A Multi Centre, Randomised, Double Blinded, Clinical Trial Comparing Cattell-Warren and Blumgart Anastomoses Following Partial Pancreato-duodenectomy: PANasta Trial.

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**Conflicts of Interest**

CMH has grants from Cancer Research UK, Pancreatic Cancer UK, National Institute of Health Research, The Royal College of Surgeons, and the Royal Liverpool University Hospital. JPN has grants from Stiftung Deutsche Krebshilfe, Heidelberger Stiftung Chirurgie and the Dietmar Hopp Stiftung. PG has grants from Cancer Research UK.

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**Contributors**

*CMH, JPN and PG conceived and designed the trial. CMH, PG, RJ, and KP supervised trial conduct, participated in data analysis and interpretation, and prepared and wrote the report. KP managed the trial and contributed to writing of the manuscript. CMH, JPN, SR, DG, DOR, AS, AP, BD and PG participated in patient recruitment and trial conduct. KP was responsible for onsite monitoring. RJ and EP participated in trial design, data analysis, and data interpretation. TMP provided independent critical review of the data and drafts. All authors have proof-read the final manuscript.*

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*Objective:*Whether a Blumgart anastomosis (BA) is superior toCattell-Warren anastomosis (CWA) in terms of post-operative pancreatic fistula (POPF) following pancreato-duodenectomy**.**

*Importance:*Complications driven by POPF following pancreatic cancer resection may hinder adjuvant therapy, shortening survival. BA may reduce complications compared to CWA, improving use of adjuvant therapy and prolonging survival.

*Methods:*A multicentre double-blind, controlled trial of patients undergoing resection for suspected pancreatic head cancer, randomized during surgery to a BA or CWA, stratified by pancreatic consistency and duct diameter. The primary end point was POPF, and secondary outcome measures were adjuvant therapy use, specified surgical complications, quality of life, and survival from the date of randomisation. For a 10% POPF reduction 416 patients were required, 208 per arm (two-sided α=0·05; power=80%).

*Results***:** Z-score at planned interim analysis was 0.474 so recruitment was held to 238 patients; 236 patients were analysed (112 BA and 124 CWA). No significant differences in POPF were observed between BA and CWA, odds ratio (95% CI) 1·04 (0·58, 1·88, p=0·887, nor in serious adverse events. Adjuvant therapy was delivered to 98 (62%) of 159 eligible patients with any malignancy; statistically unrelated to arm or post-operative complications. 12-month overall survival, hazard ratio (95% CI), did not differ between anastomoses; BA 0·787 (0·713, 0·868) and CWA 0·854 (0·792, 0·921), p=0·266 nor for the 58 patients with complications, median (IQR), 0.83 (0.74, 0.91) compared to 101 patients without complications 0.82 (0.76, 0.89) (p=0.977).

*Conclusions:*PANasta represents the most robust analysis of Blumgart versus Cattell-Warren anastomoses to date.

**Mini Abstract** word count (Microsoft word) 50/50

Post Operative Pancreatic Fistulae were not dissimilar between Blumgart and Cattell-Warren anastomoses. Although POPF drive post-operative complications they do not affect the rate of adjuvant treatment administration nor affect overall patient survival. As efficacy is similar between BA and CWA the choice of anastomosis can be left to surgical discretion.

**INTRODUCTION.**

Pancreatic ductal adenocarcinoma (PDAC) is a major surgical and oncological challenge 1–3 with only 20% of patients presenting with localised disease and without metastases undergoing surgical resection. 1The 5-year survival rates increase from an estimated 8% with surgery alone to 30-50% with adjuvant combination cytotoxic regimens. 4–6There is some evidence to support the use of preoperative neoadjuvant therapy in locally advanced disease 1,7 aiming to improve resectabilty and/or overall survival rates. 8–11However, the proportion of patients who overcome surgical complications well enough in the first instance to commence adjuvant therapy is uncertain. 5,6,12,13

The driver of serious post-operative complications following pancreatic head resection is post-operative pancreatic fistula (POPF) arising from failure of the pancreatic remnant anastomosis. 14,15 Most POPF are harmless biochemical rises (type A). However, CR-POPF (type B or C) change clinical care and may, initiate systemic complications and can lead to death. 13,16,17

