

## Peer Review File

Article information: <https://dx.doi.org/10.21037/hbsn-23-426>

### Reviewer A:

*In this manuscript, they underlined that preoperative chemotherapy allows secondary resectability of primarily unresectable patients with locally advanced pancreatic cancer without increasing perioperative mortality and morbidity. This analysis may be useful for clinical practice to treat advanced pancreatic cancer, however, the manuscript has several flaws.*

Thank you very much for your thoughtful and benevolent review. All of your remarks helped to increase the quality of the script. In the following, you will find point-by-point replies to your comments.

#### Comment 1:

*The authors mentioned all tumors were initially staged as locally advanced pancreatic ductal adenocarcinoma, classified as unresectable according to NCCN criteria at diagnosis. Given the extremely high percentage of patients who became resectable with preoperative chemotherapy, it is questionable whether all were unresectable pancreatic cancers. How did you ascertain whether the initial determination that all cases were unresectable was valid?*

#### Reply 1:

We completely agree with the reviewer that declaring a PDAC unresectable based alone on CT/MRI cannot be 100% certain. However, we performed a thin-slice contrast-enhanced dual-phased CT in all patients and an additional all-in-one MRI whenever possible. Imaging studies were then demonstrated in the interdisciplinary preoperative tumor board and decision on resectability based on NCCN and IAP criteria was made together by experienced radiologists and pancreatic surgeons with more than 20 years of experience in pancreatic imaging/surgery. A standard template was used for the radiological findings to describe vessel involvement according to the standards of NCCN and German Society of Radiology. We added this information to the methods section (please see Page 7, lines 108-110).

#### Comment 2:

*The lack of results on how preoperative treatment may or may not alter patient status, e.g., nutritional status or bone marrow suppression, seems insufficient to make claims about the safety of chemotherapy and subsequent surgery.*

Reply 2:

Yes, absolutely. Chemotherapy had certain negative effects on the patients, especially concerning their blood tests as sign of bone marrow suppression. On the other side, most patients improved their nutritional status during chemotherapy. Due to the different regimes of preoperative chemotherapy and small subgroups we intentionally did not search any correlation between type of chemotherapy and safety of applied surgery. Instead, we focused on the final results of surgery as a consistent parameter.

Comment 3:

*In Figure 3A, comparison of postoperative complications in resected and non-resected patients, is this a meaningful comparison?*

Reply 3:

Certainly not from a statistical point of view. From the patient's point of view, however, very relevant. The risk of postoperative complications is an important part of the informed consent when discussing an explorative laparotomy in patients with tumors that may be secondarily resectable. We aim for a high transparency; therefore, the presentation of results is much more meant to present an objective picture of the results in the group and actually aims at no statistical comparison between these results.

**Reviewer B:**

*The authors investigated the safety and feasibility of chemotherapy followed by surgery for initially unresectable pancreatic cancer. The resection rate was more than 60%, which is satisfactory. The mortality rate was only 1.4%, while the morbidity was comparable with the results previously reported. This is an interesting study, however, there are several problems, as shown below.*

We are grateful for your detailed and constructive criticism. All requested changes were made and certainly helped to elaborate the script. You will find a point-by-point-reply in the following:

Comment 1:

*The criteria to regard a tumor as unresectable are unclear, which had better be clarified. What was a cause of unresectability? Who did decide?*

Reply 1:

All decisions concerning resectability were based on NCCN and IAP recommendations and definitions (NCCN guideline, PubMed-ID 33845462; IAP guideline, PubMed-ID 29191513). We performed a thin-slice contrast-enhanced dual-phased CT in all patients and an additional all-in-one MRI whenever possible. Imaging studies were then demonstrated in the interdisciplinary preoperative tumor board and decision on resectability based on NCCN criteria was made together by experienced radiologists and pancreatic surgeons with more than 20 years of experience in pancreatic imaging/surgery. A standard template was used for the radiological findings to describe vessel involvement according to the standards of NCCN and German Society of Radiology. We added this information to the methods section (please see Page 7, lines 108-110).

