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Dutch Pancreatic Cancer Group; de Jong, Evelien J M; van der Geest, Lydia G; Besselink, Marc G; Bouwense, Stefan A W; Buijsen, Jeroen; Dejong, C H C; Koerkamp, Bas G; Heij, Lara R; de Hingh, Ignace H J T

Published in:
Hpb

DOI:
10.1016/j.hpb.2022.01.009

Publication date:
2022

https://doi.org/10.1016/j.hpb.2022.01.009 HPB

ORIGINAL ARTICLE

Treatment and overall survival of four types of non-metastatic periampullary cancer: nationwide population-based cohort study

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Abstract

Background: Periampullary adenocarcinoma consists of pancreatic adenocarcinoma (PDAC), distal cholangiocarcinoma (DC), ampullary cancer (AC), and duodenal adenocarcinoma (DA). The aim of this study was to assess treatment modalities and overall survival by tumor origin.

Methods: Patients diagnosed with non-metastatic periampullary cancer in 2012–2018 were identified from the Netherlands Cancer Registry. OS was studied with Kaplan–Meier analysis and multivariable Cox regression analyses, stratified by origin.

Results: Among the 8758 patients included, 68% had PDAC, 13% DC, 12% AC, and 7% DA. Resection was performed in 35% of PDAC, 56% of DC, 70% of AC, and 59% of DA. Neoadjuvant and/or adjuvant therapy was administered in 22% of PDAC, 7% of DC, 7% of AC, and 12% of DA. Three-year OS was highest for AC (37%) and DA (34%), followed by DC (21%) and PDAC (11%). Adjuvant therapy was associated with improved OS among PDAC (HR = 0.62; 95% CI 0.55–0.69) and DC (HR = 0.69; 95% CI 0.48–0.98), but not AC (HR = 0.87; 95% CI 0.62–1.22) and DA (HR = 0.85; 95% CI 0.48–1.50).

Conclusion: This retrospective study identified considerable differences in treatment modalities and OS between the four periampullary cancer origins in daily clinical practice. An improved OS after adjuvant chemotherapy could not be demonstrated in patients with AC and DA.

Received 13 August 2021; accepted 17 January 2022

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☆ This article is not based on previous communication.

Introduction

Periampullary cancer comprises four different cancer types: pancreatic ductal adenocarcinoma (PDAC), distal cholangiocarcinoma (DC), ampullary cancer (AC), and duodenal adenocarcinoma (DA). Together, they form 5% of all gastrointestinal tract malignancies.[1,2] Adenocarcinoma of the pancreatic head is the most common origin of periampullary cancers with 15.56 new diagnoses per 100,000 persons in the Netherlands in 2017, but the other origins are rare (DC 1.29 per 100,000, DA 0.98 per 100,000, and AC 0.96 per 100,000; crude incidence rates).[3] However, pre-operative differentiation on imaging between these four origins is challenging, due to anatomical close proximity. Often, pathological assessment is therefore needed. Importantly, treatment choices and the prognosis are affected by the primary tumor origin.[2]

Pancreatoduodenectomy (PD) and segmental resection for DA, are the only potentially curative treatment options for all four tumors.[2,4] International and Dutch guidelines for PDAC recommend resection and adjuvant therapy, whereas international guidelines for DC are inconsistent in terms of adjuvant chemotherapy.[5,6] Neoadjuvant therapy is only recommended in patients diagnosed with borderline PDAC. For AC and DA, no conclusive evidence-based recommendations on neoadjuvant and adjuvant therapy exist and the available evidence on the effectiveness of neoadjuvant and adjuvant therapy is limited.

The reported 5-year overall survival (OS) in population-based studies, irrespective of metastatic disease status, was highest for patients with AC (21–32%), and lowest for patients with PDAC (3–7%).[7,8] No recent nationwide study on resection rates, neoadjuvant and adjuvant therapy and OS in non-metastatic periampullary cancer origins is available.

Therefore, the primary aim of this study was to study the treatment modalities and overall survival in patients diagnosed with non-metastatic periampullary cancer. The secondary aim was to assess the effect of adjuvant therapy on OS for each different anatomic type of periampullary cancer.

Methods

Patient selection

Data of patients initially diagnosed as non-metastatic periampullary adenocarcinoma based on radiological (clinical) staging from January 2012 to December 2018 (International Classification of Disease-Oncology (ICD-O-3) C17.0, C24.0, C24.1 and C25.0; morphology codes listed in Supplementary Table 1) were retrieved from the Netherlands Cancer Registry (NCR).[9] The NCR is a population-based cancer registry in the Netherlands (approx. 17 million inhabitants since 2017), which is linked to the national pathological archive (PALGA), and National Registry of Hospital Discharge Diagnosis to identify all new cancer diagnoses. The notifications are verified in hospital medical records by trained, independent registrars, who also extract information on the patient, tumor, and treatment characteristics.