The International Study group of Pancreatic Surgery (ISGPS) recommends the use of a pancreato-jejunostomy18, following pancreato-duodenectomy. This is typified by the Cattell and Warren anastomosis (CWA) with an inner pancreatic duct to jejunum mucosal anastomosis, and a second outer layer between the anterior and posterior cut edges of the pancreatic remnant to the seromuscular layer of the jejunum. 19 This type of reconstruction is associated with a high-rate of CR-POPF, in the region of 23%, when undertaken in patients with a soft pancreatic texture and a main pancreatic duct maximum diameter ≤ 3mm. 20 An alternative pancreato-jejunal reconstruction is the Blumgart anastomosis (BA) which also involves a similar inner duct-to-mucosa anastomosis, but the outer layer is a full-thickness jejunal wrap-around of the pancreatic stump. 21 Non-randomized comparative studies suggest the BA substantially reduces the rate of CR-POPF compared to the CWA. 22–24 The PANasta trial was designed to be the first multi-centre, masked randomised trial to compare these two anastomotic techniques with the rate of POPF (any grade) as the primary outcome measure and key secondary outcome measures included other specified post-pancreatectomy complications, the proportion of patients commencing adjuvant therapy, and overall survival from the date of randomisation prior to resection.

**METHODS.**

This blinded multicentre two-arm randomised controlled trial was conducted at seven UK specialist pancreas centres, coordinated from the Cancer Research UK (CRUK) Liverpool Cancer Trials Unit (LCTU).

*Patient Selection.*

Patients with suspected peri-pancreatic head malignancy underwent standard evaluation 25 before local Multi-Disciplinary Team (MDT) discussion. Histological diagnosis of malignancy before surgery, was not necessary, provided that the MDT outcome was to proceed with pancreas head resection26–29. Patients were eligible if they were due to undergo an elective pancreato-duodenectomy for presumed malignancy, understood the nature or consequences of the trial, were able to provide written informed consent, and be aged 18 years or older. Patients were excluded if they were due to undergo extended partial pancreato-duodenectomy; left, central or total pancreatectomy; arterial resection or multi-visceral resection, previous pancreatic resection, surgery for known chronic pancreatitis, recruitment to any other pancreatic resection trial; women of childbearing potential or were unable or unwilling to use adequate contraception from time of consent up to the day of surgery (this latter point was stipulated under the terms of the sponsor, the University of Liverpool, and regulatory requirements of the Liverpool Clinical Trials Unit). Patients who had undergone neo-adjuvant chemotherapy with or without radiotherapy, were excluded as manifestations of POPF in such a case, would be more likely related to that of systemic treatments rather than the anastomosis construction itself.

*Randomisation and Blinding.*

Eligible patients were randomised using a 1:1 allocation ratio using randomly permuted blocks including pancreatic texture (soft versus hard), pancreatic duct diameter (≤ 3mm versus >3mm), and research site as stratification factors. Randomisation was undertaken intra-operatively by the operating surgeon, following pancreatic head excision and before reconstruction, via a bespoke password-controlled web-based tool called the Treatment Allocation Randomisation System (TARDIS), allocations were time-stamped. Patients and site staff were blinded to the treatment allocation, with the surgeon stating in the operation notes “pancreatic anastomosis was constructed according to trial protocol”.

*Procedures.*

The index procedure was pancreato-duodenectomy undertaken either as pylorus-preserving partial pancreato-duodenectomy (PPPD) or a Kausch-Whipple partial pancreato-duodenectomy with distal partial gastrectomy (KW-PD), dependent upon the clinical requirements. A single jejunal limb was brought up to the pancreas for the pancreatic anastomosis, either a Cattell and Warren anastomosis (CWA) or a Blumgart anastomosis (BA), as detailed in *Halloran et al* 25 The same jejunal loop was then used to anastomose the bile duct and either the first part of the duodenum or gastric remnant stomach. The placement of an internal pancreatic duct stent across the duct-mucosal anastomosis was mandatory for all patients. Surgical drains were positioned in proximity to the pancreatic, biliary, and gastric anastomoses. 100 μg of octreotide was administered subcutaneously on the evening before surgery and 100 μg three times a day subcutaneously on the day of surgery (day 0) and on post-operative days 1 to 6 to all patients.

