Randomized Controlled Trial

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A Multicenter, Randomized, Double-Blinded, Clinical Trial Comparing Cattell-Warren and Blumgart Anastomoses Following Partial Pancreatoduodenectomy

PANasta Trial

Christopher M. Halloran, MD,*,† John P. Neoptolemos, MD,‡ Richard Jackson, PhD,* Kellie Platt, MSc* Eftychia-Eirini Psarelli, MSc* Srikanth Reddy, PhD,§ Dhanwant Gomez, MD,‖ Derek A. O'Reilly, PhD,¶,# Andrew Smith, MD,** Thomas M. Pausch, MD,‡ Andreas Prachalias, MD,†† Brian Davidson, MD,‡‡§§ and Paula Ghaneh, MD*,†

Objective: Whether a Blumgart anastomosis (BA) is superior to Cattell-Warren anastomosis (CWA) in terms of postoperative pancreatic fistula (POPF) following pancreatoduodenectomy.

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

Methods: A multicenter 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 randomization. For a 10% POPF reduction, 416 patients were required, 208 per arm (two-sided $\alpha = 0{\cdot}05$; power = 80%).

Results: Z-score at planned interim analysis was 0.474 so recruitment was held to 238 patients; 236 patients were analyzed (112 BA and 124 CWA). No significant differences in POPF were observed between BA and CWA, odds ratio (95% confidence interval [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 postoperative complications. Twelve-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 BA versus CWA to date.

Keywords: pancreatico-jejunostomy, blumgart anastomosis, cattell-warren anastomosis, post operative pancreatic fistula, complications, survival, pancreatic adenocarcinoma

INTRODUCTION

Pancreatic ductal adenocarcinoma (PDAC) is a major surgical and oncological challenge[1–3] with only 20% of patients presenting with localized disease and without metastases undergoing surgical resection.[1] The 5-year survival rates increase from an estimated 8% with surgery alone to 30%–50% with adjuvant

*From the *University of Liverpool, Liverpool, UK; †Liverpool University Hospitals Foundation Trust, Liverpool, UK; ‡University of Heidelberg, Heidelberg, Germany; §Oxford University Hospitals, Oxford, UK; ‖Queens Medical Centre, Nottingham, UK; ¶Manchester Royal Infirmary, Manchester, UK; #Beijing United Family Hospital and Clinics, Beijing, China; **St James's University Hospital, Leeds, UK; ††Kings College Hospital, London, UK; ‡‡University College London, UK; and §§Royal Free Hospital, London, UK.*

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Data are available upon reasonable request. Individual participant data that underlie the results reported in this article, after de-identification (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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Reprints: Christopher M. Halloran, MD, Institute of Systems, Molecular & Integrative Biology, Department of Molecular & Clinical Cancer Medicine, University of Liverpool, 2nd Floor Sherrington Building, Ashton Street, LiverpoolL69 3GE, UK. E-mail: halloran@liverpool.ac.uk.

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combination cytotoxic regimens.[4–6] There is some evidence to support the use of preoperative neo-adjuvant therapy in locally advanced disease[1,7] aiming to improve resectabilty and/or overall survival rates.[8–11] However, 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 postoperative complications following pancreatic head resection is postoperative 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) changes 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 pancreatojejunostomy,[18] following pancreatoduodenectomy. This is typified by the Cattell-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 ≤3 mm.[20] An alternative pancreatojejunal 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] Nonrandomized 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 multicenter, masked randomized trial to compare these 2 anastomotic techniques with the rate of POPF (any grade) as the primary outcome measures and key secondary outcome measures included other specified postpancreatectomy complications, the proportion of patients commencing adjuvant therapy, and overall survival from the date of randomization before resection.

METHODS

This blinded multicenter two-arm randomized controlled trial was conducted at 7 UK specialist pancreas centers, coordinated from the Cancer Research UK (CRUK) Liverpool Cancer Trials Unit.

