Benefit of gemcitabine-based adjuvant chemotherapy in the subtypes of resected ampullary adenocarcinoma: an international propensity-score matched cohort study

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ABSTRACT

Background Whether patients who are resected for ampullary adenocarcinoma have a survival benefit from adjuvant chemotherapy is currently not known. The aim of this study was to compare propensity score-matched survival between patients with and without adjuvant chemotherapy after resection of ampullary adenocarcinoma.

Methods An international multicentre cohort study was conducted, including patients who underwent pancreatoduodenectomy for ampullary adenocarcinoma (2006-2017) in 13 centres in six countries. Propensity scores were used to match patients who received adjuvant chemotherapy to those who did not; both in the entire cohort and in two subgroups (pancreaticobiliary/mixed and intestinal subtype). Survival was assessed using the Kaplan-Meier method and Cox regressions.

Results Overall, 1163 patients underwent pancreatoduodenectomy for ampullary adenocarcinoma. After excluding 179 patients, median survival in the resulting 976 patients was 67 months (95 per cent confidence interval 56-78), of which a total of 520 (53 per cent) patients received adjuvant chemotherapy. In a propensity-matched cohort (194 vs 194 patients), median survival was better after adjuvant chemotherapy compared to those without adjuvant chemotherapy (median survival not reached vs 60 months, respectively; p=0.051). In the pancreaticobiliary/mixed subtype a survival benefit was seen; median survival was not reached in patients receiving adjuvant chemotherapy vs 32 months in the group without chemotherapy, p=0.020. The intestinal subtype did not show survival benefit from adjuvant chemotherapy.

Conclusions Patients with resected ampullary adenocarcinoma may benefit from gemcitabine-based adjuvant chemotherapy, but this effect may be reserved for those with the pancreaticobiliary and/or mixed subtype.

INTRODUCTION

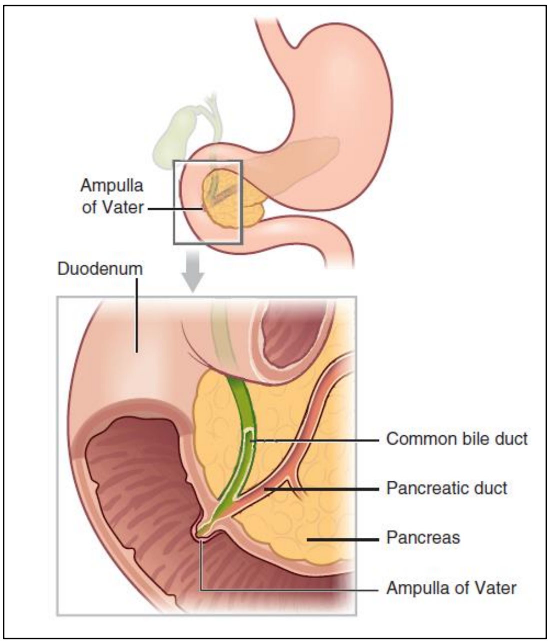
Ampullary adenocarcinoma accounts for seven per cent of pancreatic head and periampullary cancers and 0.2 per cent - 0.5 per cent of all gastro-intestinal cancers[1–3]. Ampullary adenocarcinoma arises from the ampulla of Vater, the confluence of the common bile duct and the pancreatic duct, or from the papilla of Vater, the protrusion of the ampulla of Vater into the duodenum[4–6] (Figure 1).

Compared with other periampullary cancers, ampullary adenocarcinoma often presents at an earlier stage, as a result of biliary obstruction[7]. Therefore, ampullary adenocarcinoma is generally more amenable to resection at the time of diagnosis, resulting in higher resection rates compared with other periampullary cancers (resection rates of 50 per cent vs 20 per cent, respectively)[8,9]. Moreover, patients with ampullary adenocarcinoma have a better prognosis, with 5-year survival rates varying from 30% to 70% after resection[1,9–13]. Despite this more favourable profile, the majority of patients with ampullary adenocarcinoma will eventually succumb to recurrent disease[14].

Given the rarity of ampullary adenocarcinomas, no single randomized clinical trial in adjuvant treatment has focused specifically on ampullary adenocarcinoma. The most recent high-level evidence concerning adjuvant chemotherapy in ampullary adenocarcinoma derives from the ESPAC-3 trial, which was conducted in patients with pancreatic head and periampullary cancer and including ampullary adenocarcinoma as a subgroup. Consequently, the subgroup analysis in this study was likely to be underpowered (e.g. only 297 patients with ampullary adenocarcinoma)[15]. Additionally, there is extensive heterogeneity within ampullary adenocarcinoma due to the different epitheliums from which ampullary adenocarcinoma may arise, which results in different histopathologic subtypes (intestinal, pancreaticobiliary and mixed type)[6,16]. At present, it is unclear whether these subtypes gain a survival benefit from adjuvant chemotherapy.

The aim of this study is to investigate the potential survival benefit of adjuvant chemotherapy in the different subtypes of resected ampullary adenocarcinoma by matching patients who received adjuvant chemotherapy to those who did not, using propensity scores.

Figure 1. Anatomy of the ampulla of Vater



METHODS

Study design and setting

An international retrospective multicentre cohort study was performed. Patients were included from 13 tertiary referral centres in six countries involving Europe and the United States (participating centres and corresponding patient contribution are presented in supplementary Table S1). The study was based on an anonymized database, according to the Health Research Authority in the United Kingdom, both Research Ethics Committee and Health Research Authority approval are not required for research databases, this includes the release of non-identifiable data for analysis. Due to the retrospective nature of the study, written informed consent was not obtained[17]. This study is reported in accordance with The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement[18].

