

## Peer Review File

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### Reviewer A

This is a retrospective study from a tertiary high volume HPB center in Finland on evolution of pancreatic resections over a 20-year period. 512 patients went through surgery and no patients were lost to follow-up. Congratulations on this and on the admirable results.

I do however have a few questions/requests for this work:

Comment 1: What surgical approach was used for whipples procedures? -artery first? -uncinate first? And did this change over time?

Reply 1: Thank you for the question. Our formal approach has been the classic Whipple procedure for a very long time, 2000-2014. After introduction of the BRPC concept and neoadjuvant therapy in our hospital in 2015, we have switched into using the posterior, uncinate or mesenteric (artery first) approaches to SMA for BRPC patients with suspected arterial affsion. The arterial approach is chosen depending on the location and extent of the tumor. This is practical, in order to determine resectability as early as possible.

Changes in text: We have added description of the evolved approach in BRPC patients to the surgical technique -section, page 5, lines 1-5.

*“After initiating operations for borderline resectable pancreatic cancer (BRPC) patients, vascular resections were increasingly performed. In cases involving portomesenteric vein resections, the reconstructions were performed according to the size of the venous defect with venorrhaphy, patching, end-to-end -anastomosis or by using an interposition graft (22). In cases where SMA involvement was suspected, a selected “artery first” -approach (23) was applied.”*

Comment 2: How many explorative laparotomies were performed (non-resectability found during surgery) and did this change over time?

Reply 2: Thank you for bringing up this interesting question. The assumption would be a significant reduction in the number of explorative laparotomies during the study period. However, to reliably determine the number of attempted resections from all the operations performed under the variable procedure codes for explorative laparotomy/ laparoscopy, cholecystectomy/ hepaticojejunostomy/ gastrojejunostomy is nearly impossible from the operational programs used in our center. It would require investigating individually each procedure with any of the forementioned procedure codes during the years 2000-2020. From a tertiary center, this number of procedures cannot, unfortunately, be reviewed in a reasonable time.

Changes in text: -

Comment 3: Were all resections done as open procedures or were laparoscopic and robotic resections included?

Reply 3: Thank you for the important notion. All PDs were done as open procedures, but during the last 12 years, laparoscopic distal resections have been increasingly performed. Robotic technology is not yet used by our HPB section, but training for robotic distal pancreatectomies, and liver resections is planned to launch soon.

Changes in text: We added information regarding the use of laparoscopy to the technique section, page 5, lines 8-10, and Table 1.

*“...in most cases performed using a stapler. Laparoscopic distal pancreatectomy was introduced in 2009 at our center, and mainly chosen in cases with premalignant indications or small, contained malignancies.”*

Comment 4. How many surgeons performed pancreatic surgery during this period? -did this change over time? -and how were young/new HPB-surgeons educated?

Reply 4: Altogether six (6) surgeons have performed pancreatic surgery in our center during this 20 -year period, usually 3 surgeons at any given time, and no relevant changes have occurred in this respect. Young HPB surgeons have been trained in pancreatic surgery only on demand. A relatively long period of observing and performing simpler procedures is first required, next assisting in HPB surgery, and finally performing, distal pancreatectomy and either the reconstruction or the resection phase in PD. Currently, we are able to perform all pancreatic resections with two specialized HPB surgeons. The learning curve in PD is especially long and when dealing with locally advanced disease, the procedures are only performed by the most experienced surgeons. In general, we feel teamwork is useful in all surgical practice, and especially in complication management.

Changes in text: -

5. What resectability-criterias were used, and did these change over time?

Reply 5: Thank you for the insight. For determining the treatment policy for each patient, we have applied the ESMO guidelines and after 2015 the NCCN guidelines. The change in guideline selection was due to NCCN adopting the BRPC concept and neoadjuvant therapy recommendation much sooner. There has obviously been a significant change in the resectability criteria over time. Conventionally, before 2010, it was not considered to operate

on PDAC when the tumor deformed the PV-SVM axis or if tumor growth extended to the arteries. When the BRPC concept started to gain ground internationally, we were long hesitant in our center. Neoadjuvant therapy for BRPC was introduced in 2015 here at Oulu University Hospital and only after that, according to the NCCN BRPC resectability criteria, the actual portomesenteric reconstructions and arterial procedures have been included to our common practice.