Patient Selection

Patients with suspected peri-pancreatic head malignancy underwent standard evaluation[25] before local multidisciplinary team (MDT) discussion. Histological diagnosis of malignancy before surgery, was not necessary, provided that the MDT outcome was to proceed with pancreas head resection.[26–29] Patients were eligible if they were due to undergo an elective pancreatoduodenectomy 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 pancreatoduodenectomy; left, central, or total pancreatectomy; arterial resection or multivisceral 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 the 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.

Randomization and Blinding

Eligible patients were randomized using a 1:1 allocation ratio using randomly permuted blocks including pancreatic texture (soft vs hard), pancreatic duct diameter (≤3 vs >3 mm), and research site as stratification factors. Randomization was undertaken intraoperatively by the operating surgeon, following pancreatic head excision and before reconstruction, via a bespoke password-controlled web-based tool called the Treatment Allocation Randomization 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 pancreatoduodenectomy undertaken either as pylorus-preserving partial pancreatoduodenectomy (PPPD) or a Kausch-Whipple partial pancreatoduodenectomy 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 CWA or a 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 postoperative 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 (Supplemental Material A and B, http://links.lww.com/AOSO/A163).[25,30,31] Notably:

1. Consensus meetings: All center 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 3 elements of reconstruction: adequate pancreatic neck mobilization, insertion of the parenchymal sutures, and in detail the sutures to the main pancreatic duct prior to tying, and finally 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 (Supplemental Material A and C, http://links.lww.com/AOSO/A163). Photographs for each case were examined by two reviewers (C.M.H. and D.G.) to determine the nature and quality of the procedure. In cases where there was no agreement, a third reviewer (D.A.O.) was involved to reach a consensus. All reviewers were blinded to the patient allocation.

Follow-Up

Each patient had 6 trial visits: An enrollment 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 (Supplemental Material B, http://links.lww.com/AOSO/A163).

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, postoperative fluid collection, intra and postoperative bleeding, reoperation and venous thromboembolism; 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 randomization until death by any cause. Patients underwent adjuvant chemotherapy if eligible: Strong indication had PDAC[4,6]; relative indication ampullary adenocarcinoma,[27] intrapancreatic 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 randomization. Updated protocol to version 6.0 on March 22, 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 noncompliance 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 standardized 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 summarized as median (IQR) and categorical data are summarized as frequencies of counts with associated percentages with tests across treatment or other patients subgroups performed using the 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 randomized 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 (CIs). 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 analyzed 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 May 15, 2015. Following the planned interim analysis of the first 208 evaluable patients, a Z-score comparing the 2 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 August 7, 2017. Following the minimum follow-up for all recruited patients, a data lock was implemented on March 1, 2019 and the final analyses were performed.

Patient Demographics

Two hundred thirty-eight patients who were successfully randomized at operation (Fig. 1). Two patients who had been randomized 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 randomized allocation are shown in Supplemental Table 1, http://links.lww.com/AOSO/A162. Histology revealed a malignant lesion in 194 (82.5%) of 235 patients (missing value for 1 patient allocated to the CWA group), and a nonmalignant lesion in the remaining 41 (17.5%) patients.

Postoperative Pancreatic Fistulae and Complications

Postoperatively, 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. Thirty-three (14%) were type A POPFs, 22 (9%) were type B, and 5 (2%) were type C with no significant differences between allocated groups (Supplemental Table 2, http://links.lww.com/AOSO/A162). Any POPF occurred in 13 (10%) of 134 patients with a hard pancreas compared to 47 (46%) 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 6 (4%) of 134 patients with a hard pancreas compared to 16 (16%) 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%) of 147 patients with a main pancreatic diameter ≤3 mm compared to 13 (15%) of 89 patients with a main pancreatic diameter >3 mm (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 ≤3 mm compared to 2 (2%) of 89 patients a main pancreatic diameter >3 mm (odds ratio = 6.42, 95% CI = 1.49–58.17; $P = 0.004$), Supplemental Table 2, http://links.lww.com/AOSO/A162. 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 postoperative complications.

