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Treatment and survival of resected and unresected distal cholangiocarcinoma: a nationwide study

Marin Strijker^a, Ali Belkouz^b, Lydia G. van der Geest^c, Thomas M. van Gulik^a, Jeanin E. van Hoof^d, Vincent E. de Meijer^e, Nadia Haj Mohammad^f, Philip R. de Reuver^g, Joanne Verheij^h, Judith de Vos-Geelenⁱ, Johanna W. Wilmink^b, Bas Groot Koerkamp^j, Heinz-Josef Klumpen^b  and Marc G. Besselink^a; for the Dutch Pancreatic Cancer Group

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ABSTRACT

Background: Population-based data on distal cholangiocarcinoma (DCC) from the Western world are not available, albeit essential to identify areas for improvement. This study investigated the incidence, treatment and outcomes, including time trends and predictors for survival, in a nationwide cohort of DCC.

Methods: This is a retrospective cohort study of patients diagnosed with DCC (2009–2016) derived from the Netherlands Cancer Registry. Overall survival (OS) and its predictors were analyzed using Kaplan–Meier and Cox regression analysis. Time trends (2009–2012 versus 2013–2016) were assessed.

Results: Overall, 1338 patients with DCC were included, with 1-, 3- and 5-year OS of 46%, 18%, and 11%. Incidence of DCC was 0.55–0.90 per 100.000 per year. Median OS was 10.4 months across all stages; 21.9 months for resected ($n = 620$, 46.3%), 6.7 months for unresected nonmetastatic ($n = 445$, 33.3%), and 3.6 months for metastatic DCC ($n = 273$, 20.4%) ($p < .001$). After resection, 30-day mortality was 4.8% and 90-day mortality 7.7%. Patients with metastatic DCC who received chemotherapy ($n = 78$, 28.6%) had a median OS of 8.2 versus 2.8 months for those not treated ($p < .001$). Over time, resection rates (53.6% to 61.7%, $p = .008$) and use of palliative chemotherapy in metastatic DCC (22.3% to 32.9%, $p = .05$) increased, without improvement in OS (10.3 vs 10.6 months, $p = .55$). Independent poor prognostic factors for OS in resected disease were increasing age, pT3/T4 stage, higher lymph node ratio, poor differentiation, and R1 resection.

Conclusions: In a nationwide cohort of DCC, resection rates and the use of chemotherapy increased whereas OS remained stable at 10.4 months.

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Introduction

Distal cholangiocarcinoma (DCC) is an uncommon cancer, accounting for 30–40% of all cholangiocarcinomas [1,2]. In the resectable setting, upfront surgery is the treatment of choice [3]. However, about half of all patients will suffer from recurrence within 3 years, leading to a median overall survival (OS) of 33 months [4,5]. In the recent randomized multicenter BILCAP trial, including patients with all subtypes of biliary tract cancer, administration of adjuvant capecitabine

led to better outcomes in the per-protocol analysis when compared to surgery alone [6]. In the unresectable setting, palliative chemotherapy consisting of gemcitabine plus cisplatin is the current standard of care. This was based on the results of the ABC-02 trial which showed improved median OS from 8.1 to 11.7 months when compared to gemcitabine alone in patients with biliary tract cancer [7].

To better inform patients and identify areas for improvement in the various stages of DCC, it is essential to study

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 Supplemental data for this article can be accessed [here](#).

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population-based outcomes. Current studies focus on resected tumors and are often derived from high-volume, non-Western centers [5]. The available all-stage cohorts typically combine DCC with other types of cholangiocarcinoma [8,9]. To our best knowledge, no population-based all-stage cohorts reporting outcomes for DCC only have been published.

Therefore, we used population-based data to (1) describe incidence, treatment and outcomes of all patients with DCC in a nationwide registry, (2) analyze time trends, and (3) determine independent prognostic factors for survival.

