PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Extended pancreatic neck transection versus conventional pancreatic neck transection during laparoscopic pancreaticoduodenectomy (LPDEXCEPT): protocol for a multicenter superiority randomised controlled trial
AUTHORS	You, Jiaying; Zhang, Jing; Cai, He; Wang, Xin; Wang, Hongjian; Li, Yongbin; Yu, Chao; Wang, Lei; Zhou, Xu; Peng, Bing; Cai, Yunqiang

VERSION 1 – REVIEW

REVIEWER	Bas Uijterwijk Fondazione Poliambulanza Istituto Ospedaliero, Surgery
REVIEW RETURNED	18-Sep-2023

GENERAL COMMENTS	The study protocol titled “Extended pancreatic neck transection versus conventional pancreatic neck transection during laparoscopic pancreaticoduodenectomy (LPDEXCEPT): protocol for a multicenter superiority randomised controlled trial” is a protocol for a multicenter randomized trial, comparing extended and traditional transecting plane of the pancreas during PD with stratifications for pre-op duct size and center. I consider this could be a valuable addition to current knowledge and has the potential to further improve PD technique. I have some minor issues to address: 1. The objective for extended pancreatic neck transection is outlined, however, it is not clear why this will only be assessed in laparoscopic approach. Following the objective, you could hypothesize the extended neck transection could be beneficial, regardless of lap/robotic/open approach. Since worldwide, the approach of choice is still up for debate, please clarify why laparoscopic is the only approach of choice in this trial over inclusion of all approaches. 2. Abstract: Introduction: The level of pancreatic transection can affect the occurrence of POPF by influencing blood supply and duct location. Please clarify how these factors are considered beneficial in a more distal transaction plane (more blood supply? More central duct?) One could say the more distal you will transect, the smaller the pancreatic duct. 3. Introduction: Are there anatomical variations in the blood supply of the pancreas that need to be considered before applying the extended transection technique? 4. Surgeons must have completed their learning curve. However, it is not defined when a surgeon is considered to have passed the learning curve.

	5. All indications are included in the trial, which I support. However, it is suggested that malignant tumors cause more fibrosis and a firmer pancreas compared to low-grade malignant and benign indications. Is it possible to implement a stratification technique to ensure an equitable distribution of malignant and non-malignant tumors in both groups, or could the authors provide further details and clarification on this matter? 6. Can the authors add a clear surgical technique description? Which landmarks to follow when applying the extended transection technique? Potential pitfalls? 7. The participating centers appear to be large experienced centers. How do the authors unsure global and general translatability of the results? Is this technique easily adoptable for surgeons in less experienced centers? 8. Can the authors explain why are patients with neoadjuvant chemotherapy excluded? With trials ongoing, suggesting benefit of neoadjuvant folfirinox for PDAC, how to address these patients?

REVIEWER	Tomoyuki Abe Onomichi General Hospital, Surgery
REVIEW RETURNED	12-Oct-2023

GENERAL COMMENTS	The authors present an original work Extended pancreatic neck transection versus conventional pancreatic neck transection during laparoscopic pancreaticoduodenectomy (LPDEXCEPT): protocol for a multicenter superiority randomised controlled trial. There are many major revise in this manuscript. Unfortunately, this manuscript can not to be accepted in its form. Major revisions 1. First of all, the development of diabetes after pancreatic resection due to a decrease in the volume of the residual pancreas should be considered. Through this study, it is necessary to examine whether excessive pancreatic resection is associated with short-term and long-term diabetes development. 2. It is expected that not only the anatomical location but also the thickness measured by CT at the pancreatic resection line will have a significant influence on the occurrence of postoperative pancreatic leak. There is also concern about the effect that cutting into the pancreas caudally may have on the pancreaticojejunostomy. It is expected that the blood supply will change due to the dissection of the pancreas just above the portal vein and the incision into the caudal pancreas. However, since the transverse pancreatic artery runs within the pancreas, it is unclear whether cutting into the caudal pancreas can be performed at a site with good blood flow. 3. There is also concern that cutting into the caudal pancreas may affect the pancreaticojejunostomy itself. The diameter of the main pancreatic duct becomes narrower toward the caudal side, and this phenomenon may also lead to the development of pancreatic leakage. Please consider the above three points.