*Standardization and Quality Assessment.*

The standardization of the operative techniques was ensured by using modified methods developed with the MRC ConDuCT-II Trials Methodology Hub (Supplementary Material A and B) 25,30,31 Notably:

1. Consensus meetings –All centre leads agreed the essentials of each anastomosis and the likely key steps, the postoperative management of drains, pancreatic duct stents, the use of octreotide and the timing of operative photographs. This information was developed into an operative manual.
2. Operative manual – A finalized operative manual for each anastomosis contained steps that were (a) mandatory to the construction of a safe anastomosis; (b) prohibited for the construction of a safe anastomosis, and (c) flexible steps where the operating surgeon can choose a method.
3. Operative photographs – digital operative photographs detailing procedures in a step-by-step method and showing the mandated photographic documentation of the three elements of reconstruction: adequate pancreatic neck mobilisation, insertion of the parenchymal sutures, and in detail the sutures to the main pancreatic duct prior to tying, and finially of the completed anastomosis. Photographs were centrally reviewed to assess quality of the procedure and ensure consistency. Immediately following the end of surgery, the pictures were uploaded to a secure portal area of the Trial (Supplementary Material A and C). Photographs for each case were examined by two reviewers (CMH, and DG) to determine the nature and quality of the procedure. In cases where there was no agreement a third reviewer (DAO) was involved to reach a consensus. All reviewers were blinded to the patient allocation.

*Follow-up.*

Each patient had six trial visits: An enrolment visit, a visit on the day of surgery, and follow-up visits to assess outcomes on the day of discharge, and at 3, 6, and 12 months after surgery. The detailed schedule is provided in the protocol (Supplementary Material B).

*Outcomes.*

The primary outcome POPF (any grade). 14 Secondary outcome measures were administration of adjuvant therapy or entry into clinical trials of adjuvant therapy; operation time; delayed gastric emptying; rates of wound infection, pulmonary infection, post-operative fluid collection, intra and post-operative bleeding, re-operation and venous thrombo-embolism; hospital stay; generic quality of life (EQ5D) and the European Organization for Research and Treatment of Cancer (EORTC) cancer specific questionnaire (QLQ-C30); health economic assessments; and survival from the date of randomisation until death by any cause. Patients underwent adjuvant chemotherapy if eligible: Strong indication had PDAC; 4,6 relative indication ampullary adenocarcinoma, 27 intra-pancreatic bile duct adenocarcinoma, 28 or periampullary duodenal adenocarcinoma. 29 Specific complications and severity were defined by those of the ISGPS and the Dindo and Clavien classification for all other major complications. 14,16–18,32,33 All adverse and serious adverse events (SAEs) were recorded from the time of surgery up until commencement of adjuvant chemotherapy. Expected events for the trial were exempt from SAE reporting unless they were classified as life- threatening or resulted in death namely grades 4 and 5. Trial follow-up ceased 12 months following randomisation. Updated protocol to version 6.0 on 22 March 2016.

*Statistical Analysis.*

Sample Size:POPF was measured as a binary outcome assuming a rate of 20% in the CWA standard treatment arm and an assumed decrease down to 10% or less in the BA test arm. 15, 19, 21 Using a two-sided α level of 0·05 and a power of 80%, 416 patients were required with 208 per arm. The sample size was estimated inclusive of a single interim analysis when 50% of the final information was available. Sample sizes were inflated to account for both non-compliance estimated at 15%, and a 3% loss-to-follow-up, equating to a final sample size of 506 patients with 253 per arm. Stopping rules for the interim analysis were based on the standardised Z-score based on an O’Brien Fleming 34 2 stage design using the SAS PROC SEQDESIGN version 9.3. The study would stop for futility if the Z score was in the interval -0·698 to 0·698 and would stop for efficacy if the Z score was outside the interval -2·736 to 2·736.