Patients diagnosed between 2012 and 2018 were included as the centralization of pancreatic surgery in the Netherlands was officially regulated from 2012 onwards.[10–12] Patients younger than 18 years at diagnosis and patients with clinically diagnosed metastatic disease were excluded. Information on vital status was obtained on January 31st 2020 through the Municipal Administrative Database. This study was approved by the scientific committee of the Dutch Pancreatic Cancer Group (DPCG) and the Privacy Review Board of the NCR.[13] According to the Central Committee on Research involving Human Subjects, this study does not require approval from an ethics committee in the Netherlands. The reporting of this study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.[14]

Definitions

Tumor topography was based on pathologic assessment or, if unavailable, on clinical (imaging) data. Tumor stage was registered according to the (clinical) Union for International Cancer Control (UICC) TNM classification 7th until 2016 and 8th edition from 2017.[15–17] Both clinical TNM (cTNM) and pathological TNM (pTNM) stage were reported. The findings of preoperative oncological work-up (i.e. imaging and consensus most likely diagnosis and staging at multidisciplinary team meeting) including peroperative findings of surgical exploration only were registered as cTNM, and the pTNM stage was based on pathological registered classifications. A final TNM stage consists of pTNM and, if missing, complemented with the clinical registered classifications. In patients treated with neoadjuvant therapy, only clinically registered classifications were used. Patients with unknown tumor classification and/or unknown lymph node involvement were categorized as TNM stage unknown. The pathology report was consulted to obtain information on the assessment of the surgical specimen (i.e. resection margin and histological subtype). Missing information was registered as unknown. Patients who underwent surgical exploration with laparotomy or laparoscopy but no resection of the primary tumor were categorized as no resection. Neoadjuvant and adjuvant therapy regimens were prescribed following the Dutch guidelines (pancreatic cancer, gallbladder cancer, and colorectal cancer), available evidence, and the recruiting trials. Registration of chemotherapy in the NCR is regardless of the number of chemotherapy cycles patients received.

Endpoints

OS was defined as the time from date of diagnosis to date of death from any cause or censored at last follow-up date. Treatment modalities were categorized as resection only, resection with neoadjuvant and/or adjuvant chemotherapy with or without radiotherapy (in figures shortened to (neo) adjuvant

chemo (radio) therapy), chemotherapy alone, radiotherapy alone, chemoradiotherapy without resection, and no (anti-cancer) treatment. A hospital stay after resection exceeding 14 days was considered a proxy for the presence of postoperative complicities (surgical and non-surgical).

Statistical analysis

Dichotomous data are presented as proportions and continuous data as medians with interquartile range. Baseline characteristics between periampullary tumor origins were compared using the chi-square test. The Kruskal–Wallis test was used to compare the median hospital stay between periampullary tumor origins. The percentage of patients undergoing a specific type of multimodality therapy was analyzed for the total group and stratified by tumor origin. The predictive value of patient- and tumor characteristics on receiving adjuvant therapy were studied in patients who underwent resection with logistic regression analyses for each tumor origin. To reduce the risk of immortal time bias, patients deceased within 30 days after resection were excluded. OS was calculated with the Kaplan–Meier method, and the logrank test was used to compare OS between the periampullary tumor origins. Multivariable Cox-regression analyses were performed to assess the association between adjuvant therapy and OS in patients who underwent resection and survived at least 30 days, adjusted for age, TNM-stage, resection margin, and postoperative hospital stay. A sensitivity analysis was performed among patients who underwent resection, survived at least 30 days, and were diagnosed with TNM-stage II or III. In case of multicollinearity, the most relevant parameter to represent a certain variable family was selected based on the -2log likelihood. Variables with a p-value <0.10 in the univariable model were selected for the multivariable model. P-values of <0.05 were considered statistically significant. Data were analyzed using IBM SPSS Statistics for Windows, version 25 (IBM Corp., Armong, NY, USA) and STATA SE for Windows, version 14 (StataCorp LP, College Station, Texas, USA).

Results

In total, 8758 patients with clinically non-metastatic periampullary adenocarcinoma were included (Table 1). Of these patients, 68% had PDAC, 13% DC, 12% AC, and 7% DA. The median age was 72 years (IQR 64–79 years) in PDAC, 73 years (IQR 65–81 years) in DC, 71 years (IQR 62–80 years) in AC, and 71 years (IQR 62–80 years) in DA. Patients with AC were most often diagnosed at clinical stage I (65%), followed by DC (40%), PDAC (36%) and DA (11%). Of all patients, 7% were found to have metastatic disease (pathological stage IV). Of the patients who underwent resection of the primary tumor, 23% of the patients diagnosed with cTNM stage I were also diagnosed as stage I according to the pathological findings.

