Title: **Patterns, timing and predictors of recurrence following pancreaticoduodenectomy for distal cholangiocarcinoma: An international multicentre retrospective cohort study**

Category: **Original article**

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Reprints

Reprints will not be available from the authors.

Conflicts of Interest

The authors have no conflicts of interest to declare.

Data availability statement

The data set will not be stored publically to ensure patient anonymity. However, parts of the anonymised data set can be made available to researchers for ethically approved research upon reasonable request.

Study registration details

ClinicalTrials.gov identifier:	NCT04596865: https://clinicaltrials.gov/ct2/show/NCT04596865
Sponsor:	University Hospitals Plymouth NHS Trust, Plymouth, UK
REC approval:	North West – Greater Manchester South Research Ethics Committee (20/NW/0397)

MeSH keywords

Cholangiocarcinoma; Pancreatic Neoplasms; Pancreaticoduodenectomy; Recurrence; Survival; Cohort Studies

Word count

3273

Abbreviations

ASA	American Society of Anesthesiologists
AUC	Area under the curve
BLR	Binomial logistic regression
BMI	Body mass index
CRP	C-reactive protein
CT	Computerised tomography
CT-PET	CT-positron emission tomography
dCCA	Cholangiocarcinoma
DGE	Delayed gastric emptying
EMT	Epithelial-to-mesenchymal transition
IQR	Interquartile range
ISGPS	International Study Group in Pancreatic Surgery
MDT	Multidisciplinary team
MRI	Magnetic resonance imaging
PDAC	Pancreatic ductal adenocarcinoma
POBL	Post-operative bile leak
POPF	Post-operative pancreatic fistula
PPH	Post-pancreatectomy haemorrhage

ROC Receiver operating characteristics

TNM Tumour-Node-Metastasis

Abstract

Introduction

Patients undergoing pancreaticoduodenectomy for distal cholangiocarcinoma (dCCA) often develop cancer recurrence. Establishing timing, patterns and risk factors for recurrence may help inform surveillance protocol strategies, or select patients who could benefit from additional systemic or locoregional therapies. This multicentre retrospective cohort study aimed to determine timing, patterns, and predictive factors of recurrence following pancreaticoduodenectomy for dCCA.

Materials and Methods

Patients who underwent pancreaticoduodenectomy for dCCA between June 2012 and May 2015 with five years of follow-up were included. The primary outcome was recurrence pattern (none, local-only, distant-only or mixed local/distant). Data were collected on comorbidities, investigations, operation details, complications, histology, adjuvant and palliative therapies, recurrence-free and overall survival. Univariable tests and regression analyses investigated factors associated with recurrence.

Results

In the cohort of 198 patients, 129 (65%) developed recurrence: 30 (15%) developed local-only recurrence, 44 (22%) developed distant-only recurrence and 55 (28%) developed mixed pattern recurrence. The most common recurrence sites were local (49%), liver (24%) and lung (11%). 94% of patients who developed recurrence did so within three years of surgery. Predictors of recurrence on univariable analysis were cancer stage, R1 resection, lymph node metastases, perineural invasion, microvascular invasion and lymphatic invasion. Predictors of recurrence on multivariable analysis were female sex, venous resection, advancing histological stage and lymphatic invasion.

Conclusion

Two thirds of patients have cancer recurrence following pancreaticoduodenectomy for dCCA, and most recur within three years of surgery. The commonest sites of recurrence are the pancreatic bed, liver and lung. Multiple histological features are associated with recurrence.

1. Introduction

Cholangiocarcinoma is a rare malignancy arising from the epithelial cells of the biliary tree.[1] In patients with resectable distal cholangiocarcinoma (dCCA), pancreaticoduodenectomy (PD) is potentially curative. However, 41-82% of patients undergoing surgery develop recurrence.[2–4] Due to the rarity of dCCA, studies examining recurrence patterns following PD are frequently limited to single-centre cohorts.[2–4] Studying the timings and pattern of recurrence can help optimise post-operative surveillance protocols to detect recurrence earlier. Identifying perioperative predictive factors of recurrence may also help to select patients who could benefit from additional systemic or locoregional therapies, potentially improving outcomes. This multicentre retrospective cohort study aimed to identify patterns and timing of recurrence following PD for dCCA, and perioperative factors associated with a higher risk of recurrence.

2. Methods

Data were extracted from the Recurrence After Whipple's (RAW) study (NCT04596865). Ethical approval was granted by the Greater Manchester South Research Ethics Committee (20/NW/0397) and University Hospitals Plymouth NHS Trust sponsored the study. Centres in the UK were invited to participate in the study by e-mail, and international centres were invited to join via Twitter. Any hepatobiliary centre that had performed PD for dCCA during the research window was eligible to participate, with no prerequisite regarding unit size or volume. Consecutive patients undergoing PD for dCCA at 29 participating centres in eight countries were screened for eligibility. Patients were included if they underwent a PD for histologically-confirmed cholangiocarcinoma between June 2012 and May 2015 (three years) inclusive, and had follow-up data available until death or five years post-operatively (whichever was sooner). Patients were excluded if their primary procedure was not PD, their histology did not confirm cholangiocarcinoma, or they were lost to follow-up within five years of surgery. Participants were identified through departmental databases or by requesting lists of patients

from histopathology or clinical coding departments. Data were collected from patient records, cancer registries and radiology systems. A REDCap electronic database was created for data collection.[5,6] Pre-operative variables collected were age, sex, weight, height, body mass index (BMI), diabetes, cardiovascular comorbidities, respiratory comorbidities, previous cancer diagnosis, radiological staging (7th Tumour-Node-Metastasis (TNM) edition),[7] biliary stenting, neoadjuvant therapy, bilirubin, C-reactive protein (CRP), albumin, neutrophils and lymphocytes. Intraoperative variables collected were American Society of Anesthesiologists (ASA) grade, classic vs. pylorus-preserving PD, pancreatic anastomosis type, vascular resection and intraoperative blood transfusion. Post-operative variables collected were complications, histological staging (7th TNM edition), R status, margin involvement, lymph node involvement, adjuvant therapies, palliative therapies, recurrence-free survival (RFS) and overall survival (OS).

The primary outcome was recurrence pattern (none, local-only, distant-only or mixed local/distant) and secondary outcomes were RFS and predictive factors for recurrence. Local-only recurrence was defined as recurrence only around any of the following structures: Superior mesenteric artery, superior mesenteric/portal vein, coeliac trunk, common hepatic artery, pancreatic anastomosis and locoregional lymph nodes. Distant-only recurrence was defined as recurrence in any other anatomical location excluding the above list of local recurrence sites. Mixed recurrence was defined as recurrence in both a local and distant recurrence site. Recurrence was defined as a radiology report identifying cancer recurrence on post-operative CT, MRI or CT-PET. The date of recurrence was defined as the date that the diagnostic imaging was performed. The recorded pattern of recurrence (local, distant or mixed) was based on the first cross-sectional imaging that diagnosed recurrence; patients were not reclassified if subsequent imaging showed more extensive recurrent disease. RFS was defined as the number of months from surgery to the first cross-sectional imaging that reported recurrence. The diagnosis and grading of post-operative pancreatic fistula (POPF; grade A/B/C) and post-operative bile leak (POBL; grade A/B/C) were as per the definitions from the International Study Group in Pancreatic Surgery (ISGPS) 2016 and the International Study Group of Liver Surgery 2011 respectively.[8,9] Post-

operative gastrojejunal leak was classified as grade A (no change to patient's management), B (requiring interventional procedures) or C (requiring surgery). Post-pancreatectomy haemorrhage (PPH) and delayed gastric emptying (DGE) were classified as per the definitions of the ISGPS 2007.[10,11] R status was defined as R0 (tumour cells >1mm from all surfaces/margins) and R1 (tumour cells <1mm from any surface/margin of the surgical specimen). Complications were also graded as per the Clavien-Dindo classification.[12] To reduce sampling bias, multiple centres in several countries participated to aim for a cohort representative of patients undergoing PD for dCCA. All consecutive eligible patients in the research window were included to reduce selection bias. To reduce attrition bias, data were extracted from medical records documented at the time of surgical intervention. To minimise recall bias, regional cancer registries, primary care data requests and regional radiology systems were used to determine if patients had developed recurrence or died.

2.1 Statistical methods

Univariable tests compared variables in patients with and without recurrence to identify predictive factors for recurrence. Medians were compared using Mann-Whitney U test, proportions using χ^2 or Fisher's exact test, and ordinal data using Kruskal Wallis H test. Univariable binary logistic regression (BLR) was performed to assess for relationships between specific involved margins and recurrence pattern. Univariable BLR was also performed to estimate the effect of selected factors in predicting recurrence. Selection of factors for univariable BLR was based on their ability to be included in a subsequent multivariable model (see **Supplementary Methods** for the list of excluded variables and reasons for exclusion). Univariable BLR was performed for age, sex, history of diabetes, previous cancer, cardiovascular or respiratory comorbidity, pre-operative radiological lymphadenopathy, indeterminate lung nodules, pre-operative stenting, bilirubin, neutrophil:lymphocyte ratio, classical vs. pylorus-preserving PD, pancreaticojejunostomy vs. pancreaticogastrostomy, venous vs. no venous resection, intraoperative or post-operative blood transfusion, histological differentiation, histological