Postoperative 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 vs 45 [26%] of 174 patients; $P = 0·002$), larger fistula volumes

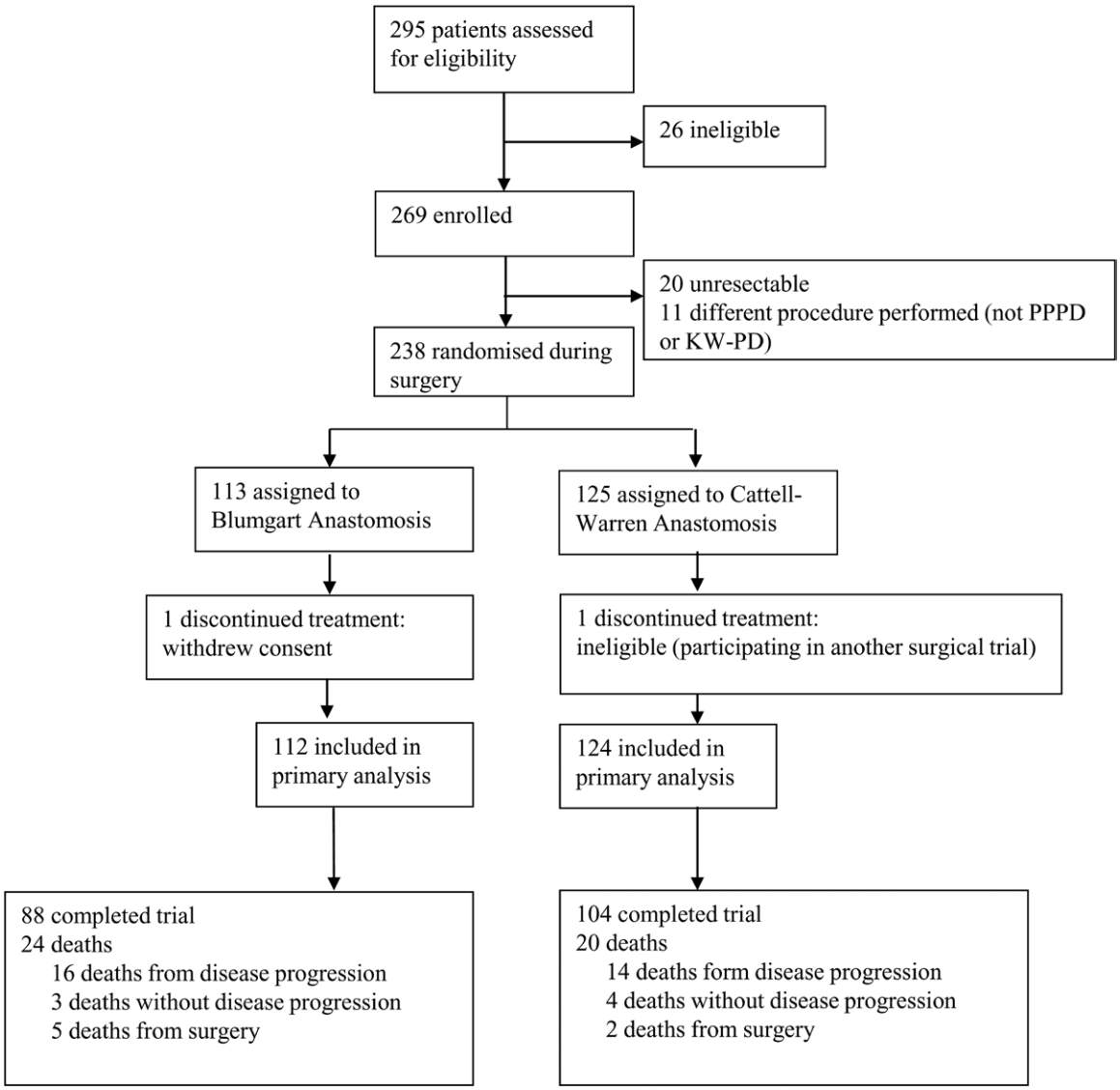

FIGURE 1. Consort diagram.

(median volume [IQR] ml = 2526 [1418, 13,128] vs 111 [40, 343]; $P < 0.001$) and a prolonged hospital stay (median [IQR] days = 16 [11, 28] vs 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 (Supplemental Material A, http://links.lww.com/AOSO/A163).