Analysis Method: Continuous data are summarised as median (IQR) and categorical data are summarised as frequencies of counts with associated percentages with tests across treatment or other patients sub-groups performed using Wilcox test for continuous covariates and fisher test/Chi-square test for categorical data. Analysis is performed on an intention to treat (ITT) retaining all patients in their randomised groups irrespective of any protocol deviations. No adjustment for missing data was planned and analyses were performed on a complete case basis. A p-value of 0.05 was used to determine statistical significance with estimated effects presented alongside 95% confidence intervals. Efficacy of the primary outcome was measured using an odds ratio and the comparison of fistula between treatment groups was performed using a stratified Cochran-Mantel-Haenszel test. Comparisons of all binary secondary endpoints followed the same methodology. The time to start of adjuvant therapy was analysed as a time-to-event endpoint, estimates obtained through the Kaplan Meier 35 approach and comparisons between groups performed using a log-rank test. 36 Continuous secondary outcomes were measured between groups using mean differences and compared using a t-test. The accuracy of a Fistula Rate Score (FRS) 37 was tested using calculation of area under the receiver operating curve (AUC). 38

**RESULTS.**

The first patent was enrolled on 15th May 2015. Following the planned interim analysis of the first 208 evaluable patients, a Z-score comparing the two treatment groups of 0.474 was observed. Both the Independent Data and Safety Monitoring Committee and the Trial Steering Committee recommended closure and the last patient was recruited on 7 August 2017. Following the minimum follow-up for all recruited patients, a data lock was implemented on 1 March 2019 and the final analyses were performed.

*Patient demographics.*

238 patients who were successfully randomised at operation, (Figure 1). Two patients who had been randomised were removed from the study analysis in line with the ITT definition specified in the protocol, leaving 124 were allocated to undergo a CWA and 112 were allocated to undergo a BA. The baseline of these and other patient demographics by randomised allocation are shown in Supplementary Table 1. Histology revealed a malignant lesion in 194 (82·5%) of 235 patients (missing value for one patient allocated to the CWA group), and a non-malignant lesion in the remaining 41 (17·5%) patients.

*Post-operative pancreatic fistulae and complications.*

Post-operatively 60 (25%) patients developed a pancreatic fistula (any POPF), in 28 (25%) of 112 patients following a BA, and in 32 (26%) of 124 patients following a CWA. 33 (14%) were type A POPFs, 22 (9%) were type B, and five (2%) were type C with no significant differences between allocated groups (Supplementary Table 2). Any POPF occurred in 13 (10%) out of 134 patients with a hard pancreas compared to 47 (46%) out of 102 patients with a soft or normal pancreas (odds ratio = 0·13, 95% CI = 0·06, 0·26; *p*<0.001). Clinically relevant fistulae, types B and C (CR-POPF) occurred in six (4%) out of 134 patients with a hard pancreas compared to 16 (16%) out of 102 patients with a soft or normal pancreas (odds ratio = 0·25, 95% CI = 0·08,0·72; *p*=0·253). Any POPF occurred in 47 (32%) out of 147 patients with a main pancreatic diameter ≤3mm compared to 13 (15%) out of 89 patients with a main pancreatic diameter >3mm (odds ratio =2·74, 95% CI = 1·34, 5·92; *p*=0·03). CR-POPF occurred in 19 (13%) out of 147 patients with a main pancreatic diameter ≤3mm compared to two (2%) out of 89 patients a main pancreatic diameter >3mm (odds ratio =6·42, 95% CI = 1·49, 58·17; *p*=0·004), Supplementary Table 2. There were no significant differences between the allocated groups with regards to operation time, length of hospital stay nor with regards to any of the other specified post-operative complications .