Changes in text: -

6. In table 2 it looks like you did pancreatic resections 4 patients with M1 disease. What was the indication for this?

Reply 6: Thank you for a very relevant question. We reinvestigated the patient data for the M1 patients thoroughly, and it was found that two patients with M1 disease were actually operated on, others were erroneous recordings. The first patient with M1 disease had an unclear mass in the right upper pulmonary lobe. This mass was biopsied preoperatively, and the result was suspicion of adenocarcinoma. The mass disappeared on CT imaging after per oral cortisone treatment and was mistakenly interpreted as being inflammatory. After distal pancreatectomy, the final PAD confirmed the identical histology for the pancreatic tumor and the biopsy material, and thus M1 tumor was unfortunately operated. The second M1 patient had an intraoperative frozen section taken from liver during PD. This was replied as a benign lesion during surgery, but in the final pathologist's report the liver lesion was confirmed as a metastasis of pancreatic adenocarcinoma. We have now corrected the Table 2 accordingly.

Changes in text: Please see the corrected Table 2.

## **Reviewer B**

A retrospective single institution evaluation of pancreatic surgery. Provides historical perspective on outcomes over time

Comments to the authors:

The submitted manuscript reports the clinical outcomes of pancreatic surgery over 20 years at a single institution. As such, it provides a perspective on the evolution of the operation as the center dramatically increased surgical volumes. The following comments are offered:

Comment 1: As a centralized referral center providing surgery only, they admit incomplete data on the use of adjuvant therapy. Why doesn't this also apply to longer term surgical followup such as 90 day mortality, or delayed complications?

Reply 1: Statistics Finland's Cause-of-Death Registry provides the complete mortality data in Finland. The reporting of death, including the cause of death, is mandatory in all Finnish health care units. Thus, our 90day mortality data is indeed valid. The unreported, delayed

complications after 90days are possible, but highly unlikely. Generally, the reports covering short-term results of pancreatic surgery do not include out-hospital complications after 90days, due to difficulties in retrieving information on delayed complications. Some guidelines have been necessary to standardize reporting, and 90day mortality with in-hospital complications are the international recommendation – 90day mortality has been shown to cover most surgery related deaths compared to other definitions (30-day or in-hospital mortality) (Talsma et al, Ann Surg 2014). Death of a patient is however always recorded in Finland at any time from surgery. Adjuvant therapy data is incomplete, as due to centralization, chemotherapy is in many cases administered at different units (secondary hospitals), than the surgical treatment (tertiary center). However, our center does also provide adjuvant therapy, but not to all Northern Finnish patients, due to long distances. The patient data systems are variable across Finland and there is no electronic communication between data systems. Thus, the adjuvant therapy data cannot be retrospectively collected, at least not with reasonable efforts.

Changes in text: -

Comment 2: Others have noted an increase in survival over time, due to both improved perioperative outcomes, increased utilization of adjuvant therapy, and improved efficacy of adjuvant therapy. While the increased T3 numbers may mitigate some of this, a multivariable analysis could be a better methodology to evaluate survival over time.

Reply 2: Thank you for the comment. We aim here to explain our reasoning for the statistical choices:

Only 23, 35, and 48 PDAC patients were operated during periods 2000-2005, 2006-2010, and 2011-2015, respectively. Complete 3-year follow-up was available only for 26 patients in the last period, and complete 1-year follow-up for 75 patients. With these values, lack of statistical power for investigating prognosis over time is evident. Based on awareness of the small PDAC numbers in the early time periods of our data, it was *a priori* decided not to conduct a Cox regression analysis. However, to address the reviewers' concerns as thoroughly as possible, we performed a univariate and multivariable analyses for the PDAC cohort. In multivariate analysis, following co-variables were used: Model A was adjusted for age (continuous), sex (male or female), RCS (0, 1 or  $\geq 2$ , excluding pancreatic cancer), preoperative ca19-9 level (continuous), pathological tumour stage (1, 2, 3 and 4), grade of differentiation (1, 2, and 3), neoadjuvant therapy (no or yes), and time period of surgery (2000-2005, 2006-2010, 2011-2015, and 2016-2020). Model B was adjusted for age (continuous), sex (male or female), RCS (0, 1 or  $\geq 2$ , excluding pancreatic cancer), preoperative ca19-9 level (continuous), tumor size (mm, continuous), N-stage (0, 1 and 2), grade of differentiation (1, 2 and 3), neoadjuvant therapy (no or yes), and time period of surgery (2000-2005, 2006-2010, 2011-2015, and 2016-2020). For missing data, multiple imputation was conducted.

