowerPoint file, and submit as “Manuscript No. -Figures.ppt” on the system, we need to edit the words in the figures. All submitted figures, including the text contained within the figures, must be editable. Please provide the text in your figure(s) in text boxes.

Author’s response: The figures has been modified and organized into a Powerpoint file entitled “Manuscript No. 48303-Figures”, the Powerpoint

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Author's response: The figures has been modified and organized into a Powerpoint file entitled "Manuscript No. 48303-Figures", the Powerpoint will uploaded as a file.

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Author's response: The figures has been modified and organized into a Powerpoint file entitled "Manuscript No. 48303-Figures", the Powerpoint will uploaded as a file.

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Author's response: The figures has been modified and organized into a Powerpoint file entitled "Manuscript No. 48303-Figures", the Powerpoint will uploaded as a file.

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Author's response: The figures has been modified and organized into a Powerpoint file entitled "Manuscript No. 48303-Figures", the Powerpoint will uploaded as a file.

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Author's response: The figures has been modified and organized into a Powerpoint file entitled "Manuscript No. 48303-Figures", the Powerpoint will uploaded as a file.

Response to reviewers:

Reviewer's code: 03477516

SPECIFIC COMMENTS TO AUTHORS

Thank you for sending your manuscript. This manuscript was "Is total laparoscopic pancreaticoduodenectomy superior to the open procedure? A meta-analysis". This manuscript was very interesting and large meta-analysis. However I wonder you should revise some important parts of it.

1. Comment: How were the background disease of TLPDs and OPDs? For example, pancreatic cancer and IPMN were difference for the complication and prognosis. So the background as pancreas texture, pancreatic duct size was important factor for some complications. You should reveal these differences.

Author's response: We thanks for your meaningful comment. We have reviewed the articles we included in our study and found four studies represented the pancreatic texture (Chopinnet, Dokmak, Poves and Zimmerman), our pooled analysis did not investigate any significant differences between the two groups in terms of pancreatic texturee (P=0.17). For the pancreatic duct size, six studies (Zimmerman, Poves, Palanivelu, Meng, Khaled and Chopinet) recorded and only three studies (Zimmerman, Poves and Meng) can we get the data, our analysis showed the pancreatic duct size was comparble between the two groups (P=0.91).

2. Comment: In these two group, you should describe the number or ratio of benign and malignant tumor. These problems were influenced for operating time and prognosis. Please try to consider again. Thank you.

Author's response: Thanks for your important suggestion. We have added a table (Table supplement. The pathological results of 28 included studies) to illustrate the number of benign and malignant tumor, and the pooled analysis showed the percentage of malignant tumors between the two groups were comparable (P=0.06).

Reviewer's code: 02484487

SPECIFIC COMMENTS TO AUTHORS

1. Comment: Extensive work but the ratio of laproscopic v/s open is too large so need more laproscopic procedures to compare.

Author's response: Thanks for your valuable suggestion, we have reviewed our manuscript and articles included in our study, we added a subgroup analysis to evaluate the safety and feasibility of TLPD in the patients with pancreaticductal adenocarcinoma (PDAC). Eventually, 3 articles were meet the requirement and the result showed that the transfusion rate was lower ($p=0.0002$) in TLPD group and the 30-day mortality was comparable between the two groups which were similar to our anterior results (in page 17-18, line 508-511, were highlighted in yellow color), but major morbidity showed an significant difference between the two groups ($P=0.02$) which was differ from the previous conclusion. But considering the small sample size, the results need to be proved by studies with larger sample and higher quality.

Reviewer's code: 00077376

SPECIFIC COMMENTS TO AUTHORS

1. Comment: This meta-analysis study has been performed very well.
Obtained results are interesting.

Author's response: Thanks for your suggestions.

Reviewer's code: 00505584

SPECIFIC COMMENTS TO AUTHORS

This is a meta-analysis comparing totally laparoscopic pancreatoduodenectomy to procedures done via an open approach. This is a well-written article, but there are some minor problems with the grammar and punctuation that need to be addressed. Also, the structure of the paper needs to be revised to make it easier for the reader to interpret the plethora of data. Lastly, the article is a bit repetitive and needs to be shortened.

