Updates in Surgery (2021) 73:439–450
https://doi.org/10.1007/s13304-021-00981-0

ORIGINAL ARTICLE

Intra-pancreatic distal cholangiocarcinoma and pancreatic ductal adenocarcinoma: a common short and long-term prognosis?

Théophile Guilbaud[1] · Edouard Girard[2] · Coralie Lemoine[3] · Ghislain Schlienger[1] · Oyekashopefoluw Alao[2] · Olivier Risse[2] · Stéphane Berdah[1] · Mircea Chirica[2] · Vincent Moutardier[1] · David Jérémie Birnbaum[1]

Received: 1 September 2020 / Accepted: 12 January 2021 / Published online: 24 January 2021

Abstract

The aim of the study was to compare histological features, postoperative outcomes, and long-term prognostic factors after pancreaticoduodenectomy for distal cholangiocarcinoma and pancreatic ductal adenocarcinoma. From 2005 to 2017, 188 pancreaticoduodenectomies (pancreatic ductal adenocarcinoma $n=151$, distal cholangiocarcinoma $n=37$) were included. Postoperative outcomes were compared after matching on pancreatic gland texture and main pancreatic duct size. Matching according to tumor size, lymph node invasion and resection margin was used to compare overall and disease-free survival. Distal cholangiocarcinoma patients had more often "soft" pancreatic gland ($P=0.002$) and small size main pancreatic duct ($P=0.001$). Pancreatic ductal adenocarcinoma patients had larger tumors ($P=0.009$), and higher lymph node ratio ($P=0.017$). Severe morbidity ($P=0.023$) and clinically relevant pancreatic fistula ($P=0.018$) were higher in distal cholangiocarcinoma patients. After matching on gland texture and main pancreatic duct diameter, clinically relevant postoperative pancreatic fistula was still more frequent in distal cholangiocarcinoma patients ($P=0.007$). Tumor size > 20 mm was predictive of impaired overall survival ($P=0.024$) and disease-free survival ($P=0.003$), tumor differentiation ($P=0.027$) was predictive of impaired overall survival. Survival outcomes for distal cholangiocarcinoma and pancreatic ductal cholangiocarcinoma were similar after matching patients according to tumor size, lymph node invasion and resection margin. Long-term outcomes after pancreaticoduodenectomy for distal cholangiocarcinoma and pancreatic ductal adenocarcinoma patients are similar. Postoperative course is more complicated after pancreaticoduodenectomy for distal cholangiocarcinoma than pancreatic ductal adenocarcinoma. After pancreaticoduodenectomy, patients with distal cholangiocarcinoma and pancreatic ductal adenocarcinoma have similar long-term oncological outcomes.

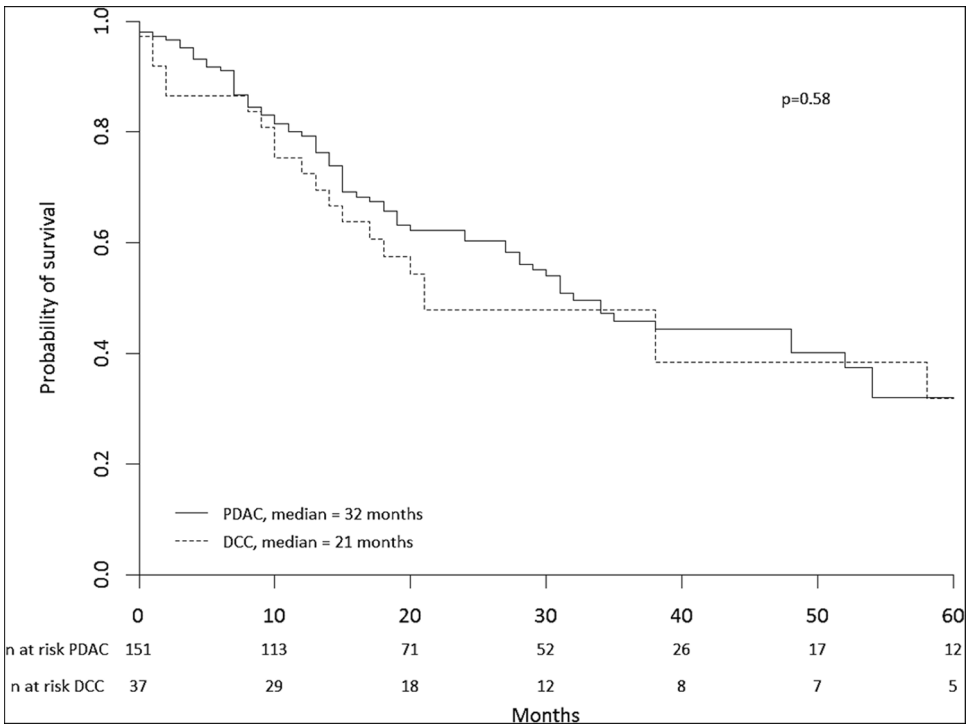
✉ Théophile Guilbaud
theo.guilbaud@gmail.com

[1] Department of Digestive Surgery, Hôpital Nord, Aix-Marseille University, Chemin des Bourrely, 13915 Marseille Cedex 20, France

[2] Department of Digestive Surgery and Liver Transplantation, Hôpital Michallon, Grenoble University, Grenoble, France

[3] Self Perceived Health Assessment Research Unit and Department of Public Health, Aix-Marseille University, Marseille, France

Graphic abstract



Keywords Distal cholangiocarcinoma · Pancreatic ductal adenocarcinoma · Pancreaticoduodenectomy · Survivals · Prognostic factors

Introduction

Periampullary malignancies include pancreatic ductal adenocarcinoma (PDAC), ampullary adenocarcinoma, distal cholangiocarcinoma (DCC), and duodenal adenocarcinoma. DCC and PDAC represent 11–20 and 70% of these tumors, respectively [1–3]. Radical resection by pancreatoduodenectomy (PD) is the only curative treatment in patients with DCC and PDAC. Because patients with DCC and PDAC are often analyzed together in reports focusing on PD outcomes [1, 4–6], it is unclear whether operative and oncological outcomes are influenced by tumor pathology.