Material and methods

Data were derived from the Netherlands Cancer Registry (NCR), which is a nationwide population-based registry recording all newly diagnosed malignancies in the Netherlands (about 17 million inhabitants). Patients are identified using the automated pathological archive (PALGA) and the National Registry of Hospital Discharge Diagnosis. Trained NCR registry administrators verify the diagnosis after approximately nine months and add data from medical files in all hospitals. This period ensures correct registration of patients in whom the diagnosis has been revised. Registry administrators across different hospitals can request each other to register additional data (e.g. when a patient was referred). Completeness of the NCR is estimated to be at least 95%; missed patients are supposed to be older, receive limited hospital care and pathological confirmation of DCC is lacking. The study was approved by the NCR review board and the scientific committee of the Dutch Pancreatic Cancer Group. The need for ethical approval was waived by the Medical Ethics Review Committee of the Amsterdam UMC, location AMC (W18_153 #18.189). The TRIPOD statement for reporting of prognostic studies was followed [10].

Patient selection and definitions

All patients registered to have primary invasive DCC diagnosed from 2009 to 2016 were included (ICD-O-3 morphological codes in Table A.1). DCC was defined as a tumor arising below the insertion of the cystic duct and above the ampulla of Vater (hence including mid-cholangiocarcinomas) [1]. Both patients with pathological and nonpathologically proven DCC were included. Patients were categorized into resected, unresected nonmetastatic, and metastatic DCC. The unresected nonmetastatic subgroup included both locally advanced tumors and patients who were unfit or unwilling to undergo surgery.

Parameters available for analysis were: year of diagnosis, tumor morphology, age, sex, details on other cancers, socioeconomic status, cTNM stage, location of metastases, basis of diagnosis (e.g. pathological confirmation), surgical exploration, chemotherapy or radiotherapy (neoadjuvant, adjuvant or palliative), survival status, time from diagnosis to death or date of last follow-up. In the case of resected tumors, type of resection, pTNM stage, lymph nodes harvested, number of positive lymph nodes, differentiation grade, radicality, length

of hospital stay, 30/90-day mortality after resection. Tumor stages were grouped based on extent of tumor growth; tumor confined to the bile duct (T1/T2) versus invasion in adjacent structures (T3/T4) according to the TNM 6th and 7th edition [11,12]. Lymph node status was evaluated using both the definition of the TNM 6/7 and the TNM 8 [11–13]. Resection margin status was classified into R0 (tumor-free resection margins) and R1 (microscopically positive margins). Adjuvant chemotherapy and palliative chemotherapy was defined as administration of at least one dose. Adjuvant therapy is not a standard treatment in the Netherlands and mainly administered in clinical trials. OS was defined as time between date of diagnosis and date of death (any cause). Vital status of the patients was checked with the Dutch civil municipal registry on 1 February 2018. Scores on social deprivation derived from income, education and occupation per 4-digit postal code area were used to assess socioeconomic status (Netherlands Institute for Social Research).

Statistical analysis

Annual incidence rates adjusted to the European standard population (ESR, version 1976) were calculated and changes were assessed by calculating the estimated annual percentage of change (EAPC) and corresponding *p* value.

Missing data occurring in eight independent baseline variables (0.5% to 17.3%) were deemed Missing at Random (unrelated to the outcome, possibly related to other parameters) [14] and estimated using multiple imputation (Predictive Mean Matching) with the creation of 10 datasets. This method assumes that missing data patterns can be modeled based on the covariates and the observed outcomes [15].

OS was analyzed using the Kaplan–Meier method. Chi-square test for trend (categorical data) and Mann–Whitney U-test (continuous non-normally distributed data) were used to assess time trends. Chi-square statistics per imputed database were combined using Rubin's rules [16]. As these rules do not apply to nonparametric tests, logistic transformation was applied when necessary in order to obtain a normal distribution.

A multivariable Cox regression model (stepwise backward selection with a *p* value >.10 in likelihood ratio tests for removal) was created using known predictors of survival from the literature [17] and factors that were of borderline significance (*p* value <.10) in univariable analysis. To avoid multicollinearity, the most relevant parameter to represent a certain variable family were selected based on the -2Log Likelihood .

Data were analyzed using IBM SPSS Statistics for Windows version 24.0 (IBM corp., Armonk, NY) and R version 3.4.3 (R Foundation for Statistical Computing, Vienna, Austria, <https://www.R-project.org>). A *p* value <.05 was considered statistically significant.