Quality and Safety

No concerns regarding the technical quality of the anastomosis construction were revealed. However, 6 (2.5%) anastomoses were identified that differed from the randomized allocation but were retained on an ITT basis: 4 patients randomized to CWA, underwent BA, and in 2 patients randomized to BA, underwent a CWA instead.

There were 39 SAEs reported in 31 (13%) of the 236 patients (Supplemental Table 3, http://links.lww.com/AOSO/A162). 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 7 patients (3%), 1 further patient developed liver metastases on restaging before adjuvant chemotherapy.

Adjuvant Treatment and Survival

Overall survival by randomization 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; $P = 0.266$) (Supplemental Table 2, http://links.lww.com/AOSO/A162 and Fig. 2A). There were 174 patients randomized 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%) 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 favor of those that had adjuvant therapy (Fig. 2B). There was no difference in overall survival by the development or absence of postoperative complications (Table 3 and Fig. 2C).

TABLE 1.

Association Between Postoperative Pancreatic Fistula and Other Postoperative Complications

Secondary Outcome		No POPF (n = 176)	Any POPF (n = 60)	*P* No POPF vs Any POPF	Type A POPF (n = 33)	CR-POPF (n = 27)	*P* Type A POPF vs Type B/CPOPF
Intraoperative hemorrhage median (IQR), mL		600 (400, 900)	800 (425, 1000)	0·365	500 (400, 931.25)	825 (500, 1000)	0.119
Missing Data	N = 2						
Postoperative hemorrhage, N (%)	No *N* = 191	146 (84)	45 (75)		25 (76)	20 (74)	
	Yes N = 43	28 (16)	15 (25)	0.179	8 (24)	7 (26)	1
Missing data	*N* = 2	n=2	..	..	..	..	
Delayed gastric emptying, N (%)	No N = 160	129 (74)	31 (52)		20 (6)	11 (41)	
	Yes N = 74	45 (26)	29 (48)	**0.002**	13 (39%)	16 (59)	0.203
Missing data	N = 2	n = 2	..		..	..	
Wound infection, N (%)	No N = 191	146 (84)	45 (75)		25 (76)	20 (74)	
	Yes N =43	28 (16)	15 (25)	0.179	8 (24)	7 (26)	1
Missing data	N = 2	n = 2	..		..	..	
Pulmonary infection, N (%)	No N = 212	162 (93)	50 (83)		28 (85)	22 (81)	
	Yes N = 22	12 (7)	10 (17)	0.048	5 (15)	5 (19)	1
Missing data	N = 2	n = 2	..		..	..	
Postoperative surgical drain fluid collection (fistula volume), median (IQR), mL		111 (40, 342·5)	2526 (1418, 13,128)	**<0.001**	1860 (1279, 3691)	8774 (1612, 35,139)	**0.014**
Missing data	N = 2						
Reoperation rate, N (%)	No N = 200	148 (94)	52 (88)		32 (97)	20 (77)	
	Yes N = 17	10 (6)	7 (12)	0·286	1 (3)	6 (23)	0.037
Missing data	N = 19	n=18	n=1				
Venous thromboembolism, N (%)	No N = 224	167 (96)	57 (95)		33 (100)	24 (89)	
	Yes N = 10	7 (4)	3 (5)	1	0 (0)	3 (11)	0.085
Missing data	N = 2						
Postoperative hospital stay, median (IQR), days		12 (9, 17)	16 (11, 28)	**<0.001**	12 (9, 16)	27.5 (21, 41)	**<0.001**
Missing data	N = 2						

Bold indicates significant results.

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 (Supplemental Material A, http://links.lww.com/AOSO/A163).