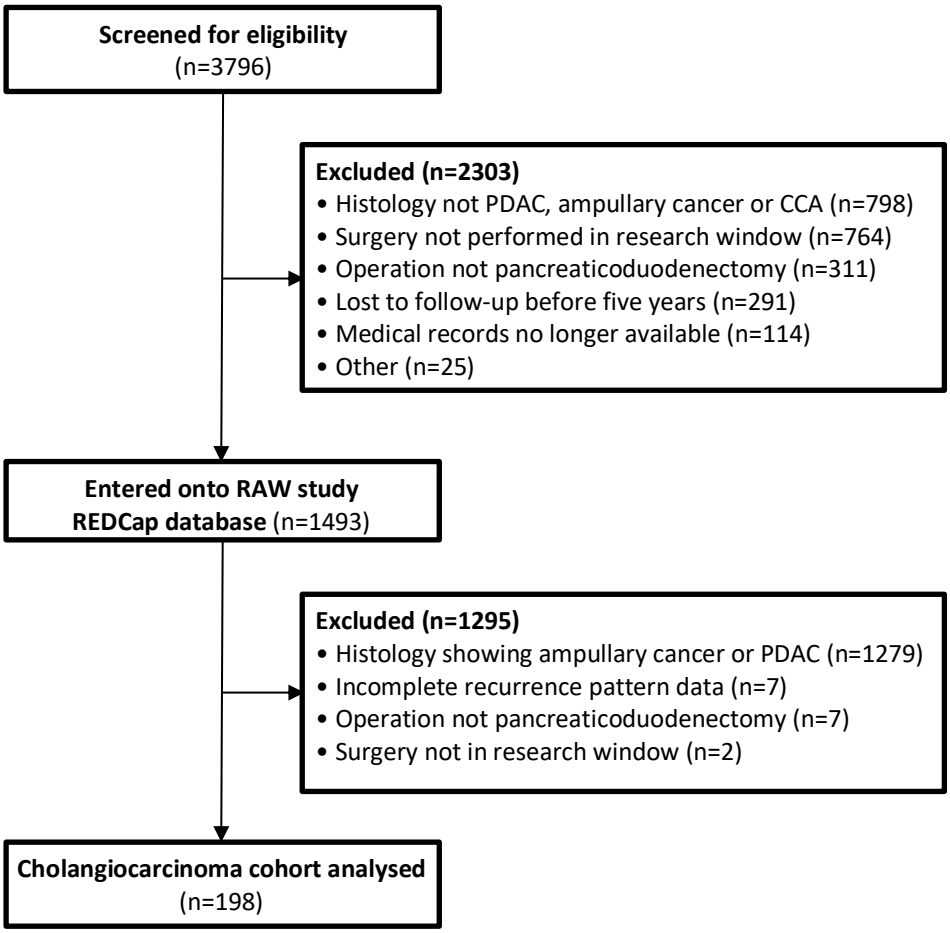
stage, R status, presence and number of metastatic lymph nodes, perineural invasion, microvascular invasion, lymphatic invasion, and completion of adjuvant chemotherapy. These factors were subsequently assessed together in a multivariable BLR model. The backward conditional method was chosen so that all included factors were considered simultaneously, accounting for collinearity between variables, prior to stepwise removal of non-predictive variables. The model was also run using forward entry method and using a complete-cases approach as a sensitivity analysis. The probability for stepwise entry was set at $p<0.05$ and stepwise removal at $p>0.10$. Times from surgery to recurrence or death were compared using the Kaplan-Meier method and the log-rank test. For all tests, a p-value <0.05 was considered significant. Analyses were performed using GraphPad Prism (v9.3.1, San Diego, CA) and IBM SPSS Statistics (v29, Chicago, IL).

3. Results

3.1 Patient demographics, investigations and management

Of the 205 patients with dCCA in the RAW study database, 198 (96.6%) were included in the final analysis (**Figure 1**). Median age at surgery was 67 and the most common comorbidities were hypertension (43.9%) and type II diabetes (14.1%) (**Table 1**). The disease was radiologically resectable in 184 (92.9%), borderline resectable in 12 (6.1%) and locally advanced in one (0.5%) patient respectively (one patient unknown). Over three-quarters of patients (77.8%) underwent pre-operative biliary drainage, but neoadjuvant therapy was rarely given (1.5%). Nineteen patients (9.6%) underwent venous resection, with arterial resection seldom performed (two patients, 1.0%). The most common complications were intra-abdominal collection (15.8%), clinically relevant POPF (15.7%) and DGE (14.2%). The R0 resection rate was 59.9%, and almost two-thirds of patients (65.7%) had histologically node-positive disease. Of the 191 patients (96.5%) with adjuvant chemotherapy data available, 91 (47.6%) received at least one cycle of chemotherapy. The most common regimens were gemcitabine (41 patients, 45%), capecitabine (16 patients, 18%), or gemcitabine with cisplatin (11 patients, 12%).

Figure 1 Participant flow diagram



CCA = cholangiocarcinoma, PDAC = pancreatic ductal adenocarcinoma

3.2 Patterns and timing of recurrence

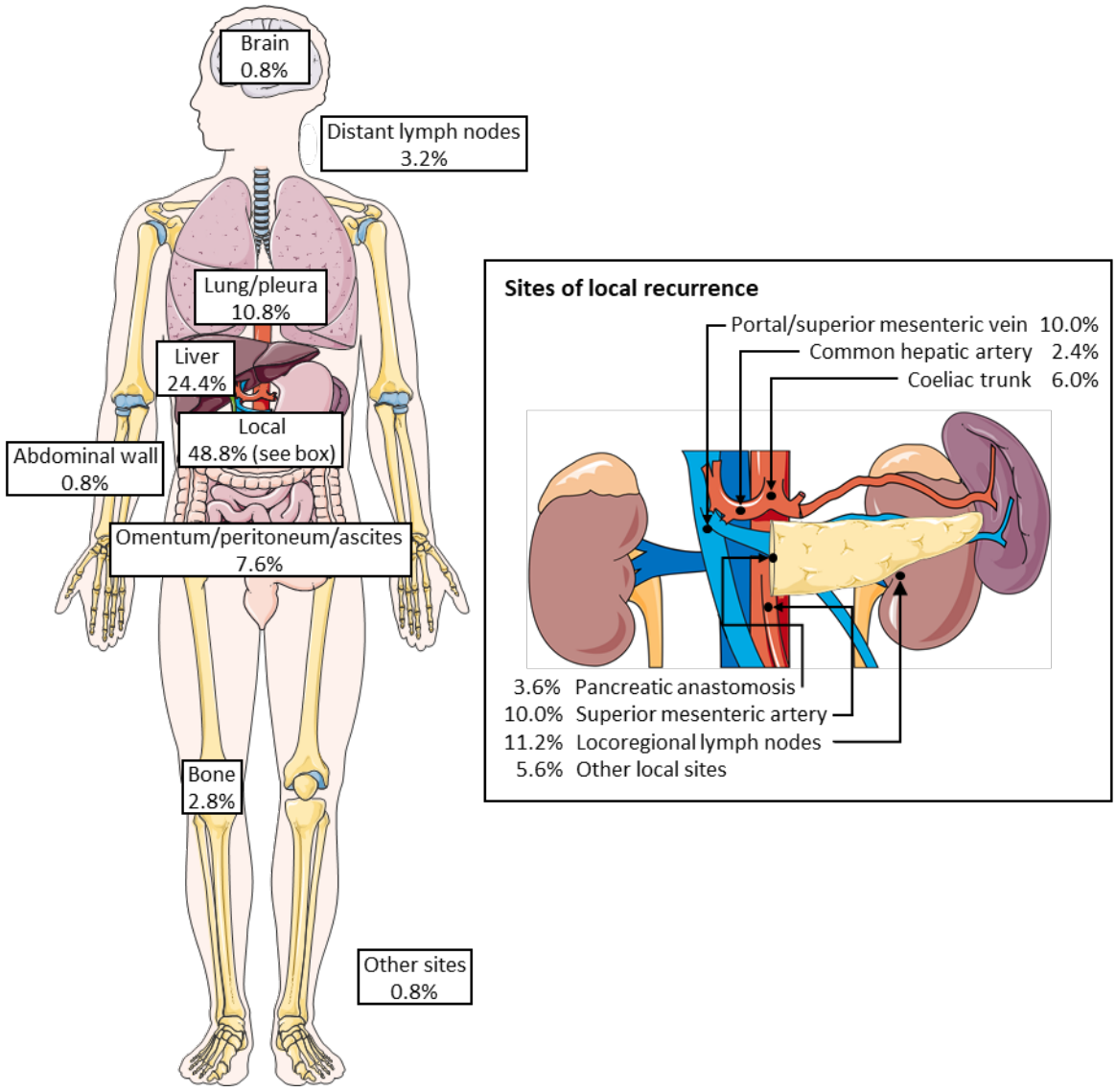
In total, 129 patients (65.2%) developed cancer recurrence within five years of surgery; 30 (15.2%) developed local-only recurrence, 44 (22.2%) developed distant-only recurrence and 55 (27.8%) developed mixed recurrence. Most patients developing recurrence did so within three years of surgery (93.8%). The most common recurrence sites were the pancreatic bed, the liver and the lung (48.8%, 24.4% and 10.8% of patients with recurrence respectively) (**Figure 2**). Local and liver recurrence were the most common sites of recurrence in the first three years post-surgery, whereas lung recurrence