Because DCC is rare, it is difficult to accumulate enough cases to establish clinical guidelines and validate prognostic factors. In DCC, R1 resection, lymph node invasion, perineural infiltration, microvascular invasion, pancreatic invasion, and pathological advanced T-stage have been associated with shorter survival [7]. For solid tumors, size represents a major predictor of oncological outcome and it has been associated with poor overall survival and disease recurrence in PDAC [8–10].

The aim of this study was to compare the histological features, postoperative outcomes, and long-term prognostic factors of DCC and PDAC patients.

Methods

Population study

From January 2005 to 2017, consecutive patients who underwent PD for histologically proven PDAC and DCC in two tertiary referral centers were extracted from a prospectively maintained database and were analyzed retrospectively. The diagnosis of malignancy was suspected on preoperative imaging data or biopsy. In case of difficulties distinguishing between DCC and PDAC, immunohistochemical analyses were done. Patients who underwent extrahepatic bile duct resection for DCC, ampullary and duodenal carcinomas were excluded from the analysis. Patients who received neoadjuvant chemotherapy were excluded. The study was conducted in accordance with the Declaration of Helsinki, and was reviewed and approved by the local ethical committees of both representative institutions (No. 2018-25-04-001).

All patients enrolled completed the informed consent for participate and publication.

Preoperative work-up and surgical procedures

All cases were discussed by a multidisciplinary pancreatic tumor board. Minimal routine work-up included 3-phase contrast-enhanced multidetector computed tomography (CT). Magnetic resonance imaging (MRI) with magnetic resonance cholangiopancreatography (MRCP) or endoscopic ultrasound (EUS) with biopsy were used when CT was inconclusive.

All procedures were done by laparotomy. If necessary, venous involvement was managed by "en bloc" resection and primary anastomosis or venous graft interposition. Intraoperatively, all resections included standard lymphadenectomy. All patients had an intraoperative frozen section examination of the proximal common bile duct and the pancreatic margins. If margins were invaded, additional resection was performed. Pancreatic reconstruction was done through a pancreaticogastrostomy and pancreatic duct stents were used systematically in cases involving a small (< 3 mm) main pancreatic duct (MPD) diameter and/or when the pancreatic gland texture was "soft". Drains were systematically placed close to the pancreato-gastrostomy and posterior to the choledocho-jejunostomy.

Data analysis

The data collected included demographics [age, sex, body mass index (BMI), American Society of Anesthesiologists (ASA) score [11]], preoperative jaundice, duration of surgery, pancreatic gland texture (i.e., "soft" or "hard") and MPD diameter. Postoperative pancreatic fistulas (POPF) were graded according to the International Study Group of Pancreatic Fistula (ISGPF) classification, and grade B and C POPFs were defined as clinically relevant [12]. Delayed gastric emptying (DGE) was categorized according to the International Study Group of Pancreatic Surgery classification (ISGPS) [13]. Postoperative bleeding was graded according to the ISGPS definition. Biliary fistula was defined as the presence of bile in the drainage fluid. Abdominal infections were defined as the presence of infectious signs requiring the administration of systemic antibiotics associated with intraabdominal collection on postoperative CT scan. Operative mortality was defined as death during the initial hospital stay or by postoperative day 90. Postoperative complications were defined as any adverse events occurring within 90 days of PD and were summarized using the Clavien–Dindo classification system. Severe morbidity was defined as Clavien–Dindo grade ≥ 3 complications [14].

Pathological analysis

In each center, a pancreatic expert pathologist reviewed all pathologic specimens and confirmed the diagnoses of PDAC or DCC. All cases were staged according to the AJCC (American Joint Committee on Cancer Staging) 7th edition [15]. Resection margins were considered R0 when at least 1 mm of clearance was observed. Histological data analyzed were tumor size, lymph node invasion, lymph node ratio, TNM stage, perineural infiltration, microvascular invasion, and tumor differentiation (well vs. moderate and poor).

Follow-up

Follow-up was scheduled every 3 months during the first 2 years and every 6 months thereafter. Follow-up included a clinical examination, measure of serum CA 19–9 levels and thoraco-abdominal CT scan. Adjuvant chemotherapy was administered when recommended and depended on the patient's physical status after PD. The main regimen given to PDAC patients was gemcitabine. The optimal adjuvant strategy has not been determined yet in DCC patients, so adjuvant regimen was based on multidisciplinary pancreatic tumor board discussions.

The end of follow-up was set at December 2018 or at the time of death. Overall survival (OS) was calculated from the date of surgery to the date of the last follow-up. Disease-free survival (DFS) was determined from the date of surgery to the date of recurrence, defined as the earliest radiologic evidence of recurrence.

