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Clinical relevance of pancreatobiliary and intestinal subtypes of ampullary and duodenal adenocarcinoma: Pattern of recurrence, chemotherapy, and survival after pancreatoduodenectomy

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ABSTRACT

Background: The clinical relevance of the classification of ampullary adenocarcinoma (AC) into pancreatobiliary (PB) or intestinal (Int) subtypes has not been resolved.
Methods: Clinicopathological factors, survival, and localization and treatment of recurrence were investigated for patients with AC and duodenal adenocarcinoma (DC) treated by pancreatoduodenectomy from 2000 to 2015.
Results: A total of 109 AC (45 PB, 64 Int) and 71 DC (all Int) were identified. Median overall survival (OS) for ACPB vs DC vs ACInt was 43.6 vs 51 vs 75 months, respectively. ACPB had significantly shorter OS than ACInt ($p = 0.036$). However, for AC stage (HR = 2.39; 95 %CI 1.23–4.64, $p = 0.010$) was the only factor associated with mortality risk in multivariate analysis. Localization of recurrence ($n = 88$) was predominantly distant (ACPB 81.5%; ACInt 92%; DC 91.7%, $p = 0.371$). Post-recurrence survival (PRS) for ACPB, ACInt and DC did not differ (6.9 vs 9.2 vs 7.5 months, $p = 0.755$). Best supportive care or palliative chemotherapy were offered for recurrent disease to 44.5%/48.1% for ACPB, 40%/56% for ACInt, and 41.7%/52.8% for DC ($p = 0.947$). The choice of chemotherapy regimen varied considerably. Five patients underwent surgical resection or ablation with curative intent. All deaths among ACPB were caused by recurrent disease, whereas 29.4% of ACInt and 23.1% of DC deaths was non-cancer related or caused by other specific cancer.
Conclusion: ACPB, ACInt and DC have similar recurrence patterns and PRS. The difference in survival between ACPB and ACInt was not statistically significant when stratified by stage. The optimal chemotherapy in patients with recurrent AC remains undefined.

Introduction

Periampullary adenocarcinomas originate from the duodenum, ampulla of Vater, bile duct or the pancreas, and pancreatoduodenectomy is the standard procedure for surgical treatment of these tumours [1]. Following curative surgery, ampullary and duodenal carcinomas have a better prognosis than pancreatic ductal adenocarcinoma and distal bile duct cancer [2,3]. Furthermore, ampullary adenocarcinomas (AC) typically have either predominant intestinal (Int) or pancreatobiliary (PB) histological differentiation which have demonstrated prognostic relevance in some [4–8], but not all studies [9]. Recently, molecular alterations of AC distinguishing the two subtypes have been identified [10–14].

Patterns of recurrence and treatment of recurrent disease have been poorly studied in AC and DC. Based on limited data, patients with recurrent liver metastases from periampullary adenocarcinomas of intestinal origin have shown improved survival following

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resection of liver metastases compared with pancreatobiliary origin [15]. Experienced centers suggest that given a likely increased chemoresponsiveness of tumours of intestinal compared to pancreatobiliary origin, resection of liver metastases from intestinal origin may be warranted [15,16]. Thus, the histological subtype may have important therapeutic implications. However, there are limited data regarding the appropriate chemotherapy for AC and DC, in the adjuvant setting, as well as for recurrent or advanced disease [3,17–21]. Analyses of metastatic AC suggest that fluoropyrimidine (Flu)-based chemotherapy may represent a more appropriate front-line chemotherapy approach [3,22]. Of note, some oncologists are now expecting that pathologists classify AC as PB or Int, and based on pathologic diagnoses will use gemcitabine (Gem)-based treatment regimens for PB tumours and Flu-based chemotherapy for Int tumours, often with inconsistent results [9].

The aim of this study was to analyse the pattern and management of recurrence and survival after pancreatoduodenectomy for AC and DC, with special emphasis on the clinical relevance of Int or PB histologic type of differentiation.

Material and methods

Study population and data collection

Patients undergoing pancreatoduodenectomy with curative intent from January 2000 to December 2015 were identified from a prospectively maintained database and reviewed retrospectively. Final date of data collection was April 30, 2017. The study was approved by the Institutional Review Board (2016/15587) according to the general guidelines provided by the Regional Ethical Committee. The study was reported to comply with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement as best as applicable [23]. Information about the patients was recorded retrospectively using hospital records. Adenocarcinoma was confirmed histologically in all cases. Preoperative workup included multidetector computed tomography (CT) with a standard protocol optimised for imaging pancreatic tumours, and chest CT to evaluate primary and metastatic tumour sites. The surgical procedure consisted of pancreatoduodenectomy with standard lymphadenectomy, as previously described [24]. Adjuvant chemotherapy was not given routinely, but at the discretion of the treating surgeon and oncologist.