Comment 2:

*The criteria to change a treatment to surgery from chemotherapy are also unknown, which should also be clarified.*

Reply 2:

After initiation of chemotherapy, patients underwent re-evaluation by the tumor board based on repetitive CT/MRI and tumor marker dynamics and taking into consideration the ABC resectability criteria every 3 months after initial diagnosis. Patients with significantly downsized tumors who fulfilled the NCCN criteria for resectability, as well as patients who had long chemotherapy (between 9-12 months) and at least an improvement to a borderline resectable situation, were also offered surgery, under consideration of patient's own will and options for alternative further non-surgical therapy.

Comment 3:

*The imaging response in all included patients and the pathological response in patients undergoing surgery should be shown.*

Reply 3:

This is an important remark to improve the transparency and expressiveness of the script. The information on imaging response (RECIST criteria) and regression grading (Le Scodan) is to be found in Table 6 and on Page 11, lines 184-186, 190-193 and in the following.

Imaging response to preoperative chemotherapy (RECIST):

	<u>Resected</u>	<u>Non-resected</u>
PR:	65.9% (n=56)	48.1% (n=26)
SD:	31.8% (n=27)	42.6% (n=23)
PD:	2.3% (n=2)	9.3% (n=5)

Regression grading in resected patients (Le Scodan):

Grade 1: 30.6% (n=26)  
 Grade 2: 42.4% (n=36)  
 Grade 3: 12.9% (n=11)  
 Grade 4: 10.6% (n=9)  
 unknown: 3.5% (n=3)

Comment 4:

*Did the authors perform postoperative adjuvant chemotherapy?*

Reply 4:

All patients were discussed postoperatively in the interdisciplinary tumor board and recommendations for adjuvant therapies were given. Chemotherapy was often administered in the patients' hometown, and the duration of treatment is often unknown due to excessive legal data protection in Germany. The known data is found in Table 6 and on Page 12, lines 212-214 and in the following.

	<u>Resected</u>	<u>Non-resected</u>
FOLFIRINOX	56.5% (n=48)	37.0% (n=20)
gemcitabine/nab-paclitaxel	12.9% (n=11)	11.1% (n=6)
other regimens	20.0% (n=17)	9.3% (n=5)
radiochemotherapy	-	27.8% (n=15)
none	8.2% (n=7)	11.1% (n=6)
unknown	2.4% (n=2)	3.7% (n=2)

**Reviewer C:**Comment:

*I read with interest the retrospective study of 85 patients who underwent pancreatic resection following preoperative chemotherapy for locally advanced pancreatic cancer - LAPC. The results are within expected norms, and the study does not add much novelty to global literature on the theme. Still, it does validate and endorse that existing practice to offer chemotherapy with neoadjuvant intent is reasonable in patients with LAPC. I have some comments.*

Reply:

We appreciate the positive evaluation by the reviewer. Indeed, similar data on the positive effects of neoadjuvant chemotherapy have been already published, mostly by colleagues in USA, UK and Japan. Neoadjuvant therapy, however, had ancillary role in Germany and only lately neoadjuvant concepts have been added to the German guidelines on PDAC. We believe that own data based on results in the German population may validate current practice and have positive effects on the management strategy in Germany and Europe.

Please find a point-by-point-reply to the comments in the following.

Comment 1:

*Line 50 - primary chemotherapy is confusion. We have secondary surgery, primary chemotherapy, and both add confusion. Rather use the standard term - preoperative chemotherapy.*

Reply 1:

Thank you, we have modified our highlight box as advised (please see Page 5, line 66).

Comment 2:

*Line 88 - 89 and line 244, omit the highly experienced pancreatic surgeons. This is vague with heterogenous interpretation of experienced vs highly experienced. Most units have competent or certified surgeons. Avoid superlative language.*

Reply 2:

We agree. Most literature on the topic recognizes experienced surgeons as those performing more than 50 resections per year. At our center, surgery is performed by three certified surgeons performing more than 100 resections per year and having performed more than 6,000 pancreatic surgeries in total. We fulfilled your recommendation avoiding superlative language and cited concrete numbers instead (please see Page 6, lines 95-97 and Page 13, line 248).