Statistical analysis

Categorical variables are described in terms of frequencies and percentages. The distribution of continuous variables was described as the mean ± standard error. Univariable associations were examined using Pearson's chi square or Fisher's exact test, and the *t* test or non-parametric Mann Whitney test, as appropriate. Factors independently associated with OS and DFS were identified by multiple logistic regression analysis that included all variables with *P* values < 0.10. All multivariable Cox proportional hazard models were systematically adjusted: tumor size, tumor differentiation, severe morbidity and postoperative chemotherapy. Survival analysis was conducted using the Kaplan–Meier method and compared using the log-rank test. A *P* value < 0.05 was significant. In addition, a matching process was used to compare PDAC and DCC groups on postoperative outcomes according to pancreatic gland texture and MPD diameter. Finally, another matching process was used to compare PDAC and DCC groups on survival (OS and DFS) according to tumor size, lymph node invasion, and resection margin status. R packages "matchit" and

"survival" were used for the propensity score and survival analyses, respectively [16]. The analysis was performed using R Studio version 1.1.447 [17].

Results

Clinical and surgical characteristics

Among the 188 patients (DCC, $n=37$; PDAC, $n=151$), DCC and PDAC groups were comparable according to demographic data (Table 1). Patients who underwent PD for DCC had more "soft" pancreatic gland texture (21 patients (67.7%) vs. 50 patients (37.6%), $P=0.002$) and small size (< 3 mm) MPD (27 patients (68.7%) vs. 108 patients (37.5%), $P=0.001$) than patients with PDAC.

Pathological findings

All patients had a tumor free proximal bile duct and pancreatic margins after frozen section analysis. Complete tumor removal (R0 resection) was achieved in 149 patients (79.3%) (Table 1). In total, 39 patients (21.7%) presented a R1 margin located on the posterior margin, mostly in the PDAC group ($n=35$, 23.2% vs. $n=4$, 10.8%, $P=0.177$), and 37 patients (94.9%) out of the 39 R1 patients had a tumor size > 20 mm ($P<0.001$). The median number of retrieved lymph nodes was 11 (range: 1–45), lymph node metastasis was found in 120 patients (63.8%) with a mean lymph node ratio of 0.20 (±0.23). Microvascular invasion was present in 108 patients (57.4%), and well differentiated tumors in 72 patients (38.3%).

The PDAC group had larger tumor size (29.5 mm (±12.1) vs. 23.0 mm (±9.9), $P=0.009$), and higher lymph node ratio (0.22 (±0.23) vs. 0.12 (±0.18), $P=0.017$) (Table 1).

Postoperative outcomes

Perioperative mortality and severe morbidity were 2.1% ($n=4$) and 28.2% ($n=53$), respectively. Postoperative complications included clinically relevant POPF (i.e., grade B/C) in 46 patients (24.5%) (Table 1).

The severe morbidity rate was higher in DCC than in PDAC patients (43.2% ($n=9$) vs. 26.0% ($n=19$), $P=0.023$). Clinically relevant POPF (i.e., grade B/C) occurred more frequently after PD for DCC. (40.5% ($n=15$) vs. 20.5% ($n=31$), $P=0.018$). The mean length of hospital stay was longer in the DCC group (29 ± 16 days) than in the PDAC group (21 ± 8 days) ($P=0.031$).

After a matching process according to pancreatic gland texture and MPD diameter (Table 2), the severe morbidity rate, postoperative hemorrhage rate and the mean length of hospital stay were similar between the two groups. However, clinically relevant POPF (i.e., grade B/C) occurred more frequently in DCC than in PDAC patients (36.7% ($n=11$) vs. 12.9% ($n=11$), $P=0.007$). Twelve patients (10.4%) presented a grade B POPF, mostly in the DCC group ($n=8$, 26.6% vs. $n=4$, 4.7%, $P=0.002$) and ten patients (8.7%) experienced a grade C POPF without difference between groups ($n=3$, 10.0% in DCC group vs. $n=7$, 8.2% in PDAC group, $P=0.719$).

Long term follow-up

Mean follow-up was 25.6 months. Median OS and 1-, 3- and 5-year OS rates were 21 months and 70.3, 29.7 and 13.5%, respectively, in the DCC group, and 32 months and 62.6, 20.5 and 7.1%, respectively, in the PDAC group. No difference was found concerning OS (Fig. 1a). Median DFS and 1-, 3- and 5-year DFS rates were 13 months and 51.4, 13.5 and 5.4%, respectively, in the DCC group, and 14 months and 56.2, 12.9 and 5.8%, respectively, in the PDAC group. No difference was found concerning DFS (Fig. 1b). Moreover, the recurrence rate and the site of recurrence were similar between the two groups (Table 1).

Postoperative chemotherapy was administered to 10 DCC patients (27.0%), while 120 PDAC patients (79.5%) received adjuvant chemotherapy ($P<0.001$). In those patients, no difference was found between DCC ($n=10$) and PDAC ($n=120$) patients concerning median OS (24 vs. 33 months, $P=0.281$) and median DFS (14 vs. 14 months, $P=0.866$). Similarly, in patients without postoperative chemotherapy (DCC group, $n=27$; PDAC group, $n=31$), no difference was found concerning median OS (DCC group, 19 months vs. PDAC group, 25 months, $P=0.454$) and median DFS (DCC group, 12 months vs. PDAC group, 11 months, $P=0.724$).

Factors influencing overall survival

In the entire cohort, the univariate analyses showed that tumor size > 20 mm, well tumor differentiation, and severe postoperative morbidity impacted OS (Table 3). Multivariate analyses identified tumor size > 20 mm (HR 2.17 [1.11–4.25], $P=0.024$) and well tumor differentiation (HR 0.47 [0.24–0.91], $P=0.027$) as independent factors influencing OS.

According to these poor prognosis factors (tumor size > 20 mm and moderate/poor tumoral differentiation), no difference was found in OS between DCC and PDAC groups (Fig. 2).