Treatment modalities in non-metastatic periampullary adenocarcinoma

Resection of the primary tumor was performed in 70% of the patients with AC, followed by 56% with DC, 59% with DA, and 35% with PDAC (Fig. 1). Characteristics of the patients who underwent resection (and not deceased within 30 days) are shown in Supplementary Table 3. The resection margin was known in 66% of these patients, and a positive resection margin was found in 11% of the patients with AC, 16% of the patients with DA, 31% of the patients with DC, and 45% of the patients with PDAC (Supplementary Table 3). Pancreatoduodenectomy was performed most often, and only a small proportion of patients diagnosed with AC (1.0%) or DA (1.2%) underwent a local resection (Supplementary Fig. 1). For patients who underwent pancreatoduodenectomy, the median length of hospital stay in days (interquartile range) was significantly shorter in patients with PDAC (11 days (9–17)), compared with patients with DC (13 days (9–21)), AC (13 days (9–20)), and DA (13 days (9–22.5); $p < 0.001$; Supplementary Table 2)). A surgical exploration, without resection, was performed in 11% of the patients with PDAC, 12% with DA, 7% with DC, and 5% with AC.

Neoadjuvant and adjuvant therapy were predominantly used in patients with PDAC (58% of resected patients), followed by DA (16%), DC (11%), and AC (11%) (data not further shown). Of the patients who received neoadjuvant and/or adjuvant therapy, the majority (86%) of the patients received adjuvant chemotherapy only, irrespective of primary tumor origin (Fig. 2).

Chemotherapy alone was administered to 12% of the patients with PDAC, in 5% of the patients with DA, 4% of the patients with DC, and 2% of the patients with AC (Fig. 1). The highest proportion of patients receiving no (anti-cancer) treatment was seen in PDAC (51%), followed by DC (41%), DA (32%), and AC (27%).

Predictors for adjuvant therapy

Within the group of patients who underwent resection, adjuvant therapy was more often administered in patients <65 years, in patients diagnosed with TNM stage II PDAC and AC, and TNM stage III AC or DC, and in patients diagnosed with PDAC, AC, and DA when hospitalized shorter than 14 days (Table 2).

Survival

Median OS for all non-metastatic periampullary cancers was 9.8 months (95% CI 9.5–10.1). Three-year and median OS rates were highest for patients diagnosed with AC (37%; 95% CI 34.3–40.1) and 22.6 months), followed by DA (34%; 95% CI 30.4–38.4) and 16.1 months), and DC (21%; 95% CI 18.4–23.4) and 13.1 months), and was lowest for patients diagnosed with PDAC (11%; 95% CI 9.8–11.5) and 8 months); Supplementary

Table 1 – Patient, tumor and treatment characteristics of patients diagnosed with non-metastatic periampullary adenocarcinoma in 2012–2018, by origin (%)

	Total (n = 8758)	PDAC (n = 5982)	DC (n = 1173)	AC (n = 1015)	DA (n = 585)	Pearson Chi-square
Age						**p = 0.046**
<65 years	24.8	24.4	23.5	25.1	31.3	
Median age [IQR], years	72 [65–80]	72 [64–79]	73 [65–81]	71 [62–80]	71 [62–80]	
Sex						**p < 0.001**
Male	51.0	48.8	57.1	56.0	52.9	
Clinical tumor classification						**p < 0.001**
T1	15.3	11.0	37.3	53.8	5.7	
T2	31.3	34.6	11.5	21.4	12.2	
T3	27.0	26.4	40.3	19.7	29.7	
T4	26.4	28.0	11.0	5.2	52.5	
Unknown	*n = 2407*	*n = 720*	*n = 773*	*n = 589*	*n = 325*	
Clinical lymph node involvement						**p < 0.001**
No	76.6	74.7	81.6	85.9	69.2	
Yes[a]	23.4	25.3	18.4	14.1	30.8	
Unknown	n = 1153	n = 756	n = 165	n = 137	n = 95	
cTNM-stage						**p < 0.001**
Stage I	37.0	36.2	39.9	64.6	10.6	
Stage II	33.7	32.9	47.1	29.0	36.3	
Stage III	29.4	30.9	13.0	6.4	53.1	
Unknown	*n = 2829*	*n = 1142*	*n = 797*	*n = 622*	*n = 268*	
TNM-stage[b]						**p < 0.001**
Stage I	15.9	16.2	10.7	25.9	6.8	
Stage II	37.8	38.8	43.0	30.3	29.6	
Stage III	23.5	26.8	9.1	14.3	34.9	
M0 NOS[c]	16.0	11.0	32.3	25.0	19.0	
Stage IV	6.8	7.3	4.9	4.4	9.7	
Differentiation grade						**p < 0.001**
Well	12.2	12.1	14.7	12.3	9.0	
Moderate	52.4	50.8	51.5	57.9	52.4	
Poorly & undifferentiated	35.4	37.2	33.7	29.8	38.7	
Unknown	*n = 5095*	*n = 3983*	*n = 583*	*n = 341*	*n = 188*	
Histology subtype						**p < 0.001**
Intestinal	6.5	2.0	1.4	27.1	27.2	
Pancreatobiliary	6.3	2.8	6.3	11.1	0.0	
Adenocarcinoma, subtype other than IT and PB	13.2	17.9	4.6	3.0	0.5	
Adenocarcinoma, not further specified	74.0	77.4	70.5	58.8	72.3	