Eligibility and data collection

Included were adults who underwent elective pancreatoduodenectomy for ampullary adenocarcinoma, with curative intent, between January 1, 2006 and December 31, 2017. Excluded were patients in whom it was unknown whether they received adjuvant chemotherapy, patients who died perioperatively, patients who received adjuvant radiotherapy and those with incomplete follow up data, which was defined as either missing vital status or no further follow-up beyond discharge after surgery. Clinical and histopathologic data were collected from electronic patient files.

Demographic variables included age, sex, body-mass-index (BMI) and American Society of Anaesthesiologists (ASA) classification. Histopathologic variables were collected from histology reports and included histopathologic subtype (intestinal, pancreaticobiliary or mixed), resection margin status, differentiation grade, pT-stage, pN-stage, pM-stage, perineural invasion and lymphovascular invasion.

Resection specimens were evaluated by certified pathologists and results documented per local protocol[19]. TNM staging was according to the 7th edition of the American Joint Committee on Cancer (AJCC)[20]. Resections were considered margin-negative if no tumour cells were found within 1mm of each microscopically assessed margin, according to the definition of the Royal College of Pathologists[19].

Referral for adjuvant chemotherapy was based on consensus of the local multi-disciplinary team. Advice on adjuvant chemotherapy and regimen was at discretion of the treating oncologist.

Outcome

The primary outcome of this study was overall survival, defined as the time in months between date of surgery and date of death, or censored at the date of last follow-up. The date of last follow-up was defined by the date of the last visit of each patient.

Histopathologic subtypes

Classification of intestinal and pancreaticobiliary subtype was according to the 4th edition of the World Health Organization (WHO) classification for tumours of the digestive system[21]. The intestinal type of ampullary adenocarcinoma arises from the adjacent duodenal mucosa and is characterized by cribriforming tubular glands with central necrosis, histologically resembling colonic adenocarcinoma. Pancreaticobiliary type ampullary adenocarcinoma derives from the terminal pancreatic or biliary ducts and is characterized by simple or branching glands within a desmoplastic stroma. Mixed type ampullary adenocarcinoma are occasionally encountered and show a combination of intestinal and pancreaticobiliary type morphology.

Reporting of ampullary adenocarcinoma was either performed according to the protocol of the Royal College of Pathologist[19], the College of American Pathologist[22] (both use the WHO classification), or according to a local protocol based on the WHO classification. Classification of histopathologic subtype was primary done based on morphology. Immunohistochemistry was not routinely performed, but on occasion only.

Propensity score matching

Propensity scores were used to match patients who received adjuvant chemotherapy to patients who did not receive adjuvant chemotherapy. Matching was performed on the complete cohort and on two subgroups, the pancreaticobiliary/mixed subtype and the intestinal subtype. The decision to merge the pancreaticobiliary and mixed subtype is a result of the most frequently administered chemotherapy (Gemcitabine) for these subtypes. The rationale for this was that patients with the mixed subtype might benefit from a gemcitabine-based regimen because a proportion of the tumour (the pancreaticobiliary-type cells) could potentially respond to such a regimen.

Propensity scores were obtained from a logistic regression model and included variables that were expected to affect survival, including: age, ASA classification, T-class, N-class, overall stage, resection margin status, differentiation grade, lymphovascular invasion and perineural invasion.

Matching was performed on a nearest neighbour basis, in a 1:1 ratio without replacement, with a calliper width of 0.01 in the complete cohort and with a calliper width of 0.02 in the two subgroups.

Balance was assessed using the standardized mean difference (SMD). Optimal balance is achieved when SMD is 0.1 or below[23].

Statistical analysis

Data were analysed using SPSS® 24.0 software (SPSS, Chicago, IL, USA). Categorical data are presented as counts with proportions and continuous data as means with standard deviations (SD) or, medians with interquartile ranges (IQR), as appropriate. Categorical data were compared using the Chi Square-test, whereas continuous data were compared by the Student's *t*-test for normally distributed data and non-normally distributed data by its nonparametric equivalent the Mann-Whitney *U* test.

Overall survival was assessed in both the unmatched and matched cohort. In the unmatched cohort uni- and multivariable Cox proportional hazards models were performed. The independent variable in this model was adjuvant chemotherapy, whereas, the dependent variable was overall survival. A potential causal effect of adjuvant chemotherapy on overall survival is assumed.

All variables that were considered potential confounders were entered in the univariable analysis, variables with a p value <0.1 were entered in the multivariable model and stepwise backward selection was applied to remove further variables from the model. Adjuvant chemotherapy, as being the variable of interest, was forced into the model regardless of the *P*-value. In addition, to assess whether the effect of adjuvant chemotherapy differs between lymph node negative and - positive patients, the interaction term pN-stage*Adjuvant chemotherapy was added to the Cox model. Pre-specified subgroup analyses were performed for the pancreaticobiliary/mixed subtype and for the intestinal subtype. The Kaplan-Meier method and log rank test were used to assess overall survival in the various matched cohorts. A *P*-value <0.050 was considered statistically significant.

RESULTS

Overall, 1163 patients underwent pancreatoduodenectomy for ampullary adenocarcinoma during the study period. Several patients did not meet the eligibility criteria as shown in the flowchart (Figure 2), either due to perioperative mortality (n=44, 3.8 per cent of patients), 105 (9.0 per cent) due to unknown receipt of adjuvant chemotherapy, 30 (2.6 per cent) patients due to receipt of adjuvant radiotherapy and 8 patients (0.7 per cent) due to incomplete follow-up.