Comment 3:

*Line 92 - patient giving written consent. This is a retrospective study. Can you please explain the enrollment and consent process? For example, did the 2015 patient provide consent in 2015 at the time of chemotherapy to publish these results? Was this a prospective study? When was ethics approval sought? Please clear my doubts with clarity of methodology. To this add, please add in title about retrospective nature of study.*

Reply 3:

All patients with PDAC, irrespective of their individual management strategy, sign informed consent for the use of their data for current and future studies on PDAC on the Ruhr-University Bochum, Bochum, Germany. Furthermore, they sign an informed consent for using data of therapy in prospective clinical register study of the StuDoQ register of the DGAV (German Society of General and Visceral Surgery) since 2015. These two signed informed consent forms are sufficient according to both German legislation and to the Declaration of Helsinki. Nevertheless, an additional allowance for the study was given by the ethics committee of the RUB (Reg. No. 22-7610), as required for all studies done by university hospitals in Bochum.

So actually, this study is a retrospective analysis of prospectively gathered data. Patients sign the informed consent for gathering and using their data as a part of a prospective ongoing study on PDAC at the RUB cancer center (ethics committee reg. no. 20-7140-bio). Additionally, an approval of the ethics committee is required before results of partial data analysis are being published (ethics committee reg. no. 22-7610).

We added some information in the methods section as advised (please see Page 7, lines 100-105).

Comment 4:

*Line 125 use short form PDAC*

Reply 4:

We have modified the text as advised (please see Page 8, line 133).

Comment 5:

*Line 165 - how 1 d versus 1 day stay is significantly different?*

Reply 5:

The results were recalculated and found to be correct. In the group of non-resected patients, the length of stay in the hospital and in the ICU was significantly shorter. Apparently, this leads to a statistically significant difference despite two medians of 1 day each in both groups.

Comment 6:

*Line 209-210. 13 patients did not receive postop chemo due to their physical condition. How much of this physical condition was due to post operative morbidity? rather than intrinsic physical comorbidity etc.*

Reply 6:

Four patients died within 90 days after surgery. Two patients recovered too slowly after complicated postoperative courses. The other seven patients did not receive chemotherapy due to a fast progression of the PDAC (e.g. peritoneal carcinomatosis). Patients unfit for chemotherapy received Best Supportive Care.

Comment 7:

*Line 254-260 about lower average mortality rate is not an apt comparison as the LAPC cases/patients that undergo such strong/toxic preoperative chemotherapy are generally fit and healthier individuals and thus there is selection bias compared to general pancreas cancer cases. Add this in discussion.*

Reply 7:

Of course, we completely agree with the reviewer. Positive selection of fit patients with ECOG 0-1 to receive chemotherapy is the most common and well-known bias of studies on PDAC, irrespective of prospective or retrospective character. We added this important remark to the discussion (please see Page 13, lines 236-239).

Comment 8:

*Line 280 arrosion should be erosion*

Reply 8:

Thank you, please see change in Page 16, line 290.

Comment 9:

*In the discussion there is no mention about CA 19-9 role and also the CT volume calculations that you have reported in table as a response to chemotherapy.*

Reply 9:

These very important topics were also added to the discussion section (please see Page 14, lines 250 and 259-262).

Comment 10:

*It is unclear if you have included the number of reoperation patients inside the major complications patients. As reoperation is a major complication and if reported separately, than your major complication statistic is falsely low. Please check and edit this.*

Reply 10:

Reoperations are the treatment of major complications (which correspond to grade 3b or higher of the Clavien-Dindo classification) and are therefore included in the calculation.

Comment 11:

*The POPF and DGE all need grading of A B and C grades.*

Reply 11:

Thank you for this remark, a clarification was added to the results section (please see Page 10, lines 165-171).