Abbreviations: AC = ampullary cancer, DA = duodenal adenocarcinoma, DC = distal cholangiocarcinoma, IT = intestinal, IQR = interquartile range, NOS = not otherwise specified, PB = pancreatobiliary, PDAC = pancreatic ductal adenocarcinoma.
[a] Positive lymph node involvement includes patients coded as N+ according to UICC 7th edition and patients coded as N1 or N2 according to UICC 8th edition.
[b] TNM stage consists of pathological TNM classification supplemented with clinical TNM classification.
[c] M0 NOS: patients without metastatic disease, but could not be grouped based on T-classification (TX) and/or N-classification (NX).

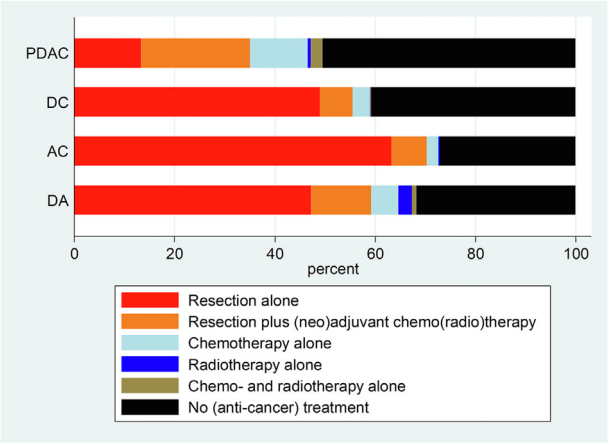

Figure 1 Treatment of 8758 patients diagnosed with non-metastatic periampullary adenocarcinoma in 2012–2018, by origin (%). Abbreviations: PDAC = pancreatic ductal adenocarcinoma; DC = distal cholangiocarcinoma; AC = ampullary cancer; DA = duodenal adenocarcinoma

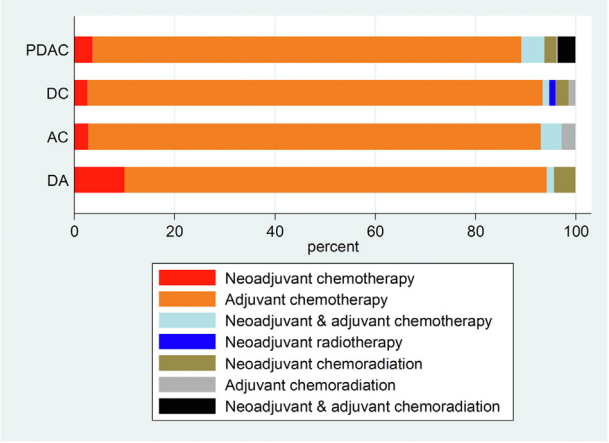

Figure 2 Details of neoadjuvant and adjuvant treatment in 1516 patients diagnosed with non-metastatic periampullary adenocarcinoma in 2012–2018, by origin (%). Abbreviations: PDAC = pancreatic ductal adenocarcinoma; DC = distal cholangiocarcinoma; AC = ampullary cancer; DA = duodenal adenocarcinoma

Fig. 2). Patients who underwent resection (Fig. 3A) had higher three-year OS, compared with patients without resection (Fig. 3B): 56% vs. 3% in DA, 52% vs. 4% in AC, 35% and 3% in DC, and 26% vs. 2% in PDAC.

Median OS was highest for patients with DA, DC and PDAC whom underwent resection with neoadjuvant and/or adjuvant therapy: 71.4 months (95% CI 18.3–124.5) in DA, 28.9 months (95% 22.0–35.7) in DC, and 23.6 months (95% CI 22.1–25.0) in PDAC (Supplementary Fig. 3). In patients with AC, median OS was highest in those who underwent resection only: 39.9 months (95% CI 32.2–47.6).