DISCUSSION

No significant difference between the 2 types of pancreatic anastomosis in terms of the primary endpoint, postoperative pancreatic fistula, were shown. The overall rate of any POPF was 28 (25%) for the BA group and 32 (26%) for CWA group, while clinically relevant POPF (types B and C) occurred in 13 (12%) and 14 (11%) patients, respectively, which compares favorably 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 2 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 (<3 mm) pancreatic ducts.[20] The importance of POPF as the initiator of other postoperative 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 postoperative hospital stay. Postoperative hemorrhage was recorded as 18% overall; 21% in BA versus 15% in CWA (mean difference [95% CI] 0.66 [0.34–1.29]), *P* = 0.225. There were 6 type B hemorrhages (BA = 4 and CWA = 2) and one further patient in the CWA arm who had a type C hemorrhage 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 2 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 enroll 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-neo-adjuvant treatment, pancreatic duct stents, and octreotide use) means that bias is minimized, 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 randomized 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 at the 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 series.[26]

To place this study in context, before PANasta; meta-analysis (Supplemental Material A, http://links.lww.com/AOSO/A163) of available evidence (n = 975)[22–24,39–41] with 40 of 489 (8%) CR-POPF for BA and 80 of 486 (16.5%) for CWA shows

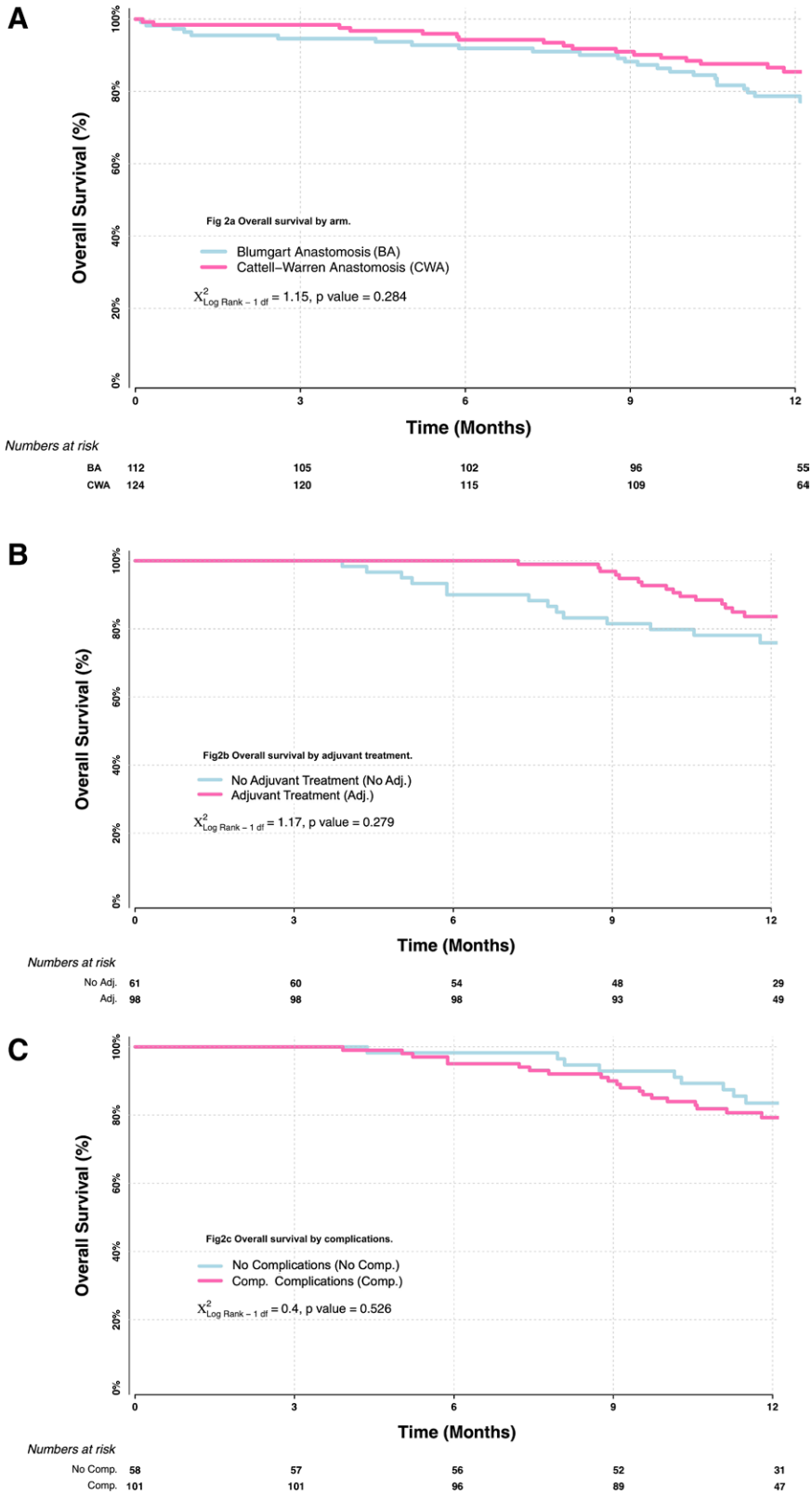

FIGURE 2. Survival. A, Overall survival by arm. B, Overall survival by adjuvant treatment. C, Overall survival by complications.

superiority for BA (relative risk [RR] 0.49, 95% CI 0.26–0.94). Only one of these studies, Hirono et al[39] is a randomized study, but is single center, unmasked 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 of 219 (11%) CR-POPF for BA and 21 of 227 (9%) for CWA confirms no advantage (relative risk [RR] 1.19, 95% CI 0.68–2.08).

The main driver of our trial was the attempt to demonstrate that by reducing postoperative complications the proportion of patients with malignancy eligible for adjuvant therapy could be

TABLE 2.

Adjuvant Therapy in Relation to Complications and Survival

