## PEER REVIEW HISTORY



## ARTICLE DETAILS

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| **TITLE (PROVISIONAL)** | Laparoscopic versus open pancreaticoduodenectomy for pancreatic ductal adenocarcinoma: study protocol for a multicentre randomised controlled trial |
| **AUTHORS** | Pan, Shutao; Qin, Tingting; Yin, Taoyuan; Yu, Xianjun; Li, Jing; Liu, Jun; Zhao, Wenxing; Chen, Xuemin; Li, Dewei; Liu, Jianhua; Li, Jingdong; Liu, Yahui; Zhu, Feng; Wang, Min; Zhang, Hang; Qin, Renyi |

## VERSION 1 – REVIEW

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| **REVIEWER** | Nickel, Felix<br>University of Heidelberg , General Surgery |
| **REVIEW RETURNED** | 03-Oct-2021 |

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| **GENERAL COMMENTS** | The authors present the protocol for an RCT comparing open and laparoscopic pancreatoduodenectomy for upfront resectable pancreatic head cancer<br><br>My main critique: Registration of the trial was on the 10th of march 2019, and the planned enrollment was 2 years. The authors state „The first enrolled patient has been given the randomised number in September 2019. All ten centres are actively recruiting patients by the time this protocol is submitted. Recruitment will approximately be completed by<br>December 2021.“ How many patients have been operated by now exactly? Why was this protocol not published much earlier? I do not see a real reason to publish this now that the study is quasi finished.<br><br>CONSORT checklist 31c: data should be available upon reasonable request from the corresponding authors at the very least, if not publicly available.<br><br>How was the estimated relevant difference in 5 year overall survival?<br><br>Concerning the abstract: Pancreatoduodenectomy is certainly the treatment of choice for resectable pancreatic head cancer but not for all pancreatic cancers.<br><br>Do the authors institutions also perform robotic assisted pancreatoduodenectomy?<br><br>A total of 4 RCTs now exist that show no relevant advantage of LPD over OPD when data are combined. On the contrary one |

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| | multicenter trial had to be stopped early due to safety issues in the LPD group. Why should another trial be performed despite these results?<br><br>Concerning: „Compared with traditional open surgery, minimally invasive surgery has many advantages, such as small incision, minimal intraoperative bleeding, fast postoperative recovery, and so on.4, which are essential factors in the development of modern surgery.“ This sentence has unclear combination of point and comma in the middle. Also, what is meant by modern surgery? This is a very unspecific statement and not very useful. Please rephrase and explain in more detail..<br><br>Concerning: „Our previous studies, including a multicentre RCT, indicated that LPD is a safe and feasible procedure associated with a shorter length of stay and comparable short-term outcomes to open PD (OPD) in highly experienced surgeons who have past the learning curve9 10.“ There is a spelling error: use „passed“ instead of „past“!<br><br>What role will Ca 19-9 play in the selection of patients? Is this standardized in any way?<br><br>Concerning: „Patients converted from LPD to open surgery will not be included in the PP set. Patients will be randomised in a 1:1 manner to either the LPD or OPD arm, with the maximum conversion rate from LPD to OPD assumed to be 10%, resulting in a ratio of up to 9:10 in the PP set. To meet these assumptions, 83 patients in the LPD group and 91 patients in the OPD group will be needed to analyse using the one-sided t test at a one-sided significance level of 0.025. PASS version15.0.5 will be used to make calculations. An additional 10% of patients will be needed to be randomised considering the non-resectable patients, patients withdrawing from the study, and patients lost to follow-up. Accordingly, 91 patients in the LPD arm and 100 patients in the OPD arm will be randomised. The randomisation ratio of this trial is 1:1, requiring 100 patients in each arm and 200 patients in total to be included for randomisation.“ It would seem more logical to me to include more patients in the LPD group than in the OPD group to account for differences in the PP analysis due to conversions from LPD to OPD. Please explain..<br><br>What is the exact time point of randomisation? Please specify! The day of presentation in the hospital? The day prior to surgery? This will influence the number of patients who convert to a different approach. |

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| | What is the study policy concerning the timing of last CT imaging before surgery? This is known to influence outcome and it is usually recommended the scans be no older than 4 weeks prior to surgery.<br><br>Concerning: „Patients can be discharged if they do not need any intravenous infusion or intravenous analgesics, do not have incision infections or any major organ dysfunction, can tolerate oral semi-liquid food, can get off bed and walk at least 250 m in a plain road without assistance, and have normal haematological parameters.“<br>Wound infections that are treated sufficiently with opening of the wound and secondary wound healing do not necessarily require in-hospital treatment but patients might be able to be discharged.<br>„Normal haematological parameters“: what exactly is meant by this? E.g. patients frequently still have a low hemoglobin level after surgery but can be safely discharged.<br><br>5-year overall survival if probably more heavily influenced by other factors than open versus laparoscopic surgery. These include type of and adherence to adjuvant treatment; compliance with adjuvant treatment and follow-up plans; systemic versus interventional or even surgical treatment of local recurrence and distant metastasis. Can the authors comment on this?<br><br>The 5 year overall survival data that the authors based their sample size calculation on is low compared to other modern results showing 5 year overall survival around 30% with modern surgery (e.g. artery-first and Triangle approaches) and adjuvant treatment (Folfirinox).<br><br>What definition for resectable vs borderline resectable will be used in the study? How is this assessed? Is this done only locally or centralized or by independent radiologists and surgeons? There is significant heterogeneity in the assessment of resectability for pancreatic cancer.<br><br>What criteria for drain removal will be used? Is this standardized?<br><br>The authors state they use very strict inclusion and exclusion criteria. There are a number of factors that can complicate this type of surgery, e.g. excessive adhesions due to previous abdominal surgeries, prior pancreatitis, cholestasis (upon what criteria will patients receive ERCP and stent placement or PTCD or surgical biliary drainage prior to resection?), cavernous transformation, chronic kidney disease, liver disease etc.. What are the guidelines and rules used in this study? Multidisciplinary boards can act heterogenously and are not a plausible explanation in my point of view. |

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| **REVIEWER** | Kathir Kamarajah, Sivesh<br>University of Birmingham, College of medical and Dental Sciences |
| **REVIEW RETURNED** | 04-Oct-2021 |