Histopathological evaluation

Resection specimens were examined according to a standardised protocol as described previously by Westgaard [25]. Briefly, after formalin fixation, the specimens were bisectioned by slicing along the ducts after inserting probes in the bile duct and main pancreatic duct. For identification of the anatomical origin of the tumour, blocks were made by sectioning parallel to these structures and including the duodenum and ampulla of Vater, in order to demonstrate the relation of the tumour to these structures. As from 2003, in the majority of cases whole mount blocks were made for identifying the critical structures. If necessary, further cross sections of the tumour were made to evaluate tumour size and infiltration into adjacent structures. The histologic type of differentiation was classified as previously described according to the criteria first suggested by Kimura et al., later revised by Albores-Saavedra et al. [8,26,27]. In brief, PB tumours typically have simple or branching glands and small solid nests of cells surrounded by a desmoplastic stroma, have cuboideal to low columnar epithelium arranged in a single layer without nuclear pseudostratification, and the nuclei are rounded but with marked variation in size and shape from one cell to the next. Int tumours typically resemble colon cancer, may consist of solid nests with cribriform areas, have tall and often pseudostratified columnar epithelium with oval nuclei located in the more basal aspects of the cytoplasm, and there may also often be presence of mucin. Cases with mixed type differentiation were classified according to the dominant pattern, without performing cut-off optimization prior to classification. All tumours were assigned to one of these two histologic types of differentiation using this approach. Until 2008 the pathologist reported a margin positive (R1) only if tumour cells were present at the surface (clearance equals 0 mm). In 2008 the definition was changed to a 1 mm clearance. Patients were staged according to the T and N definitions proposed by the 7th edition of the American Joint Committee on Cancer (AJCC) staging manual [28].

Follow up

All patients were followed regularly with history and physical examination to pursue postoperative complications and symptoms and signs of recurrence. Chest and abdominal CT were performed every 6 months or if the patients had symptoms suspect of a recurrence. Recurrence was defined as radiological evidence of intra-abdominal soft tissue around the surgical site or of distant metastasis. Patients with recurrence were referred to the Department of Oncology at their local hospital to be considered for chemotherapy.

Statistical analysis

Data were described with median and range (continuous variables) and with counts and percentages (categorical variables). Crude clinicopathological and treatment characteristics were compared between patients with ACPB, ACint and DC using the Kruskal-Wallis test for continuous variables and the chi-square test or Fisher's exact tests for categorical variables. Overall survival (OS), disease free survival (DFS), crude OS and post recurrence survival (PRS) were estimated using the Kaplan-Meier method and compared between patients' groups using the log-rank test. Survival was defined as time from surgery to death of any cause or the end of follow up through April 30, 2017, which ever came first. Similarly, DFS was defined as time from surgery to reccurence, death of any causes or end of follow up and finally, PRS was defined as time from reccurence to death or end of follow up. Cancer specific survival was computed using the Fine and Gray method and adjusted for the competing risk of death of other causes.

Cox regression analyses were used to evaluate possible associations between selected patient, tumour and treatment related variables and the mortality risk. Clinipathological relevant prognostic variables associated with mortality risk from univariate regressions were entered into a multivariate model. As T status, nodal status and lymph node ratio are highly associated with AJCC, only stage was entered into the final multivariate model. Backward stepwise selection was used to identify independent prognostic factors. The results are presented as hazard ratios (HR) with 95% confidence intervals (CI). We regarded our study as exploratory so no correction for multiple testing was performed and p-values <0.05 were considered statistically significant. All tests were two-sided. All analyses were performed using SPSS ver 24 and Stata ver 14.

Results

Patient characteristics

A total of 180 patients underwent pancreatoduodenectomy; 45 for ACPB, 64 for ACInt, and 71 for DC (all Int). There were 81 women

and 99 men. Median age at surgery was 65 years (range 32–89 years). Six patients (3.3%), two in each group, died of postoperative complications within 90 days of surgery and were excluded from further analysis. Thus, 174 patients were included in further analysis.

Clinicopathological characteristics of ACPB, ACInt, and DC are presented in Table 1. AJCC stage differed significantly among the three groups ($p < 0.001$). ACPB and DC had significantly higher AJCC stage than ACInt. AJCC stage III was found in 44.2% of patients with ACPB and 49.3% of patients with DC, but only 6.7% with ACInt. AJCC stage I was found in 51.7% of patients with ACInt, but only 11.6% of patients with ACPB and 14.5% with DC. Tumour size was significantly higher in DC (3.5 cm) vs ACPB (2.5 cm) vs ACInt (2 cm) ($p < 0.001$). Adjuvant chemotherapy was significantly more often prescribed in patients with ACPB (51.2%) vs DC (24.6%) vs ACInt (11.3%) ($p < 0.001$).