Univariate and multivariate analyses of clinicopathological factors that may influence OS in PDAC and DCC, respectively, are shown in Table 4. In PDAC patients, tumor size > 20 mm (HR 2.04 [1.10–3.77], $P=0.023$), well tumor differentiation (HR 0.49 [0.29–0.84], $P=0.009$), and postoperative chemotherapy (HR 0.45 [0.26–0.79], $P=0.005$) were

Table 1 Comparisons of demographics, intraoperative and outcomes data of the two groups (PDAC and DCC)

Variables	All ($N=188$)		PDAC ($N=151$)		DCC ($N=37$)		P value
Demographic							
Sex ratio (F:M)	77:111		69:82		8:29		**0.008**
Age (mean ± SD, years)	65.3	(±8.7)	65.2	(±8.5)	65.9	(±9.6)	0.684
BMI (mean ± SD, kg/m^2)	25.4	(±4.6)	25.3	(±4.4)	25.9	(±4.1)	0.272
ASA score							
1	38	(20.2)	29	(19.2)	9	(24.3)	0.773
2	88	(46.8)	72	(47.7)	16	(43.3)	
3	62	(33.0)	50	(33.1)	12	(32.4)	
Diabetes	49	(26.1)	43	(38.5)	6	(16.2)	0.128
Jaundice	132	(70.2)	107	(70.9)	25	(67.6)	0.695
Biliary stent	94	(50.0)	71	(47.0)	23	(62.2)	0.100
Surgery							
Operative time (mean ± SD, min)	367.2	(±104.1)	368.9	(±96.8)	355.2	(±131.3)	0.382
Adjacent organ resection	11	(5.9)	8	(5.3)	2	(5.4)	1.000
Venous resection	19	(10.1)	19	(12.6)	0	(0.0)	0.108
Soft pancreatic gland texture	71	(37.7)	50	(37.6)	21	(67.7)	**0.002**
Large MPD (> 3 mm)	90	(47.9)	80	(62.5)	10	(31.3)	**0.001**
Pathology							
Tumor size (mean ± SD, mm)	28	(±11)	29.5	(±12.1)	23.0	(±9.9)	**0.009**
R1 resection	39	(20.7)	35	(23.2)	4	(10.8)	0.177
Lymph node invasion	120	(63.8)	102	(67.6)	18	(48.7)	0.083
Lymph node ratio (mean ± SD)	0.20	(±0.23)	0.22	(±0.23)	0.12	(±0.22)	**0.017**
Microvascular invasion	108	(57.4)	89	(58.9)	19	(51.4)	0.403
Perineural infiltration	150	(79.7)	124	(82.1)	26	(70.3)	0.108
Tumor differentiation							
Well	72	(38.3)	60	(39.7)	12	(32.4)	0.159
Moderate/poor	116	(61.7)	91	(60.3)	25	(67.6)	
Early postoperative outcomes							
Severe morbidity	53	(28.2)	37	(24.5)	16	(43.2)	**0.023**
Mortality	4	(2.1)	3	(1.9)	1	(2.7)	1.000
Grade B/C pancreatic fistula	46	(24.5)	31	(20.5)	15	(40.5)	**0.018**
Biliary fistula	19	(10.1)	16	(10.6)	3	(8.1)	1.000
Postoperative hemorrhage	17	(9.0)	13	(8.6)	4	(10.8)	0.749
DGE	74	(39.4)	55	(36.5)	19	(51.4)	0.180
Abdominal infection	40	(21.3)	31	(20.5)	9	(24.3)	0.613
Length of hospital stay (mean ± SD, days)	25	(±15)	21	(±8)	29	(±16)	**0.031**
Long term outcomes							
Postoperative chemotherapy	130	(69.1)	120	(79.5)	10	(27.0)	**< 0.001**
Recurrence	116	(61.7)	94	(62.3)	22	(59.5)	0.754
Local	45	(23.9)	40	(26.5)	5	(13.5)	0.100
Liver metastasis	75	(39.9)	60	(39.7)	15	(40.5)	0.928
Peritoneal carcinomatosis	38	(20.2)	33	(21.9)	5	(13.5)	0.258

Bold values are considered significant ($P < 0.05$)

BMI indicates body mass index (calculated as weight in kilograms divided by height in meters squared), *ASA* American Society of Anesthesiologists, *MPD* main pancreatic duct, *DGE* delayed gastric empty

identified as independent factors influencing OS. In DCC patients, only tumor size > 20 mm (HR 1.24 [1.12–2.75], $P = 0.035$) and well tumor differentiation (HR 0.26

Table 2 Comparisons of demographics, intraoperative and postoperative outcomes data of the two groups (PDAC and DCC) after matching process according to pancreatic gland texture and MPD diameter