Patient Groups	Levels	BA	CWA	*P*	Missing Data: Adjuvant Therapy Yes	Missing Data: Adjuvant Therapy No	No Adjuvant Chemotherapy	Adjuvant Chemotherapy	*P*	Three Month Adjuvant Chemotherapy Rate	12-month Overall Survival Rate: No Adjuvant Chemotherapy	12-month Overall Survival Rate: Adjuvant Chemotherapy	12-month Overall Survival Rate: Total	Hazard Ratio (95% CI)	*P*
All Patients N = 236*	No complication	41	43	..	11	0	23	42	..	0.58 (0.48–0.7)	0.8 (0.6–0.94)	0.85 (0.75–0.97)	0.83 (0.75–0.91)	0.74 (0.319–1.695)	0.471
	Complication	70	80	..	6	0	49	62	..	0.7 (0.63–0.78)	0.8 (0.72–0.89)	0.84 (0.76–0.94)	0.82 (0.76–0.89)	0.84 (0.416–1.705)	0.633
	Total	111	123	0.863	17	1	72/176 (41%)	104/176 (59%)	0.326	0.65 (0.6–0.72)	0.8 (0.73–0.87)	0.85 (0.78–0.92)	0.82 (0.77–0.87)	0.8 (0.437–1.455)	0.46
PDAC N = 75	No complication	18	17	..	8	0	5	22	..	0.38 (0.25–0.59)	0.76 (0.56–1)	0.9 (0.79–1)	0.85 (0.74–0.98)	**0.18 (0.039–0.84)**	**0.029**
	Complication	20	20	..	2	0	9	29	..	0.37 (0.24–0.56)	0.44 (0.22–0.87)	0.78 (0.64–0.95)	0.68 (0.54–0.85)	0.49 (0.175–1.386)	0.18
	Total	38	37	0.399	10	0	14/65 (22%)	51/65 (78%)	0.850	0.38 (0.28–0.5)	0.6 (0.43–0.85)	0.83 (0.73–0.95)	0.76 (0.67–0.87)	**0.35 (0.133–0.895)**	0.029
Cholangiocarcinoma N = 50	No Complication	11	4	..	2	0	9	4	..	0.69 (0.48–0.99)	0.62 (0.39–1)	1 (1–1)	0.73 (0.53–1)	0 (0, Inf)	0.998
	Complication	18	17	..	2	0	17	16	..	0.7 (0.56–0.87)	0.63 (0.45–0.89)	0.94 (0.83–1)	0.77 (0.64–0.92)	0.28 (0.061–1.25)	0.095
	Total	29	21	0.867	4	0	26/46 (57%)	20/46 (43%)	0.447	0.7 (0.57–0.84)	0.63 (0.48–0.83)	0.95 (0.86–1)	0.76 (0.65–0.89)	0.22 (0.049–1)	0.05
Ampullary carcinoma N = 40	No complication	8	11	..	1	0	5	13	..	0.67 (0.49–0·93)	0.8 (0.52–1)	0.69 (0.48–0.99)	0.72 (0.54–0.96)	3.61 (0.698–18.618)	0.126
	Complication	9	12	..	0	0	13	8	…	0.76 (0.6–0.97)	0.92 (0.79–1)	0.75 (0.5–1)	0.86 (0.72–1)	2.23 (0.314–15.872)	0.422
	Total	17	23	1·00	1	0	18/39 (46%)	21/39 (54%)	0.070	0.72 (0.59–0.87)	0.89 (0.75–1)	0.71 (0.54–0.94)	0.79 (0.68–0.93)	3.07 (0.636–14.78)	0.163
Duodenal carcinoma N = 9	No complication	0	0	..	0	0	0	0	..	..	..	..	..	..	..
	Complication	1	8	..	0	0	3	6	..	0.78 (0.55–1)	1 (1–1)	1 (1–1)	1 (1–1)	1 (1–1)	Unobt.
	Total	1	8	1	0	0	3/9 (33%)	6/9 (67%)	1.00	0.78 (0.55–1)	1 (1–1)	1 (1–1)	1 (1–1)	1 (1–1)	Unobt.
Other—malignant N = 20*	No Complication	1	6	..	0	0	4	3	..	0.57 (0.3–1)	1 (1–1)	1 (1–1)	1 (1–1)	0 (0–Inf)	0.999
	Complication	5	7	..	2	0	7	3	..	0.8 (0.59–1)	0.78 (0.55–1)	1 (1–1)	0.83 (0.65–1)	1.04 (0.106–10.217)	0.973
	Total	6	13	0.381	2	1	11/17 (65%)	6/17 (35%)	0·644	0.71 (0.52–0·96)	0.85 (0.67–1)	1 (1–1)	0.89 (0.77–1)	0.63 (0.065–6.083)	0.69