Adjustment with adjuvant treatment in multivariable models produces a so-called immortal-time bias, i.e., adjusting for factors that happened after the beginning of the follow-up. (Levesque et al, BMJ 2010). Only patients who have recovered adequately from the operation,

or survived the initial postoperative phase, are able to start the planned adjuvant chemotherapy. Adjustment with adjuvant treatment would therefore eventually lead to biased mitigation of differences in the long-term survival.

Due to our arguments above, and lack of events (only 1), we would prefer to present the 1- and 3-year mortality results of the multivariable analysis in this response letter only.

Hazard ratios (HR) with 95% confidence intervals (CI) after surgery for pancreatic ductal adenocarcinoma (PDAC) stratified by time period of pancreatic cancer surgery

	2016-2020	2011-2015	2006-2010	2000-2005
	HR (95%CI)	HR (95%CI)	HR (95%CI)	HR (95%CI)
<b>1-year mortality</b>				
Crude	1 (reference)	0.98 (0.31 – 3.10)	1.43 (0.59– 3.48)	1.22 (0.53 – 2.83)
Adjusted <sup>a</sup>	1 (reference)	0.84 (0.20 – 3.55)	1.64 (0.62 – 4.30)	1.44 (0.57 – 3.61)
<b>3-year mortality</b>				
Crude	1 (reference)	0.99 (0.50 – 1.96)	0.74 (0.58 – 2.18)	0.98 (0.55 – 1.86)
Adjusted <sup>a</sup>	1 (reference)	0.98 (0.45 – 2.13)	1.19 (0.58 – 2.43)	1.20 (0.60 – 2.39)

Changes in text: We modified the Statistics-section, accordingly, please see page 6, lines 21-24 and page 7, lines 1-14.

*“...Cox’s regression model was used to analyze the relative risks of mortality, and to obtain hazard ratios (HR) with 95% confidence intervals (CI) for 30-day, 90-day, 1-year and 3-year survival, by using three models. In the crude model no adjustment was performed. Model a was adjusted for potential confounding factors: Age (continuous), sex (male or female), RCS (0, 1 or  $\geq 2$ , excluding pancreatic cancer), preoperative ca19-9 level (continuous), pathological tumour stage (1, 2, 3 and 4), grade of differentiation (1, 2 and 3), neoadjuvant therapy (no or yes), and time period of surgery (2000-2005, 2006-2010, 2011-2015, and 2016-2020). Model b was adjusted for age (continuous), sex (male or female), RCS (0, 1 or  $\geq 2$ , excluding pancreatic cancer), preoperative ca19-9 level (continuous), tumor size (mm, continuous), N-stage (0, 1 and 2), grade of differentiation (1, 2 and 3), neoadjuvant therapy (no or yes), and time period of surgery (2000-2005, 2006-2010, 2011-2015 and 2016-2020). For the analysis of 3-year survival last time periods (2016-2020) contain only year 2016 due to complete 3-year follow up and for 1-year survival*

*years 2016 – 2018. Up to 20% (48/240) of the patient data were incomplete on tumor size, T- and N-stage, grade of differentiation, or ca19-9. Thus, both complete case analysis and multiple imputation were conducted. All confounding variables categorized as above, and all-cause mortality, were included as imputation variables. The number of imputed datasets was twenty (20). The fully conditional specification was used under the assumption, that the data were missing at random. ...”*

And Results-section, please see page 6, lines 19-21.

*“In crude or adjusted multivariate models with multiple imputations, no improvement in 3-year, 1-year, 90-day, and 30-day prognosis were found (data not shown).”*

Comment 3: The authors report 30 day readmission rate as 7.8% and 90 day readmission as 3.3 %. This reviewer suspects the authors mean an additional 3.3% readmissions occurred between 30 and 90 days, but the correct number would be 11.1% at 90 days since that is a cumulative number. Perhaps the same is true for complications and mortality, as a 1.2% mortality rate is extremely low (though see also comment #1 above).

Reply 3: Thank you very much for your careful review. After completing the data with enucleations (as asked by the Reviewer B), we came across several patients, that were incorrectly excluded from the cohort. The cohort was eventually supplemented with 49 patients. After the revision of the new data, the 30d readmission rate is 7.8% and 90d readmission rate is 11.3%. In the text, we originally made the very mistake you noted. Both the Table 3, and the text have now been revised accordingly.

The 90d mortality (1,2% = 6 patients) was originally the correct cumulative 90d mortality, but after revision of the data, two more patients who suffered a post-operative complication leading to death were included. Thus, the correct number for 90d mortality is 8 (1,4%) patients.