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| **GENERAL COMMENTS** | This is a good paper for a study protocol and results / findings of this trial will be useful to the HPB community |

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| **REVIEWER** | Grande, L.<br>Hospital del Mar |
| **REVIEW RETURNED** | 04-Oct-2021 |

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| **GENERAL COMMENTS** | This is a protocol for conducting a prospective randomized study between open and laparoscopic surgery in PD whose main variable is 5-year survival. Few objections to the protocol itself and especially when the possible suggestions/modifications that the reviewer may suggest are practically impossible to assume since, according to the proposed schedule, I understand that the recruitment period is almost over.<br>Although several studies have shown that oncological outcomes, including 5-year survival, are similar between both approaches, it is right that at the time of writing the protocol there were no prospective studies conducted with this objective. However, it is intriguing that 5-year survival was chosen as the main variable, which in the best cases does not exceed 20%. In addition, the sample calculation is based on a retrospective Dutch study with only 62 laparoscopic resections, in which a higher rate of free resection margins in the laparoscopic group had been obtained (87% vs. 71%, $p < 0.01$), with no statistically significant differences in survival between the laparoscopic and open group.<br>It is also noteworthy that within the secondary variables, the specific complications of pancreatic surgery (hemorrhage / fistula, gastric emptying, etc.) are not analyzed in accordance with the ISGPS consensus. It could also be of interest to assess the overall number of complications and the cumulative severity (using, for example, the Comprehensive Complication Index) and not only the most serious complication in each patient. On the other hand, although several studies use > III as a cut-off point to classified severe complications from mild ones, there seems to be more and more consensus in considering IIIa as a mild complication.<br>I understand that the standardization of the intervention, one of the key point of the protocol, is not easy in a multicenter study, but it would have been a good idea to have made an attempt to standardize the type of reconstruction or anastomosis. This will force an analysis by centers of some variables to show that there are no differences between them. |

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| **REVIEWER** | Kang, Chang Moo<br>Yonsei Univ |
| **REVIEW RETURNED** | 04-Oct-2021 |

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| **GENERAL COMMENTS** | 1. Histologically confirmed pancreatic cancer= pancreatic ductal adenocarcinoma? Please be specific.<br>2. As exclusion criteria, followings need to be considered;<br>1) previous major upper GI surgery<br>2) Combine major vascular resection (tangential? segmental resection?)<br>3) Other concomittant cancerous condition within 2 years? or 3 years? or 5 years?<br><br>3. End point need to be re-considered;<br>1) Primary end point : short-term oncologic outcomes including pathological characteristics (please be more specific including # of retrieved LNs and margin-status, complication,....postoperative adjuvant CTx, 30-/90-day mortality.<br>2) Secondary end point: long-term oncologic outocmes including OS, and DFS |

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| | *Transfusion need to be considered.<br><br>4. at least two interim analysis a year regarding short-term oncologic outcomes need to be investigated for patients' safety. There should be some system to check If short-term oncologic outcomes and postoperative morbidity, and morality is deviated in order to have rationale for early study termination.<br><br>5. In determining sample size, I'm not sure if the reference is appropriate. According to most literatures, long-term OS is reported to be similar. 86 patients in each group may not enough to reach the conclusion in my opinion.<br><br>6. How do authors define surgical extent of PD? extended or standard? How are you going to confirm the appropriate surgical extent of each operators? |

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| **REVIEWER** | Probst, Pascal<br>University of Heidelberg, Department of General, Visceral and Transplantation Surgery |
| **REVIEW RETURNED** | 15-Oct-2021 |

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| **GENERAL COMMENTS** | Pan et al. present a protocol for a randomised-controlled trial comparing open vs laparoscopic pancreaoduodenectomy in pancreatic cancer. The rationale to perform this study is given. The methods are adequte.<br>I have some concerns to be addressed:<br>The presentation of the existing literature on this topic should be improved please see emps.evidencemap.surgery and cite the ISGPS Evidence Map of Pancreatic Surgery (Evidence Map of Pancreatic Surgery – a living systematic review with meta-analyses by the International Study Group of Pancreatic Surgery (ISGPS). Surgery. 2021;EPUB). Currently there are 4 RCT (three of them are not cited) and 45 systematic reviews. This should be part of the introduction.<br>Please rephrase "To the best of our knowledge, this will be the first randomised controlled trial to compare LPD and OPD for resectable pancreatic cancer treatment in a large multicentre setting and will provide convincing evidence on performance of pancreatic cancer resection." in the light of the ISGPS Evidence Map of Pancreatic Surgery. |

## VERSION 1 – AUTHOR RESPONSE

**Reviewer: 1**

***Dr. Felix Nickel, University of Heidelberg***

***Comments to the Author:***

***The authors present the protocol for an RCT comparing open and laparoscopic pancreatoduodenectomy for upfront resectable pancreatic head cancer***

***My main critique: Registration of the trial was on the 10th of march 2019, and the planned enrollment was 2 years. The authors state "The first enrolled patient has been given the randomised number in September 2019. All ten centres are actively recruiting patients by the time this protocol is submitted. Recruitment will approximately be completed by December 2021." How many patients have been operated by now exactly? Why was this protocol not published much earlier? I do not see a real reason to publish this now that the study is quasi finished.***

**Response:** Thanks for your comments. One hundred and eighty-one patients have been enrolled in this trial, and they have undergone surgery. This protocol has been prepared for publication since the start of this trial. The study was registered on the March 10, 2019, and the first case was enrolled on August 14, 2019. However, due to the outbreak of COVID-19, this study was interrupted and delayed for around 1 year. When the COVID-19 epidemic was controlled, we continued the study, as well as the preparations of the protocol. This trial has a recruiting period estimated to be 2 years and a follow-up period of 5 years, and we hope that the protocol can be published before the end of the recruiting period.

***CONSORT checklist 31c: data should be available upon reasonable request from the corresponding authors at the very least, if not publicly available.***

**Response:** Thanks for your kind comment. We have indicated the availability of data in the "Data Availability Statement" section (Page 12 in the revised manuscript), as shown below.

