

Response to editor and reviewer's comments:

Dear editor:

Thank you for your giving us an opportunity to revise our manuscript! Now we are submitting the revised manuscript entitled “Efficacy and safety of laparoscopic radical resection following neoadjuvant therapy for pancreatic ductal adenocarcinoma: A retrospective study” for consideration for publication in World Journal of Gastrointestinal Oncology

During the revision, we added four contributing authors: Lu Zheng, Yu-Ming Li. Lu Zheng contributed to the conception and design of the study and drafted the manuscript; Lu Zheng and Yu-Ming Li adjusted the article's overall structure, modified the article's sentences to increase its readability. Lu Zheng, Yu-Ming Li revised the article directly according to the reviewer's comments, searching for the new literature and adding the corresponding content in the discussion according to the reviewer's comments.

Thank you again for your help.

Best regards

Yours sincerely,

Xiaobing Huang and Yong-Gang He

#Reviewer 1

Good work, important topic. Small number of patients, this topic deserve multicentric study.

Response: We agree with the reviewer's view that a larger sample size should be required for further validation of the findings of our study. And we plan to register a prospective multicentric study of laparoscopic radical resection following neoadjuvant therapy for pancreatic cancer in the near future.

#Reviewer 2:

In this manuscript, the authors report on 15 cases of patients affected by pancreatic ductal adenocarcinoma (PDAC), who underwent a laparoscopic pancreatic resection (in 8 cases a Laparoscopic Pancreatoduodenectomy (LPD) for a PDAC of the pancreatic head and in 7 cases a laparoscopic RAMPS (L-RAMPS) for a PDAC of the pancreatic body/tail). All patients were affected by a borderline resectable or locally advanced tumor, for which an upfront resection was contraindicated, and all had a partial response to preop CHT which allowed for the surgical resection. In the era of multimodal oncosurgical management to PDAC and of development of minimally invasive surgical approach, a manuscript reporting the results of laparoscopic pancreatic resection after PDAC downstaging with preop CHT is

welcome, however this manuscript deserves many comments:

1.the manuscript contains many grammatical, ortographic, and sinthax errors: a review from an English mother tongue scientific editor is strongly recommended.

Response: We thank the reviewer for this nice comment and the expression of this manuscript has been modified and polished by the scientific editor in American Journal Experts; we also have revised the grammatical and spelling errors throughout the manuscript.

2 Methods: I suggest to define the term AG (regimen), the first time it is used.

Response: Thanks the reviewer for this suggestion! We have added the description of AG regimen and modified FOLFIRINOX regimen in the Method section (Page 2 line 44 to line 48 and Page 3 line 49 to line 50).

3. surgical procedures: please specify the pneumoperitoneumo pressure value, the resection - reconstruction performed during LPD, how many drains were placed at the end of surgeries and where they were placed.

Response: Thanks for the reviewer's good suggestion. The pneumoperitoneumo pressure value is 12-14 mmHg (Page 7 line 160); After the operation, one abdominal drainage tube was placed above the pancreatic duct-jejunal anastomosis and below the bile duct-jejunal

anastomosis, respectively (Page 8 line 174 to line 176).

4. The "easy first" approach is not clear to me: please explain it in detail.

Response: Thanks for your comments. The surgical pathway of “Easy First” for LPD is to free the simple part that without tumor adhesion or invasion, then place a vascular sling at the superior mesenteric, portal, and splenic veins, and even the superior mesenteric artery. Afterward, the tumor adhesion part is separated, or vascular resection and reconstruction are performed. This strategy fully considers the possibility of bleeding when separating tumor adhesions, which can easily control bleeding by tightening the vascular sling, and provide time for conversion to open laparotomy. Moreover, it also makes the operation most likely to be performed laparoscopically. Even if conversion to laparotomy is required, only a small incision is required to partially cut off the tissue, so that the patients can enjoy the advantages of minimally invasive surgery to the greatest extent. And we also added literature 22 as a reference.

[22]Jin W-W, Ajoodhea H, Mou Y-P, Zhang R-C, Lu C, Xu X-WJ: Tips of laparoscopic pancreaticoduodenectomy for borderline resectable pancreatic cancer: “easy first” approach. *Transpl Can Res*, 2016, 5(5):613-617doi 10.21037/tcr.2016.08.20.

5.Results: - General outcome: "all werre sucessfully converted to laparoscopic surgery after neoadjuvant....": this sentence sounds not adequate: actually, all patients were converted from borderline resectable

or unresectable, to resectable.

Response: We thank the reviewer for this suggestion. We have made changes in the manuscript (Page 10 line 220 to line 228 and Page 11 line 229 to line 231)..

6. results of pathological examination: "... and residual cancer was detected by multipoint sampling in one patients": what does it mean? please explain.

Response: Thanks for your comments. There was one case had no cancerous tissue found in routine sampling postoperative in the pathology department; Subsequently, the pathology department sampled multiple sample sites, and residual cancer tissue was found in additional pathological sections.

7. Discussion: - the discussion is too long, it should be shortened. - the first paragraph is not clear, please correct or delete. The list of criteria for resectability after preop CHT is a repetition of a list already shown in the Methods section: please delete it.

Response:

Thanks for the reviewer's good suggestion. The first paragraph of the discussion has been deleted. The methodology incorporates the inclusion and exclusion criteria for patients receiving neoadjuvant chemotherapy.