Changes in text: We have made corrections also to the text accordingly, pages 9, lines 7-10.

*“...Readmission rate was 7.8% within 30 days and 11.3% within 90 days. 30-day and 90-day mortality rates were 1.0% and 1.4%, respectively. The complication profile of all pancreatectomies and the benchmarking reference rates are presented in Table 3. ...”*

Comment 4: The increase over time in reoperation is quite surprising as most Interventional Radiology has dramatically decreased reoperation in most high-volume centers. The authors should explain why this trend was observed, as well as reasons for the reoperations.

Reply 4: Thank you for the justified question. We have speculated the reasons for the trend in the Discussion, page 12, lines 21-25 and page 13, lines 1-11. It may be worth adding, that while internationally an invasive approach (i.e. completion pancreatectomy) has been used widely for septic pancreatic fistulas, especially before emergence of interventional radiology, we have never performed a completion pancreatectomy in our center so far – although relaparotomies have been made with this intention. Thus, it seems, that while the international trend has shifted to a more conservative approach, this has always been the prevailing fistula management regime in our center. Also, what might confuse the reader, is the division of the reoperations into “under general anesthesia” and “in local anesthesia”, which we have now deleted. Majority of the post operative endoscopies (for anastomotic bleed or to manage or investigate DGE), were performed under general anesthesia. The actual relaparotomy rate was 8.8%, subcutaneous wound revisions were performed in 3.4% of the cases, and endoscopy rate was 4.6%. The most common reasons for relaparotomy were fascial dehiscence (16/50), followed by leakage of any of the anastomoses (11/50), post pancreatectomy hemorrhage (9/50), and colonic ischemia (6/50). Singular relaparotomies were also performed for various reasons, such as a stricture of GJ anastomose, occlusion caused by an adhesion, persisting chyle leak, and a surgical drape accidentally left into the abdomen.

Changes in text: We have added information regarding the reasons for reoperations to the results and discussion sections, pages 12-13, lines 21-25 and 1-11.

*Results: “... Total amount of reoperations was 95/566 (16,8%), including 50 (8.8%) relaparotomies, 19 (3,4%) superficial wound revisions, and 26 (4,6%) endoscopic procedures. The most common indications for relaparotomy were fascial dehiscence (16/50), followed by leakage of any of the anastomoses (11/50), post pancreatectomy hemorrhage (9/50), and colonic ischemia (6/50). Postoperative, interventional radiology was required in 12.9% of cases. Endovascular techniques or percutaneous biliary procedures were employed in 1.4% cases, and image-guided drainage or needle aspiration in 11.5% cases. Readmission rate was 7.8% within 30 days...”*

*Discussion: “...Increment in reoperation rate may also indicate a prompter approach to addressing complications, supported by the corresponding decrease in 90-day mortality. The highly conservative approach to septic fistula complications in our center probably also influences the observed trend in reoperations– no completion pancreatectomies have been performed during the 20-year study period. Instead, the most common indication for relaparotomy was fascial dehiscence, which may reflect the poorer performance status of the patients in the later time periods...”*



Comment 5: The authors did not observe some time-related trends that have been reported by others. This includes not just morbidity and mortality, but also length of stay. This is surprising as well as the center moved into a high-volume center, with multiple studies demonstrating improvement on all of these outcomes as volumes increase.

Reply 5: Thank you for the feedback. We did report on other time-related trends as well, such as improving the resection rate, and lymph node yield during the study period (Figure 4). However, the length of stay seems to be the Achilles' heel in our center. In 2020, we launched the ERAS program for pancreatic surgery, and we are currently collecting data to evaluate its effects. Shortening the length of stay is presently one of our main goals, also because of the poor health care economy prospects in Finland, and worldwide.

Changes in text: -

Comment 6: Did the use of neo-adjuvant therapy and adjuvant therapy change over time? Others have reported that as volume and perioperative outcomes improve, so will the use of adjuvant therapy, and thus survival outcomes.

Reply 6: Thank you for raising this topic. Changes in the use of adjuvant and neoadjuvant therapies are outlined in the Results section, page 11, lines 7-10. We agree that better perioperative results enable better access to adjuvant therapy, and thus long-term survival. Please also see the Reply 2 to Comment 2 for the newly added multivariable model exploring the factors affecting survival and further discussion on the long-term outcomes.

### **Reviewer C**

In this article, Nortunen et al. summarize their single center experience with pancreas resections from 2000-2020. A total of 512 patients were included of which 67 % underwent Whipple procedure, 28% distal pancreatectomy, and 5% total pancreatectomy. The time period was divided into quartiles and trends in patient characteristics as well as outcomes were analyzed over time.