All clinical and histopathologic characteristics of the unmatched and matched cohort are reported in Table 1. A total of 520 patients received adjuvant chemotherapy, whereas 456 patients did not. The adjuvant chemotherapy regimen was known in 515 of the 520 patients.

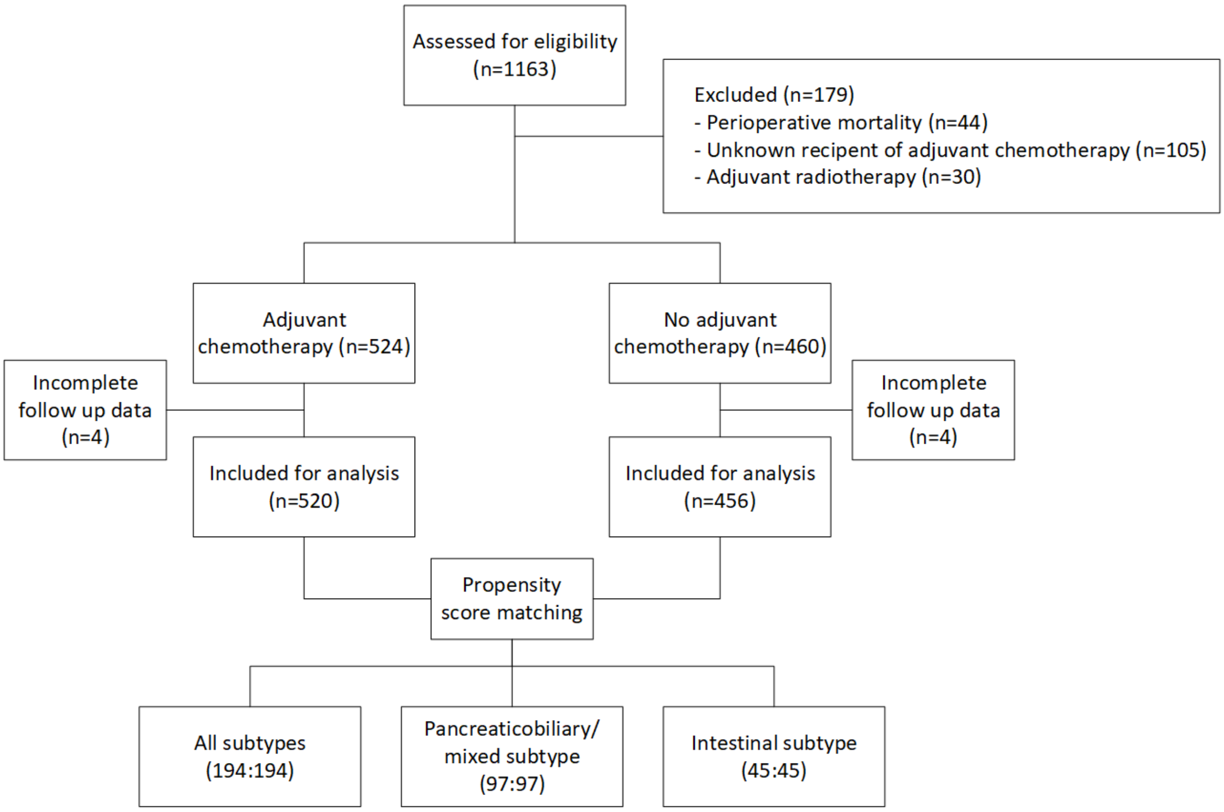
Table 1. Baseline characteristics of the unmatched and matched cohort of patients with resected AAC.