*One patient does not have complications data (1 other patient who had no adjuvant therapy). Bold indicates significant results.

inf indicates infinity; Unobt., unobtainable.

TABLE 3.
The Association Between Survival, Complications, and Adjuvant Therapy

		No Complications N = 58	Any Complication N = 101	OR/HR (95%CI)	*P*	No POPF N = 128	Any POPF N = 31	OR/HR (95%CI)	No vs Any POPF *P*	Grade A POPF N = 17	CR-POPF N = 14	OR/HR (95%CI)	Grade A vs CR-POPF *P*
Adjuvant treatment received	No N (%)	19 (33%)	42 (42%)	..	..	47 (37%)	14 (45%)	..	..	7 (41%)	7 (50%)	..	..
	Yes N (%)	39 (67%)	59 (58%)	0.69 (0.33–1.41)	0.351	81 (63%)	17 (55%)	0.71 (0.30–1.70)	0.508	10 (59%)	7 (50%)	0.71 (0.13, 3.62)	0.897
Time to start adjuvant treatment in months (95% CI)		2.185 (1.815–2.62)	2.546 (2.135–3.08)	0.68 (0.45–1.01)	0.060	2.3 (1.955–2.907)	2.628 (2.004–3.909)	0.71 (0.42–1.20)	0.197	2.628 (2.267–3.367)	3.679 (1.889–4.484)	0.77 (0.29–2.04)	0.883
Overall survival at 12 months, Rate (95% CI)		0.83 (0.74–0.91)	0.82 (0.76–0.89)	1.28 (0.60–2.71)	0.527	0.81 (0.75–0.87)	0.86 (0.78–0.96)	0.96 (0.39–2.34)	0.926	0.90 (0.89–1.00)	0.81 (0.67–0.98)	0.66 (0.12–3.62)	0.633

increased and thereby an increase in overall survival. The start point for survival was based on randomization at the time of surgery with no statistically significant evidence that postoperative 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 postoperative complications on overall survival, although in these trials the start point for survival was based on randomization 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 3 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 BA technique did not contribute to a reduction in complications compared to the CWA 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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