I want to congratulate the authors for what they have accomplished at Oulu University Hospital. By regionalizing the care for pancreatic cancer they have build a robust pancreas cancer center.

Unfortunately, I believe that the impact of this manuscript is limited and does not significantly add to the existing body of literature.

Below a few specific questions and concerns:

1. What was your trend in the operative time over the years? You grouped all resections together which I think is not appropriate since a Whipple procedure usually takes much longer than a distal pancreatectomy. It would be helpful for the readers to have operative times separate for Whipple procedure and distal pancreatectomy and the trends over time.

Reply 1: Thank you for this notion. We have now reported the operative time according to the procedure in Table 1. The time trends were originally only depicted in the figures, and not tables. For clearer presentation of our results, we would prefer not to draw an additional single figure for time trends in duration of surgeries. Thus, the time trend in duration of surgeries is now stated in Time trends and Discussion sections as follows (page 10, lines 18-17, and page 13, lines 9-10):

Changes in text:

*“Mean duration of surgery was stable 6:50 hours in 2000-2015 but grew substantially to 8:11 hours in 2016-2020.”*

*“Longer duration of surgeries in the last time periods is similarly most likely due to more advanced procedures.”*

2. What percentage of patients underwent minimally invasive resection especially in the cohort of distal pancreatectomies?

Reply 2: Thank you for the relevant point. Please see the reply for Reviewer A Comment 3.

3. Five patients are listed to have undergone resection for stage IV pancreatic cancer (table 2). Please explain who those patients are? Does your center have a study protocol for patients with metastatic PDAC?

Reply 3: Thank you, a justified question. Please see the Reply 6 for Reviewer A. We have only very recently entered a prospective multicenter SCANPAN-1 trial for oligometastatic or recurrent PDAC (NCT05271110), but these patients are not included in the current data reaching only 2020.

4. In the discussion the authors state that the cohort is complete, and no patient was lost to follow-up. This is only true for the short-term data since the data about adjuvant chemotherapy is very incomplete.

Reply 4: Thank you for the correction. We have modified the text accordingly, Discussion page 11, line 22. Please also see the explanation for missing adjuvant data in our Reply 3 to Reviewer B, Comment 3.

Changes in text:

*“The strength of our study is in the detailed data collection in a single-institution -setting. The cohort is complete with respect to short-term results, and survival follow-up.”*

5. When analyzing the complications, the authors calculated the rate of complications for the entire cohort (n=512). This however is incorrect. For example, the biliary fistula rate is reported as 3.3%. The 30% of patients with distal pancreatectomy are included in this calculation but the rate of biliary fistula for this cohort should be 0% and therefore should be excluded. The actual biliary fistula rate for the Whipple and total pancreatectomy patients is 4.6%. The same mistake was made for the rate of DGE, which is not a classic complication after distal pancreatectomy.

Reply 5: Thank you for the diligent review, your observation on the biliary leaks is correct. We have corrected both Table 3, and the text accordingly. DGE is however a known complication for distal pancreatectomy as well (Fahlbush et.al, J Clin Med. 2022; Glowka et.al, Langenbecks Arch Surg, 2016), although the mechanisms remain unclear, especially when no fistula is present. Thus, the DGE rate is still reported for the entire cohort.

We have modified Table 3 and the Results section page 8-9, and lines 23-1.

Changes to text:

*“Grade A-C bile leakages were seen in 4.0% cases after PD or TP.”*

6. The reoperation and reintervention data described in the results section don't match the data in Table 3. Please double check and revise as needed.

Reply 6: Thank you for the comment. The data is correct but misleadingly presented in the sense that in the results section we refer to the time trends of reoperations and interventions, while Table 3 describes the complications in the entire cohort. We attempted to improve the graphic representation by modifying the Figure 3 to better demonstrate the trends in complication management. Figure 3 now presents time trends in relaparotomies, endoscopic procedures and procedures performed by interventional radiologists. We have also edited the text in the Results -section to better describe the reoperations and radiological interventions. Please see the Reply 4 for Reviewer B for detailed answer.

Low impact manuscript with some flaws in data analysis where whipple and distal pancreatectomy patients were inappropriately grouped.

## **Reviewer D**

### **General**

The manuscript presents a Northern European single centre retrospective analysis on pancreatic resections over two decades, its evolution in light of centralisation and reporting of short and long term outcome trends.