Pattern and treatment of recurrence

Overall, 88 patients (50.6%) had radiologic or histologic evidence of recurrence. Site of first recurrence is presented in Table 2. There was no statistical significant difference in the recurrence pattern between ACPB, ACInt or DC ($p = 0.371$). Most patients first recurred at isolated distant sites ($n = 65$, 73.9%), while isolated local recurrence was seen in 10 patients (11.4%). The remaining 13 patients (14.8%) had both a local and distant site as first recurrence location.

The choice of best supportive care or palliative chemotherapy as treatment options for recurrent disease for ACPB, ACInt and DC did not differ (44.5% versus 48.1%, 40% versus 56%, 41.7% versus 52.8% respectively, $p = 0.947$). Five patients with recurrence underwent surgical intervention (lung resection: ACPB and ACInt, $n = 2$; liver resection: ACPB, $n = 1$; lymph node resection: DC, $n = 1$) or radiofrequency ablation of liver metastases (DC, $n = 1$) with curative intent. The choice of Flu- or Gem-based palliative chemotherapy regimen for recurrent disease varied considerably among the three groups (Table 2). When excluding 90 day postoperative mortality ($n = 6$, two in each group), all deaths among patients with ACPB were associated with recurrent AC, whereas 29.4% and 23.1% of the deaths among patients with ACInt and DC were associated with other cancer-specific or non-cancer related causes (Table 2).

Patient survival and prognostic factors

Median OS was 43.6 (95% CI 23.6–63.6) months for ACPB, 75 (95% CI 18.5–130.7) months for ACInt, and 51 (95% CI 21.6–80.3) months for DC ($p = 0.142$) (Fig. 1a). When we performed pairwise comparisons using the Kaplan Meier method, there were no statistically significant differences in OS between ACInt and DC ($p = 0.290$) and ACPB and DC ($p = 0.283$). However, ACPB had significantly shorter OS than ACInt ($p = 0.036$). Median DFS was 29.4 (95% CI 12.1–46.8) months for ACPB, and 30.7 (95% CI 15.9-not computed) months for DC ($p = 0.026$) (Fig. 1b). For ACInt median DFS was not reached. Five-year survival was 36% (95% CI 20–50) for ACPB, 56% (95% CI 42–68) for ACInt, and 49% (95% CI 36–60) for DC

Table 1
Clinicopathological characteristics for patients undergoing pancreatoduodenectomy for ampullary adenocarcinoma of pancreatobiliary or intestinal subtype, or duodenal adenocarcinoma ($n = 174$).

Variable	ACPB n = 43	ACInt n = 62	DC n = 69	p-value
Gender, n (%)				
Female	23 (53.5)	20 (32.3)	36 (52.2)	0.035[a]
Male	20 (46.5)	42 (67.7)	33 (47.8)	
Age, years, median (range)	64.0 (35.0–88.8)	67.5 (32.0–83.0)	67.0 (40.3–86.0)	0.881[b]
Tumour stage, n (%)				
T1	1 (2.3)	13 (21)	1 (1.4)	<0.001[a]
T2	5 (11.6)	34 (54.8)	17 (24.6)	
T3	18 (41.9)	11 (17.7)	29 (42.0)	
T4	19 (44.2)	4 (6.5)	22 (31.9)	
Nodal status n, (%)[c]				
N0	17 (39.5)	36 (60.0)	35 (50.7)	0.122[a]
N1	26 (60.5)	24 (40.0)	34 (49.3)	
Lymph node ratio, median (range)	0.06 (0.00–0.60)	0.00 (0.00–1.00)	0.00 (0.00–0.94)	0.181[b]
Tumour grade, n (%)				
G1/G2 well-moderate	22 (53.5)	53 (85.5)	50 (72.5)	0.001[a]
G3/G4 poor-undiff	20 (46.5)	9 (14.5)	19 (27.5)	
Tumour size, mm, median (range)	25 (10–70)	20 (10–80)	35 (5–80)	<0.001[b]
R = Resection margins, n (%)				
R0	28 (65.1)	59 (95.2)	62 (89.9)	<0.001[a]
R1	15 (34.9)	3 (4.8)	7 (10.1)	
Perineural infiltration, n (%)				
0	15 (34.9)	47 (75.8)	41 (59.4)	<0.001[a]
1	28 (65.1)	15 (24.2)	28 (40.6)	
Vascular involvement, n (%)				
0	22 (51.2)	40 (64.5)	46 (66.7)	0.229[a]
1	21 (48.8)	22 (35.5)	23 (33.3)	
AJCC stage, n (%)[c]				
I	5 (11.6)	31 (51.7)	10 (14.5)	<0.001[a]
II	19 (44.2)	25 (41.7)	25 (36.2)	
III	19 (44.2)	4 (6.7)	34 (49.3)	
Adjuvant chemotherapy, n (%)				
Yes	22 (51.2)	7 (11.3)	17 (24.6)	<0.001[a]
Flu based	17	7	17	
Gem based	5	0	0	
No	21 (48.8)	55 (88.7)	52 (75.4)	

[a] Chi square test.
[b] Median lymph node ratio was calculated with Kruskall Wallis test.
[c] Lymph node status missing in two patients with ACInt.