*"Data Availability Statement*

*The final datasets will not be available to the public. However, researchers will have access to the study data in de-identified form from the corresponding author after reasonable request when the study is completed."*

***How was the estimated relevant difference in 5 year overall survival?***

**Response:** Thanks for your comment. We reviewed the publications comparing the long-term survival of patients with resectable pancreatic ductal adenocarcinoma (PDAC) treated with LPD and OPD when this trial was designed. Croome et al.[1] found that the median survival was 25.3 months for the LPD group and 21.8 months for the OPD group ($P$ = 0.12) in the setting of pancreatic ductal adenocarcinoma (PDAC), which showed no significant difference. Song et al.[2] reported that the 5-year overall survival rates of the patients with PDAC in the laparoscopic pylorus-preserving PD and open pylorus-preserving PD groups were 53.6% and 28.8% ($P$ = 0.81), respectively. Results from the research of Stauffer et al.[3] showed that long-term survival was similar for LPD and OPD for the treatment of PDAC, with the 5-year survival of 15% for OPD and 32% for LPD ($P$ = 0.249). As reported by Delitto er al.[4], overall survival was not statistically different between patients undergoing LPD vs. OPD for pancreatic adenocarcinoma (median survival 20.7 vs. 21.1 months; P= 0.703). Kuesters et al.[5] found that in the setting of PDAC, the calculated 5-year survival rates were 20% for the LPD versus 14% for the OPD group ($P$ = 0.51). Based on these findings, we suppose that the 5-year survival did not differ after LPD and OPD. To demonstrate the assumptions, we designed the non-inferiority study to estimate the difference in the 5-year overall survival after the LPD and OPD. The sample size calculation was based on the research of Kuesters et al.[5], which showed that the 5-year overall survival rate of LPD was comparable to that of OPD for the treatment of resectable PDAC, and the estimated difference between the two groups was 6% (20% vs 14% for LPD vs OPD). This study has the largest sample size and has provided the latest findings on the 5-year overall

survival after LPD and OPD for treating PDAC. Based on this study, we assume that the estimated difference in the 5-year overall survival is 6% and the non-inferiority margin is -10%.

***Concerning the abstract: Pancreatoduodenectomy is certainly the treatment of choice for resectable pancreatic head cancer but not for all pancreatic cancers.***

**Response:** Thank you for the comment. We have revised this description in the revised manuscript (Page 3), as shown below.

"*Pancreatic cancer is one of the deadliest cancers and pancreaticoduodenectomy (PD) is recommended as the optimal operation for resectable pancreatic head cancer.*"

***Do the authors institutions also perform robotic assisted pancreatoduodenectomy?***

**Response:** Thanks for your comment. In this study, all the patients enrolled in the LPD arm were requested to receive laparoscopic pancreaticoduodenectomy, but not robot-assisted pancreatoduodenectomy. Some of the participating centres perform robot-assisted pancreaticoduodenectomy daily in actual practice.

***A total of 4 RCTs now exist that show no relevant advantage of LPD over OPD when data are combined. On the contrary one multicenter trial had to be stopped early due to safety issues in the LPD group. Why should another trial be performed despite these results?***

**Response:** Thanks for your comments. The previous published RCTs comparing the LPD to OPD were mainly focused on pancreatic or periampullary diseases and reported the short-term outcomes. Few studies have investigated PDAC specifically or monitored the long-term oncological safety. The long-term survival benefits of minimally invasive surgery in patients with cancer remains controversial. For example, minimally invasive radical hysterectomy showed poorer overall survival and disease-free survival than open surgery for patients with early-stage cervical cancer[6]. This study will be the first trial to compare the long-term safety of LPD and OPD for resectable PDAC in a large multicentre setting and aims to provide high-level evidence on the long-term survival results of LPD and OPD in the treatment of PDAC. In addition, in a large RCT (N=656) completed by Wang et al.[7], which involved participating surgeons that had completed the learning curve (≥104 LPDs), demonstrated the safety and feasibility of LPD. However, the other three RCTs set no requirement for the learning curve for the participating surgeons. In this case, the safety of LPD can be guaranteed for experienced surgeons who have completed the learning curve of LPD. In this trial, participating surgeons are required to have completed no less than 104 cases of LPDs and no less than 104 cases of OPDs, which guarantees the short-term safety of patients. The long-term outcomes and oncological safety of this new technology are still to be established. Together with the findings of previous RCTs and the concerns regarding LPD, as well as the previous RCT completed by Wang et al.[7], we were determined to carry out an RCT to further investigate these key issues.

***Concerning: "Compared with traditional open surgery, minimally invasive surgery has many advantages, such as small incision, minimal intraoperative bleeding, fast postoperative recovery, and so on.4, which are essential factors in the development of modern surgery." This sentence has unclear combination of point and comma in the middle. Also, what is meant***

***by modern surgery? This is a very unspecific statement and not very useful. Please rephrase and explain in more detail.***

**Response:** Thanks for your comments. We have revised this description in the revised manuscript (Page 5), as shown below.

*"Compared with traditional open surgery, minimally invasive surgery has several advantages, such as small incision, minimal intraoperative bleeding, and fast postoperative recovery, among others, which are essential factors promoting the development of surgical treatments."*

***Concerning: "Our previous studies, including a multicentre RCT, indicated that LPD is a safe and feasible procedure associated with a shorter length of stay and comparable short-term outcomes to open PD (OPD) in highly experienced surgeons who have past the learning curve9 10." There is a spelling error: use "passed" instead of "past"!***

**Response:** Thanks for your comment. We have respelled the word in the corresponding place.

***What role will Ca 19-9 play in the selection of patients? Is this standardized in any way?***

**Response:** Thanks for your comment. In this trial, patients diagnosed with resectable PDAC and planning to undergo PD will be included. CA19-9 is a common tumour marker for PDAC, and its increased serum concentration provides an indication of the diagnosis of PDAC. Studies have reported the important roles of CA19-9 in assessing the resectability of PDAC [8-11]. However, results of these publications remain controversial. According to the NCCN guideline, the resectability status of PDAC is mainly defined based on CT imaging, while CA19-9 is not a routine indicator for resectability status of PDAC. The diagnostic criteria of PDAC in our study follows the criteria of NCCN. Therefore, CA19-9 is not included in the criteria of patient selection in this trial and is not standardized. However, in our study, CA19-9 will be recorded, and included in the final analysis.