Comment 12:

*There is no QoL data and this has to be acknowledged as a limitation*

Reply 12:

We strongly support the need for QoL analysis for PDAC patients. Our institution is therefore participating in two large multicentre prospective trials on QoL after surgery for PDAC. A significant part of the patients in this study also took part in these QoL studies, however we are not allowed to publish data on our own before the QoL studies are finished. We have acknowledged the absence of QoL data in the discussion section (please see Page 14, lines 248-249).

Comment 13:

*Many patients did not have resection. This calls to discuss the imaging modality that is used to determine resectability after the chemotherapy. If the imaging is good/accurate, can one avoid the open-close/bypass procedures? Pls comment on this. Endoscopic/Radiologic palliation is feasible and can be attractive in such LAPC patients who dont need to undergo surgery.*

Reply 13:

As already well-known, CT imaging (even if assessed by experienced surgeons/radiologists) is not very accurate in the prediction of resectability of PDAC, especially in the course of chemotherapy / radiochemotherapy. The PIs of this study published their experience based on the CONKO-007



study recently, where this issue was discussed in detail (Wittel UA, Lubgan D, Ghadimi M, Belyaev O, Uhl W, Bechstein WO, Grützmann R, Hohenberger WM, Schmid A, Jacobash L, Croner RS, Reinacher-Schick A, Hopt UT, Pirkl A, Oettle H, Fietkau R, Golcher H. Consensus in determining the resectability of locally progressed pancreatic ductal adenocarcinoma – results of the Conko-007 multicenter trial. BMC Cancer. 2019;19(1):979).

We realize that CT is not the perfect modality; however, it is the most standardized and widely available at the moment. It represents the standard modality in the primary diagnostics of PDAC, so it is normal that it is used in the consecutive re-evaluation of resectability. The dynamic changes in CA19-9 values may be used only in secretors, where it is indicative, some 85% of all cases. The role of functional imaging such as PET-CT or PET-MRI is still controversial and none of the patients in our study got that modality. Regarding the role of bypass surgery and its comparison to endoscopic/radiologic alternative palliative procedures, the evidence is still sparse. We performed our own retrospective analysis comparing more than 400 bypass surgeries with results of 250 endoscopic palliative procedures – the manuscript is still under construction, but unofficial preliminary results show some significant advantages of bypass surgery on the long term, including better patency of anastomosis on the long term as well as better QoL with less need of forced interruptions of palliative chemotherapy. Further prospective studies are needed to answer the question on the role of different palliative options; however, some ethical issues prevent such studies.

#### Comment 14:

*Do you give somatostatin analogues after PD or DP in your hospital? PMID: 31980352. If so please mention in method section and discuss their role in reducing POPF.*

#### Reply 14:

All patients receive octreotide 100 µg in the induction of anaesthesia. Octreotide is continued postoperatively in PD only in patients with soft, fragile pancreas and small duct with a high-risk PJ. All DP patients receive octreotide 3 x 100 µg per day for a week after surgery as a standard. Since January 2022, all resected patients receive hydrocortisone perioperatively for 48 hours as indicated by some recent Scandinavian studies. The role of somatostatin analogues remains unclear. We believe that it is much more important that all patients receive the same regimen perioperatively and not individually on the discretion of the surgeon. References to octreotide were added to the methods and discussion sections (please see Page 7, lines 98-99 and Page 15, lines 279-280).

Comment 15:

*How many patients had portal vein resection and recon? Any cases with arterial resection?*

Reply 15:

This data was added to the results section (please see Page 9, lines 144-145). Therefore, transparency of surgical procedures could be elaborated.

Comment 16:

*You have not recorded 90 day mortality. Please report this.*

Reply 16:

30-day mortality was 1.4% (n=2), 90-day mortality was 2.9% (n=4). We have added this information to the text (please see Page 10, line 162) and Table 1.