Table 2
Pattern and treatment of recurrence in patients undergoing pancreatoduodenectomy for ampullary adenocarcinoma of pancreatobiliary or intestinal subtype, or duodenal adenocarcinoma (n = 174).

Variable	ACPB n = 43	ACInt n = 62	DC n = 69	p-value
Recurrence, n (%)				
Yes	27 (62.8)	25 (40.3)	36 (52.2)	0.073[a]
No	16 (37.2)	37 (59.7)	33 (47.8)	
First site of recurrence (n = 88), n (%)				
Locoregional	5 (18.5)	2 (8.0)	3 (8.3)	
Distant	15 (55.6)	21 (84.0)	29 (80.6)	0.371[a b]
Liver	6	5	11	
Lung	1	1	1	
Lymph nodes	1	4	8	
Peritoneum	0	0	0	
Multiple sites	7	11	9	
Locoregional + distant	7 (25.9)	2 (8.0)	4 (11.1)	
Liver	3	1	2	
Lung	0	0	0	
Lymph nodes	2	1	0	
Peritoneum	2	0	1	
Multiple sites	0	0	1	
Cause of death, (n = 98), n (%)				
AC or DC- specific death	25 (100)	24 (70.6)	30 (76.9)	
Other cancer -specific death	0 (0)	5 (14.7)	3 (7.7)	
Non-cancer related death	0 (0)	5 (14.7)	6 (15.4)	
Treatment of first recurrence, (n = 88), n (%)				
BSC	12 (44.5)	10 (40.0)	15 (41.7)	
Chemotherapy	13 (48.1)	14 (56.0)	19 (52.8)	0.947[a c]
Gemcitabine-based	10	8	8	
Fluoropyrimidine-based	3	6	11	
Surgery or ablation	2 (7.4)	1 (4.0)	2 (5.5)	
Postrecurrence survival (n = 88), (median, months (95%CI)				
Overall	6.9 (4.3–9.5)	9.2 (4.4–14)	7.5 (5.3–9.7)	
Best supportive care	4.3 (2.3–6.2)	4.5 (3.5–5.5)	2.1 (0.87–3.28)	ACPB: 0.032[c] ACInt: 0.076[c]
Chemotherapy	10.3 (5.6–14.9)	13.5 (3.5–23.3)	13.9 (7.9–19.8)	DC: <0.001[c]
Gemcitabine-based	10	9.2	11.9	
Fluoropyrimidine-based	7.5	19.5	13.5	

[a] Chi square test.
[b] Distant and locoregional + distant versus locoregional.
[c] Chemotherapy versus best supportive care.

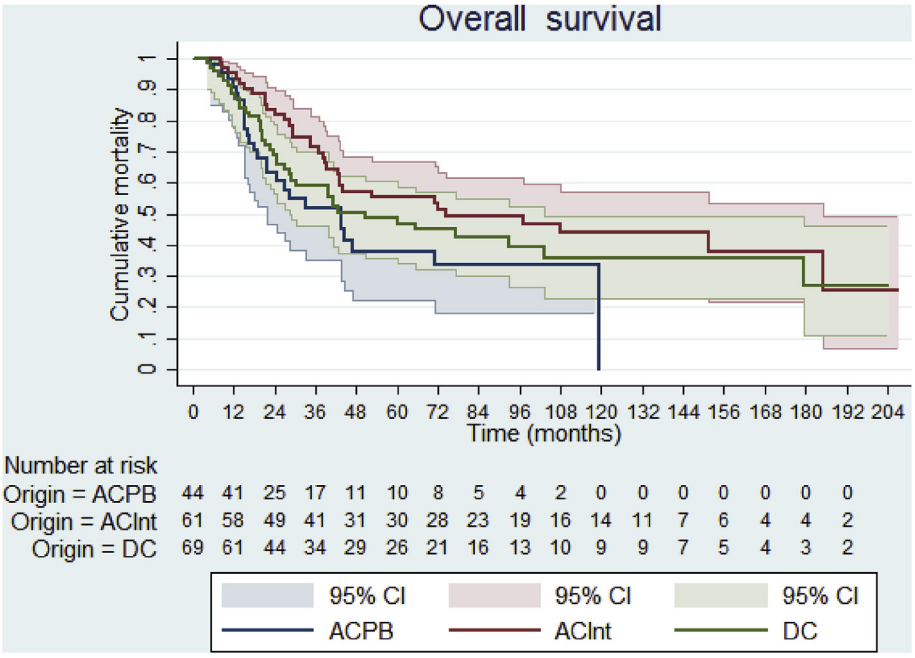

Fig. 1a. Overall survival in patients undergoing pancreatoduodenectomy for ampullary or duodenal adenocarcinoma (n = 174).