***Concerning: "Patients converted from LPD to open surgery will not be included in the PP set. Patients will be randomised in a 1:1 manner to either the LPD or OPD arm, with the maximum conversion rate from LPD to OPD assumed to be 10%, resulting in a ratio of up to 9:10 in the PP set. To meet these assumptions, 83 patients in the LPD group and 91 patients in the OPD group will be needed to analyse using the one-sided t test at a one-sided significance level of 0.025. PASS version15.0.5 will be used to make calculations. An additional 10% of patients will be needed to be randomised considering the non-resectable patients, patients withdrawing from the study, and patients lost to follow-up. Accordingly, 91 patients in the LPD arm and 100 patients in the OPD arm will be randomised. The randomisation ratio of this trial is 1:1, requiring 100 patients in each arm and 200 patients in total to be included for randomisation." It would seem more logical to me to include more patients in the LPD group than in the OPD group to account for differences in the PP analysis due to conversions from LPD to OPD. Please explain.***

**Response:** Thank you so much for pointing out this mistake. The sample included 100 patients in the LPD arm and 91 patients in the OPD arm. We have made corresponding changes in the main text. The details can be seen in the revised manuscript on Page 8.

***What is the exact time point of randomisation? Please specify! The day of presentation in the hospital? The day prior to surgery? This will influence the number of patients who convert to a different approach.***

**Response:** Thank you for pointing this out. Randomisation will be assigned on the day the preoperative evaluation is completed, and the patient is diagnosed with PDAC eligible for PD. We have stated this in the "Randomisation and blinding" section (Page 9), as shown below.

*"Randomisation will be assigned on the day the preoperative evaluation is finished and the patient is diagnosed with PDAC, eligible for PD."*

***What is the study policy concerning the timing of last CT imaging before surgery? This is known to influence outcome and it is usually recommended the scans be no older than 4 weeks prior to surgery.***

**Response:** Thank you for pointing this out. We agree with your opinion and this criterion is used in this trial. We have described this in the "Population and eligibility criteria" section (Page 6), as shown below.

*"The last CT imaging should be performed within 4 weeks before the surgery."*

***Concerning: "Patients can be discharged if they do not need any intravenous infusion or intravenous analgesics, do not have incision infections or any major organ dysfunction, can tolerate oral semi-liquid food, can get off bed and walk at least 250 m in a plain road without assistance, and have normal haematological parameters." Wound infections that are treated sufficiently with opening of the wound and secondary wound healing do not necessarily require in-hospital treatment but patients might be able to be discharged. "Normal haematological parameters": what exactly is meant by this? E.g. patients frequently still have a low hemoglobin level after surgery but can be safely discharged.***

**Response:** Thank you for the comments. We agree with your opinion. Patients with wound infections that are treated sufficiently with opening of the wound and secondary wound healing that do not require in-hospital treatment can be discharged. "Normal haematological parameters" here is written mistakenly, and should be "near-normal haematological parameters" as defined in our previous RCT[7] [12], which means that the haematological parameters become acceptable for patients evaluated by the investigators, including normal value and abnormal value with no clinical significance.

We have rephrased the discharge criteria, as shown below. And corresponding revision was made in the revised manuscript, on Page 10.

*"Patients can be discharged if they meet the following discharge criteria: no need for intravenous infusion, well tolerance of oral solid or semisolid food, no need for intravenous analgesics, well wound healing, well tolerance of independent walking at least 250 m in a plain road, well major organ function with near-normal haematological parameters."*

***5-year overall survival if probably more heavily influenced by other factors than open versus laparoscopic surgery. These include type of and adherence to adjuvant treatment; compliance with adjuvant treatment and follow-up plans; systemic versus interventional or even surgical treatment of local recurrence and distant metastasis. Can the authors comment on this?***

**Response:** Thanks for your comments. We agree that the 5-year overall survival will be influenced by several factors besides surgical technique. For each RCT, questions will be considered when evaluating the long-term outcomes in an oncological study, and that's why RCTs require strict inclusion/exclusion criteria, well-controlled follow-up schedules, and well-planned protocols. All study procedures will follow the protocol. In this trial, all included patients are required to comply with the standard treatment in accordance with the NCCN guideline. If they don't, they won't be included. All patients will receive standard adjuvant treatment as recommended in the NCCN guideline. If the first-line regimen cannot be tolerated, a second-line regimen will be used. Local recurrence and distant metastasis will be treated according to the recommendations of the NCCN guideline at the corresponding participating centres. Furthermore, there are strict and complete follow-up plans for each patient. These plans and guidelines will help to balance those factors in the two groups and minimise the influence of confounding factors on the 5-year overall survival.

***The 5 year overall survival data that the authors based their sample size calculation on is low compared to other modern results showing 5 year overall survival around 30% with modern surgery (e.g. artery-first and Triangle approaches) and adjuvant treatment (Folfirinox).***

**Response:** Thank you for this comment. At the time this trial was designed, five references reported the overall survival of LPD and OPD, and the details are shown in table 1, as shown below.

**Table 1 Survival of patients who underwent LPD or OPD for PDAC[1-5]**

| Author | Published year (study period) | Surgery | Cases | 1-year survival(%) | 2-year survival(%) | 3-year survival(%) | 4-year survival(%) | 5-year survival(%) | Median OS (month) |
|---|---|---|---|---|---|---|---|---|---|
| Croome et al. | 2014 (2008-2013) | LPD | 108 | 80.0 | 54.0 | 41.0 | 25.0 | NA | 25.3 |
| | | OPD | 214 | 71.0 | 47.0 | 31.0 | 21.0 | NA | 21.8 |
| Song et al. | 2015 (2007-2012) | LPD | 11 | 81.8 | 53.6 | 53.6 | 53.6 | 53.6 | NA |
| | | OPD | 261 | 73.2 | 58.0 | 41.8 | 28.8 | 28.8 | NA |
| Stauffer et al. | 2016 (1995-2014) | LPD | 58 | 66.5 | 43.3 | 43.3 | 38.5 | 32.1 | NA |
| | | OPD | 193 | 67.5 | 40.2 | 24.3 | 17.1 | 15.3 | NA |
| Delitto er al. | 2016 (2010-2014) | LPD | 28 | 72.5 | 45.0 | 22.5 | NA | NA | 20.7 |
| | | OPD | 22 | 77.5 | 47.5 | 42.5 | NA | NA | 21.1 |
| Kuesters et al. | 2018 (2001-2016) | LPD | 62 | 72.0 | 51.0 | 32.5 | 20.0 | 20.0 | NA |
| | | OPD | 278 | 70.0 | 42.0 | 26.5 | 18.0 | 14.0 | NA |