- 1. Comment:** Introduction Laparoscopic techniques have been widely applied in general surgeries and have been proved to be beneficial for some selected patients in terms of postoperative recovery and a shorter hospital stay(Huscher, Mingoli et al. 2005, Qiu, Wu et al. 2011). General surgeries should either be “general surgical procedures” or “general surgery.” This is a problem throughout the paper.

Author's response: Thanks for you suggestions and corrections. We revised our manuscript and replaced “General surgeries” with “general surgical procedures” in page3, line 65-66, page 5, line 141-142, page 16, line 466 and were highlighted in yellow color.

- 2. Comment:** Statistical analysis Continuous variables in this analysis were evaluate with the inverse variance statistical method, and the weighted mean difference (WMD) was calculated. Is awkward, do you mean: “Continuous variables in this analysis were evaluateD with the inverse variance statistical method, and the weighted mean difference (WMD) was (also ?) calculated.”

Author's response: Thanks for you advices. We reviewed the manuscript and consulted the statisticians, we think the expression as “Continuous variables in this analysis were evaluated with the inverse variance statistical method, and the weighted mean difference (WMD) was also calculated” was much appropriate and we have replaced in our manuscript in page 9,line 245-247 and were highlighted in yellow color.

- 3. Comment:** Results Subsequently, we reviewed over the titles to identify

literature that was not relevant to our topic, and these articles excluded from our study. Do you mean: "Subsequently, we reviewed the titles to identify literature that was not relevant to our topic, and these articles WERE excluded from our study." With advancement in anastomosis, the incidence of bile leak has been decreased. Should be: "With advancements in anastomosis, the incidence of bile leak has decreased."

Author's response: Thanks for your careful comment, we have revised it in our manuscript in page 9, line 261-262 and page 12, line 355-356 and were highlighted in yellow color.

- 4. Comment:** In the section below, differences are expressed with Confidence intervals and then with percentages in the second paragraph. I believe percentages should be included in all variables studied. This will make analysis and reading of the paper easier. CI can also be included in the body of the paper if desired: A total of 1425 patients in thirteen studies (Asbun and Stauffer 2012, Hakeem, Verbeke et al. 2014, Dokmak, Fteriche et al. 2015, Tan, Zhang et al. 2015, Delitto, Luckhurst et al. 2016, Palanivelu, Senthilnathan et al. 2017, Stauffer, Coppola et al. 2017, Chen, Sun et al. 2018, Chopinet, Fuks et al. 2018, Khaled, Fatania et al. 2018, Lee, Kim et al. 2018, Meng, Cai et al. 2018, Zimmerman, Roye et al. 2018) developed PPH. Although Chopinet (Chopinet, Fuks et al. 2018) and Dokmak (Dokmak, Fteriche et al. 2015) found that the application of TLPD increased the incidence of PPH, our pooled analysis of all the included studies did not demonstrate any significant differences between the two groups (OR=1.12, 95% CI=0.89 ~ 1.42, P=0.34) (Fig. 10). Similarly, this analysis of included articles (Asbun and Stauffer 2012, Croome, Farnell et al. 2014, Tee, Croome et al. 2015, Palanivelu, Senthilnathan et al. 2017, Stauffer, Coppola et al. 2017, Meng, Cai et al. 2018, Poves, Burdion et al. 2018) did not show any statistically significant differences in terms of severe PPH (Grade B/C) (OR=1.02, 95% CI=0.65 ~ 1.60, P=0.95). A total of 762 patients in ten studies (Asbun and Stauffer 2012, Hakeem, Verbeke et

al. 2014, Speicher, Nussbaum et al. 2014, Delitto, Luckhurst et al. 2016, Palanivelu, Senthilnathan et al. 2017, Stauffer, Coppola et al. 2017, Chapman, Gleisner et al. 2018, Chen, Sun et al. 2018, Lee, Kim et al. 2018, Zimmerman, Roye et al. 2018) developed wound infections in our study, and the overall incidence was 8.33% in the TLPD group and 10.11% in the OPD group. The results of our analysis showed that the frequency of wound infections in the TLPD group was significantly lower than that in the OPD group (OR=0.48, 95% CI=0.34 ~ 0.67, P<0.0001) (Fig. 11).