Table 1 Demographics, pre-operative imaging and endoscopic/surgical management

Variables	All patients [n=198 (%)]
Demographics	
Age (years), median (IQR)	67 (61-73)
Female	61 (30.8)
Body mass index (kg/m^2), median (IQR)	26.0 (23.0-28.4)
Pre-operative diabetes	
No	160 (80.8)
Yes - Type II	28 (14.1)
Yes – Type I	3 (1.5)
Unknown	7
Cardiovascular comorbidities	
None	98 (49.5)
One or more	100 (50.5)
Hypertension	*87 (43.9)*
Cardiac arrhythmia	*15 (7.6)*
Ischaemic heart disease	*10 (5.1)*
Other	*(9.6)*
Unknown	0
Respiratory comorbidities	
None	177 (89.4)
One or more	21 (10.6)
Asthma	*11 (5.6)*
Chronic obstructive pulmonary disease	*7 (3.5)*
Other	*5 (2.5)*
Unknown	0
Pre-operative imaging	
CT	193 (97.5)
Endoscopic ultrasound	52 (26.3)
MRI	48 (24.2)
CT-PET	18 (9.1)
Staging laparoscopy	10 (5.1)
Radiological staging	
IA (T1 N0 M0)	50 (41.3)
IB (T2 N0 M0)	32 (26.4)
IIA (T3 N0 M0)	8 (6.6)
IIB (T1-3 N1 M0)	31 (25.6)
III (T4 N0-1 M0)	22 (18.2)
Unknown	77
Pre-operative biliary drainage	
Yes – Endoscopic and/or percutaneous	154 (77.8)
No – Not required (patient not jaundiced)	25 (12.6)
No – Decision to operate whilst jaundiced	14 (7.1)
No – Stenting attempted but failed	5 (2.5)
Unknown	0
Surgery	
Pancreaticoduodenectomy type	
Pylorus preserving	*103 (52.3)*
Classic	*94 (47.7)*
Unknown	*1*
Pancreatic anastomosis	
Pancreaticojejunostomy	*146 (75.6)*
Pancreaticogastrostomy	*47 (24.4)*
Unknown	*5*
Vascular resection	
Venous	
No	*168 (89.8)*
Partial resection (cuff) +/- patch	*10 (5.3)*
Complete resection with reconstruction	*9 (4.8)*
Unknown	*11*
Arterial	
No	*185 (98.9)*
Yes	*2 (1.1)*
Unknown	*11*

IQR=Interquartile range. CT = Computerised tomography. CT-PET = CT-positron emission tomography. MRI = Magnetic resonance imaging.

Figure 2 Patterns of cancer recurrence following pancreaticoduodenectomy performed for distal cholangiocarcinoma



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was the most common in years 4-5 (**Figure S1**). Median RFS was similar regardless of whether the recurrence pattern was local-only, distant-only or mixed (11.5 vs. 13.0 vs. 11.5 months respectively, p=0.175) (**Figure S2a**). However, patients with distant-only recurrence had a significantly higher median OS compared to those with mixed recurrence (24 vs. 20.5 months, p=0.008) (**Figure S2b**). When subdividing patients with distant-only recurrence into lung-only recurrence, liver-only recurrence, and multi-site distant recurrence, patients with lung-only recurrence had a significantly

higher median RFS compared to patients with multi-site distant recurrence (26 vs. 11 months, p=0.003), liver-only recurrence (26 vs. 9 months, p=0.001) or local-only recurrence (26 vs. 11.5 months, p=0.003) (**Figure S3a**). This translated into a higher median OS in lung-only recurrence compared to liver-only (not reached vs. 23 months, p=0.004), multisite distant-only (not reached vs. 22 months, p=0.004) and local-only recurrence (not reached vs. 25.5 months, p=0.001) (**Figure S3b**).

3.3 Predictors of recurrence

The study variables were compared between patients who developed recurrence and those who did not (**Table 2**). Patients with recurrence had significantly higher pre-operative lymphocyte count (2.1 vs. $1.8x10^9$ L^{-1}, p=0.045) and neutrophil:lymphocyte ratio (NLR) (2.95 vs. 2.26, p=0.035). However, receiver operating characteristics (ROC) analyses did not find these to be discerning predictors of recurrence (lymphocyte count area under the curve (AUC)=0.408 and NLR AUC=0.571, **Figures S4a** and **S4b**). Histologically, patients with recurrence were more likely to have poorly-differentiated, higher stage tumours and an R1 resection (50% vs. 33%, p=0.022). Whilst no particular surgical margin was more commonly involved in patients with recurrence overall, univariable BLR of individual margins found involvement of the bile duct transection margin to be associated with local-only recurrence, and involvement of the anterior surface or SMV groove margin to be associated with mixed recurrence (**Table S1**). Patients with recurrence were more likely to have lymph node metastases (76% vs. 46%, p<0.001) and a higher number of lymph node metastases (2 vs. 0 nodes, p<0.001), leading to a higher median lymph node ratio (LNR, 1.13 vs. 0.00, p<0.001). However, the AUC for both of these factors was low (AUC=0.699 and 0.666 respectively, **Figures S5a** and **S5b**). Perineural, microvascular and lymphatic invasion were also significantly more common in patients with recurrence. No significant differences were observed in the rates of adjuvant chemotherapy use between those with or without recurrence.

Table 2 Factors associated with recurrence following pancreaticoduodenectomy for distal cholangiocarcinoma

Variables	Recurrence n=129 (%)	No recurrence n=69 (%)	p value
Demographics			
Age (years), median (IQR) (n=198)	67 (60-73)	67 (62-74)	0.397
Male (%) (n=198)	93 (72.1)	44 (63.8)	0.227
Body mass index (kg/m^2), median (IQR) (n=129)	25.4 (23.1-28.4)	26.6 (23.0-28.7)	0.566
Pre-operative comorbidities			
Diabetes (n=191)	19 (14.7)	12 (17.4)	0.595
One or more cardiovascular comorbidities (n=198)	61 (47.3)	39 (56.5)	0.216
One or more respiratory comorbidities (n=198)	16 (12.4)	5 (7.2)	0.261
Previous history of other cancer (n=198)	20 (15.5)	5 (7.2)	0.096
Radiological features			
Radiological stage (TNM 7th edition) (n=121)	-	-	0.538
IA (T1 N0 M0)	31 (39.7)	19 (44.2)	0.635
IB (T2 N0 M0)	20 (25.6)	12 (27.9)	0.787
IIA (T3 N0 M0)	6 (7.7)	2 (4.7)	0.710
IIB (T1-3 N1 M0)	21 (26.9)	10 (23.3)	0.658
III (T4 N0-1 M0)	0 (0.0)	0 (0.0)	1.000
Unknown	51	26	0.799
Radiologically-detected lymphadenopathy (n=162)	23 (21.9)	12 (21.1)	0.900
Indeterminate lung nodules (n=154)	12 (12.6)	6 (10.2)	0.644
MDT opinion			
Resectability (n=197)	-	-	0.374
Resectable	121 (94.5)	63 (91.3)	0.384
Borderline resectable	7 (5.5)	5 (7.2)	0.619
Locally advanced	0 (0.0)	1 (1.4)	0.352
Unknown	1	0	1.000
Pre-operative treatments			
Biliary stenting (percutaneous or endoscopic) (n=198)	100 (77.5)	54 (78.3)	0.905
Neoadjuvant chemotherapy ± radiotherapy (n=198)	3 (2.3)	0 (0.0)	0.202
Pre-operative blood results			
Bilirubin (µmol L^{-1}), median (IQR) (n=197)	27 (13-68)	24 (13-50)	0.433
C-reactive protein (mg L^{-1}), median (IQR) (n=96)	10 (3-25)	10 (4-24)	0.791
Albumin (g L^{-1}), median (IQR) (n=174)	37 (34-42)	36 (30-42)	0.869
CRP:Albumin Ratio (CAR), median (IQR) (n=91)	0.27 (0.08-0.76)	0.29 (0.12-0.80)	0.767
Neutrophils (x 10^9 L^{-1}), median (IQR) (n=187)	5.0 (3.8-6.9)	4.9 (4.0-6.7)	0.578
Lymphocytes (x 10^9 L^{-1}), median (IQR) (n=187)	1.8 (1.2-2.3)	2.1 (1.5-2.6)	**0.045**
Neutrophil:Lymphocyte Ratio (NLR), median (IQR) (n=187)	2.95 (1.96-4.08)	2.26 (1.72-3.85)	**0.035**
Operative factors			
American Society of Anesthesia (ASA) grade (n=183)	-	-	0.191
I	19 (16.1)	15 (23.1)	0.246
II	68 (57.6)	37 (56.9)	0.927
III	31 (26.3)	13 (20.0)	0.342
Unknown	11	4	0.583
Pylorus-preserving (vs. classical) pancreaticoduodenectomy (n=197)	68 (52.7)	35 (50.7)	0.868
Pancreaticojejunostomy (vs. pancreaticogastrostomy) (n=191)	96 (77.4)	50 (72.5)	0.442
Venous resection (partial or complete) (n=187)	15 (12.5)	4 (6.0)	0.209
Arterial resection (n=187)	1 (0.8)	1 (1.5)	1.00
Intraoperative blood transfusion received (n=139)	15 (17.0)	5 (9.8)	0.241
Complications			
Post-operative pancreatic fistula (all grades) (n=190)	34 (27.2)	19 (29.2)	0.767
Clinically relevant pancreatic fistula (grade B/C)	17 (13.6)	13 (20.0)	0.251
Post-operative bile leak (n=190)	5 (4.0)	4 (6.2)	0.495
Post-operative gastrojejunal leak (n=190)	1 (0.8)	0 (0.0)	1.000
Post-pancreatectomy haemorrhage (n=190)	11 (8.8)	8 (12.3)	0.445
Post-operative blood transfusion received (n=184)	19 (15.7)	15 (23.8)	0.179
Intra-abdominal collection (n=198)	17 (13.2)	13 (18.8)	0.290
Delayed gastric emptying (n=190)	15 (12.4)	12 (17.4)	0.343
Histological factors			
Differentiation (n=180)	-	-	0.121
Well	6 (5.1)	7 (11.3)	0.126
Well/moderate	4 (3.4)	0 (0.0)	0.300
Moderate	60 (50.8)	35 (56.5)	0.474
Moderate/poor	15 (12.7)	11 (17.7)	0.361
Poor	33 (28.0)	9 (14.5)	**0.043**
Unknown	11	7	0.705
Maximum tumour diameter (mm), median (IQR) (n=166)	25 (18-31)	20 (15-28)	0.140
Histological stage (TNM 7th edition) (n=195)	-	-	**<0.001**
IA (T1 N0 M0)	0 (0.0)	10 (14.5)	**<0.001**
IB (T2 N0 M0)	6 (4.8)	7 (10.1)	0.228
IIA (T3 N0 M0)	22 (17.5)	19 (27.5)	0.103
IIB (T1-3 N1 M0)	92 (73.0)	31 (44.9)	**<0.001**
III (T4 N0-1 M0)	6 (4.8)	2 (2.9)	0.714
Unknown	3	0	0.553