The effort of reporting and publishing such valuable results with the STROCSS guideline is certainly commendable and must be encouraged.

The question/aim of the paper is however twofolds, contemporarily analysing access to service and short term outcome of all pancreatic surgery, and the long term of PDAC patients. While the former necessarily conditions the latter, it is hard to study both topics at the same time, as the latter is markedly influenced by several different and external factors which are well beyond surgery.

I would suggest keeping the focus of the paper on the single centre cohort presentation, of course including the PDAC outcome, however not putting the issue at the centre of the study, as the observation here has insufficient data to relate the clinical practice to the outcome.

Comment 1: Especially in the first parts of the manuscript the written English is often slightly unclear to me, and possibly not medical-scientific enough. It requires in my view major revision and documented English motherlanguage professional medical writer review.

Reply 1: Thank you for reporting this flaw. We have now had the manuscript thoroughly revised by a professional, English mother-language editor, and all the language-related issues Reviewer D raises here and in further comments, have been carefully addressed.

Title

Comment 2: The title does some justice to the paper, however does not include the background hypothesis of centralisation of referrals and surgery (which improves outcomes in pancreatic surgery if quality is also ensured).

Reply 2: Thank you for the assessment regarding the title. Our revised suggestion:

### **Evolution of pancreatic surgery over time and effects of centralization -a single-center retrospective cohort study**

Abstract

Comment 3: The meaning of the sentence “prognosis of resectable PDAC has also shown minor improvement” is not clear to me: is it meaning that there is actual improvement or that such improvement is still “minor”? Please clarify. Analogously, the abstract shows in my views several minor flaws in the English language.

Reply 3: Please see the Reply 1.

Comment 4: "...of all-cause pancreatic surgery". This expression is not medical (i.e. indication, diagnosis, condition etc.) and is probably wrong, as we understand from the text that this does not include for example enucleations, surgery for acute or chronic pancreatitis.

Reply 4: Please see the Reply 1. However, the term "all-cause pancreatic" surgery, is correct, since the cohort does include surgery for acute and chronic pancreatitis, trauma, and now after the revision, also enucleations.

Comment 5: I cannot find The Type of study design here (STROCSS 2021 2b)

Reply 5: Thank you for the comment, the type of study is outlined in the title, please see the STROCSS checklist also.

Comment 6: I am not sure that "Time quartiles" is appropriate as this rather is a division in four periods of time, irrespective of the distribution of events (surgeries) in the "quartile" periods. Please ensure this is technically correct and consider this still sounds unusual to me.

Reply 6: Thank you for your concern, we have replaced the term "quartile" with "period".

Changes in text: *"quartile"* changed into *"period"* throughout the text.

Comment 7: How about Neo-adjuvant therapy, was that recorded?

Reply 7: Thank you for the question. The recording of neoadjuvant therapy is now mentioned in the abstract, line 10.

Changes to text:

*"...and administration rates of neo-, and/or adjuvant therapy of PDAC patients were analyzed."*

Comment 8: The term "receipt" related to adjuvant therapy is rather unusual. Additionally, does it refer to completion of chemotherapy?

Reply 8: Thank you for this point. receipt. Information regarding the adjuvant therapy (incl. how many cycles, any dose reductions, early ceasing) cannot be retrospectively retrieved from secondary hospitals' patient registries. Receipt here refers to having any adjuvant therapy, but we have modified the phrasing throughout the text. Please also see the Reply 1 to Reviewer B.

Comment 9: Results should mention the total number of cases, age and gender distribution, main diagnosis, type of surgery. The series presentation should be consistent and tidy for all four periods (as this is the main investigated variable), even if short.

Reply 9: Thank you for the comment, we agree with your view. We have added the demographic description to the abstract, lines 11-14.

Changes to text:

*“A total of 566 pancreatectomies were performed during the study period: 369 (67%) pancreatoduodenectomies (PDs), 130 (28%) open left pancreatectomies (LPs), 45 laparoscopic LPs, 26 (5%) total pancreatectomies (TPs), and six (1.1%) enucleations. Median age of patients was 63 (57-71) years, and 50% (283) of patients were men.”*

Comment 10: Did “all” (not medical attribute) complication rates really remain at constant “low” levels? Is not reoperation rate a type of complication? This is a broad definition of severity which is determinant in the Dindo-Clavien classification.

Reply 10: Thank you for the clarification. We have corrected the phrasing in the Abstract, line 16 accordingly.