After adjusting for age, TNM stage, resection margin, and postoperative hospital stay, resection combined with adjuvant therapy was associated with a higher OS in patients with PDAC (HR = 0.62 (95% CI 0.55–0.69), $p < 0.001$), and DC (HR = 0.69 (95% CI 0.48–0.98), $p = 0.038$) compared with resection alone, but not in patients with AC (HR = 0.87 (95% CI 0.62–1.22), $p = 0.423$), and DA (HR = 0.85 (95% CI 0.48–1.50), $p = 0.580$; Table 3). The results remained similar when only patients diagnosed with pathological stage II or III were included (data not shown).

Discussion

This first nationwide population-based cohort study on non-metastatic periampullary cancers demonstrated that almost two thirds of the patients diagnosed with DC, AC, and DA underwent resection, versus only one third of the patients with PDAC. One out of five patients diagnosed with PDAC and who underwent resection, received at least one cycle of neoadjuvant and/or adjuvant therapy, compared with only one out of ten patients diagnosed with DC, AC, and DA. Between 2012 and 2018, three-year OS was highest with 37% for patients diagnosed with AC, followed by 34% in DA, 21% in DC, and 11% in PDAC. This retrospective study could not demonstrate an improved OS after adjuvant chemotherapy in patients diagnosed with AC and DA.

The higher resection rates in patients diagnosed with AC, followed by patients with DA, DC, and PDAC were also observed in a population-based study performed in the USA (2004–2012).[7] PDAC grow in closer proximity to the veins compared with DC, AC, and DA, and therefore complicates the resectability. In addition, patients with AC tend to present relatively early due to symptoms. In the current study, 65% of patients with AC was diagnosed at clinical stage I, compared with 11%–40% in patients with other periampullary cancers.[1,18] The low resection rate in patients diagnosed with PDAC might also be partly explained by misclassification of the exact primary tumor origin in patients who did not undergo resection.[19] Without pathological examination of the tumor, these patients can be – based on clinical data – classified as the most common tumor origin in that area, i.e. PDAC, automatically resulting in a lower proportion of these patients without resection. Furthermore, patients might have been not fit enough for, or not willing to undergo surgery and/or other (anti-cancer) treatment.

Differences in three year OS found in patients diagnosed with non-metastatic AC (37%), DA (34%), and DC (29%) compared with the lower three year OS in patients with PDAC (11%) are similar to previous population-based studies.[7,8,20] The variation in OS between tumor origins might be explained by differences in tumor stage at diagnosis and resection rates. In addition, histological subtype, response to systemic therapy, and differences in biological behavior, e.g. lymph node metastases, neural invasion, and resection margin status, have been shown to be

Table 2 – Multivariable model for characteristics potentially related with receiving adjuvant therapy after resection of the primary tumor, by origin

Group (no. adjuvant/ resected patients)	Total (1374/3689 = 37%)[a] OR (95% CI); p-value		PDAC (1184/2041 = 58%)[a]		DC (68/625 = 11%)[a]		AC (70/691 = 10%)[a]		DA (52/332 = 16%)[a]	
Age										
<65 years	Ref.		Ref.		Ref.		Ref.		Ref.	
65–75 years	0.66 (0.56–0.77)	**<0.001**	0.61 (0.49–0.77)	**<0.001**	0.88 (0.51–1.56)	0.688	0.39 (0.22–0.70)	**0.001**	0.53 (0.25–1.10)	0.088
>75 years	0.24 (0.20–0.30)	**<0.001**	0.17 (0.13–0.22)	**<0.001**	0.46 (0.20–1.03)	0.058	0.30 (0.14–0.65)	**0.002**	0.04 (0.01–0.30)	**0.002**
TNM Stage[b]										
Stage I	Ref.		Ref.		Ref.		Ref.		Ref.	
Stage II	2.25 (1.78–2.83)	**<0.001**	1.53 (1.11–2.12)	**0.010**	3.41 (0.80–14.49)	0.097	3.70 (1.66–8.26)	**0.001**	1.14 (0.23–5.74)	0.878
Stage III	1.64 (1.25–2.18)	**<0.001**	1.19 (0.79–1.77)	0.408	8.84 (1.89–41.33)	**0.006**	3.41 (1.39–8.38)	**0.007**	4.71 (0.99–22.41)	0.051
M0 NOS	0.58 (0.34–1.00)	0.049	1.46 (0.43–4.94)	0.547	7.10 (1.32–39.32)	**0.023**	1.88 (0.51–6.93)	0.345	0.84 (0.06–11.12)	0.893
Stage IV	0.78 (0.43–1.39)	0.394	0.47 (0.23–0.95)	**0.034**	–	–	4.87 (0.85–28.04)	0.076	–	–
Resection margin status										
R0 resection	Ref.		Ref.		Ref.		Ref.		Ref.	
R1 resection	1.65 (1.34–2.02)	**<0.001**	0.99 (0.76–1.29)	0.912	1.42 (0.73–2.75)	0.306	0.55 (0.15–1.98)	0.356	0.70 (0.20–2.51)	0.588
Unknown	1.00 (0.85–1.18)	0.984	0.89 (0.70–1.12)	0.316	0.78 (0.42–1.44)	0.419	1.30 (0.74–2.29)	0.364	0.63 (0.30–1.33)	0.227
Postoperative hospital stay										
≤14 days	Ref.		Ref.		Ref.		Ref.		Ref.	
>14 days	0.40 (0.34–0.47)	**<0.001**	0.36 (0.29–0.44)	**<0.001**	0.67 (0.38–1.18)	0.164	0.34 (0.17–0.65)	**0.001**	0.37 (0.18–0.78)	**0.008**