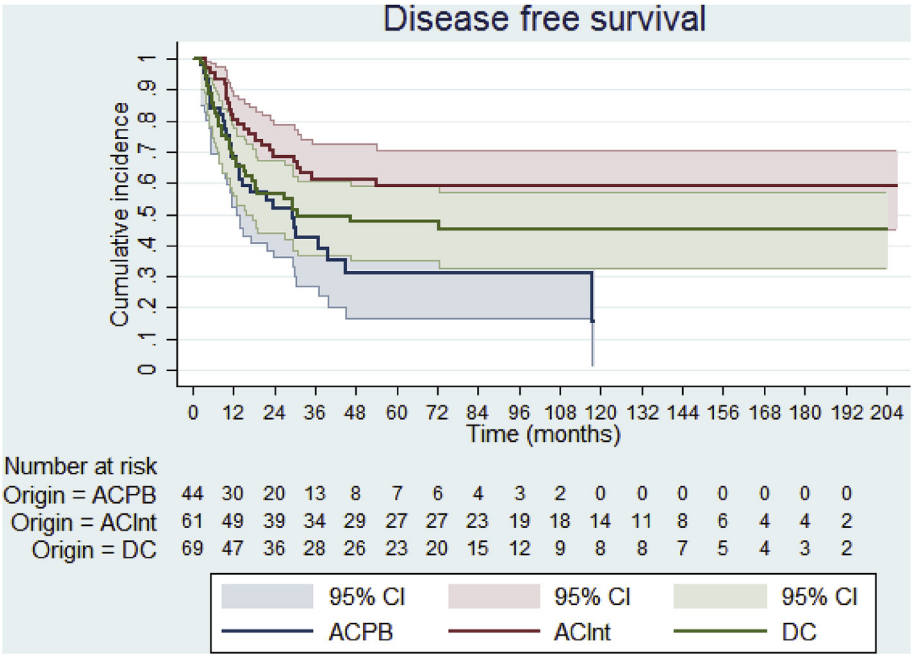

Fig. 1b. Disease free survival in patients undergoing pancreatoduodenectomy for ampullary or duodenal adenocarcinoma (n = 174).

(p = 0.150). The cumulative mortality by other causes was similar for DC and ACInt, however the cancer-specific mortality was the highest for ACPB and lowest for ACInt (Fig. 1c). The difference in cumulative cancer-specific mortality between the diagnostic groups did not reach the level of statistical significance.

However, when accounting for stage the difference in OS between ACPB and ACInt was not statistically significant (Table 3). For AC, stage (p = 0.01) and perineural invasion (p = 0.04) were the only significant factors associated with mortality risk on multivariate analysis, but when adjusted for cancer specific death, stage (p = 0.033) was the only significant factor associated with mortality risk (Table 3).

PRS for ACPB, ACInt and DC did not differ (6.9 versus 9.2 versus 7.5 months, respectively (p = 0.755)) (Fig. 2, Table 2). For ACPB and DC patients undergoing palliative chemotherapy had significantly better survival than patients undergoing best supportive care (10.3 vs 4.3 months for ACPB; p = 0.03, 13.9 vs 2.1 months for DC; p < 0.001), whereas there was no significant difference for ACInt (13.5 vs 4.5 months, p = 0.076) (Table 2). No difference between Gem- or Flu-based palliative chemotherapy on PRS was revealed, but because of the small study sample in each group (<10 in 4 of the 6 subgroups) conclusions regarding the effect of specific