Table 2 (continued)

Variables	Recurrence n=129 (%)	No recurrence n=69 (%)	p value
Histological factors (continued)			
Incomplete (R1) resection (n=195)	64 (50.0)	22 (32.8)	**0.022**
Involved surface/margin: (n=195)	-	-	-
Anterior surface	6 (4.7)	1 (1.5)	0.425
Bile duct transection	15 (11.7)	2 (3.0)	0.059
Pancreatic transection	9 (7.0)	2 (3.0)	0.337
Periductal circumferential margin	6 (4.7)	4 (9.0)	0.739
Vessel margin (if resected), n=13	8 (80.0)	1 (33.3)	0.203
SMA/posterior margin	33 (25.8)	13 (19.4)	0.377
SMV groove	19 (14.8)	7 (10.4)	0.507
Any tumour positive nodes on histology (n=194)	98 (76.0)	32 (46.4)	**<0.001**
Number of resected lymph nodes positive for tumour, median (IQR) (n=194)	2 (1-4)	0 (0-2)	**<0.001**
Total number of resected lymph nodes, median (IQR) (n=194)	16 (11-22)	14 (10-20)	0.346
Lymph Node Ratio (LNR), median (IQR) (n=194)	0.13 (0.03-0.26)	0.00 (0.00-0.12)	**<0.001**
Perineural invasion (n=162)	14 (25.5)	10 (9.3)	**0.010**
Microvascular invasion (n=135)	22 (44.9)	19 (22.1)	**0.006**
Lymphatic invasion (n=140)	23 (50.0)	18 (19.1)	**<0.001**
Adjuvant treatments			
Adjuvant chemotherapy commenced (n=191)	65 (51.6)	26 (40.0)	0.129
Cycles of chemotherapy administered, median (IQR) (n=176)	6 (5-6)	6 (6-6)	0.533
Planned course of adjuvant chemotherapy completed (n=191)	50 (82.0)	19 (82.6)	0.945
Adjuvant radiotherapy (n=189)	3 (2.4)	2 (3.1)	0.769

Bold p values are significant at p<0.05. n = The number of patients with data for the named variable. CRP = C-reactive protein, IQR = Interquartile range, MDT = multidisciplinary team, TNM = Tumour-Node-Metastasis. Continuous variables are compared using the Mann-Whitney U test, proportions using $\chi 2$ or Fisher's exact test, and ordinal data using the Kruskal Wallis H test.

Univariable and multivariable BLR assessed the strength of relationship between selected study variables and the risk of recurrence (**Table 3**). All variables associated with recurrence on univariable regression were histological: TNM stage, R1 resection, presence and number of lymph node metastases, perineural invasion, microvascular invasion and lymphatic invasion. Multivariable analysis found that female sex, venous resection, advancing histological stage, presence of lymph node metastases and lymphatic invasion were predictors of recurrence. Multivariable models using a complete-cases approach and forward entry method returned consistent results (**Table S2**). Whilst most of the above identified factors are biologically plausible risk factors for recurrence, female sex was an unexpected finding. To further investigate this, all variables were compared between males and females (**Table S3**). Compared to males, female patients were less likely to have post-operative DGE (18% vs. 5%, p=0.01), more likely to have lymphatic invasion (29% vs. 24%, p=0.042) and less likely to complete adjuvant chemotherapy (69% vs. 88%, p=0.039).

Table 3 Univariable and multivariable regression analysis of selected potential predictors of recurrence following pancreaticoduodenectomy for distal cholangiocarcinoma

Variables	Univariable model [OR (95% CI)]	p value	Multivariable model [a] [OR (95% CI)]	p value
Demographics				
Age (per year)	0.98 (0.95-1.01)	0.179	-	-
Female vs. male	1.47 (0.79-2.70)	0.228	2.56 (1.14-5.88)	**0.022**
Pre-operative comorbidities				
Pre-operative diabetes*	0.81 (0.37-1.78)	0.596	-	-
One or more cardiovascular comorbidities*	0.69 (0.38-1.24)	0.216	-	-
One or more respiratory comorbidities*	1.81 (0.63-5.18)	0.267	-	-
Previous history of other cancer	2.35 (0.84-6.56)	0.103	3.39 (0.84-13.78)	0.088
Radiological features				
Radiologically-detected lymphadenopathy*	1.05 (0.48-2.31)	0.900	-	-
Indeterminate lung nodules*	1.28 (0.45-3.61)	0.644	1.25 (0.33-4.73)	0.738
Pre-operative treatments				
Biliary stenting	0.96 (0.47-1.94)	0.905	-	-
Pre-operative blood results				
Serum bilirubin (per µmol L^{-1})	1.00 (1.00-1.01)	0.230	-	-
Neutrophil:Lymphocyte ratio (NLR)	1.04 (0.97-1.13)	0.297	-	-
Operative factors				
Classical (vs. pylorus-preserving) PD	1.05 (0.58-1.89)	0.868	-	-
PJ (vs. PG) anastomosis	0.77 (0.39-1.51)	0.443	-	-
Venous resection*	2.25 (0.72-7.08)	0.166	4.87 (1.06-22.34)	**0.042**
Intraoperative blood transfusion received*	1.89 (0.64-5.55)	0.247	-	-
Post-operative blood transfusion received*	0.60 (0.28-1.27)	0.181	0.62 (0.24-1.63)	0.332
Histological factors				
Differentiation*	-	0.689	-	-
Moderate vs. well	1.20 (0.42-3.44)	0.734	-	-
Poor vs. well	1.68 (0.56-5.04)	0.354	-	-
Histological stage (TNM 7th edition)*	-	**0.003**	-	0.091
II vs. I	6.46 (2.40-17.36)	**<0.001**	4.71 (1.43-15.53)	**0.011**
III vs. I	8.50 (1.34-54.13)	**0.023**	3.49 (0.41-29.33)	0.250
Incomplete (R1) resection*	2.05 (1.10-3.79)	**0.023**	-	-
Any metastatic lymph nodes on histology*	3.66 (1.96-6.81)	**<0.001**	1.43 (1.17-1.74)	**<0.001**
Number of metastatic lymph nodes on histology (per node)	1.40 (1.18-1.66)	**<0.001**	-	-
Adequate lymphadenectomy (≥15 nodes resected)*	1.39 (0.77-2.52)	0.274	-	-
Perineural invasion*	3.31 (1.36-8.06)	**0.008**	-	-
Microvascular invasion*	2.87 (1.34-6.14)	**0.006**	-	-
Lymphatic invasion*	4.22 (1.94-9.15)	**<0.001**	5.75 (2.15-15.40)	**<0.001**
Adjuvant treatments				
Adjuvant chemotherapy course completed*	0.96 (0.27-3.38)	0.945	-	-

Results are from binary logistic regression models, with odds ratios (ORs) reported for the stated category, relative to the reference category for nominal variables, or per the stated number of units increase for continuous variables. Initially, separate univariable models were produced for each of the factors. A multivariable model was then produced, which considered all factors for inclusion, and used a backwards stepwise method for variable selection; the resulting model was based on n=187 cases (n=123 outcomes). Bold p values are significant at p<0.05. *Patients where data were not available were grouped into an "Unknown" category for the stated variable in the multivariable model, in order to minimise exclusions on complete-cases analysis; the resulting ORs and p-values for these categories are not reported in the table for brevity, but are reported in Table S2 (Model A) for the factors included in the final model. PD = pancreaticoduodenectomy, PG = pancreaticogastrostomy, PJ = pancreaticojejunostomy, TNM = Tumour-Node-Metastasis.

1. Discussion

4.1 Patterns and timing of recurrence

Our results found that 65% of patients undergoing PD for dCCA developed recurrence within five years of surgery; 15% developed local-only recurrence, 22% developed distant-only recurrence, and 28% developed mixed recurrence. Zhou et al. (China, n=124) found a recurrence rate of 56%; 22%

developed local-only recurrence, 19% distant-only recurrence and 15% mixed recurrence.[4] Exclusion of R1 resections from their cohort may explain their lower overall recurrence rate, but would not their higher rate of local-only recurrence. Kim et al. (South Korea, n=132) published a retrospective cohort study on recurrence patterns following PD and adjuvant chemoradiotherapy for dCCA.[13] Recurrence occurred in 66 patients (50%), usually with distant metastases (58 patients, 44% of the cohort). Whilst our distant recurrence rate was similar (50% developed either mixed or distant-only recurrence), their local and local-only recurrence rates were lower than in our study (26% vs. 49% and 10% vs. 15% respectively). This may be explained by the use of chemoradiotherapy in their cohort. Komaya et al. investigated timing and recurrence patterns following PD for dCCA (Japan, n=389).[14] Despite only including patients with R0 resection, their 5-year recurrence rate was similar to our study (60% vs. 65%) and most patients also recurred within three years (86%). Their local-only and distant recurrence rates were also similar (12% vs. 15% and 43% vs. 50% respectively), but they observed a much lower rate of mixed recurrence (3% vs. 28%). Possible explanations are their exclusion of R1 resections in their cohort and an intensive imaging surveillance protocol that may have identified patients who would have developed mixed recurrence at a time when only local recurrence was radiologically apparent.