Abbreviations: AC = ampullary cancer, CI = confidence interval, DA = duodenal adenocarcinoma, DC = distal cholangiocarcinoma, IQR = interquartile range, NOS = not otherwise specified, PDAC = pancreatic ductal adenocarcinoma.
Differentiation grade was, despite a p-value<0.05 in the univariable model, not included in the multivariable model based on medical expertise.
[a] 123 patients died <30 days after resection (PDAC = 58; DC = 26; AC = 16; DA = 23) and were excluded.
[b] TNM stage consists of pathological TNM classification supplemented with clinical TNM classification.

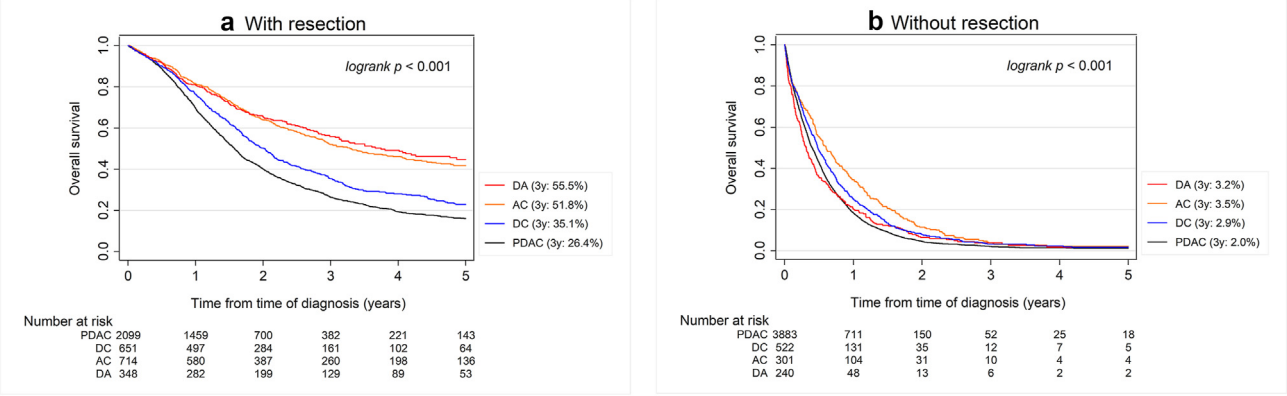

Figure 3 – Overall survival in patients with non-metastatic periampullary cancer (A) with resection and (B) without resection. Abbreviations: PDAC = pancreatic ductal adenocarcinoma; DC = distal cholangiocarcinoma; AC = ampullary cancer; DA = duodenal adenocarcinoma

Table 3 Multivariable analysis for the association of adjuvant therapy with overall survival in patients who underwent resection of the primary tumor, by origin