Sensitivity analyses

Guarantee-time bias (also known as immortal bias or survivor treatment selection bias) could possibly lead to an overestimation of the effect of treatment, as a patient can only receive a therapy if this patients survives until start of treatment. In order to reduce this effect, in the first sensitivity analysis patients who died within 90 days after resection (resected tumors) or diagnosis (unresected tumors) were excluded [18,19]. In the second sensitivity analysis, complete case analyses were performed in order to evaluate the influence of methods of handling missing data. In the third sensitivity analysis, we excluded patients without a pathologically confirmed diagnosis and with tumor morphology associated with other tumors than DCC (i.e. pancreatic or ampullary cancer) as assessed by an expert pathologist (J.V.) (Table A.1).

Quality control

Completeness and correctness of diagnoses as registered in the NCR were assessed for all patient undergoing resection (as only in these cases a reliable reference standard is available) in the Amsterdam UMC, location AMC.

Results

In total, 1338 patients were registered to have DCC; 620 patients underwent resection (46.3%), 445 (33.3%) had unresected nonmetastatic disease and 273 (20.4%) had metastatic disease (Figure 1, Table 1 original data, Table A.2 imputed data). The incidence of DCC was between 0.55 and 0.90 per 100.000 inhabitants per year in the period 2009–2016. The incidence did not change significantly over the years (estimated annual percentage of change 3.5%; $p = .18$). Of the patients with resected, unresected nonmetastatic and metastatic DCC, 17.3% ($n = 107$), 70.8% ($n = 315$) and 30.8% ($n = 84$) were >75 years, respectively ($p < .001$). The diagnosis of adenocarcinoma was confirmed by pathology in 85.8% of all patients. After resection, 30-day mortality was 4.8% ($n = 30$), 90-day mortality was 7.7% ($n = 48$) and 7.4% ($n = 46$) received adjuvant chemotherapy. Palliative chemotherapy was administered in 21 (4.7%) patients with unresected nonmetastatic DCC and in 78 (28.6%) with metastatic disease. In patients with unresected nonmetastatic tumors, 134 (30.1%) died within 90 days after diagnosis, of whom median age was 80 (IQR 74–86), 50.7% ($n = 68/134$) were male, and only one patient received palliative chemotherapy. In the patients with metastatic tumors, 90-day mortality was 43.2% ($n = 118$). Reasons for not starting tumor-targeted treatment were known in a subset of patients with nonresected tumors. The most frequently reported reasons were