Of note, there is no standard anatomical definition for local recurrence, which impacts how recurrence patterns are classified. However, this should not affect the overall recurrence rate, which is consistent between studies (50-66%).[4,13–16] Acknowledging this limitation, one can conclude that 10-22% of patients develop local-only recurrence, 43-50% of patients develop distant metastases, and ~90% of patients recur within three years of surgery. These figures are consistent regardless of whether the cohorts are comprised of only R0 resections or include R1 resections. Our results support the use of more intensive surveillance follow up in the first three years after resection compared to later years. However, we do not have data to support a particular frequency of imaging because surveillance protocols for patients in this study were variable between centres. The ESMO 2023 guidelines

acknowledge that there is a lack of data on the survival benefit and cost effectiveness of intensive post-operative surveillance in resected cholangiocarcinoma.[17]

The subset of patients with lung-only recurrence may benefit from a curative-intent treatment strategy; their longer OS compared to other recurrence patterns suggests that lung-only recurrence has a comparatively favourable prognosis. Whilst multifocal lung disease is likely best treated with systemic agents, limited lung recurrence may be treated with surgery or locoregional therapies such as stereotactic ablative body radiotherapy.[18,19] The authors recommend that locoregional treatments are considered in patients diagnosed with lung-only metastases.

Whilst adjuvant chemoradiotherapy has been employed in some centres, it is not standard practice. The phase II SWOG S0809 trial treated patients with T2-4, lymph node positive, or R1 resected perihilar CCA, dCCA and gallbladder cancer with gemcitabine and capecitabine followed by capecitabine-based chemoradiotherapy.[20] Of the 38 patients with resected dCCA who developed recurrence, eight (21%) had local recurrence, three of which (8%) had local-only recurrence. These figures are lower than those seen in our study (66% had local recurrence, 23% had local-only recurrence). No phase III trials comparing adjuvant chemotherapy with chemoradiotherapy have been conducted to date, and further studies are warranted.

4.2 Predictors of recurrence

On multivariable analysis, factors associated with recurrence were female sex, venous resection, histological stage, lymph node metastases and lymphatic invasion. Our results bear similarities to previous studies. Choi et al. (South Korea, n=122) found that worsening tumour differentiation and lymph node metastases were independent risk factors for shorter RFS on multivariable analysis.[16] Sallinen et al. (Finland, n=47) found pre-operative CA 19-9 >30 U ml^{-1} and lymph node metastases were independent risk factors for shorter RFS. [15] Similar results were found in Kim et al., with poor

differentiation, lymph node metastases and high pre-operative CA 19-9 identified as predictors of recurrence.[13] Komaya et al. also found that vascular resection was associated with a significantly lower median RFS (0.8 vs 3.1 years).[14] As vascular resection is only performed if there are concerns regarding oncological clearance, it is likely that vascular resection is associated with more extensive local disease at the time of surgery rather than being a cause of recurrence itself.

However, some factors identified in other studies did not predict recurrence in our cohort. Komaya et al.[14] identified many of the same predictive factors for recurrence as our study, but also bilirubin >85.5µmol L^{-1}, biliary drainage and receiving adjuvant chemotherapy. Di Martino et al. (Spain/Italy/Singapore, n=232) found LNR >15%, perineural invasion and R1 resection to be independent predictors of recurrence on multivariable analysis.[21] Whilst LNR was also associated with recurrence in our cohort ($p<0.001$), our AUC was lower than the AUC in their study (0.666 vs. 0.755). As their study had a higher median lymph node yield (20 vs. 15), the LNR may have been more discerning in their cohort.

Our study is the first to report on specific involved margins and the risk of particular recurrence patterns in resected dCCA (**Table S1**). An involved bile duct margin may feasibly lead to local-only recurrence in the porta hepatis or at the hepatojejunal anastomosis. As the anterior surface of the pancreas and the SMV groove margin are in contact with peritoneal surfaces, this may facilitate transcoelomic spread and subsequent mixed recurrence. However, caution in extrapolating these data is advised due to the low numbers of patients with specific involved margins in particular recurrence patterns.

4.3 Female sex as a risk factor for recurrence

A comparison of outcomes between males and females in our cohort found higher rates of lymphatic invasion and a lower chance of completing adjuvant chemotherapy. Female sex was a risk factor for

recurrence on the multivariable model even after correcting for the higher rate of lymphatic invasion. There is recent evidence suggesting sex-based outcome differences from chemotherapy. A systematic review by Ledenko et al. investigated variations in sex-related outcomes of patients with inoperable cholangiocarcinoma in chemotherapy treatment trials (15 studies, n=309 males, 278 females).[22] Whilst these studies did not find evidence of an overall difference in progression-free survival (PFS) between males and females, they did identify varying responses to different chemotherapy regimens between the sexes. For example, females had a higher median PFS compared to males when receiving gemcitabine with S-1, but males had a higher median PFS when receiving capecitabine with nab-paclitaxel. Unfortunately capecitabine monotherapy, the current standard of care in clinical guidelines,[17] was not assessed. Future studies investigating adjuvant therapies in resected dCCA should include sex-based treatment outcomes to identify possible variations in treatment efficacy between males and females.

4.4 Limitations

Despite being a large cohort for studies of this nature, the small number of patients puts our results at risk of both type I errors (high number of comparative statistics) and type II errors (having an inadequate number of patients to detect small but significant differences). Preoperative CA 19-9 was not collected as part of the data set, which has been associated with an increased risk of recurrence and could have been incorporated into our multivariable model. Due to the complexity of the multivariable model, several investigated variables were excluded due to issues with missing data, collinearity or loss of degrees of freedom. It is possible that a larger, more complete data set that addressed these issues may influence the results of our multivariable model.

2. Conclusions

This multicentre retrospective cohort study found that 65% of patients who underwent PD for dCCA developed recurrence within five years of surgery. Most patients recurred within three years, most commonly in the pancreatic bed, the liver and the lung. Predictors of recurrence were female sex, histological stage, venous resection, R1 resection, any lymph node metastases, increasing number of metastatic lymph nodes, perineural invasion, microvascular invasion and lymphatic invasion.

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Supplementary Methods

Selection of factors for univariate and multivariate binary logistic regression

The predictive factors selected for univariable binary logistic regression (BLR) were determined by their ability to be included in the multivariate BLR model. Ideally, all factors investigated in this study would have been included in the multivariate BLR model. However, the multivariate model failed when all factors were entered. Reasons for this included:

- More than 30% of missing data points in any one variable.
- Loss of degrees of freedom (i.e. all of one option from a categorical variable were in the same category as an option from another categorical variable. Factors with very few cases, e.g. use of neoadjuvant therapy, were particularly prone to this).
- Highly correlated variables (e.g. tumour diameter and TNM stage, as the T stage is determined by the diameter of the tumour).

To try and include as many variables as possible, factors were removed one by one once identified as causing one of the above reasons for model failure. Factors with >30% data missing were removed first, followed by those that caused loss of degrees of freedom, and lastly highly related variables. The following factors were removed:

- >30% data points missing: Body mass index, Radiological stage, CRP, CRP:albumin ratio.
- Loss of degrees of freedom: Neoadjuvant chemotherapy, Resectability (low numbers of borderline and locally advanced cases), ASA grade (low numbers of ASA III), Postoperative pancreatic fistula, intra-abdominal collection, Postoperative bile leak, Postoperative gastrojejunal leak, Post-pancreatectomy haemorrhage, Arterial resection, Adjuvant radiotherapy.
- Highly correlated variables: Involved/surface margin (highly correlated with R1 resection), Lymph node ratio (highly correlated to any metastatic lymph nodes on histology, and number of metastatic lymph nodes on histology, Adjuvant chemotherapy commenced (highly correlated with adjuvant chemotherapy completed), Cycles of chemotherapy administered (highly correlated with adjuvant chemotherapy completed).

Albumin, neutrophils, lymphocytes and delayed gastric emptying were excluded *a priori* as they were not considered likely to be predictors of recurrence.

When the above variables were excluded, the multivariate BLR model produced a valid result. All factors included in the multivariate BLR model were also assessed using univariate BLR (Table 3).

Figure S1 Site and timing of recurrence following pancreaticoduodenectomy for cholangiocarcinoma