	Unmatched cohort				**Matched cohort**			
	Adjuvant chemotherapy (N=520)	No adjuvant chemotherapy (N=456)	SMD	P value	Adjuvant chemotherapy (N=194)	No adjuvant chemotherapy (N=194)	SMD	P value
Age, years (SD)	64 (10)	69 (10)	0.50	<0.001	69 (9)	68 (10)	0.01	0.564
Female[a]	219 (42.2)	201 (44.3)	0.04	0.514	76 (39.2)	93 (47.9)	0.20	0.082
ASA classification (%)[b]			0.08	0.544			0.10	0.643
1	71 (17.7)	54 (15.3)			27 (13.9)	28 (14.4)		
2	237 (59.1)	205 (58.2)			111 (57.2)	121 (62.4)		
3	89 (22.2)	91 (25.9)			55 (28.4)	44 (22.7)		
4	4 (1.0)	2 (0.6)			1 (0.5)	1 (0.5)		
BMI, kg/m^2 (SD)[c]	25.9 (4.4)	25.8 (4.7)	0.02	0.762	25.6 (4.1)	25.6 (4.6)	0.00	0.983
Resection margin[d]			0.35	<0.001			0.05	0.721
R0	393 (75.9)	388 (85.5)			146 (75.3)	149 (76.8)		
R1	125 (24.1)	66 (14.5)			48 (24.7)	45 (23.2)		
Tumour size, mm (SD)[e]	24.1 (12.5)	22.5 (13.2)	0.12	0.064	23.4 (12.8)	23.4 (13.5)	0.00	0.978
Stage (7th AJCC)[f]			0.75	<0.001			0.10	0.271
0	-	5 (1.1)			-	-		
1A	15 (2.9)	64 (14.2)			10 (5.2)	14 (7.2)		
1B	52 (10.0)	123 (27.3)			36 (18.6)	43 (22.2)		
2A	35 (6.7)	52 (11.6)			26 (13.4)	24 (12.4)		
2B	239 (46.1)	131 (29.1)			83 (42.8)	69 (35.6)		
3	167 (32.2)	68 (15.1)			34 (17.5)	43 (22.2)		
4	11 (2.1)	7 (1.6)			5 (2.6)	1 (0.5)		
pT-stage (7th AJCC)[g]			0.62	<0.001			0.01	0.838
0	-	5 (1.1)			-	-		
1	23 (4.4)	77 (17.1)			15 (7.7)	16 (8.2)		
2	145 (27.9)	178 (39.6)			70 (36.1)	72 (37.1)		
3	179 (34.5)	118 (26.2)			71 (36.6)	63 (32.5)		
4	172 (33.1)	72 (16.0)			38 (19.6)	43 (22.2)		
pN-stage (7th AJCC)			0.76	<0.001			0.11	0.305
N0	128 (24.6)	258 (56.6)			78 (40.2)	88 (45.4)		
N1	392 (75.4)	198 (43.4)			116 (59.8)	106 (54.6)		
Histopathologic subtype[h]			0.36	<0.001			0.26	0.032
Intestinal	83 (27.1)	139 (49.1)			36 (29.5)	55 (45.1)		
Pancreaticobiliary	197 (64.4)	119 (42.0)			80 (65.6)	60 (49.2)		
Mixed	26 (8.5)	25 (8.8)			6 (4.9)	7 (5.7)		
Differentiation grade[i]			0.35	<0.001			0.02	0.914
Well	25 (4.9)	51 (11.4)			15 (7.7)	16 (8.2)		
Moderately	273 (53.4)	275 (61.2)			127 (65.5)	123 (63.4)		
Poorly	213 (41.7)	123 (27.4)			52 (26.8)	55 (28.4)		
Perineural invasion[j]			0.37	<0.001			0.02	0.834
Present	247 (48.2)	129 (32.3)			75 (38.7)	73 (37.6)		
Absent	265 (51.8)	271 (67.8)			119 (61.3)	121 (62.4)		
Lymphovascular invasion[k]			0.50	<0.001			0.01	0.919
Present	354 (69.0)	199 (47.4)			108 (55.7)	107 (55.2)		
Absent	159 (31.0)	221 (52.6)			86 (44.3)	87 (44.8)		

Data are given as No. (per cent) unless noted otherwise. Missing values unmatched cohort: [a]3 missing sex, [b]223 missing ASA classification, [c]257 missing BMI, [d]4 missing resection margin, [e]37 missing tumour size, [f]7 missing overall stage, [g]7 missing T-class, [h]387 missing histopathologic subtype, [i]16 missing differentiation grade, j64 missing perineural invasion, [k]40 missing lymphovascular invasion. Missing values in the matched cohort: [c]102 missing BMI, [e]16 missing tumour size, [h]144 missing histopathologic subtype.

The most frequently administered regimen was Gemcitabine monotherapy in 390 (75.7 per cent patients, followed by Gemcitabine in combination with Capecitabine in 34 (6.6 per cent patients. The proportion of patients completing six cycles was 74 per cent and 91 per cent, respectively. Details on all adjuvant chemotherapy regimens, including number of cycles received, are given in supplementary Table S2 and S3.

Figure 2. CONSORT diagram



Overall survival

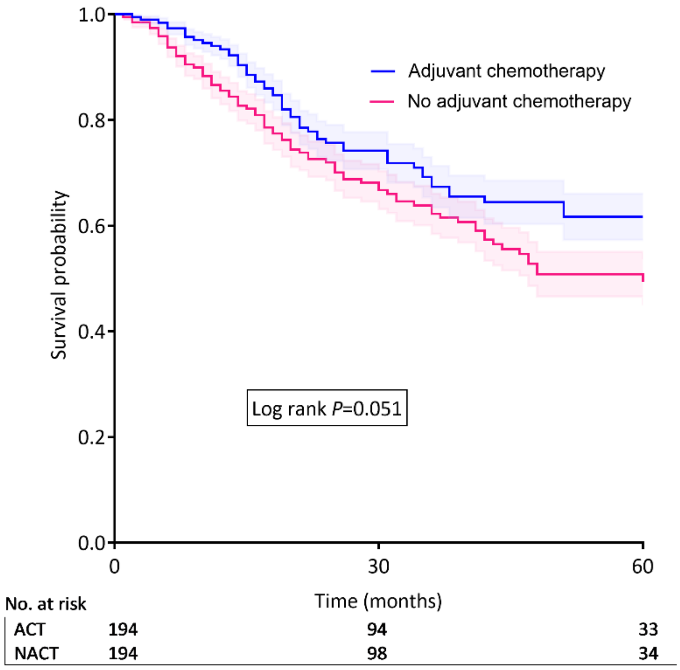
At the end of follow-up, 592 (60.7 per cent) patients were alive with a median follow-up time of 41 (IQR 18-64) months. The median survival of the complete cohort was 67 (95 per cent confidence interval 56-78) months and 1-, 3-, and 5-year overall survival rates were 89 per cent, 63 per cent and 54 per cent, respectively. There was no survival difference between patients with a histopathologic subtype and patients in whom the subtype was missing (67 months; 95 per cent confidence interval 49-85 months and 65 months; 95 per cent confidence interval 48-82), respectively, p=0.985).