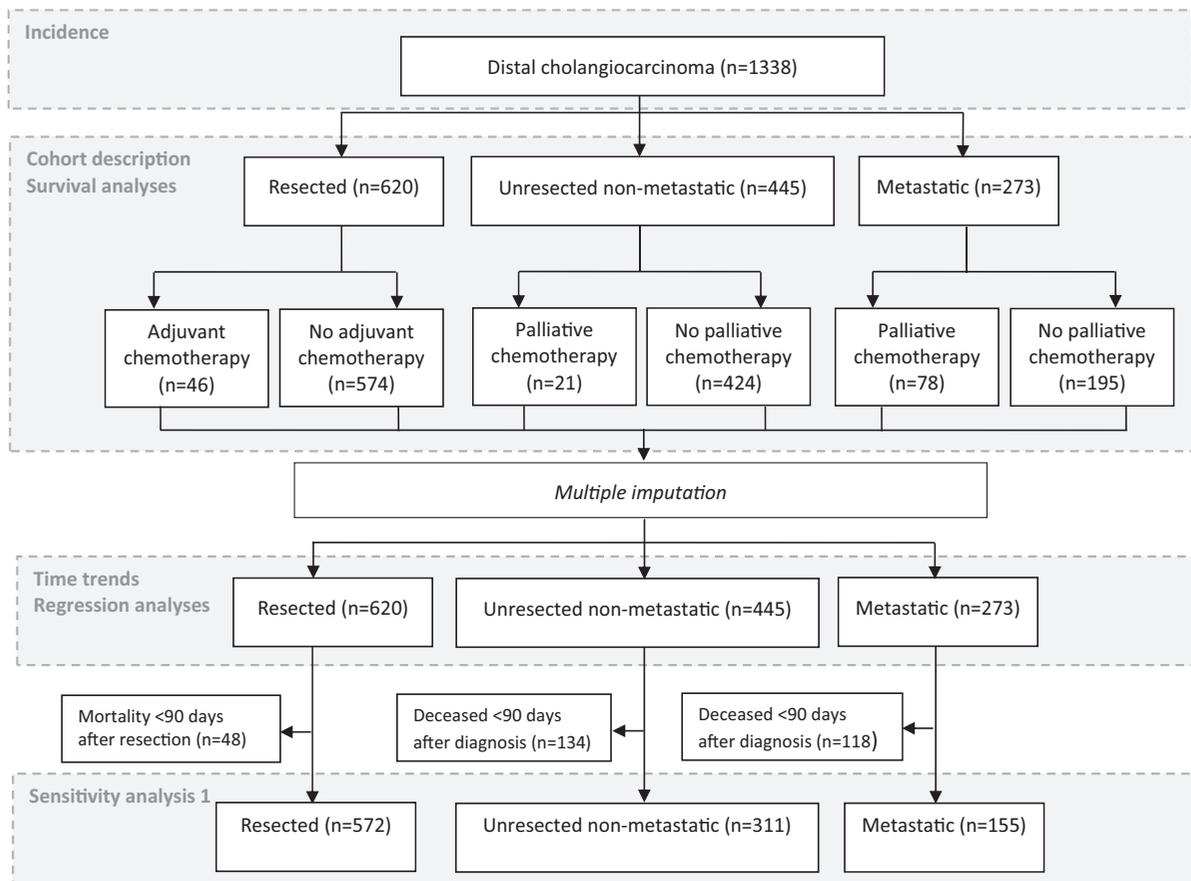


Figure 1. Patient flow. This figures describes the analyses as presented in the main manuscript, and the first sensitivity analysis. Two additional sensitivity analyses (complete case analyses and pathologically proven DCC) were performed using different selections of patients.

Table 1. Characteristics and short-term outcomes of patients with distal cholangiocarcinoma in the Netherlands (2009–2016).

	Total (n = 1338)	Resected (n = 620)	Unresected nonmetastatic (n = 445)	Metastatic(n = 273)
Patient and tumor characteristics				
Age	72 (64–79)	67 (60–73)	80 (74–86)	71 (63–77)
Age > 75 years	506 (37.8)	107 (17.3)	315 (70.8)	84 (30.8)
Male sex	760 (56.8)	387 (62.4)	235 (52.8)	138 (50.5)
Other cancer before diagnosis DCC (yes)	206 (15.4)	75 (12.1)	93 (20.9)	38 (13.9)
Other cancer after diagnosis DCC (yes)	48 (3.6)	30 (4.8)	14 (3.1)	4 (1.5)
Socioeconomic Status				
High	385 (28.8)	183 (29.5)	128 (28.8)	74 (27.1)
Medium	533 (39.8)	266 (42.9)	164 (36.9)	103 (37.8)
Low	414 (30.9)	166 (26.7)	153 (34.4)	95 (34.8)
Unknown	6 (0.5)	5 (0.8)	0	1 (0.4)
Clinical T stage				
Tis/T0/T1/T2	260 (19.4)	144 (23.2)	73 (16.4)	43 (15.8)
T3/T4	265 (19.8)	123 (19.8)	79 (12.7)	63 (23.1)
TX	730 (54.6)	346 (55.8)	233 (37.6)	151 (55.3)
Unknown	83 (6.0)	7 (1.1)	60 (13.5)	16 (5.8)
Clinical N stage				
N0	785 (58.7)	484 (78.1)	203 (45.6)	98 (35.9)
N1	258 (19.3)	78 (12.6)	76 (17.1)	104 (38.1)
NX	212 (15.8)	51 (8.2)	106 (23.8)	55 (20.1)
Unknown	83 (6.0)	7 (1.1)	60 (13.5)	16 (5.8)
Location metastases ^a				
Liver	N/A	4 (0.6)	N/A	178 (63.7)
Peritoneal		1 (0.2)		59 (21.6)
Lymph node		4 (0.6)		50 (18.3)
Lung		0		45 (16.5)
Other		0		35 (12.8)
Pathology confirmation of diagnosis (yes)	1148 (85.8)	620 (100)	291 (65.4)	237 (86.8)
Pathological T stage				
T0/T1/T2	N/A	158 (25.5)	N/A	N/A
T3/T4		451 (72.7)		
TX		4 (0.6)		
Unknown		7 (1.1)		
Pathological N stage				
N0	N/A	255 (41.1)	N/A	N/A
N1		348 (56.1)		
NX		10 (1.6)		
Unknown		7 (1.1)		
Differentiation grade				
Well differentiated	N/A	64 (10.3)	N/A	N/A
Moderately differentiated		256 (41.3)		
Poorly differentiated		193 (31.1)		
Unknown/not determined		107 (17.3)		
Radicality				
No residual disease	N/A	427 (68.9)	N/A	N/A
Microscopic residual disease		140 (22.6)		
Unknown		53 (8.5)		
Treatment characteristic and short term outcomes				
Neoadjuvant chemotherapy (yes)	N/A	3 (0.5)	N/A	N/A
Surgical exploration +/- resection (yes)	707 (52.8)	620 (100)	48 (10.8)	39 (14.3)
Type of resection				
Pancreatoduodenectomy	N/A	603 (97.3)	N/A	N/A
Bile duct resection		17 (2.7)		
Adjuvant chemotherapy (yes)	N/A	46 (7.4)	N/A	N/A
Palliative chemotherapy (yes)	N/A	N/A	21 (4.7)	78 (28.6)
Radiotherapy, any (yes)		4 (0.6)	3 (0.6)	1 (0.4)
Length of hospital stay in days ^b	N/A	13 (9–21)	N/A	N/A
30-day mortality after resection/diagnosis	N/A	30 (4.8)	65 (14.5)	39 (14.3)
90-day mortality after resection/diagnosis	N/A	48 (7.7)	134 (30.1)	118 (43.2)