Variables	All ($N=115$)		PDAC ($N=85$)		DCC ($N=30$)		P value
Demographic							
Sex ratio (F:M)	44/71		38/47		6/24		**0.017**
Age (mean ± SD, years)	64.8	(±8.6)	64.5	(±8.1)	65.5	(±10.1)	0.626
BMI (mean ± SD, kg/m^2)	25.2	(±4.4)	25.1	(±4.2)	25.6	(±3.9)	0.321
ASA score							
1	33	(28.7)	24	(28.2)	9	(30.0)	0.976
2	42	(36.5)	31	(36.5)	11	(36.7)	
3	40	(34.8)	30	(35.3)	10	(33.3)	
Diabetes	27	(23.5)	23	(27.1)	4	(13.3)	0.127
Jaundice	84	(73.0)	63	(74.1)	21	(70.0)	0.662
Biliary stent	61	(53.0)	41	(48.2)	20	(66.7)	0.082
Surgery							
Operative time (mean ± SD, min)	365	(±134.7)	367.5	(±111.6)	358.2	(±143.2)	0.627
Adjacent organ resection	9	(7.8)	7	(8.2)	2	(6.7)	1.000
Venous resection	18	(15.7)	18	(21.2)	0	(0.0)	**0.003**
Pathology							
Tumor size (mean ± SD, mm)	27.7	(±10.6)	29.3	(±10.6)	23.0	(±9.5)	**0.004**
R1 resection	23	(20.0)	20	(23.5)	3	(10.0)	0.111
Lymph node invasion	73	(63.5)	59	(69.4)	14	(46.7)	**0.026**
Lymph node ratio (mean ± SD)	0.18	(±0.20)	0.21	(±0.21)	0.11	(±0.17)	**0.016**
Microvascular invasion	68	(59.2)	53	(62.4)	15	(50.0)	0.237
Perineural infiltration	94	(81.7)	74	(87.1)	20	(66.7)	**0.013**
Tumor differentiation							
Well	46	(40.0)	37	(43.5)	9	(30.0)	0.193
Moderate/Poor	69	(60.0)	48	(56.5)	21	(70.0)	
Early postoperative outcomes							
Severe morbidity	34	(29.6)	23	(27.1)	11	(36.7)	0.322
Mortality	4	(3.5)	3	(3.5)	1	(3.3)	1.000
Grade B/C pancreatic fistula	22	(19.1)	11	(12.9)	11	(36.7)	**0.007**
Biliary fistula	10	(8.7)	8	(9.4)	2	(6.7)	1.000
Postoperative hemorrhage	12	(10.4)	9	(10.6)	3	(10.0)	1.000
DGE	50	(43.5)	35	(41.2)	15	(50.0)	0.402
Abdominal infection	27	(23.5)	20	(23.5)	7	(23.3)	0.983
Length of hospital stay (mean ± SD, days)	23.9	(±13.1)	23.2	(±13.3)	26.1	(±12.6)	0.289

Bold values are considered significant ($P < 0.05$)

BMI indicates body mass index (calculated as weight in kilograms divided by height in meters squared), *ASA* American Society of Anesthesiologists, *MPD* main pancreatic duct, *DGE* delayed gastric empty

[0.08–0.88], $P=0.031$) were highlighted as independent factors influencing OS.

Factors influencing disease-free survival

In the entire cohort, the univariate analyses showed that tumor size > 20 mm and well tumor differentiation impacted DFS (Table 2). Multivariate analyses identified tumor size > 20 mm (HR 2.32 [1.33–4.06], $P=0.003$) as the only independent factor influencing DFS.

Univariate and multivariate analyses of clinicopathological factors that may influence DFS in PDAC and DCC respectively are shown in Table 4. In PDAC patients, tumor size > 20 mm (HR 1.91 [1.16–3.14], $P=0.011$) was identified as the only independent factor influencing DFS, while in DCC patients no independent factor influencing DFS was highlighted.

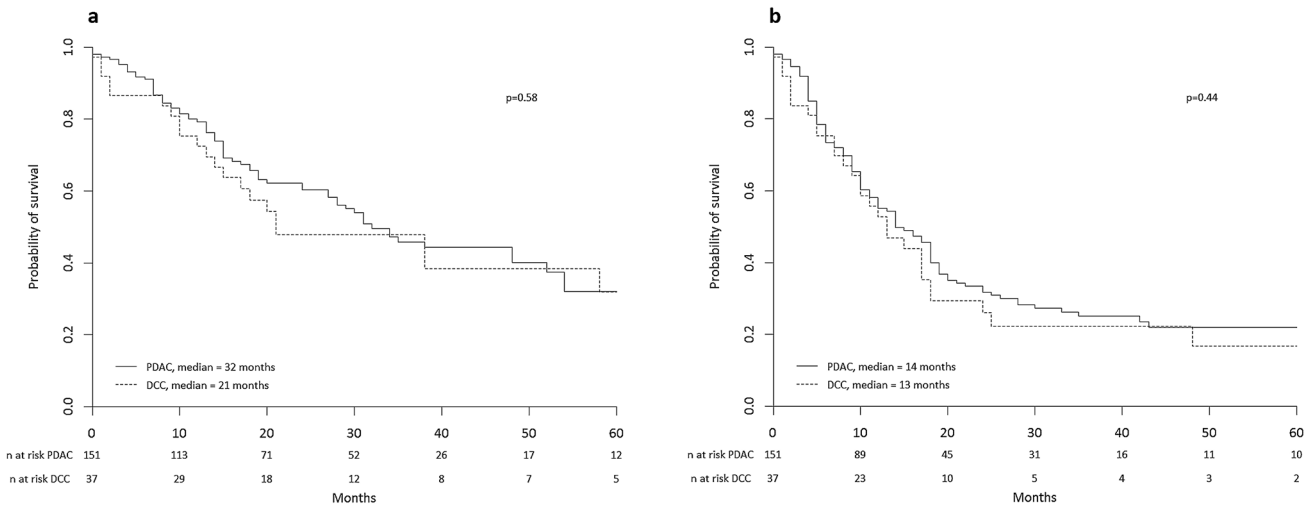


Fig. 1 Overall and disease-free survivals compared between patients who underwent PD with curative intent for DCC and PDAC. **a** Overall survival. **b** Disease-free survival

Table 3 Univariable and multivariable analyses of clinicopathological factors that may influence Overall and Disease-Free Survivals