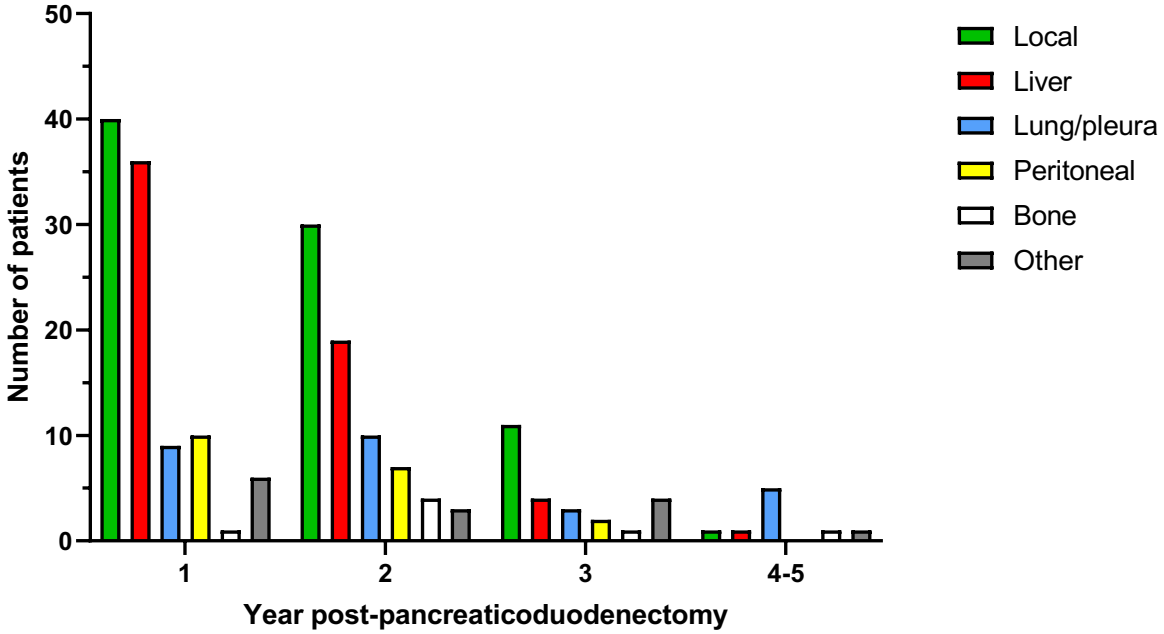
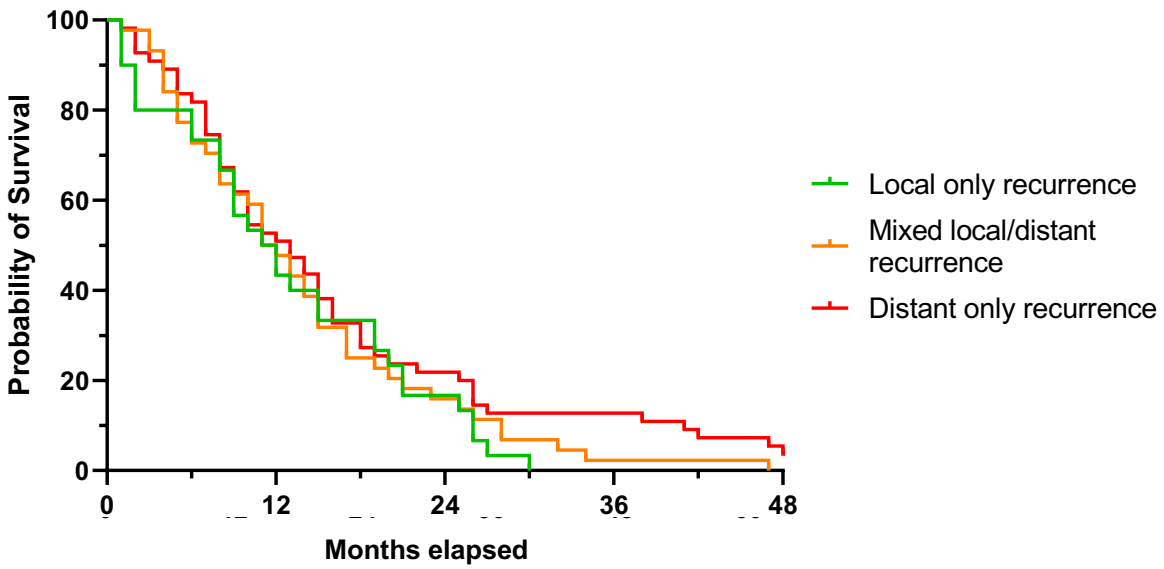
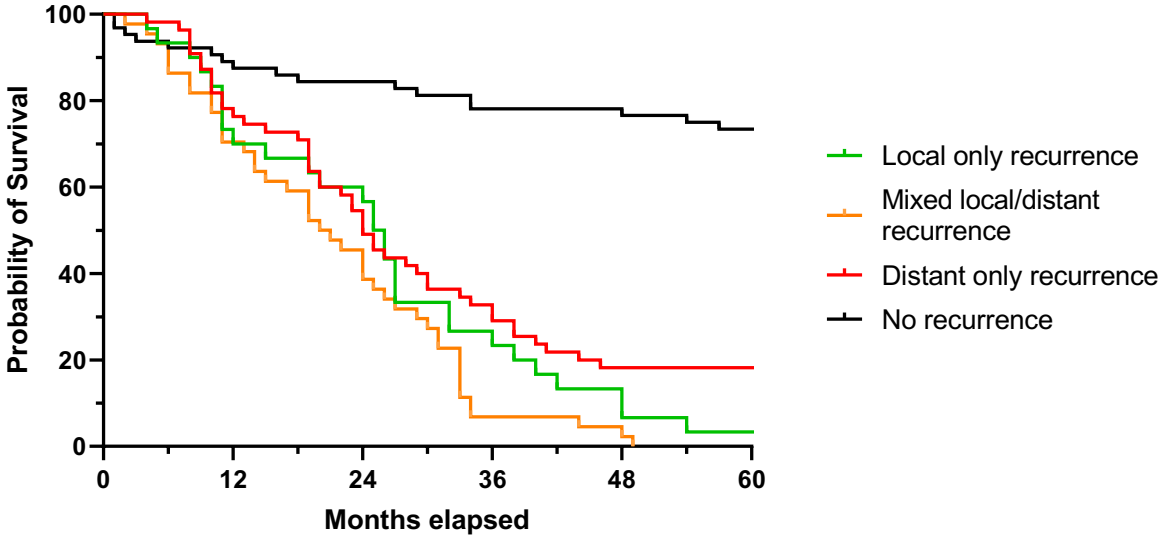


Figure S2a Recurrence-free survival following pancreaticoduodenectomy for cholangiocarcinoma



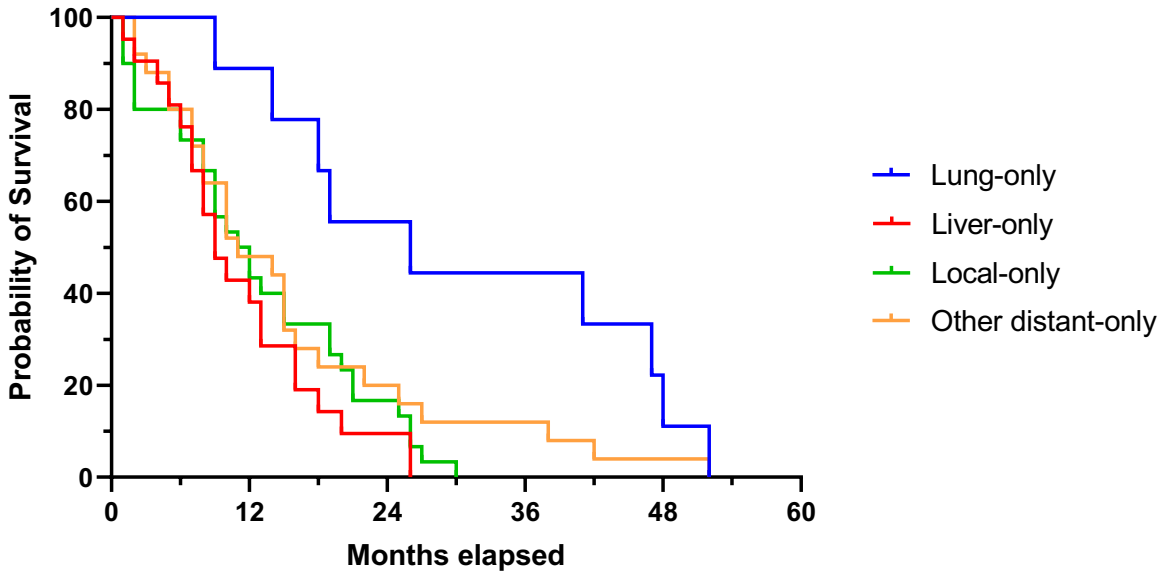
Number at risk	Time since surgery (months)							
	0	6	12	18	24	30	36	42
Local-only recurrence	30	24	15	12	7	1	1	1
Mixed local/distant recurrence	44	34	22	14	8	5	2	2
Distant-only recurrence	55	46	29	18	13	8	8	5

Figure S2b Overall survival following pancreaticoduodenectomy for cholangiocarcinoma



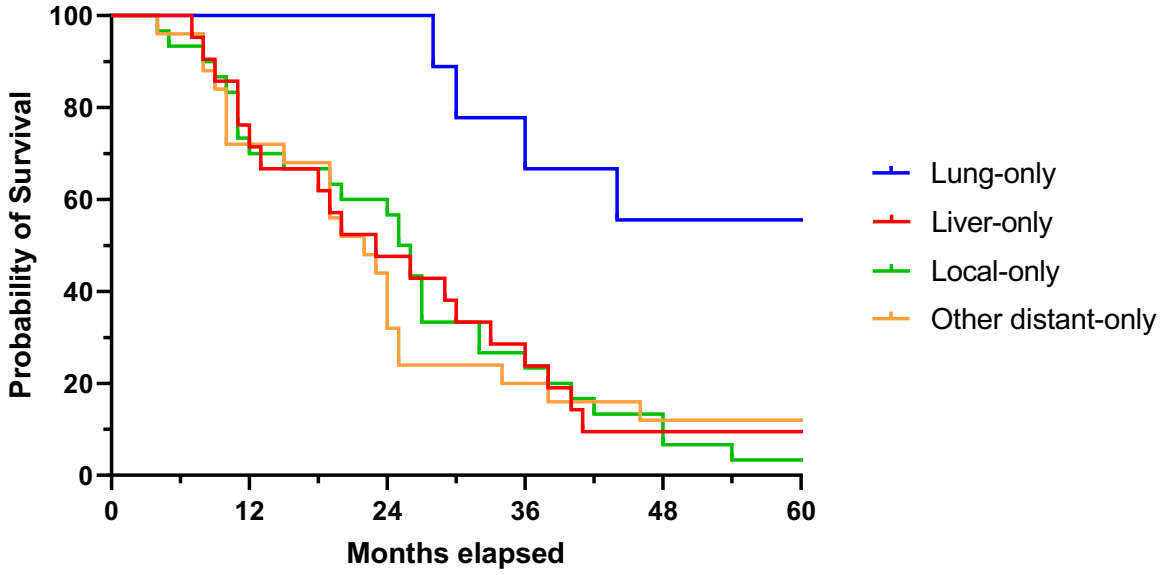
Number at risk	Time since surgery (months)								
	0	6	12	18	24	30	36	42	48
No recurrence	64	60	57	55	55	53	52	52	50
Local-only recurrence	30	29	22	21	18	13	8	5	4
Mixed local/distant recurrence	44	41	34	27	20	14	5	5	2
Distant-only recurrence	55	55	43	40	30	23	18	13	11