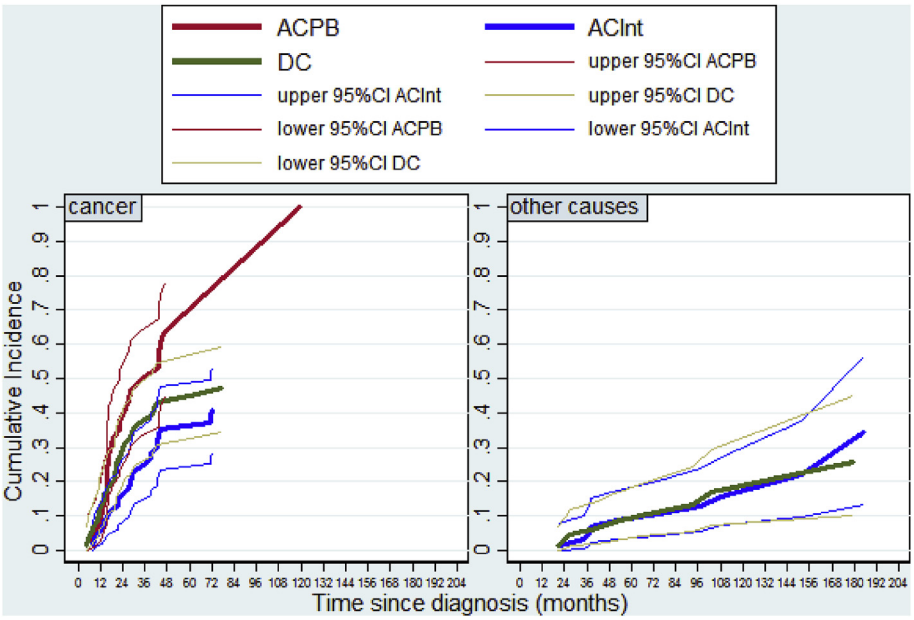

Fig. 1c. Cancer-specific mortality for patients undergoing pancreatoduodenectomy for ampullary or duodenal adenocarcinoma (n = 174) adjusted for the competing risk of death of other causes.

Table 3
Uni- and multivariable Cox regression analysis of clinical and histopathologic factors in ampullary adenocarcinoma (n = 105) associated with mortality risk.

UNIVARIABLE			
Variable	HR	95% CI	p
Age, years	1.02	1.00–1.04	0.097
Gender (female/male), Ref = female	1.02	1.00–1.04	0.501
T (T1/T2 vs T3/T4), Ref = T3/T4	3.67	2.09–6.45	<0.001
N (0/1), Ref = N1	3.51	1.00–6.18	<0.001
Tumour diameter, mm	1.17	1.00–1.36	0.049
Stage (I and II vs III), Ref stage = III	3.39	1.87–6.16	<0.001
R (0/1), Ref = R1	4.82	2.46–9.44	<0.001
Grade (G1/G2 (well) vs G3/G4 (poor)), Ref = G3/G4	1.37	0.78–2.42	0.278
Histological subtype (PB/Int), Ref = PB	1.75	1.03–2.99	0.039
Perineural infiltration (Yes/No), Ref = Yes	2.68	1.58–4.54	<0.001
Vascular involvement (Yes/No), Ref = Yes	2.20	1.31–3.71	0.003
Adjuvant chemotherapy (Yes/No), Ref = Yes	0.94	0.51–1.72	0.828

MULTIVARIABLE						
Variable	Overall survival			Cancer-specific survial		
	HR	95% CI	p	HR	95% CI	p
Stage (I and II vs III), Ref = III	2.39	1.23–4.64	0.010	2.16	1.07–4.36	0.033
Histological subtype (PB vs Int), Ref = PB	1.08	0.56–2.08	0.827	0.86	0.42–1.75	0.675
Perineural infiltration (Yes/No), Ref = Yes	2.01	1.03–3.90	0.040	1.99	0.95–4.16	0.066
Vascular involvement (Yes/No), Ref = Yes	1.60	0.91–2.81	0.103	1.83	0.99–3.40	0.056

PB = pancreatobiliary, Int = intestinal.

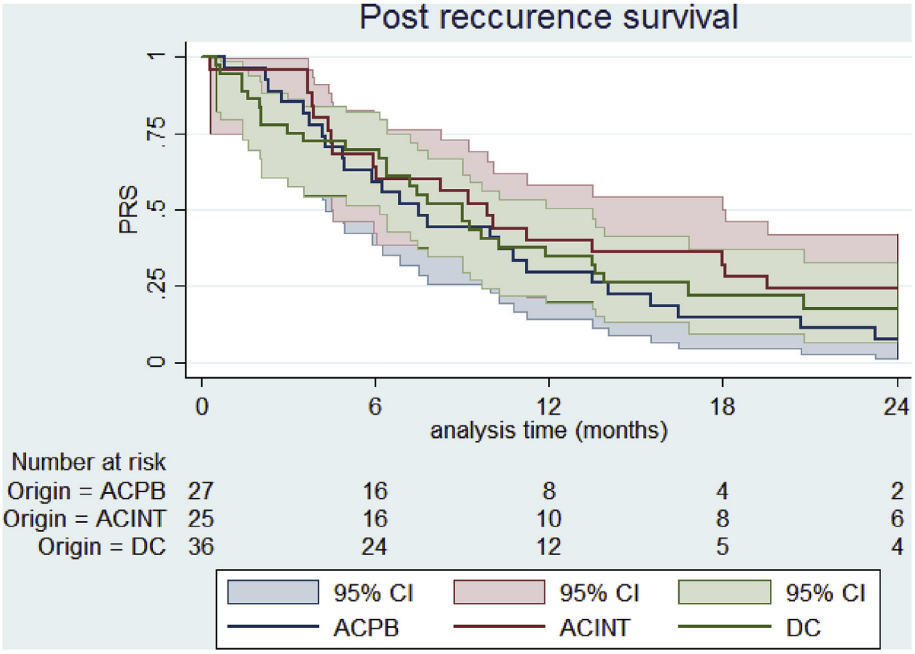

Fig. 2. Postrecurrence survival in patients undergoing pancreatoduodenectomy for ampullary or duodenal adenocarcinoma stratified by tumour origin and histological subtype (n = 88).

chemotherapy regimens on survival could not be drawn from this study (Table 2).