Predictive factors	Univariate analysis	Multivariate analysis		*P* value
	P value	Hazard ratio (95% CI)		
Overall survival				
Age	0.203	–		–
Gender	0.391	–		–
Biliary stent	0.884	–		–
PDAC	0.407	–		–
DCC				
Tumor size > 20 mm	0.024	2.17	(1.11–4.25)	**0.024**
R1 resection	0.954	–		–
Lymph node ratio	0.133	–		–
Microvascular invasion	0.263	–		–
Perineural infiltration	0.327	–		–
Well differentiation	0.027	0.47	(0.24–0.91)	**0.027**
Severe morbidity	0.030	1.91	(0.97–3.75)	0.063
Postoperative chemotherapy	0.052	0.62	(0.32–1.19)	0.150
Disease-free survival				
Age	0.322	–		–
Gender	0.152	–		–
PDAC	0.164	–		–
DCC				
Biliary stent	0.937	–		–
Tumor size > 20 mm	0.003	2.32	(1.33–4.06)	**0.003**
R1 resection	0.916	–		–
Lymph node ratio	0.124	–		–
Microvascular invasion	0.110	–		–
Perineural infiltration	0.151	–		–
Well differentiation	0.024	0.53	(0.31–1.25)	0.191
Severe morbidity	0.444	–		–
Postoperative chemotherapy	0.282	–		–

Bold values are considered significant ($P < 0.05$)

PDAC indicates pancreatic ductal adenocarcinoma, *DCC* distal cholangiocarcinoma

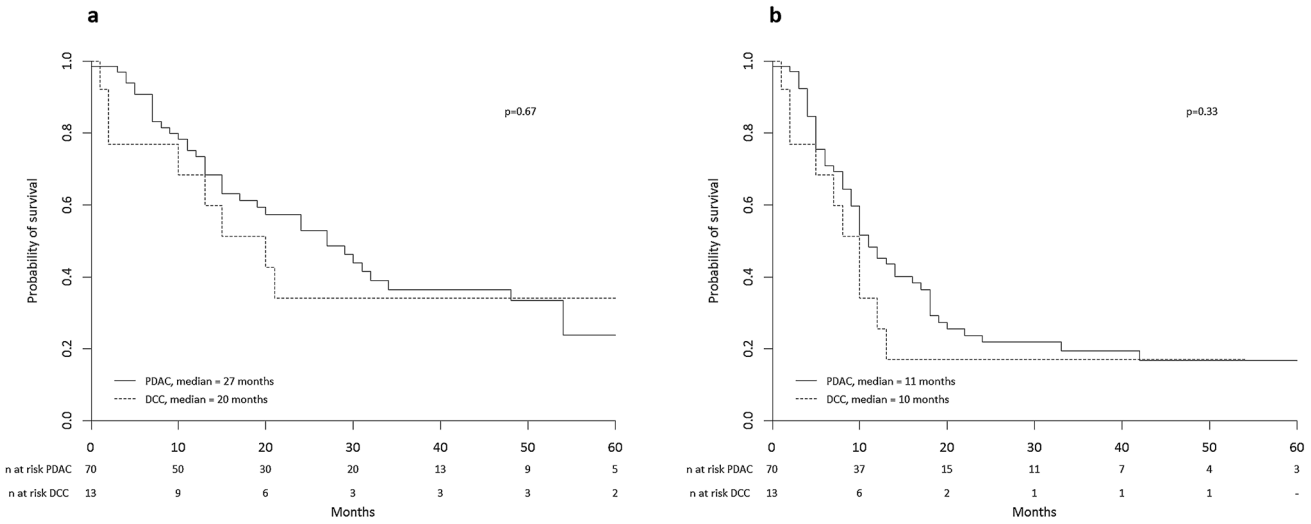


Fig. 2 Overall and disease-free survivals compared between patients associated with tumor size > 20 mm and moderate/poor tumor differentiation, who underwent PD in curative intent for DCC and PDAC. **a** Overall survival. **b** Disease-free survival

Table 4 Univariable and multivariable analyses of clinicopathological factors that may influence Overall and Disease-Free Survivals in pancreatic ductal adenocarcinoma (PDAC) and distal cholangiocarcinoma (DCC) respectively

Predictive factors	PDAC				DCC			
	Univariate analysis	Multivariate analysis		*P* value	Univariate analysis	Multivariate analysis		*P* value
	P value	Hazard ratio (95% CI)			*P* value	Hazard ratio (95% CI)		
Overall survival								
Age	0.744	–		–	0.127	–		–
Gender	0.982	–		–	0.673	–		–
Biliary stent	0.701	–		–	0.884	–		–
Tumoral size > 20 mm	0.043	2.04	(1.10–3.77)	**0.023**	0.036	1.24	(1.12–2.75)	0.035
R1 resection	0.136	–		–	0.709	–		–
Lymph node ratio	0.125	–		–	0.135	–		–
Microvascular invasion	0.550	–		–	0.370	–		–
Perineural infiltration	0.126	–		–	0.761	–		–
Well differentiation	0.032	0.49	(0.29–0.84)	**0.009**	0.037	0.26	(0.08–0.88)	**0.031**
Severe morbidity	0.115				0.332	–		–
Postoperative chemotherapy	0.031	0.45	(0.26–0.79)	**0.005**	0.508	–		–
Disease-free survival								
Age	0.709	–		–	0.335	–		–
Gender	0.174	–		–	0.361	–		–
Biliary stent	0.582	–		–	0.709	–		–
Tumoral size > 20 mm	0.003	1.91	(1.16–3.14)	**0.011**	0.054	1.90	(0.91–4.05)	0.069
R1 resection	0.111	–		–	0.427	–		–
Lymph node ratio	0.174	–		–	0.178	–		–
Microvascular invasion	0.281	–		–	0.678	–		–
Perineural infiltration	0.169	–		–	0.730	–		–
Well differentiation	0.051	0.83	(0.54–1.25)	0.371	0.064	0.58	(0.25–1.32)	0.191
Severe morbidity	0.109				0.402	–		–
Postoperative chemotherapy	0.808	–		–	0.185	–		–