Figure S3a Recurrence-free survival in patients with liver-only, lung-only, other distant-only and local-only recurrence following pancreaticoduodenectomy for cholangiocarcinoma



Number at risk	Time since surgery (months)								
	0	6	12	18	24	30	36	42	48
Lung-only recurrence	9	9	9	7	6	5	5	4	2
Liver-only recurrence	21	17	10	4	3	0	0	0	0
Other distant-only recurrence	25	22	13	7	6	4	4	2	1
Local-only recurrence	30	24	15	12	7	1	0	0	0

Figure S3b Overall survival in patients with liver-only, lung-only, other distant-only and local-only recurrence following pancreaticoduodenectomy for cholangiocarcinoma



Number at risk	Time since surgery (months)								
	0	6	12	18	24	30	36	42	48
Lung-only recurrence	9	9	9	9	9	8	6	5	4
Liver-only recurrence	21	21	16	14	11	8	6	3	3
Other distant-only recurrence	25	25	21	18	11	8	6	5	4
Local-only recurrence	30	29	22	21	18	13	8	5	4

Figure S4a Receiver operating characteristics (ROC) area under the curve (AUC) for lymphocyte count

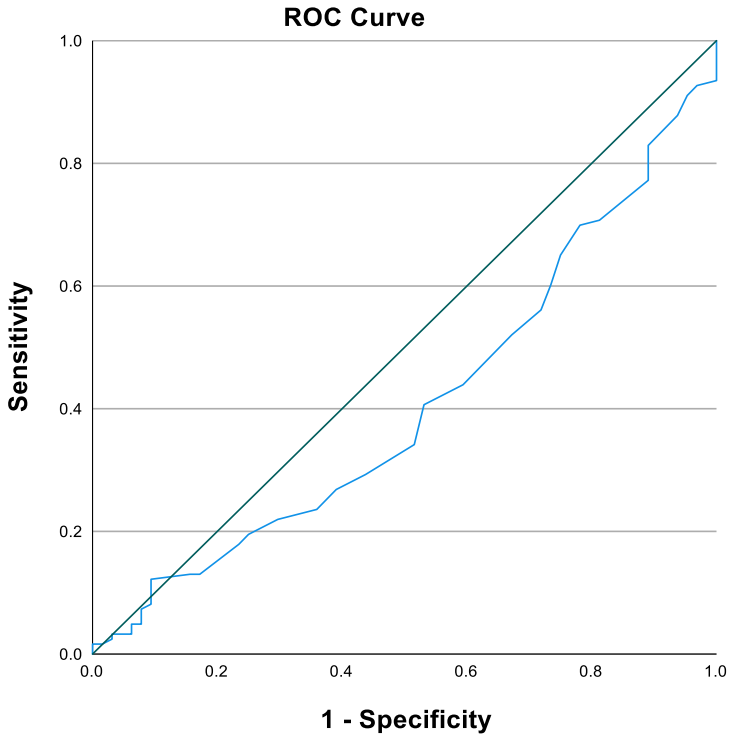


Figure S4b Receiver operating characteristics (ROC) area under the curve (AUC) for neutrophil: lymphocyte ratio (NLR)

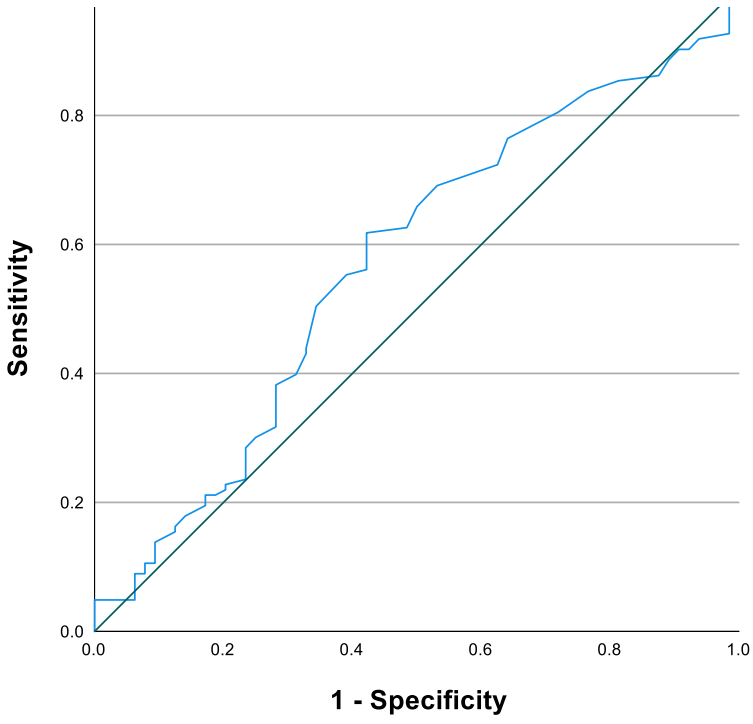


Figure S5a Receiver operating characteristics (ROC) area under the curve (AUC) for number of positive lymph nodes

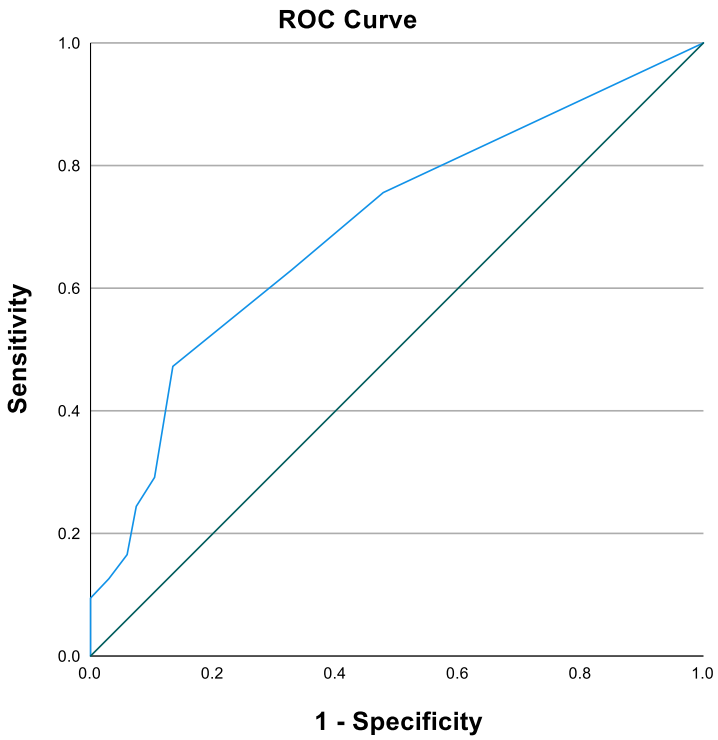


Figure S5b Receiver operating characteristics (ROC) area under the curve (AUC) for lymph node ratio (LNR)

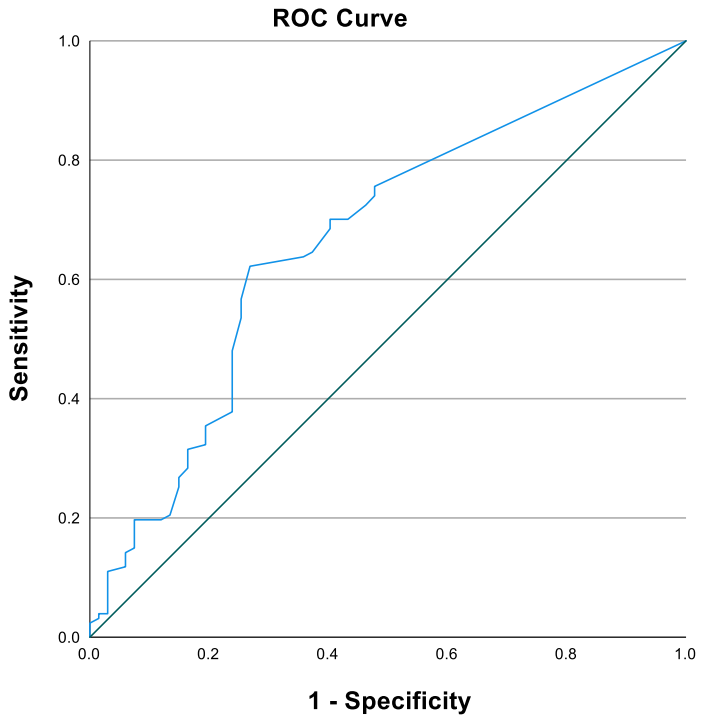


Table S1 Univariable regression analysis of association between specific involved margins and pattern of recurrence

Margin involved	Number of patients (n)	OR (95% CI)	p value
Local-only recurrence			
Anterior surface	1	0.91 (0.11-7.87)	0.935
Bile duct transection	6	3.50 (1.18-10.35)	**0.023**
Pancreatic transection	3	2.18 (0.54-8.74)	0.271
Periductal circumferential margin	3	2.51 (0.61-10.30)	0.202
SMA/posterior margin	11	2.15 (0.94-4.94)	0.071
SMV groove	6	1.81 (0.66-4.97)	0.248
Mixed recurrence			
Anterior	5	9.55 (1.79-51.11)	**0.008**
Bile duct	7	2.67 (0.95-7.48)	0.062
Pancreatic	3	1.31 (0.33-5.16)	0.701
Periductal	1	0.37 (0.05-2.98)	0.348
SMA/posterior	14	1.74 (0.82-3.66)	0.147
SMV groove	10	2.48 (1.03-5.95)	**0.042**
Distant-only recurrence			
Anterior	0	-	-
Bile duct	2	0.32 (0.07-1.46)	0.143
Pancreatic	3	0.98 (0.25-3.83)	0.974
Periductal	2	0.64 (0.13-3.11)	0.580
SMA/posterior	8	0.47 (0.20-1.09)	0.079
SMV groove	3	0.30 (0.09-1.05)	0.060