Original data including missing data are presented; Continuous data are presented as median with Interquartile Ranges; Categorical data are presented as counts with percentages.

^aMore than one possible.

^bRegistered since 2011, missing data in 7 patients; N/A: Not Applicable.

the patient's performance status (35/119 documented reasons) and choice of patient and/or family (32/119) in the nonresected nonmetastatic group. This was extent of disease (16/51), performance status (11/51) and choice of patient and/or family (11/51) in the patients with metastatic tumors.

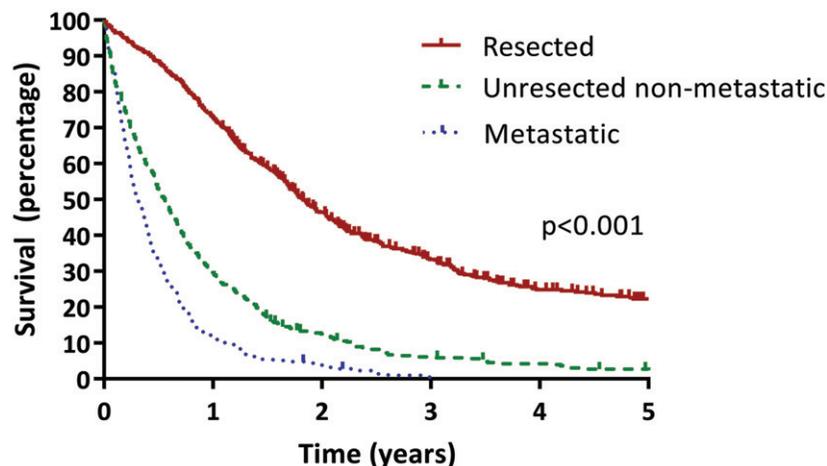
Over time, resection rates in patients with nonmetastatic tumors increased from 53.6% in 2009–2012 to 61.7% in 2013–2016 ($p = .008$) and more extensive tumors (T3/T4) were resected ($p = .003$; Table A.3). Also administration of palliative chemotherapy in the metastatic group increased

Table 2. Survival of patients with distal cholangiocarcinoma.