Bold values are considered significant ($P < 0.05$)

Long term prognosis after matching process

After a matching process according to tumor size, lymph node invasion, and resection margin status, 30 DCC patients were compared to 101 PDAC patients. Patients who underwent PD for DCC were more often male (24 patients (80.0%) vs. 56 patients (55.5%), $P=0.015$), had more "soft" pancreatic gland texture (20 patients (66.7%) vs. 35 patients (34.7%), $P=0.018$), and small size MPD (21 patients (70.0%) vs. 38 patients (37.6%), $P=0.018$) than PDAC patients. The severe complication rate was similar between the two matched groups (22.7% ($n=23$) in the PDAC group vs. 36.7% ($n=11$) in the DCC group, $P=0.127$). However, clinically relevant POPF (i.e., grade B/C) occurred more frequently in the DCC group than in the PDAC group (36.7% ($n=11$) vs. 12.9% ($n=13$), $P=0.006$). PDAC and DCC patients were similar regarding perineural infiltration (83.3% vs. 66.7%, $P=0.070$), microvascular invasion (56.4% vs. 50.0%, $P=0.534$), and well tumor differentiation rates (45.5% vs. 30.0%, $P=0.130$). Postoperative chemotherapy was administered to 9 DCC patients (30.0%) and 86 PDAC patients (85.2%) ($P<0.001$).

Long term prognosis factors influencing OS and DFS in the matched cohort are shown in Table 5. Univariate analyses found that tumor size, well tumor differentiation, severe morbidity, and postoperative chemotherapy influenced OS, and that tumor size, lymph node ratio, and well tumor differentiation impacted DFS. In multivariate analyses, well tumor differentiation (HR 0.43 [0.24–0.78], $P=0.005$) and severe morbidity (HR 2.39 [1.33–4.28], $P=0.004$) were the two independent factors influencing OS, whereas tumor size (HR 2.03 [1.17–3.52], $P=0.012$) was the only independent factor associated with DFS. Pathological diagnosis (DCC vs. PDAC) did not impact OS and DFS.

Table 5 Univariable and multivariable analyses of clinicopathological factors that may influence Overall and Disease-Free Survivals in the matched cohort according to tumor size, lymph node invasion and resection margin status

Predictive factors	Univariate analysis	Multivariate analysis		*P* value
	P value	Hazard ratio (95% CI)		
Overall survival				
Age	0.258	–		–
Gender	0.945	–		–
Biliary stent	0.329	–		–
PDAC	0.244	–		–
DCC				
Tumor size	0.068	1.63	(0.94–2.83)	0.087
R1 resection	0.296	–		–
Lymph node ratio	0.191	–		–
Microvascular invasion	0.828	–		–
Perineural infiltration	0.335	–		–
Well differentiation	0.022	0.43	(0.24–0.78)	**0.005**
Severe morbidity	0.021	2.39	(1.33–4.28)	**0.004**
Postoperative chemotherapy	0.062	0.55	(0.14–1.06)	0.065
Disease-free survival				
Age	0.957	–		–
Gender	0.722	–		–
PDAC	0.626	–		–
DCC				
Biliary stent	0.332	–		–
Tumor size	0.002	2.03	(1.17–3.52)	**0.012**
R1 resection	0.767	–		–
Lymph node ratio	0.046	1.61	(0.63–4.09)	0.321
Microvascular invasion	0.108	–		–
Perineural infiltration	0.167	–		–
Well differentiation	0.088	0.74	(0.47–1.15)	0.180
Severe morbidity	0.529	–		–
Postoperative chemotherapy	0.644	–		–

Bold values are considered significant ($P<0.05$)

PDAC indicates pancreatic ductal adenocarcinoma, *DCC* distal cholangiocarcinoma

Discussion

Periampullary tumors have variable outcomes following resection. It is difficult to establish prognostic factors and appropriate guidelines because DCC is uncommon and most studies are concerned with small, retrospective and heterogeneous series.

We studied 188 patients who underwent PD with curative intent; the main finding was that long-term oncological outcomes were not influenced by the pathological diagnosis. PDAC patients more often had larger tumors and higher lymph node ratio at presentation. In PDAC patients, tumor size, tumor differentiation, and postoperative chemotherapy independently predicted long-term survival. In DCC, only tumor size and tumor differentiation were predictors of independent long-term survival. The multivariate analysis did not highlight postoperative chemotherapy as a prognostic factor, probably because of the small sample size of DCC patients who received adjuvant therapy, which is not recognized as a standard of care. After matching patients according to tumor size, lymph node invasion and resection margin status, which are major prognosis factors in both PDAC and DCC [6, 8–10, 18, 19], the pathological diagnosis (DCC vs. PDAC) still did not influence survival.

Studies on PDAC and DCC survival and prognosis remain discordant. Some studies reporting better survival after PD for DCC when compared to PDAC [6, 20, 21] included ampullary and duodenal tumors in the analysis. Recently, a large study showed that DCC has a better prognosis than PDAC [5]. DCC patients were less likely to be margin positive (19 vs. 25%; $P < 0.005$), to have lymph node invasion (55 vs. 69%; $P < 0.001$), and to receive adjuvant therapy (57 vs. 71%; $P < 0.001$). DCC was associated with improved median OS (40 months) compared with PDAC (22 months; $P < 0.001$). Lymph node invasion was the only factor independently associated with decreased OS for both DCC and PDAC. However, this study included patients who underwent extended resection for both DCC and PDAC, which highlights locally advanced tumors.