Post-operative complications associated with the presence of any POPF and CR-POPF are shown in Table 1. Patients with any POPF when compared to patients with no POPF were more likely to have delayed gastric emptying (29 (48%) of 60 versus 45 (26%) of 174 patients; p=0·002), larger fistula volumes (median volume (IQR) m1 = 2526 (1418, 13128) versus 111 (40, 343); *p*<0·001) and a prolonged hospital stay (median (IQR) days = 16 (11, 28) versus 12 (9, 17); *p*<0·001). Both fistula volume and prolonged hospital stay were also associated with higher grades of fistula, (Table 1). The FRS based on pancreatic texture, main pancreatic duct diameter, and body mass index when applied to the whole data set had an AUC (95% CI), of 0·61 (0·53, 0·68) for any POPF and 0·54 (0·44, 1·64) for CR-POPF (Supplementary Material A).

*Quality and Safety.*

No concerns regarding the technical quality of the anastomosis construction were revealed. However, six (2·5%) anastomoses, were identified that differed from the randomised allocation but were retained on an ITT basis: four patients randomised to CWA, underwent BA, and in two patients randomised to BA, underwent a CWA instead.

There were 39 SAEs reported in 31 (13%) of the 236 patients (Supplementary Table 3). There were 21 SAEs observed from 16 (13%) of 124 patients undergoing a CWA and 18 events from 15 (13%) of 112 patients undergoing a BA. There were 10 grade V SAEs, leading to surgically related deaths in seven patients (3%), one further patient developed liver metastases on restaging prior to adjuvant chemotherapy.

*Adjuvant Treatment and survival.*

Overall survival by randomisation arm showed no statistically significant differences between the BA and CWA groups, with a hazard ratio of 0·72 (95% CI = 0·40, 1.31; *p*=0·266) (Supplementary Table 2 and Figure 2a). There were 174 patients randomised who could potentially be considered for adjuvant therapy, including those with a definite indication, PDAC (75), and those with relative indications cholangiocarcinoma (50), ampullary adenocarcinoma (40), and duodenal adenocarcinoma (9) (Table 2). There were 15 patients with missing data leaving 159 patients; adjuvant therapy was delivered to 98 (62%) and in those with PDAC this was 51 (78%) out of 65 patients (Table 2). Overall survival by adjuvant therapy for these 159 patients demonstrated a hazard ratio of 0·51 (95% CI = 0·24, 1·10; *p*=0·176) in favour of those that had adjuvant therapy (Figure 2b). There was no difference in overall survival by the development or absence of post-operative complications (Table 3 and Figure 2c).

In patients specifically with PDAC, complications did not affect the rate of adjuvant treatment given; 29 (73%) of 40 patients with complications compared with 22 (65%) of 35 patients without complications. Those without complications who had adjuvant therapy survival might be more compared to those who did not have adjuvant therapy, survival was not significantly different between those who had adjuvant therapy and no adjuvant therapy if complications occurred (Table 2). Overall, there were no significant associations between survival, complications, and adjuvant therapy in the 159 eligible patients for adjuvant therapy (Table 3). There were no statistically significant differences, between the groups, in terms of quality of life using either the EQ5D or EORTC-QCQ30 instruments (Supplementary Material A).

**DISCUSSION.**

No significant difference between the two types of pancreatic anastomosis in terms of the primary endpoint, post-operative pancreatic fistula, were shown. The overall rate of any POPF was 28 (25%) for the Blumgart anastomosis group and 32 (26%) for Cattell-Warren anastomosis group, whilst clinically relevant POPF (types B and C) occurred in 13 (12%) and 14 (11%) patients respectively, which compares favourably with other series. 14,15,20,39 The clinically relevant POPF rate in this series was 27 (11·4%) of 236 cases which is similar when compared to 752 (13·6%) of 5533 cases collected by the Pancreatic Fistula Study Group. 20 There were also no significant differences between the two types of anastomoses with respect to other specific complications. Moreover, PANasta is consistent with International Study Groups in terms of all POPF and CR-POPF occurrence in soft glands and narrow (<3mm) pancreatic ducts 20 The importance of POPF as the initiator of other post-operative complications was demonstrated by the significant association between any POPF and delayed gastric emptying, and any POPF or clinically relevant POPF with POPF volume, and prolonged post-operative hospital stay. Post-operative haemorrhage was recorded as 18% overall; 21% in BA vs. 15% in CWA (mean difference (95% CI) 0·66 (0·34-1·29)), p=0.225. There were six type B haemorrhages (BA=4 and CWA=2) and one further patient in the CWA arm who had a type C haemorrhage associated with a type C POPF and died. We could not show predictability of the FRS, when applied to the current series. The systematic employment of the two POPF mitigation procedures (internal pancreatic duct stent and octreotide) may account for this. PANasta recruitment coincided with that of ESPAC-5 (both CRUK funded), therefore a decision was taken that the straight to surgery group in ESPAC-5 could enrol into PANasta, but those undergoing systemic neo-adjuvant treatment would not, primarily to maintain ESPAC-5 recruitment. Another important consideration was that the healing properties of reconstructed pancreata following either neo-adjuvant chemotherapy and or radiotherapy will be completely different. Thus, the assessment of POPF in such cases cannot be purely attributed to the anastomosis technique.