Number of events	Total (n = 3689)		PDAC (n = 2041)[a]		DC (n = 625)[a]		AC (n = 691)[a]		DA (n = 332)[a]	
	2462		1538		423		344		157	
	HR (95%CI); p-value									
Adjuvant therapy										
No	Ref.		Ref.		Ref.		Ref.		Ref.	
Yes	0.90 (0.82–0.98)	**0.013**	0.62 (0.55–0.69)	**<0.001**	0.69 (0.48–0.98)	**0.038**	0.87 (0.62–1.22)	0.423	0.85 (0.48–1.50)	0.580
Age										
<65 years	Ref.		Ref.		Ref.		Ref.		Ref.	
65–75 years	1.14 (1.04–1.25)	**0.007**	1.06 (0.94–1.19)	0.321	0.96 (0.77–1.20)	0.747	1.16 (0.90–1.50)	0.264	1.77 (1.16–2.68)	**0.008**
≥75 years	1.28 (1.14–1.43)	**<0.001**	1.13 (0.97–1.31)	0.109	1.23 (0.94–1.61)	0.134	1.07 (0.80–1.44)	0.654	2.30 (1.39–3.83)	**0.001**
TNM-classification[b]										
Stage I	Ref.		Ref.		Ref.		Ref.		Ref.	
Stage II	3.02 (2.58–3.54)	**<0.001**	1.79 (1.46–2.18)	**<0.001**	3.50 (2.35–5.21)	**<0.001**	4.67 (3.26–6.70)	**<0.001**	3.36 (1.21–9.35)	**0.020**
Stage III	2.86 (2.39–3.44)	**<0.001**	1.90 (1.50–2.43)	**<0.001**	4.76 (2.86–7.94)	**<0.001**	6.86 (4.65–10.13)	**<0.001**	3.32 (1.18–9.33)	**0.023**
Stage M0 NOS	1.42 (1.01–1.99)	0.041	0.49 (0.15–1.54)	0.219	2.62 (1.41–4.85)	**0.002**	2.52 (1.37–4.64)	**0.003**	3.66 (1.06–12.62)	**0.040**
Stage IV	8.05 (6.09–10.65)	**<0.001**	4.25 (3.00–6.02)	**<0.001**	19.71 (9.44–41.14)	**<0.001**	16.04 (7.80–33.00)	**<0.001**	8.15 (1.98–33.49)	**0.004**
Resection margin status										
R0 resection	Ref.		Ref.		Ref.		Ref.		Ref.	
R1 resection	1.74 (1.55–1.96)	**<0.001**	1.47 (1.27–1.70)	**<0.001**	1.60 (1.21–2.14)	**0.001**	1.23 (0.77–1.95)	0.392	2.67 (1.49–4.79)	**0.001**
Unknown	1.29 (1.17–1.42)	**<0.001**	1.26 (1.11–1.42)	**<0.001**	1.15 (0.92–1.45)	0.226	1.16 (0.90–1.48)	0.248	1.65 (1.09–2.49)	**0.017**
Postoperative hospital stay										
≤14 days	Ref.		Ref.		Ref.		Ref.		Ref.	
>14 days	1.20 (1.10–1.30)	**<0.001**	1.22 (1.10–1.36)	**<0.001**	1.25 (1.02–1.52)	**0.033**	1.14 (0.91–1.43)	0.245	1.33 (0.92–1.93)	0.132

Abbreviations: AC = ampullary cancer, CI = confidence interval, DA = duodenal adenocarcinoma, DC = distal cholangiocarcinoma, IQR = interquartile range, NOS = not otherwise specified, PDAC = pancreatic ductal adenocarcinoma.
[a] 123 patients died <30 days after resection (PDAC = 58; DC = 26; AC = 16; DA = 23) and were excluded.
[b] TNM stage consists of pathological TNM classification supplemented with clinical TNM classification.

prognostic factors for survival.[21–23] The proportion of patients with a positive resection margin in this study is remarkably high for patients diagnosed with AC (84%) and DA (69%). This might be explained by differences in pathological examination.

In addition, the use of neoadjuvant and/or adjuvant therapy varied widely between periampullary cancer origins. Patients diagnosed with PDAC received neoadjuvant and/or adjuvant therapy most frequently. Following national guidelines, patients with resectable PDAC receive adjuvant therapy, and neoadjuvant strategies were mostly applied in prospective trials, such as the phase 3 PREOPANC-1 trial, investigating neoadjuvant chemoradiotherapy vs. upfront surgery.[24,25] International and Dutch guidelines advise not to administer neoadjuvant and adjuvant therapy outside clinical trials in DC and the lack of guidelines for AC and DA might explain the low numbers of these patients treated with neoadjuvant and/or adjuvant therapy.[5,25]

We demonstrated that adjuvant therapy is associated with improved OS in patients diagnosed with PDAC and DC, but this association could not be shown for DA and AC. The benefit of adjuvant therapy in patients with PDAC has been shown by the

CONKO-001 trial, and the chemotherapeutic agents demonstrated to be effective in the ESPAC-4 trial and PRODIGE-24 trial are now recommended in the international guidelines.[26–28] In patients with DC, the BILCAP study including biliary cancers (including gallbladder cancer), showed that adjuvant capecitabine resulted in better overall survival compared to observation (HR = 0.81 (95% CI 0.63–1.04), p = 0.10), and the ACTICCA-1 trial (recruiting since 2014) currently investigates different adjuvant treatment strategies.[29,30] The type of adjuvant treatment in patients with DC in the present study is unknown, but might be similar to these clinical studies and thus may have contributed to the OS difference between patients with DC with and without adjuvant therapy.