VERSION 1 – AUTHOR RESPONSE

Comment 1. The objective for extended pancreatic neck transection is outlined, however, it is not clear why this will only be assessed in laparoscopic approach. Following the objective, you could hypothesize the extended neck transection could be beneficial, regardless of lap/robotic/open approach. Since worldwide, the approach of choice is still up for debate, please clarify why laparoscopic is the only approach of choice in this trial over inclusion of all approaches.

Response: Thank you for this question. There are many aspects that differ between open and minimally invasive (laparoscopic and robotic) pancreaticoduodenectomy, including some of the postoperative complications, duration of surgery, intraoperative bleeding, length of hospitalization, and so on [1-4]. And it is still up for debate to choose the approach. Studies would inevitably introduce additional confounding factors once multiple approaches are included. The process of study design and study implementation would also become more complex to eliminate the bias introduced by these confounding factors. In order to control for these biases more simply and to obtain more accurate and trustworthy results, also because laparoscopic surgery is practiced more in our research team, we chose only laparoscopic surgery for this trial. This is the first randomised trial to validate the benefits of extended pancreatic neck transection, additional studies could be conducted in the future to confirm the advantages of it regardless of the approaches.

Ref.:

1. Uijterwijk BA, Kasai M, Lemmers DHL, et al. The clinical implication of minimally invasive versus open pancreatoduodenectomy for non-pancreatic periampullary cancer: a systematic review and individual patient data meta-analysis. Langenbecks Arch Surg. 2023;408(1):311. Published 2023 Aug 15.
2. Uijterwijk BA, Wei K, Kasai M, et al. Minimally invasive versus open pancreatoduodenectomy for pancreatic ductal adenocarcinoma: Individual patient data meta-analysis of randomized trials. Eur J Surg Oncol. 2023;49(8):1351-1361.
3. Sattari SA, Sattari AR, Makary MA, Hu C, He J. Laparoscopic versus Open Pancreatoduodenectomy in Patients with Periampullary Tumors: A Systematic Review and Meta-analysis [published online ahead of print, 2022 Dec 15]. Ann Surg. 2022;10.1097/SLA.0000000000005785.
4. Pfister M, Probst P, Müller PC, et al. Minimally invasive versus open pancreatic surgery: meta-analysis of randomized clinical trials. BJS Open. 2023;7(2):zrad007.

Comment 2. Abstract: Introduction: The level of pancreatic transection can affect the occurrence of POPF by influencing blood supply and duct location. Please clarify how these factors are considered beneficial in a more distal transaction plane (more blood supply? More central duct?) One could say the more distal you will transect, the smaller the pancreatic duct.

Response: We appreciate this valuable question, which makes the foothold of the trial clearer. Theoretically, there are both advantages (more blood supply, and more central duct) and disadvantages (maybe smaller the pancreatic duct) to transect the pancreatic neck more distally. This theoretical contradiction pushed us to organize this trial to explore the impact of the level of pancreatic transection in clinical practice. We will measure the pancreatic duct diameter intraoperatively. By comparing the pancreatic duct diameters of the study and control groups in each subgroup (≤3mm, ＞3mm), it is able to confirm whether there is a significant difference in the pancreatic duct diameter at different transection level, and also to determine whether the difference in the pancreatic duct diameter at different transection level is a major factor influencing the occurrence of pancreatic fistula.

Comment 3. Introduction: Are there anatomical variations in the blood supply of the pancreas that need to be considered before applying the extended transection technique?

Response: There are many patterns of variation in vascularization of the pancreas [1-3]. However, it is not easy to use preoperative enhanced CT to determine accurately, and selective arteriography is usually required [4,5]. The variation of superior mesenteric artery and vein (SMA and SMV), and hepatic artery is the focus of attention during pancreaticoduodenectomy, but it does not influence transection of pancreatic neck [6]. We will record the variation of vessels of the pancreas in this trial.

Ref.:

1. Bertelli E, Di Gregorio F, Mosca S, Bastianini A. The arterial blood supply of the pancreas: a review. V. The dorsal pancreatic artery. An anatomic review and a radiologic study. Surg Radiol Anat. 1998;20(6):445-452.

2. Mosca S, Di Gregorio F, Regoli M, Bertelli E. The superior horizontal pancreatic artery of Popova: a review and an anatomoradiological study of an important morphological variant of the pancreatica magna artery. Surg Radiol Anat. 2014;36(10):1043-1049.