In contrast, our results are consistent with previous series that have showed no difference in survival between resected DCC and PDAC patients [1, 4, 22]. Among these studies, only one was based on a matching analysis using a propensity score [4]. Of the 290 patients analyzed, 56 (19%) had DCC [4]. Median OS and DFS was 36.9 and 14.6 months, respectively. Combined organ resection, R1 resection, vascular invasion, postoperative hemorrhage, and postoperative abdominal infection were independent risk factors for worse survival. However, lymph node invasion did not influence long-term prognosis. According to pathological characteristics, matching analysis found no difference between DCC and PDAC in terms of OS or DFS. In another study, 346 consecutive periampullary malignancies (249 PDAC, 79 ampullary carcinomas, 18 DCC) treated by PD were analyzed [1]. Median OS was not different between PDAC and DCC. Only lymph node invasion (median 16.2 vs. 29.9 months, $P < 0.001$) and perineural invasion (median 17.7 vs. 47.9 months, $P < 0.001$) predicted OS on multivariate analysis. In another study of 204 patients with PDAC ($n = 108$), DCC ($n = 32$), or ampullary carcinoma ($n = 64$) [22], median OS for resected PDAC, DCC, and ampullary carcinoma were 16, 25, and 24 months, respectively, without difference between PDAC and DCC. In the multivariate analysis, positive resection margin, lymph node invasion, and poor tumor differentiation independently influenced OS. In our study, only PDAC and DCC were compared. OS and DFS were similar in the two groups. After matching patients on recognized poor prognosis factors, such as tumor size, lymph node invasion and resection margin status, OS and DFS were similar, regardless of the pathological diagnosis. The multivariate analyses found that poor tumor differentiation and severe morbidity were the two independent factors impairing OS, whereas tumor size > 20 mm was the only independent factor influencing DFS.

Recently, histopathologic phenotype has been highlighted as a better prognostic factor of long-term survival and adjuvant chemotherapy response than tumor anatomic location in patients with periampullary adenocarcinomas [23, 24]. Immunohistochemical staining against specific markers, such as cytokeratins 7 (CK7) and 20 (CK20), mucins 1 (MUC1) and 2 (MUC2), as well as caudal-type homeodomain (CDX2) protein, have been proven to be relevant in determining the exact histological subtype in large or mixed-type tumors [25]. CK20, MUC2, and CDX2 expression were found to be more prevalent in intestinal type tumors, while MUC1 was more frequently expressed in pancreatobiliary type tumors [26, 27]. In a large series including 510 periampullary adenocarcinomas (13 duodenal, 110 ampullary, 43 DCC and 344 PDAC), the median overall survival was similar between DCC and PDAC [23]. Most duodenal (61.5%) and ampullary (51.8%) cancers were of intestinal type, whereas most DCC were of pancreaticobiliary type (86.0%). Those with intestinal type tumors had longer median overall survival than those with pancreaticobiliary type tumors (71.7 vs. 33.3 months, $P = 0.02$) or PDAC (31.4 months, $P = 0.003$). These findings suggest that DCC and PDAC are not separate tumor entities but share many immunohistochemical characteristics of the pancreatobiliary type and the same poor long-term prognosis.

The second major finding was that DCC patients had more complicated postoperative courses than PDAC patients. Higher severe morbidity rates were probably due to higher rates of clinically significant POPF after PD for DCC

and led to longer in hospital stay. This could be expected because DCC patients more often had soft pancreatic texture and small MPD size, which are well known risk factors for developing POPF. After a matching process on these two risk factors, severe morbidity and postoperative hemorrhage rates were similar between DCC and PDAC patients. Clinically relevant POPF was significantly higher in the DCC group due to more grade B POPF than in the PDAC group, which did not require intensive care unit admission or invasive drainage.

Several reports have highlighted the benefit of neoadjuvant chemotherapy in patients with borderline and advanced PDAC. Interestingly, beside improving oncological outcome, preoperative chemotherapy also improved postoperative course by decreasing POPF rates [28]. Because the place of neoadjuvant chemotherapy in the management of patients with DCC is still to be defined [5, 18], these differences in postoperative course are likely to persist in the near future.

Possible weaknesses of our study include a limited sample size and a long period of recruitment, as well as the retrospective statistical analyses. Frequent inaccurate diagnosis between periampullary tumors was recently described [29, 30]. Even after expert pathologist assessment, we may assume that there was some misdiagnosis. The low incidence of DCC explains the long duration of recruitment and the small sample size of this study, which was comparable to previous studies.

Conclusions

In summary, long-term oncological outcomes after PD for DCC and PDAC patients are similar. On presentation, DCC patients are more likely to have soft pancreas texture, smaller MPD and smaller tumors than PDAC patients. The postoperative course of PD is more complicated for DCC than for PDAC.

Author contributions TG, GS, VM, and DJB: conception and design; SB, MC, VM, and DJB: administrative support; TG, EG, GS, OA, OR, and DJB: provision of study materials or patients; TG, EG, CL, GS, OA: collection and assembly of data; TG, CL, MC, DJB: data analysis and interpretation; the first draft of the manuscript was written by TG, DJB, and MC. All authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Data availability In two tertiary referral centers, data was extracted from a prospectively maintained database and were analyzed retrospectively.

Compliance with ethical standards

Conflicts of interest There are no conflicts of interest or financial disclosure to declare.

Ethics approval The study was conducted in accordance with the Declaration of Helsinki, and was reviewed and approved by the local ethical committees of both representative institutions (No. 2018-25-04-001).

Consent for participate and publication All patients enrolled completed the informed consent for participate and publication.

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