The seemingly lack of benefit of adjuvant therapy in DA and AC in our study should be interpreted with caution because of the observational study design, the small number of patients receiving adjuvant therapy, and the possible risk of confounding by indication. And although the association between adjuvant therapy and OS was adjusted for age, TNM-classification, resection margin, and postoperative hospital stay, not all possible confounders (i.e. performance status, histologic subtype) were available. The association is thus studied in a heterogeneous study population. Some retrospective studies have reported more favorable OS with adjuvant chemotherapy in patients diagnosed with DA and AC (DA: HR = 0.77 (95% CI 0.68–0.8) and AC: HR = 0.82 (95% CI 0.71 to 0.95).[31,32] Only one trial among patients with DC, AC, and DA, on adjuvant therapy is available and shows a survival benefit for adjuvant gemcitabine (HR = 0.70 (95%CI 0.51–0.97), p = 0.03) and for fluorouracil plus folinic acid (HR = 0.79 (95% CI 0.58–18), p = 0.13) compared with observation after adjusting for prognostic variables.[33] Moreover, it could be suggested to cluster periampullary cancer, especially AC, based on histologic subtype (i.e. intestinal vs. pancreatobiliary) instead of anatomic location or origin.[34] In a retrospective study on gemcitabine-based adjuvant chemotherapy among patients diagnosed with AC, an improvement in survival was only seen in patients with the pancreatobiliary subtype and not in those with the intestinal subtype.[35] High level evidence should therefore be obtained for patients with pancreatobiliary tumors and patients with intestinal tumors separately.

The results of this study should be interpreted in light of some limitations. In addition to the risks associated with the retrospective cohort design, treatment allocation was not at random and survival differences may be (partly) the result of selection bias. Second, the retrospective and nationwide study design limits the availability of data on patient and tumor characteristics (e.g. comorbidity, performance status), recurrences, number of chemotherapy cycles, and type of systemic therapies. The presence and size of the association between adjuvant chemotherapy and overall survival per periampullary tumor origin might have been affected by the number of chemotherapy cycles and type of systemic therapies. Third, without resection specimens for pathological assessment, the diagnosis of the exact anatomic site of periampullary tumors is difficult.[1,36] However, this represents daily clinical practice in which the exact anatomic site is not always known and also pathological assessment is not always conclusive.[19] Fourth, no distinction could be made between resectable, borderline resectable, and locally advanced disease, while clinical decisions for treatment – especially in PDAC – are often made based on this classification. Therefore, our study includes a heterogeneous patient population with resectable and locally advanced disease status.

Yet, this is the first study among a European population diagnosed with periampullary cancer studying resection rates, neoadjuvant and adjuvant therapy, and overall survival, and assessing the association between adjuvant therapy and overall survival per periampullary origin. This study gives therefore insight in daily clinical practice and identifies areas for future studies to obtain high level evidence.

In conclusion, this nationwide study showed that among the four periampullary cancers, i.e. pancreatic adenocarcinoma, distal cholangiocarcinoma, ampullary cancer, and duodenal adenocarcinoma, each have different treatment approaches and outcomes in clinically non-metastatic disease. Data from randomized controlled trials on the effectiveness of neoadjuvant and adjuvant strategies are to be awaited in patients with ampullary cancer and duodenal adenocarcinoma, but also distal cholangiocarcinoma.

Acknowledgments

The authors thank the registration team of the Netherlands Comprehensive Cancer Organisation (IKNL) for the collection of data for the Netherlands Cancer Registry as well as IKNL staff for scientific advice.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflict of interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:JDV has served as a consultant for Amgen, AstraZeneca, MSD, Pierre Fabre, and Servier, and has received institutional research funding from Servier. All outside the submitted work.

SG reports grants from Roche, grants from Pfizer, grants from Novartis, grants from Eisai, grants from Lilly. All outside the submitted work; HVL reports grants and non-financial support from BMS, grants and non-financial support from Celgene, grants and non-financial support from Lilly, grants and non-financial support from Nordic, grants and non-financial support from Servier, grants from Bayer, grants from Merck Serono, grants from MSD, grants from Philips. All outside the submitted work;

VT-H reports grants and personal fees from Roche, grants and personal fees from Novartis, grants and personal fees from Pfizer, grants and personal fees from Lilly, personal fees from Accord Healthcare, grants from AstraZeneca, grants from Eisai, grants from Daiichi Sankyo. All outside the submitted work;

LV-VI reports non-financial support from Servier, non-financial support from Pierre Fabre, non-financial support from Roche. All outside the submitted work; JW reports grants and non-financial support from Servier, non-financial support from MSD, non-financial support from AstraZeneca, grants and non-

financial support from Celgene, grants from Halozyme, grants from Merck, grants from Roche, grants from Pfizer, grants from Amgen, grants from Novartis. All outside the submitted work;
VM reports a VENI grant by the Netherlands Organization for Scientific Research (NWO; grant #09150161810030) and a grant from the Dutch Ministry of Economic Affairs (Health ~ Holland Public Private Partnership grant #PPP-2019-024). All outside the submitted work; IDH received grants from Roche and RanD Biotechnology. All outside the submitted work;
The other authors have declared no conflicts of interests.
ICMJE-COI forms are obtained and can be provided.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.hpb.2022.01.009.