	n	1-year survival	3-year survival	5-year survival	Median survival, months (95% CI)	p value
Total	1338	46%	18%	11%	10.4 (9.5–11.4)	
Resected	620	73%	34%	22%	21.9 (20.1–23.8)	
Adjuvant chemotherapy	46	83%	29%	16%	22.8 (18.8–26.9)	.80
No adjuvant chemotherapy	574	72%	34%	23%	21.9 (19.9–23.8)	
Unresected non-metastatic	445	30%	6%	3%	6.7 (5.8–7.6)	
Palliative chemotherapy	21	38%	5%	0%	9.9 (7.9–11.9)	.17
No palliative chemotherapy	424	29%	6%	3% ^a	6.3 (5.4–7.2)	
Metastatic	273	11%	1%	0%	3.6 (2.9–4.4)	
Palliative chemotherapy	78	26%	2%	0%	8.2 (6.7–9.7)	<.001*
No palliative chemotherapy	195	5%	0%	0%	2.8 (2.4–3.2)	

Original data were used in this analysis (no missing data on described variables). *Significance ($p < .0001$).

^aMedical files of the 8 patients with unresected tumors were checked by the NCR registry administrators; in 4 patients there were doubts about the diagnosis of DCC and/or diagnosis was revised during the clinical course.



Resected	No. at risk	620	452	257	153	86	61
Unresected M0	No. at risk	445	132	50	24	15	7
M1	No. at risk	273	30	9	1	0	0

Figure 2. Survival of patients with distal cholangiocarcinoma per stage in a nationwide cohort. Original data were used in this analysis (no missing data on described variables); N = Number at risk; M0: nonmetastatic; M1: metastatic.

from 22.3% ($n = 25$) in 2009–2012 to 32.9% ($n = 53$) in 2013–2016 ($p = .05$).

Survival and prognostic factors

Median follow-up time of censored patients was 39.3 months (IQR 24.4–62.4). Overall 1-, 3- and 5-year survival across all stages was 46%, 18%, and 11%. Median OS was 10.4 months (95% CI 9.5–11.4). For patients with resected, unresected nonmetastatic and metastatic tumors, median OS was 21.9 months (95% CI 20.1–23.8), 6.7 months (95% CI 5.8–7.6) and 3.6 months (95% CI 2.9–4.4), respectively ($p < .001$; Table 2, Figure 2). Survival did not significantly improve over time in the total cohort ($p = .55$, Table A.3) or any of the subgroups. In metastatic disease, median OS with palliative chemotherapy was 8.2 (95% CI 6.7–9.7) versus 2.8 months (95% CI 2.4–3.2) without ($p < .001$). Independent prognostic factors for poor OS in resected disease were increasing age, T3/T4 stage, higher lymph node ratio, poor differentiation, and R1 resection (Table 3). In metastatic tumors, administration of palliative chemotherapy was the strongest independent

predictor of survival (HR 0.54, 95% CI 0.38–0.77, $p < .001$) (Table A.4).

Quality control

Some 94 patients underwent resection in the Amsterdam UMC, location AMC (Table A.5). After reassessment, two patients (2.1%) were found to be incorrectly registered as DCC by the NCR (one pancreatic cancer, one duodenal cancer) and three cases were incorrectly registered as non-DCC (3.2%).

Sensitivity analyses

In resected disease, the same prognostic factors were detected in multivariable regression analysis. For patients with metastatic DCC surviving at least 90 days after diagnosis ($n = 155$) OS was 9.4 months (95% CI 8.2–10.5) versus 5.2 months (4.5–5.8) with and without palliative chemotherapy ($p < .001$) (Table A.6). Moreover, palliative chemotherapy was the only independent predictor of OS (HR 0.56, 95% CI 0.40–0.77, $p < .001$) (data not shown).

Table 3. Predictors for overall survival in patients with resected distal cholangiocarcinoma ($n = 620$).