LPD laparoscopic pancreaticoduodenectomy, OPD open pancreaticoduodenectomy, OS overall survival, NA not available

We referred to the study conducted by Kuesters et al.[5], which showed that the 5-year overall survival rate of LPD is comparable to that of OPD for the treatment of resectable PDAC, and the estimated difference between the two group is 6% (20% vs 14% for LPD vs OPD). This reference was the latest study with the most patients in the LPD and OPD group that had reported the 5-year overall survival rate in treatment of PDAC. Thus, the sample size was calculated based on this reported data. The prognosis of pancreatic was poor, even after surgery or receiving adjuvant chemoradiotherapy. The 5-year overall survival following surgery for resectable PDAC has rarely improved. In the ESPAC-1 trial reported in 2004, the estimated 5-year survival was 21.1% for the chemotherapy group (5-fluorouracil plus folinic acid), 8.0% in the no chemotherapy group, and 10.8% for the group randomised to chemoradiotherapy[13]. In the ESPAC-3(v2) trial reported in 2010, the estimated 5-year survival was 17.5% for patients in the gemcitabine group and 15.9% for patients in the 5-fluorouracil plus folinic acid group[14]. In the ESPAC-4 trial reported in 2017, the estimated 5-year survival was 16.3% for the patients randomised to gemcitabine, and 28.8% for the patients randomised to gemcitabine plus capecitabine[15]. At present, for patients diagnosed with a localised, resectable tumour, the prognosis remains poor with around 20% surviving 5 years after surgery[16]. Furthermore, with the development of modern surgery, the surgical techniques of LPD and OPD are both constantly being refined.

***What definition for resectable vs borderline resectable will be used in the study? How is this assessed? Is this done only locally or centralized or by independent radiologists and surgeons? There is significant heterogeneity in the assessment of resectability for pancreatic cancer.***

**Response:** Thank you for pointing this out. We define the resectable and borderline resectable according to the NCCN guideline, as given below.

*"Resectable: No distant metastasis; No radiographic evidence of SMV or PV distortion; Clear fat planes around CA, HA, and SMA.*

*Borderline resectable: No distant metastasis; Venous involvement of the SMV or PV with distortion or narrowing of the vein or occlusion of the vein with suitable vessel proximal and distal, allowing for safe resection and replacement; GA encasement up to the hepatic artery with either short segment encasement or direct abutment of the HA without extension to the CA; Tumour abutment of the SMA not to exceed 180° of the circumference of the vessel wall."*

The resectability status of PDAC is determined locally by responsible surgeons of each centre according to the principle of the NCCN guideline.

***What criteria for drain removal will be used? Is this standardized?***

**Response:** Thank you for pointing this out. The criteria for drain removal after pancreaticoduodenectomy are important. However, there is a lack of high-level evidence guiding relevant clinical practice. Though several RCTs have been published[17-19], to drain or not, drain with early or late removal, and how to better stratify patients with different risk level of POPF remain to be settled[18 19].

In this trial, the abdominal drains will be placed routinely for patients. Surgeons will decide the timepoint of drain removal according to every participant's manifestation, laboratory examination results (the concentration of drain fluid amylase (DFA) on postoperative day (POD) 1 and POD3), and imaging findings. This is similar to previous multicentre RCTs[7 20-22]. In general, the drain will be kept for at least three days, and removed if there is no evidence of pancreatic fistula or sign of large amount of ascites due to other reasons. Several indicators, such as the DFA value on POD1 (cut-off value was set at 5000 U/L according to many experts' perspectives)[19] and pancreatic fistula risk score (FRS, based on the pancreatic duct diameters, pathology, pancreatic texture, and the estimated intraoperative blood loss)[23] will be used by some surgeons for decision making. Nevertheless, the accuracy of POD1 DFA for predicting POPF is limited. For FRS, it is not easy to accurately measure the pancreatic duct diameters (in most cases, only several millimetres), and the evaluation of pancreatic texture is difficult to be standardized among different centres. Thus, the criteria for drain removal will not be standardized.

Several studies, including four RCTs[7 20-22], support that laparoscopic technique in pancreaticoduodenectomy is not associated with the occurrence of POPF. Moreover, as you know, the diagnosis of POPF is based on the concentration of amylase in ascites and is not directly related to the duration of drain placement. Based on this knowledge, surgeons are unlikely to subjectively prolong or shorten drain time in either the LPD group or the OPD group. Therefore, despite lacking standardization, our outcomes of interests probably will not be significantly affected by the no standardization in drain removal.

We have described this in the "Concomitant treatment" section (Page 10), as shown below.

*"The abdominal drains will be placed routinely for patients. The timepoint of drain removal depends on every patient's manifestation, laboratory examination results (the concentration of drain fluid amylase (DFA) on postoperative days (PODs) 1 and 3), and imaging findings. In patients with a DFA concentration of less than 5000 U/L on POD 1, early drain removal at 72 h is recommended. In patients with a DFA concentration of more than 5000 U/L on POD 1, drain removal will be decided by the corresponding surgeon according to the patient's situation."*

***The authors state they use very strict inclusion and exclusion criteria. There are a number of factors that can complicate this type of surgery, e.g. excessive adhesions due to previous abdominal surgeries, prior pancreatitis, cholestasis (upon what criteria will patients receive ERCP and stent placement or PTCD or surgical biliary drainage prior to resection?), cavernous transformation, chronic kidney disease, liver disease etc.. What are the guidelines and rules used in this study? Multidisciplinary boards can act heterogenously and are not a plausible explanation in my point of view.***

**Response:** Thanks for your comments. We agree that several factors, such as those mentioned above, can complicate the surgery. The inclusion and exclusion criteria can only restrict the homogeneity of the included patients to a certain extent. In this study, the MDT will be consulted to evaluate the feasibility of surgery, to assess the impact of these factors on surgical safety and patient survival, and decide whether the patient meets the curative treatment criteria according to clinical guidelines. The evaluation and decision from the MDT can improve the homogeneity of included patients. Besides, the randomization will balance the observed and unobserved factors between the two groups, and minimize the influencing factors of surgery evaluation between the two surgical groups. Furthermore, since this trial was designed to assess the long-term survival of patients treated with LPD and OPD, it is of great importance that participants assigned to the two arms are balanced and comparable, the enrolled patients are highly homogeneous, and the included patients can benefit from the treatments of both arms.