Comment 17:

*You have not mentioned blood transfusion details. Would be good to add if have data.*

Reply 17:

Only two patients received a transfusion of two PRBCs (packed red blood cell transfusion) each, not because of relevant blood loss, but because of low initial hemoglobin levels. This information was added to the text (please see Page 9, lines 145-148).

Comment 18:

*ICU readmission is reported and is confusing as ICU admission is not reported. So all patients were postop admitted to ICU? Do have have something in between general ward and ICU - like high dependency unit? Many units routinely admit whipples to high dependency unit and not ICU. Please shed clarity on the care delivery at your hospital.*

Reply 18:

All patients with PD and TP are admitted postoperatively to the ICU – standard SOP at our institution. DP and bypass procedures usually spend a night postoperatively at the Intermediate Care Ward, which is our equivalent of high dependency unit. Of course, some cases with DP and bypass procedures may be admitted as an exception to the ICU if intraoperative problems occur.

Comment 19:

*Drain removal policy? please mention if any specific perioperative care plan is modified in patients who have preop chemo?*

Reply 19:

Drain fluid quantity is measured daily. Amylase, lipase, and bilirubin are measured at day 3 and day 7 after surgery. Triglycerides are only measured if a chyle leak is suspected. If laboratory values are within the normal range and quantity of fluid decreases, drains are removed on day 7. In cases of POPF, drains are first pulled several inches out every 48 hours and removed later considering clinical and laboratory or also imaging findings.

Comment 20:

*When was the postop chemo started? How soon after surgery?*

Reply 20:

Postoperative chemotherapy was normally started after complete recovery of the patient, but not later than the 12<sup>th</sup> week postoperatively. Usually, this means 2-3 weeks of postoperative hospital stay and directly after it 3 more weeks in the rehabilitation facility – therefore, most of the patients started postoperative chemotherapy about 6-8 weeks after surgery. An explanation is now included in the text (please see Page 12, line 213-214).

**Reviewer D:**Comment:

*This manuscript attempts to describe what the authors say is the “real world results” and therefore have included all patients undergoing an attempt at resection of locally advanced PDAC after neoadjuvant chemotherapy. The primary endpoint is comparison of postoperative morbidity and mortality in patients who were operated but resected or not resected. In order to assess the impact of preoperative chemotherapy on perioperative complications the appropriate comparison would be between patients undergoing pancreatic resection with and without preoperative chemotherapy. Although the well-informed pancreatic surgeon will recognize that the complication rates in this cohort of patients is in the expected range for non-pretreated patients, the comparison group used does not allow the stated conclusions. I recommend eliminating the current control group and identify a cohort of patients that are untreated with chemotherapy as the control group. Propensity score matching would yield the best comparison group.*

Reply:

Dear Reviewer, thank you very much for your constructive criticism and your great ideas how to improve the quality of the script. You will find replies to all comments in the following.

We agree that a comparison group consisting of patients undergoing upfront surgery may be adequate to better illustrate the surgical results of the study. We published plenty of papers with detailed analysis of our patients with upfront surgery in previous reports and these did not differ substantially from literature data by other institutions and multicentre reports. These citations are based on our own data on upfront surgery for PDAC as well as on data of the German national registry for pancreatic surgery and fully correspond to cited data in the manuscript:

- Fahlbusch T, Luu AM, Höhn P, Klinger C, Werner J, Keck T, Friess H, Köninger J, Kraus T, Alsfasser G, Padberg W, Ritz JP, Uhl W, Belyaev O. Impact of pylorus preservation on delayed gastric emptying after pancreaticoduodenectomy – analysis of 5.000 patients based on the German StuDoQ/Pancreas-Registry. *Gland Surg* 2022; 11(1): 67-76.
- Pyras C, Lukas C, Janot-Matuschek M, Herzog T, Tannapfel A, Uhl W, Belyaev O. Preservation of aberrant right hepatic arteries does not affect safety and oncological radicality of pancreaticoduodenectomy – own results and a systematic review of the literature. *Hepatobiliary Surg Nutr* 2022; 11(1): 25-37.
- Fahlbusch T, Höhn P, Klinger C, Werner J, Keck T, Friess H, Köninger J, Kraus T, Alsfasser G, Padberg W, Ritz JP, Uhl W, Belyaev O. Risk factor identification for delayed gastric emptying after distal pancreatectomy – an evaluation of 1.688 patients based on the German StuDoQ/Pancreas-Registry. *J Clin Med* 2022; 11(19): 5539.