Discussion

The results of the current study show that ACPB was associated with worse overall survival compared with ACInt and DC. However, for AC AJCC stage was the only factor associated with mortality risk on multivariate analysis. The first site of recurrence was predominantly distant for all groups, and approximately 50% of the patients started palliative chemotherapy. The study revealed a considerable variation in the choice of chemotherapy regimen for recurrent disease for both AC and DC. Initiation of palliative chemotherapy was associated with improved survival in ACPB and DC, whereas PRS was not statistically significant between ACPB, ACInt and DC.

Several studies have shown that PB type of differentiation is a significant prognostic factor for survival in AC, also supported by earlier studies in smaller case numbers from our group [4,8] and others [5–7,29,30]. However, the current study including 109 patients with resected AC supports the findings from the Atlanta group showing that while ACPB has a worse prognosis than ACInt, histological subtype is not an independent prognostic factor [9]. Importantly, a significantly higher proportion of patients with ACPB had AJCC stage III tumours. Thus, the current study emphasizes the

strong prognostic impact of the anatomic extent of disease in AC classified according to the AJCC staging system [28].

A significant proportion of patients with ACPB received adjuvant chemotherapy, most probably due to the anticipated association to pancreatic ductal adenocarcinoma and worse prognosis [4,8]. However, adjuvant chemotherapy was not associated with improved survival in AC. A recent study on 4190 patients with AC from the National Cancer Database showed that the use of adjuvant therapy was associated with significantly improved OS [31]. Only one randomized clinical trial has addressed the role of adjuvant chemotherapy after resection of periampullary adenocarcinomas, but no clear survival advantage for any of the specific tumour types was found [18]. However, the dichotomized classification ACPB or ACInt was not consistently applied within the patient cohort [18]. In the current study, only 25% of the patients with DC received adjuvant chemotherapy, that compares well with recent studies [32,33]. Indication for adjuvant chemotherapy in DC is often extrapolated from colon cancer and given to AJCC stage III patients, and a potential survival benefit in this group of patients with DC has recently been found [33].

In the current study, patients receiving palliative chemotherapy for ACPB and DC showed significantly better PRS than patients receiving best supportive care only for recurrent disease. Of note PRS in the three groups was similar to that reported in recurrent pancreatic ductal adenocarcinoma [34]. The choice of chemotherapy regimen varied considerably among the three groups [17]. The median PRS of 10–14 months in patients initiating palliative chemotherapy are comparable to prior evidence from selected reports in the literature summarized in Table 4. Some authors consider that Gem-based regimens is not generally effective for carcinomas of Int origin [7]. Furthermore, it is suggested that it may be reasonable to apply current treatment guidelines for pancreatic ductal adenocarcinoma to periampullary PB type cancers [7]. Thus, there has been a tendency to vary the treatment of patients with AC based on whether the tumour displayed a PB or Int histological phenotype [18]. The literature is scarce on this topic and there is only low level evidence to support such an approach for AC. However, FOLFOX seems to be a promising first-line chemotherapy regimen for unresectable or recurrent DC [35,36]. Most studies on adjuvant and palliative chemotherapy for DC include ileal and jejunal adenocarcinomas (Table 4) [33]. Patients with tumours located in the duodenum are often slightly older, and have shown to have more advanced disease stages and a different metastatic pattern compared to ileal and jejunal adenocarcinomas [32]. Thus, it could be questioned whether these tumours should be considered as one entity.

No difference in PRS between Gem- or Flu-based chemotherapy was revealed in this study, but the small study sample did not permit a statistically meaningful result. Thus, it is difficult to draw conclusions regarding the effect of specific chemotherapy regimens on PRS from this study. Given all the reports on the better prognosis for ACInt and DC, a window of opportunity to treat recurrent disease in the same way as for metastatic colorectal cancer has been expected. Consequently, the possibility of resection of liver metastases has been considered in ACInt and DC [15,16]. However, the current study showed no significant difference in PRS between the three groups. Interestingly, two patients with ACInt and ACPB who developed lung metastases 10 and 24 months after surgery underwent lung resection for recurrent disease. The patients are still alive and free of recurrence 69 and 98 months after PD. This suggests a favorable outcome of patients with isolated lung metastases [37]. Given the rarity of AC and DC, it is difficult to perform well-powered randomized controlled clinical trials to evaluate the role of different chemotherapy regimens or a potentially curative surgical approach for recurrent disease. Interestingly, Mafficini et al. recently identified a subset of patients with AC that might benefit

Table 4
Summary of selected single or multi-institutional studies from the last decade reporting chemotherapy regimen and postrecurrence survival in patients with recurrent or metastatic ampullary or duodenal adenocarcinoma.