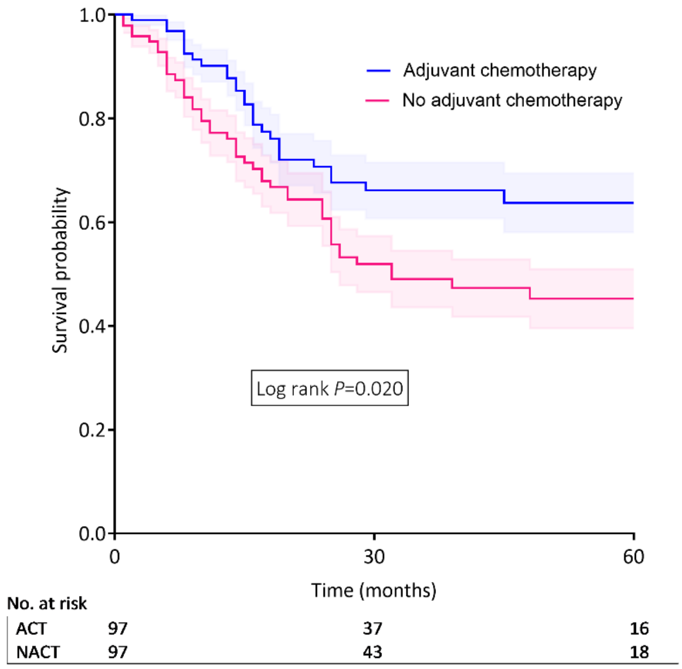
A total of 194 patients who received adjuvant chemotherapy were matched to 194 patients who had no adjuvant chemotherapy (Table 1). Optimal balance was achieved for age, ASA classification, BMI, resection margin status, tumour size, overall stage, pT-stage, differentiation grade, perineural invasion and lymphovascular invasion. Some degree of unbalance remained for the variables sex, pN-stage and histopathologic subtype.

Figure 3A shows the overall survival of the matched cohort; adjuvant chemotherapy versus no adjuvant chemotherapy. Median survival was not reached in the adjuvant chemotherapy group versus 60 months in the no adjuvant chemotherapy group, p=0.051. Corresponding 1-, 3-, and 5-year overall survival rates were 93 per cent, 68 per cent and 62 per cent in the adjuvant chemotherapy group versus 86 per cent, 62 per cent and 49 per cent in the no adjuvant chemotherapy group, respectively. The Cox proportional hazards model for overall survival is shown in Table 2. Variables associated with survival in univariable analysis were age >65 years, R1 resection, pT-stage 3/4, pN-stage 1, pancreaticobiliary/mixed subtype, poor tumour differentiation, and lymphovascular- and perineural invasion.

Figure 3a. Overall survival by adjuvant chemotherapy, in the matched cohort of all subtypes.

Figure 3b. Overall survival by adjuvant chemotherapy, in the matched cohort of pancreaticobiliary/ mixed subtype.





ACT = Adjuvant chemotherapy, NACT = No adjuvant chemotherapy

Multivariable analysis revealed that adjuvant chemotherapy (mono-agent regimen HR=0.70 [95 per cent confidence interval 0.50-0.99] p=0.042; multi-agent regimen HR=0.38 [95 per cent confidence interval 0.17-0.83, *P*=0.015) was associated with an improved overall survival after adjusting for other variables associated with overall survival. The interaction term pN-stage*Adjuvant chemotherapy was not statistically significant in the multivariable Cox model and was therefore removed from the model.

Table 2. Cox proportional hazards model for overall survival in patients with resected AAC.

	Univariable		**Multivariable**	
	Hazard ratio (95% CI)	P value	Hazard ratio (95% CI)	P value
Age >65 years	1.392 (1.132 – 1.712)	0.002		
Female sex	1.022 (0.835 – 1.250)	0.834		
ASA 3/4	1.266 (0.973 – 1.649)	0.079		
Adjuvant chemotherapy				
Mono-agent regimen[a]	1.209 (0.970 – 1.508)	0.092	0.699 (0.495 – 0.988)	0.042
Multi-agent regimen[a]	1.219 (0.839 – 1.771)	0.298	0.380 (0.174 – 0.830)	0.015
R1 resection	2.62 (2.09 – 3.29)	<0.001	1.473 (1.018 – 2.132)	0.040
pT-stage 3/4	2.750 (2.199 – 3.39)	<0.001		
pN-stage 1	4.02 (3.13 – 5.16)	<0.001	3.487 (2.184 – 5.566)	<0.001
Histopathologic subtype				
Pancreaticobiliary/mixed[b]	1.536 (1.158 – 2.038)	0.003		
Tumour differentiation				
Poorly[c]	1.849 (1.509 – 2.265)	<0.001		
Lymphovascular invasion	2.575 (2.049 – 3.235)	<0.001		
Perineural invasion	2.167 (1.755 – 2.676)	<0.001	1.657 (1.148 – 2.390)	0.007

[a]Compared with no adjuvant chemotherapy. [b]Compared with intestinal type. [c]Compared with well/moderately differentiated tumour

Pancreaticobiliary and mixed subtype

Table 3 shows the baseline characteristics of the two matched subgroups. A total of 97 patients with pancreaticobiliary/mixed subtype who received adjuvant chemotherapy were matched to 97 comparable patients who did not receive adjuvant chemotherapy. Optimal balance was obtained for sex, ASA classification, BMI, resection margin status, tumour size, overall stage, pN-stage, differentiation grade, perineural- and lymphovascular invasion. For age, histopathologic subtype and pT-stage some degree of unbalance remained. Figure 3B shows the overall survival of the matched cohort; adjuvant chemotherapy versus no adjuvant chemotherapy in the pancreaticobiliary/mixed subtype.