Attention to standardization, (non-neoadjuvant treatment, pancreatic duct stents and octreotide use) means that bias is minimised, when measuring the primary end point of POPF, and as a consequence it should be possible to compare the two different anastomoses without confounders. Of the 235 patients randomised with known histology 194 (82·5%) had malignancy and 41 (17·5%) had a benign histology, including 15 (6%) patients with intraductal papillary mucinous neoplasm (IPMN) at risk of developing invasive cancer in whom surgery was recommended. The remaining 26 (11%) patients had suspicious lesions, but were found to be benign on histology, which is in line with documented series26.

To place this study in context, before PANasta; meta-analysis (Supplementary Material A) of available evidence (n=975) 22–24,39–41 with 40/489 (8%) CR-POPF for BA and 80/486 (16·5%) for CWA shows superiority for BA (relative risk [RR] 0·49, 95% CI 0·26 to 0·94). Only one of these studies, Hirono et al 39, is a randomized study, but is single centre, un masked and has fewer malignant cases. It reports a CR-POPF rate of 6·8% in the CWA arm and 10·3% in the BA arm, which is consistent with PANasta. Further meta-analysis restricted to randomized evidence, PANasta and Hirono 39 (n=446) with 24/219 (11%) CR-POPF for BA and 21/227 (9%) for CWA confirms no advantage (relative risk [RR] 1·19, 95% CI 0·68 to 2·08).

The main driver of our trial was the attempt to demonstrate that by reducing post-operative complications the proportion of patients with malignancy eligible for adjuvant therapy could be increased and thereby an increase in overall survival. The start point for survival was based on randomisation at the time of surgery with no statistically significant evidence that post-operative complications impacted on the delivery of adjuvant therapy, nor on overall survival. The 78% of patients with PDAC that received adjuvant chemotherapy, compares to the 77% reported by the American College of Surgeons study. 13 ESPAC-1, -3 and -4 adjuvant trials also show no significant association between post-operative complications on overall survival, although in these

 trials the start point for survival was based on randomisation at 2-12 weeks after surgery. 5,6,12 However, it is suggested in patients with PDAC who had complications, overall survival was decreased.

*Limitations.*

The multiple malignant pathologies and their distinct prognoses with follow-up restricted to 12-months following randomization, limits the generalizability of the long-term survival analysis presented here. Although, all patients that were discharged with a POPF or a POPF driven complication had completely resolved by month three of follow up, it is unclear whether these initial complications had an effect on longer term survival after 12-months. This is particularly pertinent in those with a malignant diagnosis. Survival of these patients must also be taken in context with 15 patients (8·5%) having missing data on adjuvant chemotherapy.

**Conclusions.** The Blumgart anastomosis technique did not contribute to a reduction in complications compared to the Cattell-Warren anastomosis and there was no statistical association between the development of complications and the delivery of adjuvant therapy as well as overall survival.

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**Data Sharing**

Data are available upon reasonable request. Individual participant data that underlie the results reported in this article, after deidentification (text, tables, figures, and appendices) will be available 9 - 36 months following article publication to investigators whose proposed use of the data has been approved by an independent review committee (“learned intermediary”) identified for this purpose, for individual participant data meta-analysis. Proposals may be submitted up to 36 months following article publication. After 36 months the data will be available in our University's data warehouse but without investigator support other than deposited metadata.