Author's response: Thanks for your advices, and the percentage has been added in the revised manuscript in page 13, line 364-365 and were highlighted in yellow color.

5. Comment: The ICU admission rate was reported in 2 studies(Tee, Croome et al. 2015, Meng, Cai et al. 2018) involving 71 patients (25 TLPDs and 46 OPDs), and the rate did not show any significant difference between the two groups (OR=0.90, 95% CI=0.53 ~ 1.54, P=0.71). However, in terms of the duration of ICU stay, we observed that the TLPD group had a significantly shorter ICU stay than the OPD group (WMD=-0.28d, 95% CI=-2.88 ~ -1.29 d, P<0.00001) (Fig. 13) through the analysis of these two studies(Asbun and Stauffer 2012, Hakeem, Verbeke et al. 2014). This is awkward, do you mean: The ICU admission rate was reported in 2 studies(Tee, Croome et al. 2015, Meng, Cai et al. 2018) involving 71 patients (25 TLPDs and 46 OPDs), and the rate did not show any significant difference between the two groups (OR=0.90, 95% CI=0.53 ~ 1.54, P=0.71). However, in terms of the duration of ICU stay, we observed that the TLPD group had a significantly shorter ICU stay than the OPD group (WMD=-0.28d, 95% CI=-2.88 ~ -1.29 d, P<0.00001) (Fig. 13)(Asbun and Stauffer 2012, Hakeem, Verbeke et al. 2014).

Author's response: Thanks for your comment. The ICU admission rate in our manuscript means the number the patient in each group who needs to be sent to the ICU for further treatment; the duration of ICU stay means

the average residence time of the patients who were sent to the ICU for intensive care.

6. **Comment:** Discussion There is a problem with the endnotes, please see the end of the paragraph: Laparoscopic techniques are minimally invasive procedures that have been applied in a wide variety of general surgeries, including some pancreatic operations(Kantor, Talamonti et al. 2017), and the techniques have proven to be more advantageous in terms of a shortened LOS, a reduced operative blood loss, a decreased incidence of postoperative complications and an enhanced postoperative recovery(Clinical Outcomes of Surgical Therapy Study, Nelson et al. 2004, Huscher, Mingoli et al. 2005, Kim, Hyung et al. 2010, Correa-Gallego, Dinkelspiel et al. 2014)[Correa-Gallego, 2014 #57][Huscher, 2005 #49].

Author's response: Thanks for your comment. We have reviewed the manuscript and confirmed the references in page 16, line 465-470 and were highlighted in yellow color.

7. **Comment:** This section is repetitive. Either keep it in the Discussion or in the Introduction, but not both: However, with regard to PD, considering its retroperitoneal operative field, proximity to the great vessels, difficult dissection, and complex biliary and pancreatic anastomosis(Pedziwiatr, Malczak et al. 2017), this procedure has only been performed at some major medical centers, and some modifications, such as hand-assisted PD and laparoscopy - assisted PD, have been introduced since PD was first introduced in 1994(Gagner and Pomp 1994). In the last decade, with the continuous advancements in instrumentation and innovations in procedures(Satyadas, Kanhere et al. 2010), TLPD has been increasingly accepted and performed by general surgeons worldwide, but this challenging procedure is still in its early stages, and only a few studies with limited series comparing TLPD and OPD have been conducted. In our review, we found two clinical RCTs, and the remaining studies included in our meta-analysis were retrospective studies with limited

quality. Therefore, whether TLPD is superior to or comparable to OPD has remained unknown until now. To our knowledge, several systematic reviews or meta-analyses comparing minimally invasive PD (MIPD) and OPD have been published (de Rooij, Klompaker et al. 2016, de Rooij, Lu et al. 2016) [1, #65], but none of them have compared TLPD and OPD specifically; hence, we performed this meta-analysis with the largest available dataset from the published literature.