- Luu AM, Braumann C, Belyaev O, Janot-Matuschek M, Rudolf H, Praktknjo M, Uhl W. Long-term survival after pancreaticoduodenectomy in patients with ductal adenocarcinoma of the pancreatic head. *Hepatobiliary Pancreat Dis Int* 2021; 20(3): 271-278.
- Luu AM, Olchanetski B, Herzog T, Tannapfel A, Uhl W, Belyaev O. Is primary total pancreatectomy in patients with high-risk pancreatic remnant justified and preferable to pancreaticoduodenectomy? – a matched-pairs analysis of 200 patients. *Gland Surgery* 2021; 10(2): 618-628.
- Luu AM\*, Belyaev O\*, Höhn P, Praktknjo M, Uhl W, Braumann C. Late recurrences of pancreatic cancer in patients with long-term survival after pancreaticoduodenectomy. *J Gastrointestinal Oncology* 2021; 12(2): 474-483.
- Luu AM, Krasemann L, Fahlbusch T, Belyaev O, Janot-Matuschek M, Uhl W, Braumann C. Facing the surgeon's nightmare: incidence and management of postoperative pancreatic fistulas grade C after pancreaticoduodenectomy based on the updated definition of the international study group (ISGPS). *J Hepatobiliary Pancreat Sci* 2020; 27(4):171-181.

That is why we believe that adding a control group of patients with upfront surgery would make the study more boring and complex without adding relevant information to the reader. At the same time, we felt obliged to include the results of non-resected patients in order to present these “real world data” and to show the “other side of the coin”.

Comment 1:

*Define the institutional definition of locally advanced pancreatic adenocarcinoma and what the process is to arrive at that determination. Ideally there would have been a secondary radiology review before including a case in this study*

Reply 1:

There is no institutional definition of LAPC – we used the NCCN and IAP criteria during the tumor board (NCCN guideline, PubMed-ID 33845462; IAP guideline, PubMed-ID 29191513). Nevertheless, for the aim of the study, all cases underwent secondary radiology review, as recommended by the reviewer.

Comment 2:

*I understand the goal of trying to get a real-world assessment of preoperative chemotherapy impact, however the 9 patients treated with gemcitabine alone and radiation with capecitabine are really outlier treatments and I suggest eliminating those cases.*

Reply 2:

We cannot eliminate them because we reported all cases of surgery after chemotherapy as defined per study protocol – this would be a protocol violation and would not represent the real-life situation, i.e. preoperative therapy is sometimes individually adapted and does not always follow the guidelines.

Comment 3:

*It is stated that 90% of tumors shrank with preoperative chemotherapy. That is an extremely high number. Please elaborate and clarify this statement with regard to the smaller partial response rate.*

Reply 3:

Thank you very much for this important remark, this concerns surely needed clarification. All tumors were measured before and after preoperative chemotherapy. At least a small shrinkage was measured in 90.6% of cases. Partial response (PR) is defined as at least a 30% decrease in the sum of diameters of target lesions in longest axis measurement (RECIST revised, Eur Radiol, 2010 Jun;20(6):1456-67, doi: 10.1007/s00330-009-1685-y). This could be achieved in 59.0% of patients. According to your valuable remark, an explanation was added to the script to clarify this circumstance (please see Page 11, lines 185-187).

Comment 4:

*I suggest eliminating the term “secondarily” resected and use the more commonly used phrase of resected after preoperative chemotherapy or after neoadjuvant chemotherapy*

Reply 4:

We eliminated the term secondary/secondarily in the text. Please see changes in lines 36, 45/46, 58/59, 61/62, 66, 189/190 and 321.