Median survival was not reached in the adjuvant chemotherapy group versus 32 months in the no adjuvant chemotherapy group, p=0.020. Corresponding 1-, 3-, and 5-year overall survival rates were 90 per cent, 66 per cent and 64 per cent in the adjuvant chemotherapy group versus 77 per cent, 49 per cent and 45 per cent in the no adjuvant chemotherapy group, respectively.

Table 3. Baseline characteristics of the matched pancreaticobiliary/mixed and intestinal subgroups of resected AAC.

	Pancreaticobiliary/mixed subtype				**Intestinal subtype**			
	Adjuvant chemotherapy (N=97)	No adjuvant chemotherapy (N=97)	SMD	P value	Adjuvant chemotherapy (N=45)	No adjuvant chemotherapy (N=45)	SMD	P value
Age, years (SD)	68 (9)	69 (9)	0.11	0.431	67 (8)	66 (11)	0.10	0.378
Female	45 (46.4)	48 (49.5)	0.07	0.666	22 (48.9)	23 (51.1)	0.05	0.833
ASA classification[a]			0.05	0.924			0.03	0.558
1	17 (21.5)	13 (17.6)			3 (8.3)	5 (11.9)		
2	39 (49.4)	40 (54.1)			26 (72.2)	27 (64.3)		
3	22 (27.8)	20 (27.0)			6 (16.7)	10 (23.8)		
4	1 (1.3)	1 (1.4)			1 (2.8)	-		
BMI, kg/m^2 (SD)[b]	25.5 (4.3)	25.7 (5.2)	0.04	0.773	27.6 (4.3)	26.1 (5.8)	0.29	0.277
Resection margin			0.03	0.869			0.07	0.803
R0	73 (75.3)	72 (74.2)			34 (75.6)	35 (77.8)		
R1	24 (24.7)	25 (25.8)			11 (24.4)	10 (22.2)		
Tumour size, mm (SD)[c]	22.6 (11.6)	22.6 (9.8)	0.00	0.974	23.2 (12.2)	22.2 (12.2)	0.08	0.708
Stage (7th AJCC)			0.07	0.742			0.10	0.716
1A	3 (3.1)	1 (1.0)			4 (8.9)	3 (6.7)		
1B	17 (17.5)	16 (16.5)			11 (24.4)	12 (26.7)		
2A	11 (11.3)	13 (13.4)			3 (6.7)	6 (13.3)		
2B	41 (42.3)	38 (39.2)			16 (35.6)	17 (37.8)		
3	21 (21.6)	27 (27.8)			11 (24.4)	7 (15.6)		
4	4 (4.1)	2 (2.1)			-	-		
pT-stage (7th AJCC)			0.18	0.531			0.05	0.541
1	5 (5.2)	2 (2.1)			5 (11.1)	3 (6.7)		
2	35 (36.1)	30 (30.9)			19 (42.2)	21 (46.7)		
3	33 (34.0)	37 (38.1)			10 (22.2)	14 (31.1)		
4	24 (24.7)	28 (28.9)			11 (24.4)	7 (15.6)		
pN-stage (7th AJCC)			0.00	1.000			0.24	0.396
N0	35 (36.1)	35 (36.1)			27 (60.0)	22 (48.9)		
N1	62 (63.9)	62 (63.9)			18 (40.0)	23 (51.1)		
Histopathologic subtype			0.34	0.174			0.00	1.00
Intestinal	-	-			45	45		
Pancreaticobiliary	89 (91.8)	83 (85.6)			-	-		
Mixed	8 (8.2)	14 (14.4)			-	-		
Differentiation			0.04	0.953			0.09	0.858
Well	5 (5.2)	5 (5.2)			2 (4.4)	2 (4.4)		
Moderately	61 (62.9)	59 (60.8)			36 (80.0)	34 (75.6)		
Poorly	31 (32.0)	33 (34.0)			7 (15.6)	9 (20.0)		
Perineural invasion			0.09	0.564			0.00	1.000
Present	42 (43.3)	46 (47.4)			14 (31.1)	14 (31.1)		
Absent	55 (56.7)	51 (52.6)			31 (68.9)	31 (68.9)		
Lymphovascular invasion			0.07	0.653			0.05	0.830
Present	61 (62.9)	64 (66.0)			26 (57.8)	27 (60.0)		
Absent	36 (37.1)	33 (34.0)			19 (42.2)	18 (40.0)		

Data are given as No. (per cent) unless noted otherwise. Missing values pancreaticobiliary/mixed subtype: [a]41 missing ASA classification, [b]44 missing BMI, [c]3 missing tumour size. Missing values intestinal subtype: [a]12 missing ASA classification, [b]24 missing BMI, [c]4 missing tumour size.

The model for overall survival in the pancreaticobiliary/mixed subtype is shown in Table 4. Characteristics associated with overall survival in univariable analysis were age >65 years, R1 resection, pT-stage 3/4, pN-stage 1, poor tumour differentiation, and lymphovascular- and perineural invasion. Multivariable analysis showed that adjuvant chemotherapy (mono-agent regimen HR=0.66 [95 per cent confidence interval 0.46-0.94] p=0.021; multi-agent regimen HR=0.36 [95 per cent confidence interval 0.17-0.77] p=0.008) was associated with an improved overall survival after adjusting for other variables associated with overall survival. The interaction term pN-stage*Adjuvant chemotherapy was not statistically significant in the multivariable Cox model and was therefore removed from the model.