Author's response: Thanks for your suggestion. We have simplified the "Discussion" in our revised manuscript in page 16, line 470-480 and were highlighted in yellow color.

8. **Comment:** POPF and DGE are considered to be the two most common and severe complications of PD, especially POPF, which is a life-threatening complication, and the occurrence... Spelling: "POPF and DGE are considered to be the two most common and severe complications of PD, especially POPF, which is a life-threatening complication, and the occurrence... In patients who undergo PD for malignant tumors, oncological safety is the most important priority. "In patients undergoing PD for malignant tumors, oncological safety is the main priority."

Author's response: Thanks for your careful correction. We have corrected them in our revised manuscript in page 18, line 525 and page 19, line 558-559 and were highlighted in yellow color.

9. **Comment:** Conclusion: I do not believe the data supports this conclusion. As mentioned the totally laparoscopic group had significantly smaller tumors, ideally, this paper would have looked at matched-controlled groups. "Therefore, we suggest that TLPD is comparable to OPD or may be better than OPD in terms of oncological outcomes." At most the authors could conclude that more matched-controlled studies are needed to adequately ascertain if totally laparoscopic approaches will have superior oncological outcomes to open PD.

Author's response: Thanks for your suggestion. After talking with our

team members, we decided to correct our expression as “Therefore, we suggest that TLPD is comparable to OPD or may be better than OPD in terms of reducing blood loss, decreasing the blood transfusion and wound infection rates, shortening the length of ICU stay and LOS, and increasing the number of lymph nodes harvested, the R0 resection rate and improve the oncological outcomes, despite having a longer operative time and being used for smaller tumors” in our revised manuscript, in page 21, line 601-606 and were highlighted in yellow color.

Reviewer's code: 01221925

SPECIFIC COMMENTS TO AUTHORS

This is an interesting paper where the authors provide us with a meta-analysis regarding the comparison of totally laparoscopic pancreaticoduodenectomy (TLPD) vs open pancreaticoduodenectomy (OPD). The authors reach the conclusion that they are essentially comparable with the main exception being operating time, which is significantly longer in the TLPD.

- 1. Comment:** The paper could benefit from significant editorial language assistance.

Author's response: Thanks for your suggestion. The manuscript have been revised by a native English speaker (AJE) before the first submission. Now, we have revised it once again.

- 2. Comment:** The authors are correct to point out the fact that a meta-analysis is only as good as the basic data that is uses and as such the fact that there were only 2 randomized controlled trials is a limitation. Furthermore, the fact that in the TLPD the tumors are smaller, may be an indication of a selection bias, where the "easier" cases wer performed laparoscopically, whereas those with more extensive involvement were perfomed in the open manner. Do we have data regarding pre-operative staging or how was it decided which patients were going to undergo a TLPD and which an OPD?

Author's response: Thanks for your suggestions. The data regarding pre-operative staging may including the tumor size, tumor location, vascular invasion and lymph node metastasis, in addition, the symptoms sometimes helpful for the staging. In recent years, with the improvement of skills and the accumulation of the experience, the indication for TLPD has expanded and similar to the OPD in some medical centers.

- 3.** The point regarding the learning curve is an excellent one and perhaps the key of any transition towards a minimally invasive procedure. Is there a

number thought of as the minimum requirement, ie in lap hepatectomies 60 procedures are deemed as necessary to achieve proficiency in the procedure?

Author's response: Thanks for your comment. Several literatures regarding the learning curve have been published, the minimum number required varied from 5 to 40. In our opinion the desired number is not less than 30 cases.

4. Is there more information regarding the cost, as this is usually the other limiting factor?

Author's response: Thanks for your comment. Four articles mentioned the cost, three found the cost between the two groups were comparable, only one drew a different conclusion that the TLPD cost more money. In our center, we did not discover the difference between the two groups in terms of expense.