Table S2 Comparison of backward conditional and entry method multivariable regression analyses of selected potential predictors of recurrence following pancreaticoduodenectomy for distal cholangiocarcinoma

Variables	Multivariable model A [OR (95% CI)]	p value	Multivariable model B [OR (95% CI)]	p value	Multivariable model C [OR (95% CI)]	p value	Multivariable model D [OR (95% CI)]	p value
Demographics								
Male vs. female	2.56 (1.14-5.88)	**0.022**	1.79 (0.85-3.70)	0.128			1.16 (0.41-3.33)	0.776
Pre-operative comorbidities								
Previous history of other cancer	3.39 (0.84-13.78)	0.088	3.48 (0.91-13.36)	0.069			2.30 (0.53-9.93)	0.265
Radiological features								
Indeterminate lung nodules*	-	**0.042**	-	0.124				
Yes vs. no	1.25 (0.33-4.73)	0.738	1.01 (0.28-3.60)	0.994	4.66 (0.75-29.21)	0.100	3.86 (0.55-27.21)	0.176
Unknown vs. no	4.12 (1.37-12.42)	**0.012**	2.92 (1.03-8.22)	**0.042**				
Operative factors								
Venous resection*	-	0.121	-	0.209				
No vs. yes	4.87 (1.06-22.34)	**0.042**	3.76 (0.84-16.75)	0.082	5.86 (0.77-44.89)	0.089	6.21 (0.68-56.51)	0.105
Unknown vs.no	1.77 (0.15-20.63)	0.648	1.80 (0.18-17.97)	0.616				
Post-operative blood transfusion*	-	0.081	-	0.060				
Yes vs. no	0.62 (0.24-1.63)	0.332	0.55 (0.22-1.38)	0.204			0.74 (0.22-2.50)	0.625
Unknown vs. no	0.17 (0.03-0.86)	**0.032**	0.18 (0.04-0.85)	**0.030**				
Histological factors								
Histological stage (TNM 7th edition)*	-	0.091	-	0.151	-	**0.005**	-	0.110
II vs. I	4.71 (1.43-15.53)	**0.011**	4.29 (1.24-14.87)	**0.022**	8.83 (2.33-33.53)	**0.001**	5.31 (1.08-26.09)	**0.040**
III vs. I	3.49 (0.41-29.33)	0.250	4.16 (0.51-33.77)	0.182	11.14 (0.90-137.17)	0.060	7.32 (0.48-111.73)	0.152
Unknown vs. I	-	0.999	-	0.999				
Any tumour positive nodes*	1.43 (1.17-1.74)	**<0.001**	1.42 (1.16-1.74)	**<0.001**			2.42 (0.77-7.62)	0.132
Lymphatic invasion*	-	**0.002**	-	**0.001**				
Yes vs. no	5.75 (2.15-15.40)	**<0.001**	5.75 (2.14-15.40)	**<0.001**	3.54 (1.34-9.34)	**0.011**	3.94 (1.41-11.04)	**0.009**
Unknown vs. no	1.96 (0.74-5.22)	0.177	1.96 (0.74-5.22)	0.177				

Model A - Backward conditional method, categories for unknown variables included (n=187). Model B - Entry method of factors identified by model A, unknown variables included (n=198). Model C - Backward conditional method of factors identified by model A, categories for unknown variables excluded (n=108). Model D - Entry method of factors identified by model A, categories for unknown variables excluded (n=108). The complete list of variables considered for inclusion are reported in **Table 3**. Bold p values are significant at p<0.05. * = variable with unknown data category included. TNM = Tumour-Node-Metastasis, N/A = not applicable (unknown category excluded from analysis), NS = not stated.

Table S3 Comparison between males and females undergoing pancreaticoduodenectomy for cholangiocarcinoma

Variables	Male n=137 (%)	Female n=61 (%)	p value
Demographics			
Age (years), median (IQR)	67 (61-74)	68 (62-74)	0.661
Body mass index (kg/m^2), median (IQR)	26.4 (23.7-28.7)	24.9 (22.1-27.8)	0.170
Pre-operative comorbidities			
Diabetes	25 (18.9)	12 (11.3)	0.143
One or more cardiovascular comorbidities	61 (47.3)	39 (56.5)	0.216
One or more respiratory comorbidities	16 (12.4)	5 (7.2)	0.261
Previous history of other cancer	20 (15.5)	5 (7.2)	0.096
Radiological features			
Radiological stage (TNM 7th edition)	-	-	0.638
Radiologically-detected lymphadenopathy	20 (18.2)	15 (28.8)	0.153
Indeterminate lung nodules	14 (12.7)	4 (9.1)	0.782
MDT opinion			
Resectability	-	-	0.258
Pre-operative treatments			
Biliary stenting (percutaneous or endoscopic)	108 (78.8)	46 (75.4)	0.584
Neoadjuvant chemotherapy ± radiotherapy	2 (1.5)	1 (1.6)	1.000
Pre-operative blood results			
Bilirubin (µmol L^{-1}), median (IQR)	28 (15-68)	18 (10-42)	0.189
C-reactive protein (mg L^{-1}), median (IQR)	10 (3-25)	11 (3-23)	0.886
Albumin (g L^{-1}), median (IQR)	36 (33-42)	37 (28-42)	0.940
CRP:Albumin Ratio (CAR), median (IQR)	0.25 (0.10-0.80)	0.37 (0.14-0.79)	0.649
Neutrophils (x 10^9 L^{-1}), median (IQR)	5.1 (3.9-7.0)	4.8 (3.6-6.6)	0.539
Lymphocytes (x 10^9 L^{-1}), median (IQR)	1.8 (1.2-2.5)	1.9 (1.4-2.4)	0.643
Neutrophil:Lymphocyte Ratio (NLR), median (IQR)	2.85 (1.85-4.23)	2.36 (1.85-3.88)	0.222
Operative factors			
American Society of Anesthesia (ASA) grade	-	-	0.942
Pylorus-preserving (vs. classical) pancreaticoduodenectomy	65 (47.8)	38 (62.3)	0.060
Pancreaticojejunostomy (vs. pancreaticogastrostomy)	99 (75.0)	47 (77.0)	0.758
Venous resection (partial or complete)	9 (7.4)	1 (1.8)	0.321
Arterial resection	2 (1.6)	0 (0.0)	0.334
Intraoperative blood transfusion received	12 (12.0)	8 (20.5)	0.199
Complications			
Post-operative pancreatic fistula (all grades)	40 (30.5)	13 (22.0)	0.227
Clinically relevant pancreatic fistula (grade B/C)	23 (16.8)	7 (11.5)	0.336
Post-operative bile leak	7 (5.3)	2 (3.4)	0.723
Post-operative gastrojejunal leak	1 (0.8)	0 (0.0)	1.000
Post-pancreatectomy haemorrhage	10 (7.6)	9 (15.3)	0.121
Post-operative blood transfusion received	21 (16.5)	13 (22.8)	0.312
Intra-abdominal collection	20 (14.6)	10 (16.4)	0.745
Delayed gastric emptying	24 (18.3)	3 (5.1)	**0.014**
Histological factors			
Differentiation	-	-	0.246
Maximum tumour diameter (mm), median (IQR)	22 (16-30)	23 (20-30)	0.488
Histological stage (TNM 7th edition)	-	-	0.547
Histological factors (continued)			
Incomplete (R1) resection	64 (47.1)	22 (37.3)	0.207
Involved surface/margin:	-	-	-
Anterior surface	6 (4.4)	1 (1.7)	0.677
Bile duct transection	13 (9.6)	4 (6.8)	0.783
Pancreatic transection	9 (6.6)	2 (3.4)	0.509
Periductal circumferential margin	7 (5.1)	3 (5.1)	1.000
Vessel margin (if resected), n=13	6 (66.7)	3 (75.0)	1.000
SMA/posterior margin	34 (25.0)	12 (20.3)	0.481
SMV groove	21 (15.4)	5 (8.5)	0.189
Any tumour positive nodes on histology	89 (65.0)	41 (67.2)	0.758
Number of resected lymph nodes positive for tumour, median (IQR)	2 (0-3)	2 (0-3)	0.342
Total number of resected lymph nodes, median (IQR)	16 (11-22)	14 (9-19)	0.119
Lymph Node Ratio (LNR), median (IQR)	0.10 (0.00-0.21)	0.16 (0.00-0.27)	0.109
Perineural invasion	18 (16.1)	6 (10.2)	0.500
Microvascular invasion	28 (30.4)	13 (30.2)	0.981
Lymphatic invasion	24 (24.2)	17 (28.8)	**0.042**
Outcome			
Recurrence vs. no recurrence	93 (67.9)	36 (59.0)	0.259
Adjuvant treatments			
Adjuvant chemotherapy commenced	64 (48.9)	27 (45.0)	0.621
Cycles of chemotherapy administered, median (IQR)	6 (6-6)	6 (4-6)	0.064
Planned course of adjuvant chemotherapy completed	51 (87.9)	18 (69.2)	**0.039**
Adjuvant radiotherapy	3 (2.3)	2 (3.4)	0.648

Bold p values are significant at p<0.05. CRP = C-reactive protein, IQR = Interquartile range, MDT = multidisciplinary team, TNM = Tumour-Node-Metastasis