Characteristics	Univariable Cox regression analysis			Multivariable Cox regression analysis		
	HR	95% CI	<i>p</i> value	HR	95% CI	<i>p</i> value
Increasing age (per year)	1.01	1.00–1.03	.005*	1.02	1.01–1.03	<.001*
Sex						
Male	1			–		
Female	1.0	0.82–1.21	.97			
Year of diagnosis						
2009–2012	1			–		
2013–2016	1.10	0.90–1.33	.35			
Socioeconomic status						
Low	1			a		
Medium	1.10	0.87–1.38	.42			
High	0.90	0.69–1.15	.39			
History of cancer						
No	1			–		
Yes	1.27	0.96–1.68	.10			
pT stage (TNM 6/7)						
T1/T2	1			1		
T3/T4	1.54	1.23–1.93	<.001*	1.28	1.01–1.63	.04*
TX	2.49	0.74–8.45	.14	1.18	0.41–4.34	.79
pN stage (TNM 6/7)						
N0	1			b		
N1	2.10	1.68–2.52	<.001*			
NX	3.18	1.67–6.04	<.001			
pN stage (TNM 8)						
N0	1			b		
N1	1.74	1.39–2.17	<.001*			
N2	2.74	2.13–3.52	<.001*			
NX	3.16	2.32–4.31	<.001*			
Lymph Node Ratio	4.80	3.29–7.01	<.001*	2.85	1.87–4.33	<.001*
Differentiation grade						
Well differentiated	1			1		
Moderately differentiated	1.22	0.85–1.76	.28	1.16	0.82–1.64	.41
Poorly differentiated	2.48	1.72–3.59	<.001*	2.28	1.60–3.25	<.001*
Radicality						
No residual disease	1			1		
Microscopic residual disease	2.01	1.68–2.57	<.001*	1.81	1.45–2.26	<.001*
Adjuvant chemotherapy ^c						
No	1			–		
Yes	1.05	0.74–1.45	.80			

Data after multiple imputation were used; Same prognostic factors were identified when excluding patients deceased within 90 days after resection.

*Significance ($p < .0001$).

^aRemoved in backward selection.

^bNot analyzed in multivariable analysis in order to avoid multicollinearity.

^cProportional hazard assumption not met.

When including only pathologically confirmed DCC no substantial differences were seen; survival was 11.3 (95% CI 10.1–12.5), 21.5 (95% CI 19.6–23.4), 6.9 (95% CI 5.8–8.1) and 4.2 (95% CI 3.6–4.9) months for the total cohort, patients with resected disease, unresected metastatic and metastatic disease, respectively. Also in complete case analyses (applicable for time trends and regression analyses, no missing data for other analyses), outcomes were similar (data not shown).

Discussion

In this first nationwide Western cohort of DCC, median OS for patients with resected, unresected nonmetastatic, and metastatic tumors was 21.9, 6.7 and 3.6 months, respectively. Over time resection rates increased from 53.6% to 61.7%. Adjuvant chemotherapy was rarely used, because this is not a standard treatment in the Netherlands. Palliative chemotherapy was used in a minority of patients; in 4.7% of patients with unresected nonmetastatic and 28.6% with metastatic DCC. In the metastatic group, administration of

palliative chemotherapy increased over the years and seemed associated with improved survival. OS, however, did not improve significantly with time.

Our study revealed a median OS of 21.9 months for resected DCC compared to 33 months (range 18–102) in a 2017 meta-analysis of 3258 patients including 776 Western patients [5]. Recent large Western cohorts including about 200 [2,20,21] and 1982 [22] patients with resected DCC revealed median OS of 18 to 39 months. Explanations for these differences could include patient selection and varying administration of adjuvant chemotherapy. Type of center may also have influenced outcomes. High-volume expert centers may treat a selected group of patients and could benefit from a volume-outcomes relation which has previously been observed in pancreatic cancer [23,24]. The effect of adjuvant chemotherapy could not be assessed as proportional hazards assumptions were violated, only a small number of selected patients received chemotherapy and chemotherapy strategies were unknown. Mortality rates after pancreatoduodenectomy in our series (4.8% 30-day mortality, 7.7% 90-day mortality) were in the higher ranges as

compared to the literature. The before mentioned 2017 meta-analysis reported perioperative mortality (no definition provided) of 4% (range 0–8%) [5]. These differences are most likely explained by the generally worse outcomes in nationwide data compared to high-volume export centers. This has also been observed in a recent German nationwide study, reporting mortality rates of 8.6% for pancreatic malignant neoplasms and even 11.9% for nonpancreatic malignancies [25,26].