Study	Year	Number of patients	Chemotherapy/Number of patients	Disease status	Overall survival (months)
Overman [39]	2008	30 DC, 50 JIC	Flu + platinum: 29 Flu based: 41 Non-Flu based: 10	Not specified	Flu + platinum: 14.8 Flu based: 12 Non-Flu based: 12 p = 0.10
Overman [40]	2009	12 AC, 7 DC, 11 JIC	CAPOX: 30	Not specified	20.4 (overall)
Valle [41]	2010	20 AC 241 Cholangiocarcinoma 149 Gallbladder cancer	Gem: 11 GemCis: 9	Not specified	Gem: 8.1 GemCis: 11.7 p < 0.001[a]
Kim [20]	2010	29 AC	GemCis: 9, FluCis: 20	Not specified	12.5 in both groups p = 0.91
Zaanan [35]	2010	55 DC, 38 JIC	5FU/LV: 10 FOLFOX: 48 FOLFIRI: 19 5FU/LV-Cis: 16	Not specified	5FU/LV: 13.5 FOLFOX: 17.8 FOLFIRI: 10.6 5FU/LV-Cis: 9.3 p = 0.25
Koo [42]	2011	28 DC, 12 JIC	Flu based: 40	Recurrent: 19 Metastatic: 21	11.8 (overall)
Zhang [43]	2011	34, DC/JIC	FOLFOX: 28 CAPOX: 6	Not specified	14.2 (overall)
Xiang [44]	2012	33, DC/JIC	FOLFOX: 33	Metastatic	15.2 (overall)
McWilliams [45]	2012	9 DC, 19 JIC	CAPOX + Irinotecan: 28	Not specified	12.7 (overall)
Jiang [3]	2013	64 AC	Flu based: 40 Gem based: 24	Recurrent: 50 Metastatic: 14	Flu based: 19.1 Gem based: 12.3 p = 0.06
Shoji [21]	2014	26 AC	Flu based: 11 Gem based: 15	Recurrent:14 Metastatic: 12	Flu based: 8.0 Gem based: 12.3 p = 0.29
Lothe (current study)	2018	27 AC	Flu based: 9 Gem based: 18	Recurrent: 27	11 (overall[b])
Lothe (current study)	2018	19 DC	Flu based: 11 Gem based: 8	Recurrent:19	13.9 (overall[b])

AC = ampullary adenocarcinoma, DC = duodenal adenocarcinoma, JIC = jejunal-ileal adenocarcinoma, Flu = fluoropyrimidine, Gem = gemcitabine, Cis = cisplatin, CAPOX = capecitabine and oxaliplatin, FOLFOX = 5-fluorouracil, leucovorin and oxaliplatin, FOLFIRI = 5-fluorouracil, leucovorin and irinotecan, 5FU/LV = 5-fluorouracil and leucovorin.

[a] No survival analysis of AC alone performed due to small sample size.

[b] No statistical analysis of AC subgroups based on chemotherapy regimen performed due to small sample size.

from therapies targeted to activating mutations of ERBB, PI3K, or WNT signaling pathways [13]. Perhaps, as our understanding of the molecular and genetic origins of AC will improve, more targeted therapeutic strategies will contribute to a better outcome.

Certain limitations of this study must be acknowledged. First, this was a retrospective analysis of patients treated at a single institution with all the inherent biases associated with this study design. However, the clinical database used was prospectively maintained and provided complete follow-up data on adjuvant and palliative chemotherapy administration, pattern of recurrence, and cause of death. Second, given the rarity of AC, the sample size was small. Despite the limitations of the small sample size, this is one of the largest series to date evaluating the effect of systemic chemotherapy for recurrent AC and DC after pancreatoduodenectomy (Table 4). Last, and most important, AC shows mixed phenotypes in 20–40% of cases which may cause substantial subjectivity in their histologic designation [9,13]. Thus, due to limitations in interobserver agreement linked to the assessment of hematoxylin-eosin stained slides and the lack of reliable diagnostic criteria a histomorphological classification on a predominant, dichotomized pattern approach (PB or Int) may be questioned [9,38].

In conclusion, this study confirmed that although ACInt carries a better prognosis than ACPB, the histological subtype is not an independent prognostic factor when accounting for stage. The optimal chemotherapy in patients with recurrent AC and DC remains undefined. Large, multicentre studies evaluating the optimal chemotherapy for AC and DC are needed.

Conflicts of interest

The authors declare that they have no conflict of interest.

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