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**Legends**

**Supplementary Table 1. Patient demographics, surgical and pathology findings**

aMalignant other: BA arm; solid pseudo-papillary tumour (n=1), colloid carcinoma + biliary intraductal papillary mucinous neoplasm (n=1), metastatic colorectal cancer (n=1), metastatic renal cell carcinoma (n=1), and pancreatic neuroendocrine tumour + ampullary adenoma (n=1). CWA arm; adenosquamous carcinoma (n=3), pancreatic neuroendocrine tumour (n=2), solid pseudo-papillary tumour (n=1), gastric adenocarcinoma (n=1), and colloid carcinoma + mixed intraductal papillary mucinous neoplasm (n=1).

**b**1 duodenal adenoma with endocrine microadenoma.

cBA group; necrotising granulomatous pancreatitis (1) and Xanthogranulomatous pancreatitis (1). CWA group;

autoimmune pancreatitis (2).

dNon-malignant other: BA arm; biliary intraductal papillary mucinous neoplasm (n=1), Brunner’s gland hyperplasia (n=1), choledochal cyst(n=1), inflammation (n=1), borderline intraductal papillary mucinous neoplasm (n=1), lymphoepithelial cyst (n=1) and lipomatosis (n=1). CWA arm; intra-ampullary papillary-tubular neoplasm (n=1), duodenal leiomyoma (n=1) and ampullary ulcer (n=1).

**Supplementary Table 2: Post-operative outcomes**

aUnless otherwise specified·

**b**DGE by POPF type· Severity A vs No Fistula1·86 (0·857, 4·05), p=0·116· Severity B/C vs No Fistula 4·17 (1·801, 9·652), p<0·001·

cEligible here refers to patients with PDAC, Cholangiocarcinoma, Ampullary Adenocarcinoma, and Neuroendocrine Carcinoma· Please note that 6 patients outside of this group also received adjuvant therapy (Table 2)

Deaths by Tumour type:

* BA: PDAC (n=10); Ampullary (n=3); Cholangiocarcinoma (n=9); Neuroendocrine Carcinoma (n=1); Other-Malignant (n=1)
* CWA: PDAC (n=7); Ampullary (n=6); Cholangiocarcinoma (n=4); Neuroendocrine Carcinoma (n=1); Other-Malignant (n=1); Other, non-malignant (n=1)

**Table 1· Association between post-operative pancreatic fistula and other postoperative complications.**

Abbreviations. POPF = post-operative pancreatic fistula, CR-POPF = clinically relevant post-operative pancreatic fistula, IQR = interquartile range.

**Table 2. Adjuvant therapy in relation to complications and survival.**

Abbreviations: PDAC = Pancreatic Ductal Adenocarcinoma, BA=Blumgart Anastomosis, CWA=Cattell-Warren Anastomosis, Unobt=unobtainable and inf=infinity.

a1 patient does not have complications data (1 Other patient who had no adjuvant therapy).

**Table 3. The association between survival, complications, and adjuvant therapy**

Abbreviations: OR = Odds rate, HR = Hazard rate, POPF = post-operative pancreatic fistula, CR-POPF = clinically relevant post-operative pancreatic fistula.

**Supplementary Table 3. Serious adverse events.**

aFive grade V events caused death in five patients in the Blumgart arm: Hospital acquired pneumonia (1 event), Respiratory Failure (1 event), Upper Gastrointestinal Bleed (1 event), Ischaemic Small Bowel (1 event) and Post-Operative bleed secondary to Type C POPF (1 event).

bFive events were causative or present at death in three patients in the Cattell-Warrant arm. 1 patient developed liver metastases (1 event). 1 patient developed a Type C POPF, underwent a relaparotomy and then subsequently died (2 events). 1 patient developed both a Type C POPF and a hepato-jejunostomy stricture causing wound dehiscence and liver abscesses, both ongoing at death (2 events).

**Figure 1. Consort diagram**

**Figure 2. Survival**

2a. Overall survival by arm.

2b. Overall survival by adjuvant treatment.

2c. Overall survival by complications.