The median OS of patients with unresected nonmetastatic disease without and with chemotherapy (6.7 and 9.9 months) and of patients with metastatic disease without and with chemotherapy (2.8 and 8.2 months) are not in line with results from previous trials. The median OS of unresected biliary tract cancer is typically reported between 8.1 and 12.7 months [7,27,28]. Obviously, patients selected for clinical trials represent a subset of the total population with better performance status and prognosis. For example, the current unresected nonmetastatic group also includes patients unfit or unwilling to undergo surgical or systemic treatment as reflected by the median age of 80 years and a 90-day mortality rate of 30%.

Our results on prognostic factors in patients undergoing resection are in line with the two recent reviews [5,17]. A recent propensity score matched cohort comparing adjuvant chemotherapy with or without radiotherapy and observation found that adjuvant therapy is only associated with improved survival in patients with high-risk features (defined as T3/T4 tumors, nodal positivity, lymphovascular invasion and moderate/poor differentiation grade) [22]. These findings highlight the importance of well-established prognostic factors. We found increased resection rates over time (53.6% vs 61.7%), which may be the result of increased awareness and increased referrals to specialized centers with experienced surgeons resecting more extensive tumors. To our knowledge, there are no previous reports on time trends in DCC, but increased resection rates have also been observed in pancreatic cancer [29,30].

Previous studies frequently combined intra- and extrahepatic cholangiocarcinomas. Although these tumors have similar morphological characteristics, there seems to be a high intertumor genetic heterogeneity within cholangiocarcinomas [31,32]. Whereas intrahepatic carcinomas often harbor IDH1/2 and FGFR mutations, extrahepatic carcinomas frequently show KRAS and P53 [33,34]. In the group of resected extrahepatic carcinomas, surgical procedures, preoperative drainage and related complications differ for DCC and perihilar cholangiocarcinoma. For patients with unresectable tumors, current systemic treatment is equal for all cholangiocarcinomas. However, timing and presentation of symptoms differ, possibly leading to different outcomes. Moreover, supportive care strategies, such as stenting techniques and its complications vary; this may influence survival directly or indirectly by delaying or cancelation of chemotherapy. Hence, it seems more sensible to separate outcomes for different subtypes of cholangiocarcinoma in accordance to, for example, the TNM classifications in which definitions for perihilar carcinomas and DCC were separated since the 7th edition (2009).

The first shortcoming of this study relates to the difficulty of establishing the diagnosis of DCC [35]. The diagnosis of adenocarcinoma was not pathologically confirmed in 14.2% of the cases. Besides, more than half of the cohort did not undergo a resection, so the origin of disease (distal bile duct versus other periampullary tumor) was determined on imaging only. Moreover, we expect that nonresected tumors in the pancreatic head in which diagnosis is unsure, are more likely to be classified as pancreatic cancer than as DCC. Therefore, the true total number of patients with nonresected DCC is probably higher. Even after resection the determination of the tumor origin may be challenging and dependent on the pathologist's macroscopic judgments of the specimen. However, as long as there are no reliable biomarkers to differentiate between these tumor types, the current study reflects the situation in clinical practice. The number of registration errors seemed small in the quality control analysis and may not have had a large impact on results. However, it should be noted that the diagnosis in the nonresected setting is even more difficult, and results from different diagnostic modalities and/or multidisciplinary meetings may show conflicting results. Therefore, one can imagine that in hindsight the patient's medical files may be challenging to interpret for registry administrators. It is expected that a small number of registration errors will occur in all countries and over all time periods. Therefore, in order to maintain comparability with other countries and time periods, patients in whom the registered diagnosis was not DCC in quality control were not excluded. Second, the treatment effect may have been overestimated. It was attempted to reduce guarantee-time bias in sensitivity analysis by excluding patients who deceased within 90 days after resection or diagnosis. Still, treated patients mostly likely differ systematically from untreated patients (treatment selection bias). At last, the lack of performance status which was not registered in the NCR during this study period.

A strength of the current study is the population-based, all-stage setting, reflecting real-life treatment and survival in a Western country. A second strength includes the statistical methods of handling of missing data combined with several sensitivity analyses in order to overcome possible limitations of registry data.

In conclusion, survival of all patients with DCC in an unselected Western population-based cohort is poor and did not improve over the time despite increased resection rates and increased use of chemotherapy. Palliative chemotherapy is rarely used in the unresected setting, even though this is considered standard of care and seemed associated with improved survival.

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