3. Kulenović A, Sarac-Hadzihalilović A. Blood vessels distribution in body and tail of pancreas - a comparative study of age related variation. Bosn J Basic Med Sci. 2010;10(2):89-93.

4. Kulenovic A, Sarac Hadzihalilovic A. Investigation of vascularization of human pancreas using method of selective arteriography with insight into significance to a surgical approach for this organ. Bosn J Basic Med Sci. 2010;10(1):15-18.

5. Rousek M, Whitley A, Kachlík D, et al. The dorsal pancreatic artery: A meta-analysis with clinical correlations. Pancreatology. 2022;22(2):325-332.

6. Nagakawa Y, Nakata K, Nishino H, et al. International expert consensus on precision anatomy for minimally invasive pancreatoduodenectomy: PAM-HBP surgery project. J Hepatobiliary Pancreat Sci. 2022;29(1):124-135.

Comment 4. Surgeons must have completed their learning curve. However, it is not defined when a surgeon is considered to have passed the learning curve.

Response: Thanks for this question. We defined that a surgeon who had performed more than 104 cases of laparoscopic pancreaticoduodenectomy is considered to have passed the learning curve, according to the study about practice patterns of laparoscopic pancreaticoduodenectomy conducted by Wang et al [1].

Ref.:

1. Wang M, Peng B, Liu J, et al. Practice Patterns and Perioperative Outcomes of Laparoscopic Pancreaticoduodenectomy in China: A Retrospective Multicenter Analysis of 1029 Patients. Ann Surg. 2021;273(1):145-53.

Comment 5. All indications are included in the trial, which I support. However, it is suggested that malignant tumors cause more fibrosis and a firmer pancreas compared to low-grade malignant and benign indications. Is it possible to implement a stratification technique to ensure an equitable distribution of malignant and non-malignant tumors in both groups, or could the authors provide further details and clarification on this matter?

Response: Thank you for your question. We understand that you are attempting to ensure an equitable distribution of pancreatic texture in both groups, considering that pancreatic texture is also a key risk factor for pancreatic fistula [1]. However, firstly, although there have been a few studies that have attempted to use CT values to represent pancreatic texture, there is a lack of a more recognized method to accurately assess pancreatic texture preoperatively [2-3]. Secondly, pancreatic texture is not only determined by the type of pathologic diagnosis, but is also influenced by the site of the tumor, size of the tumor, and so on. Besides, it is also difficult to accurately determine the pathologic diagnosis preoperatively, especially to differentiate the CT manifestations of chronic mass pancreatitis and pancreatic adenocarcinoma, both of whose pancreatic texture is firm. Thirdly, too many stratification factors can add to the difficulties in the implementation of the study. Thus, we did not consider the pancreatic texture or pathologic diagnosis as the stratification factor. Since pancreatic duct diameter is the main risk factor for pancreatic fistula [1], we included pancreatic duct diameter as a stratification factor. Also, because of the differences in healthcare delivery and quality, the study center was included as another stratification factor, which could allow extrapolability of the study results to other hospitals.

Ref.:

1. Schuh F, Mihaljevic AL, Probst P, et al. A Simple Classification of Pancreatic Duct Size and Texture Predicts Postoperative Pancreatic Fistula: A classification of the International Study Group of Pancreatic Surgery. Ann Surg. 2023;277(3): e597-e608.

2. Shi Y, Gao F, Qi Y, et al. Computed tomography-adjusted fistula risk score for predicting clinically relevant postoperative pancreatic fistula after pancreatoduodenectomy: Training and external validation of model upgrade. *EBioMedicine*. 2020;62:103096.
3. Lapshyn H, Petruch N, Thomaschewski M, et al. A simple preoperative stratification tool predicting the risk of postoperative pancreatic fistula after pancreatoduodenectomy. *Pancreatology*. 2021;21(5):957-964.

Comment 6. Can the authors add a clear surgical technique description? Which landmarks to follow when applying the extended transection technique? Potential pitfalls?