Changes to text:

*“...frequently operated on in later time periods. Complication rates remained at constant low levels...”*

Comment 11: Despite the short-term (assuming short means 30 days) mortality values are low, such values need definition (at least type of operations, time threshold etc.)

Reply 11: Thank you for an excellent point. We have now added 90-day mortality for clarification of short-term mortality to Abstract, line 18.

Changes in text:

*“Short-term (90-day) mortality after pancreatectomy decreased from 3.1% to 0.45%, while 5-year survival...”*

Comment 12: 5year survival (supposedly for PDAC) is presented in no-decimal figures (usually present), with an increase from 17% to 20%, in line with the largest series recently published. That would be a positive result, however that would require distinction (i.e. stage, neo- or adjuvant chemotherapy).

Reply 12: Thank you for the assessment. We have now added decimals. Applying the multivariate model in this setting is not recommendable in our view, please see Reply 2 for Reviewer B.

Comment 13: I could understand that the “resection rate” figures refer to incidence (is that correct?) only down in the manuscript read. Such proportion with the epidemiological figures should be made clearer as it refers to centralisation of referral and otherwise might imply resection rete at time of laparotomy. Is that figure compared to the national incidence?

Reply 13: Thank you for this question. Resection rate here is calculated by using data on all the diagnosed PDAC cases in our catchment area, retrieved from the Finnish Cancer Registry. The resection rate obviously reflects the centralization, but it is noteworthy that the most prominent rise in resection rate was gained between the last two time periods, while centralization took place between the second and third time period. This phenomenon is mainly caused by the expanded resection criteria (incl. neoadjuvant therapy) and stronger inclination to operate elderly and less fit patients. We have modified the phrasing in Abstract, lines 20-21, to better describe the definition of resection rate.

Changes in text:

*” Resection rate of diagnosed PDAC cases, as reported by the Finnish Cancer Registry (FCR) for the catchment area, increased from 3.2% ...”*

Comment 14: In the conclusion there is mention of significance of the increase in number of procedures (even if a value of significance is not provided), and a defined a 5year overall survival improvement from 17% to 20%, suggesting a surprising (“even with..”) non obvious correlation with the Centre volume. Such absence of relation might be due to several factors, such as type and completion of chemotherapy and quality of care, usually unrelated to the early complication rates or the main centre, as chemotherapy can be performed in district hospitals.

Reply 14: Thank you for the comment. We have replaced the misused word “significant” with “substantial” in Abstract, line 22. “even with...” is still in the remaining phrasing to emphasize the clinical significance of non-significant survival figures.

Changes in text:

*“Conclusions: The hospital volume of pancreatectomies has increased substantially, while complications and postoperative mortality have remained at acceptable levels. Long-term survival of PDAC patients has improved over two decades to 21.4%, and a nearly doubled resection rate to 14.9%.”*

## Introduction

Comment 15: The wording is sometimes not fluent, the use of articles incorrect.

Reply 15: Thank you for the fair assessment, please see the Reply 1.

Comment 16: The aim of the study is not entirely clear to me, I.e. whether it is a general case-series presentation or the study of a specific question, with the hypothesis that quality enhancement with centralization might reflect both short and long term results.

Reply 16: Thank you for the relevant question and we apologize for the confusing presentation of aims. The primary aim of the study is to present the case-series of our center and the secondary aim is to describe the effect of time-related developments – such as centralization - to quality of pancreatic surgery.

Changes to text: -

## Methods

Comment 17: Why were the enucleations excluded? They are part of the “all-cause” pancreatic surgery and carry the risk of pancreatic leaks. It is not easy at this stage for the reader to understand whether this is a pancreatic surgeries or a pancreatic resections series.

Reply 17: Thank you for this opinion. We agree enucleations should after all be included and we have retrieved the enucleation data from years 2000-2020. This data is now included in the series. The search for the enucleations data was very useful, since it revealed several (6 enucleations + 43 other) other pancreatectomies, that were originally falsely excluded from the cohort. Thus, the cohort now includes 566 pancreatectomies and corresponding changes have been made to text and Tables 1- 3.

Changes in text: Numeral changes throughout the text. Enucleations first presented in Results page 7, lines 22-24 and page 8, line 1.

*“The cohort included 369 (67%) pancreatoduodenectomies (PDs), 130 (28%) open left pancreatectomies (LPs), 45 laparoscopic left pancreatectomies, 26 (5%) total pancreatectomies (TPs), and six (1.1%) enucleations.”*

Comment 18: Were PDAC incidences collected from the Finnish Cancer Registry?