Table 4. Cox proportional hazards model for overall survival in pancreaticobiliary/mixed subtype of resected ampullary adenocarcinoma.

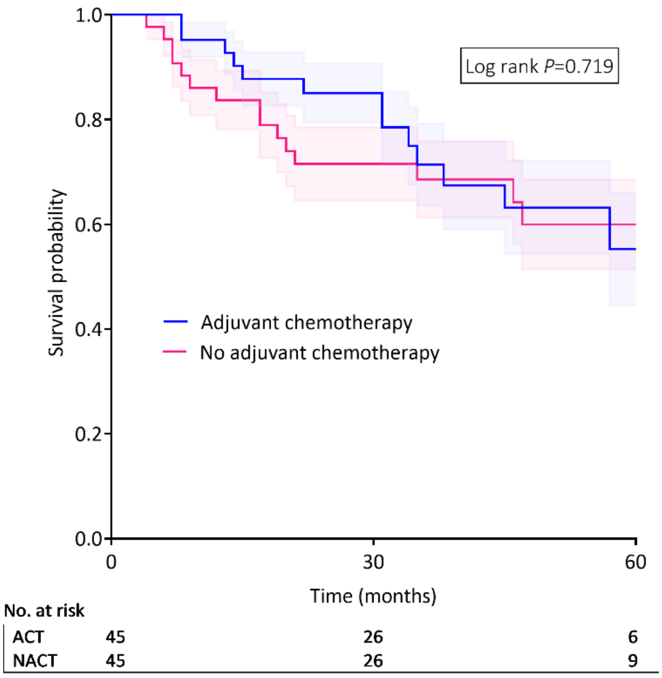
	Univariable		**Multivariable**	
	Hazard ratio (95% CI)	P value	Hazard ratio (95% CI)	P value
Age >65 years	1.420 (1.023 – 1.973)	0.036		
Female sex	0.984 (0.714 – 1.356)	0.922		
ASA 3/4	1.358 (0.887 – 2.078)	0.159		
Adjuvant chemotherapy				
Mono-agent regimen[a]	0.904 (0.642 – 1.272)	0.563	0.655 (0.456 – 0.939)	0.021
Multi-agent regimen[a]	0.665 (0.341 – 1.296)	0.231	0.363 (0.172 – 0.768)	0.008
R1 resection	2.45 (1.75 – 3.42)	<0.001	1.511 (1.032 – 2.214)	0.034
pT-stage 3/4	2.179 (1.484 – 3.200)	<0.001		
pN-stage 1	3.69 (2.38 – 5.70)	<0.001	2.724 (1.616 – 4.590)	<0.001
Tumour differentiation				
Poor[b]	1.572 (1.138 – 2.170)	0.006		
Lymphovascular invasion	3.054 (2.016 – 4.627)	<0.001	1.635 (1.007 – 2.654)	0.047
Perineural invasion	2.120 (1.516 – 2.966)	<0.001	1.571 (1.063 – 2.320)	0.023

[a]Compared with no adjuvant chemotherapy. [b]Compared with well/moderately differentiated tumour.

Intestinal subtype

A total of 45 patients with intestinal subtype who received adjuvant chemotherapy were matched to 45 comparable patients who did not receive adjuvant chemotherapy (Table 3). There was optimal balance for the following variables: age, sex, ASA classification, resection margin status, overall stage, pT-stage, differentiation grade, perineural invasion and lymphovascular invasion. The groups were not well balanced in terms of BMI and pN-stage. Figure 3C shows the overall survival of the matched cohort; adjuvant chemotherapy versus no adjuvant chemotherapy in the Intestinal subtype. Median survival was not reached in both the adjuvant chemotherapy group and in the no adjuvant chemotherapy group, p=0.719. Corresponding 1-, 3-, and 5-year overall survival rates were 95 per cent, 71 per cent and 55 per cent in the adjuvant chemotherapy group and 84 per cent, 69 per cent and 60 per cent in the no adjuvant chemotherapy group.

Figure 3c. Overall survival by adjuvant chemotherapy, in the matched cohort of intestinal subtype



ACT=Adjuvant chemotherapy, NACT=No adjuvant chemotherapy.

The model for overall survival in intestinal subtype is shown in supplementary Table S4. Associated with survival in univariable analysis were R1 resection, pT-stage 3/4, pN+, and lymphovascular- and perineural invasion. After adjusting for these variables, adjuvant chemotherapy, both mono or multi agent regimen, was not found to be associated with overall survival. The interaction term pN-stage*Adjuvant chemotherapy was not statistically significant in the multivariable Cox model and was therefore removed from the model.

DISCUSSION

In this study, patients with the pancreaticobiliary or mixed subtype of resected ampullary adenocarcinoma had a survival benefit from an adjuvant Gemcitabine-based regimen. In lack of randomized data, this large international multi-centre cohort study used propensity scores to match patients. In the matched cohort, an improved overall survival was found in patients who received adjuvant chemotherapy compared with patients who did not receive chemotherapy. The benefit from adjuvant treatment was only seen in patients with the pancreaticobiliary or mixed subtype, but not in the intestinal subtype.