**Reviewer: 2**

***Dr. Sivesh Kathir Kamarajah, University of Birmingham***

***Comments to the Author:***

***This is a good paper for a study protocol and results / findings of this trial will be useful to the HPB community.***

**Response:** Thank you for the comment.

**Reviewer: 3**

***Dr. L. Grande, Hospital del Mar***

***Comments to the Author:***

***This is a protocol for conducting a prospective randomized study between open and laparoscopic surgery in PD whose main variable is 5-year survival. Few objections to the protocol itself and especially when the possible suggestions/modifications that the reviewer may suggest are practically impossible to assume since, according to the proposed schedule, I understand that the recruitment period is almost over.***

***Although several studies have shown that oncological outcomes, including 5-year survival, are similar between both approaches, it is right that at the time of writing the protocol there were no prospective studies conducted with this objective. However, it is intriguing that 5-year survival was chosen as the main variable, which in the best cases does not exceed 20%.***

**Response:** Thank you for your comment. Long-term survival is a major concern of cancer treatment. RCTs with short-term outcomes as the primary outcome have proved that LPD has certain advantages over OPD in the treatment of pancreatic or periampullary tumours. However, no RCT has compared the long-term survival after LPD and OPD. Previously, we carried out a multicentre RCT for short-term outcomes[7]. Based on the previous study, we further carried out this clinical trial to explore the long-term benefits of patients with PDAC after PD. The 5-year survival rate is a meaningful efficacy indicator for cancer treatment. Although the 5-year survival rate for PDAC is low, it also has great clinical significance, which is selected as the primary outcome in this trial. Furthermore, a longer follow-up duration is associated with more outcomes we can evaluate. During the study period, we can also evaluate the 1-year and 2-year survival rates, among others, which will provide meaningful clinical significance.

***In addition, the sample calculation is based on a retrospective Dutch study with only 62 laparoscopic resections, in which a higher rate of free resection margins in the laparoscopic group had been obtained (87% vs. 71%, p < 0.01), with no statistically significant differences in survival between the laparoscopic and open group.***

**Response:** Thank you for your comment. Some studies have confirmed that the resection margins can influence the long-term outcome[24-26]. However, the long-term survival of PDAC is influenced by many factors, not just R0 resection. The difference in R0 resection rate (87% vs. 71% for LPD vs. OPD in the reference) does not necessarily lead to a difference in the 5-year survival. We reviewed published studies that reported the 5-year overall survival after LPD and OPD for the treatment of PDAC, and by the time we designed this trial, this was the latest study with the most patients in the LPD (n=62) and OPD (n=278) groups. Thus, we referred to this study for sample size calculation.

***It is also noteworthy that within the secondary variables, the specific complications of pancreatic surgery (hemorrhage/fistula, gastric emptying, etc.) are not analyzed in accordance with the ISGPS consensus. It could also be of interest to assess the overall number of complications and the cumulative severity (using, for example, the Comprehensive Complication Index) and not only the most serious complication in each patient. On the other hand, although several studies use > III as a cut-off point to classified severe complications from mild ones, there seems to be more and more consensus in considering IIIa as a mild complication.***

**Response:** Thank you for your comments. The primary outcome of this trial is the 5-year survival rate, and complications are analysed as secondary outcomes. The complications are recorded, managed, and will be analysed according to the ISGPS consensus. To better report the outcomes of this trial, complication rate and comprehensive complication index will be analysed as secondary outcomes, as shown below. And corresponding revision was made in the revised manuscript, on Page 7.

*"(4) complication rate (complications related to PD are defined according to the International Study Group of Pancreatic Surgery; complication grades are defined according to the Clavien-Dindo classification system) (5) comprehensive complication index (CCI, calculated as the sum of all complications that are weighted for their severity, available at www.assessurgery.com);"*

In this trial, Clavien-Dindo ≥ Ⅲ is used as a cut-off point to classify severe complications from mild ones, as most studies did. While the distribution of exact Clavien-Dindo grade will be listed and analysed in the statistical analysis, which will provide the full information of the Clavien-Dindo grade distribution to readers.

***I understand that the standardization of the intervention, one of the key point of the protocol, is not easy in a multicentre study, but it would have been a good idea to have made an attempt to standardize the type of reconstruction or anastomosis. This will force an analysis by centres of some variables to show that there are no differences between them.***

**Response:** Thank you for your comment. There were two aspects to consider about the standardization of reconstruction and anastomosis. First, it was widely accepted that the method of pancreatic anastomosis that was familiar to the surgeon produced the best results. To ensure the surgical quality and safety of the participating patients, this trial encouraged the surgeon to use their most familiar reconstruction methods, as well as the pancreatic anastomosis. Second, each pancreatic anastomosis required time and experience to master, it was impossible for the surgeons who were qualified to take part in this trial to master a specific anastomosis method in such a short period. Based on the above, the type of reconstruction was determined by the surgeon's experience and preference.

Moreover, methods used for reconstruction during OPD must be consistent with those during LPD in the same centre, as we described in the main text. We do not require uniformity across different centres. We adopted block randomization in this trial, which can ensure that the distribution of the reconstruction and anastomosis types in the LPD and OPD groups are balanced, and will not interfere with the analysis of outcomes. In addition, the impact of different reconstruction and anastomosis types on the outcomes will be analysed during the final statistical analysis.