Reply 18: Thank you for the question. Yes, please see the Data collection -section.



Changes in text: -

Comment 19: The use of the benchmark model should be utilised carefully, as it refers only to benchmark cases (i.e. low comorbidity and no vascular/borderline surgery), hence the comparison should be made only benchmark-to-benchmark.

Comment 19: Thank you for the comment. We agree on the definition and purpose of the benchmark modelling. However, our aim was to present the quality of our centers' performance, and the benchmark model serves well as a well-known reference system to quality surgery. Here it is used to emphasize that even when including high risk cases, our center performs on a high-quality level.

Changes in text: -

Comment 20: There is no survival prediction uni-multivariate analysis, make sure this is not required to answer the study aim/question/hypothesis (usually this is required to search for predictors of survival)

Reply 20: Please see the answers to Comment 2 for Reviewer B and Comment 12 for yourself.

Comment 21: The wording is sometimes not fluent, the use of articles incorrect.

Reply 21: Please see the Reply 1.

## Results

Comment 22: Standard presentation usually includes gender distribution at first, along with age of patients.

Reply 22: Thank you for the suggestion. We have modified the Results section, accordingly, please see page 7, lines 21.

Changes in text:

*“Median age of patients was 63 (57-71) years, and 50% (283) of patients were men. “*

Comment 23: PDAC diagnosis presented in 48% of cases, and follow up information was available only in 141 (57%) of cases, of which 102 had referral to adjuvant chemotherapy (but how often was it completed?). Unfortunately data is not enough to draw any conclusion.

Reply 24: Thank you for the comment. We have explained reasons for the incomplete

adjuvant data in Reply 1 to Reviewer B.

Comment 24: Neoadjuvant chemotherapy was administered to 28 patients: to what total population such figure is given at 11%?

Reply 24: Thank you for the careful review. There is a mistake with 11%. Only 2 (4%) patients received neoadjuvant therapy during 2011-2015, while 26/130 (20%) PDAC patients were administered neoadjuvant therapy during the last time period. Please see Results, page 11, lines 14-15.

Changes in text:

*“Neoadjuvant therapy was administered to only 4% (2) of PDAC patients in 2011-2015, but to 20% (26) in 2016-2020.”*

Comment 25: In the short term outcome paragraph, I would suggest mentioning causes of endovascular (i.e. bleed) or percutaneous (i.e. collections, PTBD). 30-day and 90-day mortality rates were 1.0% and 1.2%, respectively. These are very positive results to be complimented, however the latter is particularly low, compared to the former, as usually 90day doubles 30day mortality. Please can you confirm and comment.

Reply 25: Thank you for the comment. We have now modified the Results section to include the endovascular and percutaneous procedures separately. The 90d mortality is indeed correct, please see the detailed Reply 1 to Reviewer B.

Changes in text: Please see Reply to Reviewer B.

Comment 26: Re “resection rate” please see comment in the abstract section.

Reply 26: Please the Reply 13.

Discussion

Comment 27: The discussion is dense of up-to-date considerations and allows the reader to better understand the work done, following the STROCSS scheme. I would however again submit the text to mother language professional medical writing review to allow a more scientific and fluent wording.

Reply 27: Please see the Reply 1.

Comment 28: Re “resection rate” please see comment in the abstract section.

Reply 28: Please see the Reply 13.

## Conclusion

Comment 29: As a baseline, the results you present are excellent. I would however suggest stating the key figures rather than only commenting, and possibly express even stronger statements (possible from your data) that centralisation has improved access to care, standard of care by evidence based guidelines, curative surgery and complications.

Reply 29: Thank you for the feedback. We have modified the conclusion by presenting the key figures. Conclusion page 15, lines 8-11.

Changes in text:

*“Despite the extension of operative indications to more advanced disease, more complex surgeries, and patients with poorer performance status, the overall 5-year survival of PDAC patients has improved to 21.4% over the study period, with a simultaneous rise in the resection rate from 3.2 to 14.9%.”*

Comment 30: Does the “overall 5-year survival in the cohort” refer to PDAC only?

Reply: Thank you for the question. The overall 5-y survival refers to PDAC only. We have also excluded the pancreatic adenocarcinomas originating from cystic neoplasms, since their prognosis is better. Thus, we have only included the true, non-cystic, duct originated PDAC.

Changes in text: Please see the previous Reply 29.

Comment 31: Again, if the “resection rate” refers to the national incidence this should be specified.

Reply 31: Thank you for your thorough review and many excellent comments. Please see the Reply 13.