In the discussion, such inclusion criteria deal with conditions under which

surgery is performed upon completion of neoadjuvant chemotherapy.

8. Similar for the paragraph where the authors describe the postoperative complications of study patients. - The paragraph describing PDAC pathological changes due to CHT is potentially interesting, however a connection between different sentences is lacking, reducing the paragraph readability and clearness.

Response: Thanks for your comments. And the expression of this manuscript has been modified and polished by the scientific editor in American Journal Experts; we also have revised the grammatical and spelling errors throughout the manuscript.

10. In the limitation section, the authors should not simply enlist the study limitation, but also actions which should/may be put in place to mitigate such limitations.

Response: Thanks for the reviewer's good suggestion. The reason for these limitations is that neoadjuvant chemotherapy followed by laparoscopic surgery for pancreatic cancer is a difficult procedure, so we provide specific solutions to intraoperative difficulties based on existing surgical experience (2, 3). Meanwhile, we set limit 1 based on our previous experience on more than 500 cases of surgery and LPD after neoadjuvant. We estimated that surgeons should be more appropriately

when at least 100 LPD have been completed and passed the learning curve.

11.in conclusion, in the discussion the authors should compare the results from their study with pre-exisitng data from previous studies, speculate on their results, and try to describe their experience in a challenging situation represented by laparoscopic pancreatic resection following preop CHT.

1. **Response:** Thanks for the reviewer’s good suggestion. In the discussion, we supplemented the existing research data on neoadjuvant chemotherapy for pancreatic cancer and compared our results with them, followed by a description of our experience in laparoscopic surgery after neoadjuvant chemotherapy.

Re-reviewer

I believe the manuscript has bee significantly improved, I have some minor comments: 1. I would change the sentence “After the operation, one abdominal drainage tube was placed above the pancreatic duct-jejunal anastomosis and below the bile duct-jejunal anastomosis, respectively” to “After the operation, one abdominal drainage tube was placed ahead the pancreatic duct-jejunal anastomosis and one behind the bile duct-jejunal anastomosis, respectively” (if I unnderstand well two

drains are placed, correct?).

Response: Thanks for the reviewer's good comments and revision. Yes, two abdominal drainage tubes were placed after the operation. We revised the sentences in the manuscript.

2. In the text I cannot find the reference #22.

Response: Thank you for your reminder. We have added reference #22 on page 7, line 163.

3. The authors should consistently use the acronims NACT and PDAC in the text, sometimes they still use the terms neoadjuvant chemotherapy and pancreatic cancer.

Response: Thanks for the reviewer's good suggestion. We have revised the manuscript and consistently use NACT and PDAC in the manuscript

4. The discussion is still too long: it should be compressed in 6-7 paragraphs (about 3 pages with double spaced lines): please begin by shortening the paragraph concerning NACT ("At present, the optimum number of NACT cycles is still uncertain. ...").

Response: We thank the reviewer's good suggestion. We have compressed the manuscript according to your comments.

5. The postoperative results (and related management) should be removed from the discussion. A paragraph reporting postoperative results should be added in the Results section.

Response: We thank the reviewer's good suggestion. We have removed

from the discussion. Postoperative results have been added to the Results section (Page 11 line 249 to line 251 and Page 12 line 252 to line 258).

6. The points 2 and 3 reported in the paragraph “Our experience includes the following:....” are quite questionable and should be rephrased: in particular, point b) In some cases, the “artery-first” approach may be selected, as it helps to identify suitable layers during the operation. (with layers, do the authors mean “anatomical dissection planes”). Point c) For patients in whom it is difficult to establish a retropancreatic tunnel during the operation, the pancreas can be separated and resected at a position 2-3 cm to the left side of the superior mesenteric vein and then toward the right side where the superior mesenteric vein can be found.” (This sentence is not clear, please explain better).

Response: We thank the reviewer’s good suggestion. We have modified this text as follows: we believe that resection is the challenging part of LPD after NACT for PDCA, and the difficulty of resection is the management of anatomical structure and vessels. Our experience is as follows: 1) Although more challenging, LPD after NACT can be performed by a surgeon with rich experience in LPD surgery. 2) It is very difficult to find a single approach that suitable for all cases. During the operation, we preferentially adopt the “early first” principle, and gradually separate and resect to complete. However, in some cases, we chose different arterial approaches according to the direction of tumor

invasion. 3) Due to portal vein adhesion and tumor invasion after NACT in some pancreatic cases, procedures of the superior mesenteric vein behind the neck of the pancreas may cause bleeding, and the establishment of a retropancreatic tunnel is more challenging. In these cases, the pancreas can be separated and resected from 2-3 cm to the left side of the superior mesenteric vein and the neck of the pancreas. The advantage of choosing here is that it is far away from the tumor, the tissue separation is easier than performing behind the neck of the pancreas, and the space between the splenic vein and the pancreas can be easily separated. It is safer to search the superior mesenteric vein after the resection of the pancreas and dissection of surrounding tissues from left to right. 4) The digestive tract reconstruction was performed according to a routine procedure after lesion resection in pancreaticoduodenectomy and was barely affected by NACT (Page 17 line 381 to line 384 and Page 18 line 385 to line 399).