**Reviewer: 4**

***Dr. Chang Moo Kang, Yonsei Univ***

***Comments to the Author:***

***1. Histologically confirmed pancreatic cancer= pancreatic ductal adenocarcinoma? Please be specific.***

**Response:** Thank you for pointing this out. In the inclusion criteria, the histologically confirmed pancreatic cancer means pancreatic ductal adenocarcinoma. We have made corresponding revision in the revised manuscript.

***2. As exclusion criteria, followings need to be considered;***

***1) previous major upper GI surgery***

***2) Combine major vascular resection (tangential? segmental resection?)***

***3) Other concomittant cancerous condition within 2 years? or 3 years? or 5 years?***

**Response:** Thank you for pointing this out.

1) We agree that patients with previous major upper gastrointestinal surgery are to be excluded for this study. As described in the 3rd inclusion criteria, all patients will be evaluated by MDT to decide the feasibility of surgery. Patients with characteristics that affect the surgical procedure and the outcome will not be included.

2) We agree that patients requiring combined major vascular resection will not be included in this trial. As described in the 4th inclusion criterion, patients without vascular invasion and not requiring vascular resection as evaluated by the MDT team according to abdominal imaging data will be included in this trial.

3) Considering the great impact of cancer history on survival, patients with a history of malignant tumours are excluded regardless of time.

According to your kind comments, we reconstructed the inclusion/exclusion criteria, without changing the contents of the criteria, as shown below. And corresponding revision was made in the revised manuscript, on Page 6.

*"Inclusion criteria*

1) *Age between 18 years and 75 years.*
2) *Histologically confirmed PDAC or clinically diagnosed PDAC by an MDT without histopathologic evidence.*
3) *Patients feasible to undergo both LPD and OPD according to MDT evaluations.*
4) *Patients understanding and willing to comply with this trial.*
5) *Provision of written informed consent before patient registration.*
6) *Patients meeting the curative treatment intent in accordance with clinical guidelines.*

*Exclusion criteria*

1) *Pregnant or breast-feeding women.*
2) *Patients with serious mental disorders.*
3) *Patients treated with neoadjuvant therapy.*
4) *Patients requiring left, central or total pancreatectomy or other palliative surgery.*
5) *Patients with vascular invasion and requiring vascular resection as evaluated by the MDT team according to abdominal imaging data.*
6) *Patients with distant metastases, including peritoneal, liver, distant lymph node metastases, and involvement of other organs.*
7) *Preoperative American Society of Anaesthesiologists (ASA) score ≥ 4.*
8) *History of other malignant disease.*
9) *Body mass index > 35 kg/m$^2$.*
10) *Patients participating in any other clinical trials within 3 months."*

***3. End point need to be re-considered;***

***1) Primary end point: short-term oncologic outcomes including pathological characteristics (please be more specific including # of retrieved LNs and margin-status, complication, .... postoperative adjuvant CTx, 30-/90-day mortality.***

***2) Secondary end point: long-term oncologic outocmes including OS, and DFS***

**Response:** Thank you for your advice. We have carried out an RCT comparing the short-term oncological outcomes of LPD and OPD for the treatment of pancreatic or periampullary tumours, and the results of the study have been published[7]. In this trial, patients with PDAC are included, and the primary outcome is the 5-year overall survival rate, which is the most important indicator for evaluating

the therapeutic effect of cancer. At the same time, the short-term oncological outcomes will also reflect in the long-term survival. The design of this trial is based on the primary outcome, namely long-term survival, which determines a series of experimental design elements, such as the non-inferiority design of the trial, sample size calculation, and data collection. While at present, recruitment for this trial is about to end, it is inappropriate to modify the outcomes.

***Transfusion need to be considered.***

**Response:** Thank you for your advice. We agree with your opinion. Transfusion is a key factor to be analysed in the complications.

***4. At least two interim analysis a year regarding short-term oncologic outcomes need to be investigated for patients' safety. There should be some system to check If short-term oncologic outcomes and postoperative morbidity, and morality is deviated in order to have rationale for early study termination.***

**Response:** Thanks for your comments. The interventions in this trial are surgical procedures, LPD or OPD. The short-term safety of the two procedures has been validated in our previous RCT[7]. Although there is no interim analysis in this trial, the safety committee will evaluate the safety of patients throughout the trial. If a major safety incident occurs, the trial will be terminated promptly.

***5. In determining sample size, I'm not sure if the reference is appropriate. According to most literatures, long-term OS is reported to be similar. 86 patients in each group may not enough to reach the conclusion in my opinion.***

**Response:** Thank you for your comment. We reviewed published studies that reported the 5-year overall survival rate of LPD and OPD for the treatment of PDAC, and by the time we designed this trial, this was the most recent study with the most patients in both the LPD (n=62) and OPD (n=278) groups. Based on the reference, 86 patients in each group was required according to the scientific and rigorous calculation. At the same time, considering the patients withdrawing from the study and those lost to follow-up, an additional 10% of patients were randomised, resulting in 100 patients in each group. This is the sample size we calculated based on historical data and experimental design.

***6. How do authors define surgical extent of PD? extended or standard? How are you going to confirm the appropriate surgical extent of each operators?***

**Response:** Thanks for your comments. Standard PD is performed in the trial. We have defined the surgical extent of PD in the protocol, and all surgeries are performed according to the PD technique standards. As we have described in the main text, the participating surgeons were required to have completed no less than 104 cases of LPDs and no less than 104 cases of OPDs in this trial, which is a guarantee that the surgeries they perform are of appropriate extent. Surgeons willing to participate had provided one recently unedited LPD and one recently unedited OPD surgery video to the research council for evaluation. The surgeons and their centres were permitted to participate in this study as a collaborator after the research council had approved the surgical techniques. Furthermore, the exact surgical extent of each patient is recorded and will be analysed.