Response: We thank the reviewer for raising this question. All study centers will perform the LPD using the optimization of operative procedure. The specific operating procedures and details are reported in our previous articles [1]. In this study, the surgical operation required attention to the following operational details: Firstly, mark the level of the transection on the surface of the pancreas according to the group of participants before transecting the pancreatic neck, and after dissecting the upper and lower margins of the pancreas and revealing the superior mesenteric vein and portal vein. The level of transection in extended transection group is at more than 5 mm and less than 10 mm beyond the left side of the portal vein, while it in the conventional transection group is at the mesenteric-portal axis. Secondly, make sure not to pull on the pancreas and surrounding tissue, and make sure the pancreas is in situ when marking. Thirdly, mark the pancreas from the superior margin to the inferior margin completely with an electrocoagulation hook, and transect the pancreas along the mark to prevent deviation.

Ref.:

1. Li YB, Cai YQ, Wang X, Meng LW, Cai H, Xu J, et al. [Optimization of Operative Procedure in Total Laparoscopic Pancreaticoduodenectomy (with Video)]. Sichuan Da Xue Xue Bao Yi Xue Ban. 2020;51(4):446-52.

Comment 7. The participating centers appear to be large experienced centers. How do the authors unsure global and general translatability of the results? Is this technique easily adoptable for surgeons in less experienced centers?

Response: Thanks for your question about why studies are not conducted in low-experience centers attempting to improve the translatability and extrapolability of the results. Studies have confirmed that low-volume hospital and low-experience surgeon are the risk factor for patient safety [1-3]. International expert consensus suggested that LPD should be performed in large volume medical centers by experienced surgeons [4]. Low-experience surgical team should select more appropriate cases for LPD [4]. Therefore, considering trial ethics and participant safety, this study will only conduct in high-experienced centers. If the results of this trial do prove that extended pancreatic neck

resection is favorable and does not have much impact on surgical operation (length of surgery and length of pancreatic-intestinal anastomosis). We believe that the results are a good guide for surgical operations in low-experience centers.

Ref.:

1. Qin H, Qiu J, Zhao Y, et al. Does minimally-invasive pancreaticoduodenectomy have advantages over its open method? A meta-analysis of retrospective studies. PLoS One 2014;9:e104274.
2. Kutlu OC, Lee JE, Katz MH, et al. Open pancreaticoduodenectomy case volume predicts outcome of laparoscopic approach: a population-based analysis. Ann Surg 2018;267:552-60.
3. Wang M, Peng B, Liu J, et al. Practice Patterns and Perioperative Outcomes of Laparoscopic Pancreaticoduodenectomy in China: A Retrospective Multicenter Analysis of 1029 Patients. Ann Surg. 2021;273(1):145-53.
4. Qin R, Kendrick ML, Wolfgang CL, Edil BH, Palanivelu C, Parks RW, et al. International expert consensus on laparoscopic pancreaticoduodenectomy. Hepatobiliary Surg Nutr. 2020;9(4):464-83.

Comment 8. Can the authors explain why are patients with neoadjuvant chemotherapy excluded? With trials ongoing, suggesting benefit of neoadjuvant folfirinox for PDAC, how to address these patients?

Response: In our study center, patients with neoadjuvant chemoradiotherapy routinely undergo open surgery. For the reasons stated in the previous question, this study was conducted only in LPD surgery. Therefore, we excluded neoadjuvant chemoradiotherapy patients.

Comment 1. First of all, the development of diabetes after pancreatic resection due to a decrease in the volume of the residual pancreas should be considered. Through this study, it is necessary to examine whether excessive pancreatic resection is associated with short-term and long-term diabetes development.

Response: Thanks for your question, which we think is very helpful in optimizing our research protocol. We plan to follow up the pancreatic endocrine and exocrine function of the participants at the third month postoperatively and at the first year postoperatively. For endocrine function, we detect diabetes mellitus development, and the diagnosis and classification of diabetes mellitus is according to the international criteria of diabetes [1]. For pancreatic exocrine function, we defined pancreatic exocrine insufficiency as that stool evacuation was >3 times/day, and pasty or greasy stool was noted, associated with patient's weight loss, and there was a need for enzyme supplementation resulting in recovery of bowel movements and cessation of steatorrhea [2], considering that not all research centers can measure fecal elastase, N-benzol-L-tyrosyl-p-aminobenzoic acid (BT-PABA), or fecal chymotrypsin. Because previous studies have reported that the level of transection have little

effect on the pancreatic exocrine and endocrine function [3], we set the pancreatic function in the long and short term as a secondary outcome.