A plausible explanation why survival benefit was noted only in the pancreaticobiliary or mixed subtype and not in intestinal subtype, is the choice of the adjuvant chemotherapy regimen, which was Gemcitabine monotherapy in the vast majority. Gemcitabine may be effective in pancreatic cancer[24], however, it is not known for its efficacy in intestinal cancer[25]. Moreover, intestinal subtype ampullary adenocarcinoma showed no sensitivity to Gemcitabine in vitro, whereas a significant growth reduction was seen in the pancreaticobiliary subtype[26]. To date, no clear guidelines or protocols exist on adjuvant chemotherapy in ampullary adenocarcinoma, consequently, the decision remains at the discretion of the treating oncologist. Until now, most evidence on the efficacy of adjuvant chemotherapy in ampullary adenocarcinoma derives from subgroup analyses of the ESPAC-3 trial. The 92 patients with ampullary adenocarcinoma treated with Gemcitabine in that study had a median survival of 70.8 months compared with 57.8 months in the 100 patients treated with 5-FU versus 40.6 months in the 105 patients who did not receive adjuvant chemotherapy[15]. This subgroup analysis failed to show a statistically significant difference, potentially due to a type II error. Subgroup analyses on the different histopathologic subtypes were not performed. The ESPAC-4 trial, comparing Gemcitabine alone with doublet Gemcitabine and Capecitabine, has extended recruitment for the periampullary cohort[27].

Similar to the current study, a German retrospective mono-centre study of 95 patients with resected ampullary adenocarcinoma, demonstrated a survival benefit in patients receiving adjuvant Gemcitabine in the pancreaticobiliary subtype only (median survival of 32 months in the Gemcitabine group versus 13 months in the patients not receiving adjuvant chemotherapy, P=0.013). However, groups were small (22 patients received Gemcitabine vs 24 controls) and no matching was performed, resulting in high risk of treatment allocation bias[28].

It is possible that patients with intestinal subtype ampullary adenocarcinoma might benefit from adjuvant chemotherapy regimens comparable to those in duodenal cancer. Although the evidence regarding adjuvant chemotherapy in duodenal cancer is limited, a survival benefit of 16 months (median survival of 42 versus 26 months) has been described in lymph node positive duodenal cancer. However, details on specific adjuvant chemotherapy regimens are lacking[29]. Another retrospective study reported an increased survival after adjuvant chemotherapy in the subgroup of patients with a lymph node ratio of 0.1 or above[30]. The ongoing BALLAD trial, investigating different adjuvant chemotherapy regimens in small bowel adenocarcinoma, may provide more evidence on this issue[31].

Even though the importance of classifying the different subtypes has been highlighted repeatedly[28,32–34], it appears that documentation of subtype is often lacking. In the current study the histopathologic subtype was not reported in 387/976 patients, nearly 40%, suggesting that subtype classification is either not considered or remains challenging[35]. The current study reveals that histopathologic subtyping of ampullary adenocarcinoma has potential therapeutic implications and therefore, every effort should be made to classify ampullary adenocarcinoma, especially prior to the administration of adjuvant chemotherapy.

Several studies have suggested that additional immunohistochemical staining may improve distinction between subtypes[35–37]. Potential markers expressed in intestinal type carcinoma include CK20, MUC2 and CDX2[38–40]. Whereas, pancreaticobiliary type carcinomas are likely to express CK7 and MUC1[39,40]. Ang and colleagues have shown that combining morphologic classification with an immunohistochemical panel of MUC1, MUC2, CDX2 and CK20 may improve consensus diagnosis[35]. Moreover, Overman and colleagues performed gene expression and proteomic analysis on fresh frozen samples of 14 patients with ampullary adenocarcinoma. Two subgroups were identified, an intestinal like and pancreaticobiliary like subtype[41].

In addition to the missing values of histopathologic subtype, there are a number of limitations to this study. First, due to the retrospective study design, the adjuvant chemotherapy group was selected, demonstrated by the more advanced overall stage and unfavourable tumour characteristics in the adjuvant chemotherapy group. By using propensity score matching, based on clinical and histopathologic variables associated with survival, treatment allocation bias was minimized. However, treatment allocation bias can only be entirely avoided by randomization. Second, no central histopathology review was done and, consequently differences in subtypes classification between centres might have occurred. Even though the WHO classification[21] was used in all centre, the use of immunohistochemistry was not routine practice but only used on occasion. Indication for the use of immunohistochemistry might have different between centres. With improved differentiation of subtypes, the observed differences in survival may possibly increase. Third, tumour staging was performed using the 7th edition of AJCC, instead of the current 8th edition. The majority of specimens in this study were assessed when the 7th edition was in use and restaging would require formal revision of all specimens. This was not feasible due to the large cohort and multi-centre aspect of the study. Further, N-stage was not optimally balanced between de adjuvant chemotherapy group and the no adjuvant chemotherapy group in the matched cohort of all subtypes and in the matched cohort of the intestinal subtype. As N-stage was associated with survival, this could have led to an underestimated survival benefit in the cohort of all subtypes. In the intestinal subtype, the estimated effect of adjuvant chemotherapy on survival could have been overestimated. However, no difference was seen in survival between adjuvant chemotherapy and no adjuvant chemotherapy. Possibly, adjuvant chemotherapy could have an unfavourable effect on survival in patients with intestinal subtype. Lastly, a number of centres from different geographical settings participated in the study.

This could have resulted in substantial heterogeneity regarding treatment strategy. The inclusion of several centres may also however, have improved the external validity of this study.

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