**Reviewer: 5**

***Dr. Pascal Probst, University of Heidelberg***

***Comments to the Author:***

***Pan et al. present a protocol for a randomised-controlled trial comparing open vs laparoscopic pancreaoduodenectomy in pancreatic cancer. The rationale to perform this study is given. The methods are adequte.***

***I have some concerns to be addressed:***

***The presentation of the existing literature on this topic should be improved please see emps.evidencemap.surgery and cite the ISGPS Evidence Map of Pancreatic Surgery (Evidence Map of Pancreatic Surgery – a living systematic review with meta-analyses by the International Study Group of Pancreatic Surgery (ISGPS). Surgery. 2021;EPUB). Currently there are 4 RCT (three of them are not cited) and 45 systematic reviews. This should be part of the introduction.***

**Response:** Thank you for your advice. We have learned a lot from this article. The ISGPS Evidence Map of Pancreatic Surgery has summarised all the publications related to pancreatic surgery and allows researchers to access research in related fields. We failed to refer to the article because the article had not been published when we wrote the protocol. We have added relevant content to the introduction, as shown below. And corresponding revision was made in the revised manuscript, on Page 5.

*"As shown by the ISGPS Evidence Map of Pancreatic Surgery[27], an increasing number of studies, including 4 large-scale randomised controlled trials (RCTs), have reported the safety and feasibility of LPD for the treatment of periampullary or pancreatic tumours[7 22 28-30]."*

***Please rephrase "To the best of our knowledge, this will be the first randomised controlled trial to compare LPD and OPD for resectable pancreatic cancer treatment in a large multicentre setting and will provide convincing evidence on performance of pancreatic cancer resection." in the light of the ISGPS Evidence Map of Pancreatic Surgery.***

**Response:** Thank you for your advice. We learned a lot from this article. We have rephrased our text based on knowledge acquired from the ISGPS Evidence Map of Pancreatic Surgery, as shown below. And corresponding revision was made in the revised manuscript, on Page 4.

*"This trial aims to compare the long-term safety of LPD and OPD for resectable* PDAC *treatment in a large multicentre setting and will provide evidence on performance of* PDAC *resection."*

Reference


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**VERSION 2 – REVIEW**

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|---|---|
| **REVIEWER** | Nickel, Felix<br>University of Heidelberg , General Surgery |
| **REVIEW RETURNED** | 28-Dec-2021 |

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|---|---|
| **GENERAL COMMENTS** | The authors have added relevant information and have improved the manuscript.<br><br>I have some minor remarks that should be addressed to improve readability and to improve comparability with existing and future studies: |

| | |
|---|---|
| | This sentence should be modified or deleted since it does not add any relevant information to argue that minimally invasive surgery is minimally invasive. "With rapid advances in minimally invasive technology, minimally invasive surgery is favoured by surgeons in more and more fields due to its minimal invasiveness and enhanced patient recovery". The term minimally invasive is used three times in one sentence although once should be sunfficient.<br><br>This sentence is too general and does not add to the manuscript: „However, more high-quality RCTs are needed to verify whether minimally invasive surgeries can bring the same long-term benefits for patients with tumours as open surgeries do“<br><br>The outcomes should include the following and these should be listed and appropriate references used:<br>-Major complications (Clavien Dindo 3 and/or higher)<br>-Postoperative pancreatic fistula according to ISGPS definition<br>-Postoperative bile leak according to ISGLS definition<br>-Postpancreatectomy hemorrhage according to ISGPS definition<br>-Delayed gastric emptying according to ISGPS definition<br>-Chyle leak according to ISGPS definition |

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| **REVIEWER** | Probst, Pascal<br>University of Heidelberg, Department of General, Visceral and Transplantation Surgery |
| **REVIEW RETURNED** | 12-Jan-2022 |

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|---|---|
| **GENERAL COMMENTS** | All queries are resolved. |

## VERSION 2 – AUTHOR RESPONSE

**Reviewer: 1**

***Dr. Felix Nickel, University of Heidelberg***

***Comments to the Author:***

***The authors have added relevant information and have improved the manuscript.***

***I have some minor remarks that should be addressed to improve readability and to improve comparability with existing and future studies:***

***This sentence should be modified or deleted since it does not add any relevant information to argue that minimally invasive surgery is minimally invasive. "With rapid advances in minimally invasive technology, minimally invasive surgery is favoured by surgeons in more and more fields due to its minimal invasiveness and enhanced patient recovery". The term minimally invasive is used three times in one sentence although once should be sufficient.***

**Response:** Thanks for your comment. We agree with your opinion that this sentence does not add to the manuscript after further consideration. Thus, we have deleted this sentence.

***This sentence is too general and does not add to the manuscript: "However, more high-quality RCTs are needed to verify whether minimally invasive surgeries can bring the same long-term benefits for patients with tumours as open surgeries do"***

**Response:** Thanks for your comment. We have revised the description in the revised manuscript (Page 14), as shown below.

"*The current guidelines of NCCN suggest that minimally invasive surgeries are feasible and safe for patients with hepatobiliary cancer[1], colon cancer[2], rectal cancer[3], ovarian cancer[4], cervical cancer[5], and pancreatic cancer[6], among others. Meanwhile, many of these guidelines state that their long-term safety needed to be further evaluated in more high-quality researches."*

***The outcomes should include the following and these should be listed and appropriate references used:***

***-Major complications (Clavien Dindo 3 and/or higher)***

***-Postoperative pancreatic fistula according to ISGPS definition***

***-Postoperative bile leak according to ISGLS definition***

***-Postpancreatectomy hemorrhage according to ISGPS definition***

***-Delayed gastric emptying according to ISGPS definition***

***-Chyle leak according to ISGPS definition***

**Response:** Thank you for your comments. We have listed the complications as secondary outcomes. And corresponding revision was made in the revised manuscript, on Page 7.

*"(4) complication rate (complications related to PD, including major complications with Clavien-Dindo ≥3[7], postoperative pancreatic fistula[8], postoperative bile leak[9], postpancreatectomy haemorrhage[10], delayed gastric emptying[11], and chyle leak[12], are defined according to the International Study Group of Pancreatic Surgery)"*

**Reviewer: 5**

***Dr. Pascal Probst, University of Heidelberg***

***Comments to the Author:***

***All queries are resolved.***

**Response:** Thank you for your comments.

Reference

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## VERSION 3 – REVIEW

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| **REVIEWER** | Nickel, Felix<br>University of Heidelberg , General Surgery |
| **REVIEW RETURNED** | 16-Feb-2022 |

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|---|---|
| **GENERAL COMMENTS** | The authors present the study protocol for an important project comparing laparoscopic and open pancreatoduodenectomy regarding survival for cancer patients. |