Ref.:

1. American Diabetes Association. Diagnosis and classification of diabetes mellitus. *Diabetes Care*. 2013;36 Suppl 1(Suppl 1):S67-S74.
2. Beger HG, Poch B, Mayer B, Siech M. New Onset of Diabetes and Pancreatic Exocrine Insufficiency After Pancreaticoduodenectomy for Benign and Malignant Tumors: A Systematic Review and Meta-analysis of Long-term Results. *Ann Surg*. 2018;267(2):259-270.
3. Jwa EK, Hwang S. Extended pancreatic transection for secure pancreatic reconstruction during pancreaticoduodenectomy. Ann Hepatobiliary Pancreat Surg. 2017;21(3):138-45.

Comment 2. It is expected that not only the anatomical location but also the thickness measured by CT at the pancreatic resection line will have a significant influence on the occurrence of postoperative pancreatic leak. There is also concern about the effect that cutting into the pancreas caudally may have on the pancreaticojejunostomy. It is expected that the blood supply will change due to the dissection of the pancreas just above the portal vein and the incision into the caudal pancreas. However, since the transverse pancreatic artery runs within the pancreas, it is unclear whether cutting into the caudal pancreas can be performed at a site with good blood flow.

Response: Thanks for your question, making the data collected for our study be more comprehensive. Pancreatic thickness mainly affects pancreatic fistula after distal pancreatectomy [1], and few studies have confirmed that pancreatic thickness is the risk factor for pancreatic fistula after pancreaticoduodenectomy [2-4]. Despite this, we believe that it is feasible and maybe valuable to measure pancreatic thickness in this study. Therefore, we planned to measure pancreatic thickness on preoperative CT in front of the portal vein-superior mesenteric vein.

Regarding blood flow, the literature does confirm extended pancreatic neck transection can get better blood supply [5,6].

Ref.:

1. Notte A, Doussot A. Postoperative pancreatic fistula after distal pancreatectomy: pancreatic thickness and duct size as the only denominators? *Hepatobiliary Surg Nutr*. 2023;12(2):229-231.
2. Xia W, Zhou Y, Lin Y, et al. A Predictive Risk Scoring System for Clinically Relevant Pancreatic Fistula After Pancreaticoduodenectomy. *Med Sci Monit*. 2018; 24:5719-5728. Published 2018 Aug 16.
3. Lin Z, Tang B, Cai J, et al. Preoperative prediction of clinically relevant postoperative pancreatic fistula after pancreaticoduodenectomy. *Eur J Radiol*. 2021; 139:109693.
4. Shi Y, Gao F, Qi Y, et al. Computed tomography-adjusted fistula risk score for predicting clinically relevant postoperative pancreatic fistula after pancreatoduodenectomy: Training and external

validation of model upgrade. *EBioMedicine*. 2020;62:103096.
5. Strasberg SM, McNevin MS. Results of a technique of pancreaticojejunostomy that optimizes blood supply to the pancreas. J Am Coll Surg. 1998;187(6):591-596.
6. Strasberg SM, Drebin JA, Mokadam NA, et al. Prospective trial of a blood supply-based technique of pancreaticojejunostomy: effect on anastomotic failure in the Whipple procedure. J Am Coll Surg. 2002;194(6):746-760.

Comment 3. There is also concern that cutting into the caudal pancreas may affect the pancreaticojejunostomy itself. The diameter of the main pancreatic duct becomes narrower toward the caudal side, and this phenomenon may also lead to the development of pancreatic leakage. Please consider the above three points.

Response: We appreciate this valuable question, which makes the foothold of the trial clearer. Theoretically, there are both advantages (more blood supply, and more central duct) and disadvantages (maybe smaller the pancreatic duct) to transect the pancreatic neck more distally. This theoretical contradiction pushed us to organize this trial so as to explore the impact of the level of pancreatic transection in clinical practice. We will measure the pancreatic duct diameter intraoperatively. By comparing the pancreatic duct diameters of the study and control groups in each subgroup (≤3mm, ＞3mm), it is able to confirm whether there is a significant difference in the pancreatic duct diameter at different transection level, and also to determine whether the difference in the pancreatic duct diameter at different transection level is a major factor influencing the occurrence of pancreatic fistula.

VERSION 2 – REVIEW

REVIEWER	Tomoyuki Abe Onomichi General Hospital, Surgery
REVIEW RETURNED	27-Nov-2023

GENERAL COMMENTS	Thank you for the opportunity to review this manuscript again. This paper is well-designed and revised clearly according to the Reviewer's comments.