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A population-based study on incidence, treatment, and survival in ampullary cancer in the Netherlands

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ABSTRACT

Introduction: Ampullary cancer is rare and as a result epidemiological data are scarce. The aim of this population-based study was to determine the trends in incidence, treatment and overall survival (OS) in patients with ampullary adenocarcinoma in the Netherlands between 1989 and 2016.
Methods: Patients diagnosed with ampullary adenocarcinoma were identified from the Netherlands Cancer Registry. Incidence rates were age-adjusted to the European standard population. Trends in treatment and OS were studied over (7 years) period of diagnosis, using Kaplan-Meier and Cox regression analyses for OS and stratified by the presence of metastatic disease.
Results: In total, 3840 patients with ampullary adenocarcinoma were diagnosed of whom, 55.0% were male and 87.1% had non-metastatic disease. The incidence increased from 0.59 per 100,000 in 1989–1995 to 0.68 per 100,000in 2010–2016. In non-metastatic disease, the resection rate increased from 49.5% in 1989–1995 to 63.9% in 2010–2016 ($p < 0.001$). The rate of adjuvant therapy increased from 3.1%

Abbreviations: EAPC, estimated annual percentage change; ESP, European standard population; NCR, Netherlands Cancer Registry; NOS, not otherwise specified; RESP, revised European standard population; UICC, Union for International Cancer Control.

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to 7.9%. In non-metastatic disease, five-year OS (95% CI) increased from 19.8% (16.9–22.8) in 1989–1995 to 29.1% (26.0–31.2) in 2010–2016 (logrank p < 0.001). In patients with metastatic disease, median OS did not significantly improve (from 4.4 months (3.6–5.0) to 5.9 months (4.7–7.1); logrank p = 0.06). Cancer treatment was an independent prognostic factor for OS among all patients.

Conclusion: Both incidence and OS of ampullary cancer increased from 1989 to 2016 which is most likely related to the observed increased resection rates and use of adjuvant therapy.

Introduction

Ampullary adenocarcinoma (hereafter: ampullary cancer), clustered in the group of periampullary cancers, is a rare cancer as it accounts for only 0.2%–0.5% of all gastrointestinal tract tumours [1–4]. Population-based studies in the United States of America (USA, 1973–2005), France (1976–2009) and England (1998–2007) reported age-adjusted incidence rates in men and women of 0.46–0.63 and 0.30–0.40 per 100,000 persons, respectively [5–7]. Over the last decades, the incidence increased in the USA (+0.9% per year) and among men in France (+4.6% per year), but remained constant in England [5–7].

In current practice, guidelines of distal biliary tract or pancreatic cancers are sometimes extrapolated to treat patients with ampullary cancer [8–10]. The standard of care for locoregional ampullary cancer is pancreatoduodenectomy [2,3,10]. Guidelines from the UK (2005), Belgium (2009), and the Netherlands (2011) recommend to restrain (neo-)adjuvant systemic or radiotherapy to study treatments, as the role of (neo-)adjuvant therapy in ampullary cancer is still debated [9,11–20]. Evidence is limited as most studies are retrospective and in clinical trials patients with ampullary cancer are often excluded [13–21].

Longitudinal population-based analyses on ampullary cancer are limited [5,7,22]. To identify areas for improvement of survival, surgical and medical oncological treatment and counselling, it is essential to gain more insight in patient characteristics, therapies and outcomes in large population-based cohorts. Therefore, the aim of this study was to determine the trends in incidence, treatment and OS in patients diagnosed with ampullary cancer in the Netherlands between 1989 and 2016.

Methods

Database

The Netherlands Cancer Registry (NCR) is a population-based cancer registry in the Netherlands (17.4 million inhabitants; 2019). All patients with newly diagnosed malignancies are automatically identified through linkage to the national automated pathological archive (PALGA) and supplemented with data from the National Registry of Hospital Discharge Diagnosis (clinical diagnosis based on hospitalization, outpatient visits or imaging data). Trained administrators consult the medical records to verify the diagnosis and register information on diagnosis and treatment. Completeness of the NCR is estimated to be at least 95% [23]. This study was approved by the Scientific Committee of the Dutch Pancreatic Cancer Group (DPCG) and the Privacy Review Board of the NCR. No approval from an ethics committee was required [24].

Patients

All patients aged 18 years or older diagnosed with ampullary adenocarcinoma between 1989 and 2016 were identified from the NCR (International Classification of Disease for Oncology, third edition; C24.1 and morphology codes listed in Supplementary Table A1) [25]. Tumour stage was registered according to the Union for International Cancer Control (UICC) TNM classification valid at time of diagnosis [26–28]. The TNM classification for all patients was converted to TNM 7th edition (Supplementary Table A2). Tumour stage was based on pathological TNM (pTNM) classification. If missing, clinical TNM classification (cTNM) was used. One digit Extent of Disease coding was recorded until 2012 for not microscopically verified malignancies (Supplementary Table A3). Patients with registered unknown metastatic disease status (MX) were categorised as no metastatic disease. Patients without any registered information on tumour classification, lymph node involvement and metastatic status were classified as 'unknown'. Patients were classified as M0 NOS (not otherwise specified) when patients had no metastatic disease, but could not be grouped based on tumour classification (TX) and/or lymph node involvement (NX). Two patients with a tumour without invasion and without lymph node involvement or metastases were excluded.

Treatment categories for patients with non-metastatic disease were: A) resection of the primary tumour (local surgical or endoscopic excision, pancreatoduodenectomy or not specified), B) resection of the primary tumour (local surgical or endoscopic excision, Whipple or pylorus preserving pancreatoduodenectomy or not specified) combined with (neo-)adjuvant chemo(radio) therapy, C) chemo- and/or radiotherapy alone, and D) no (anti-cancer) treatment (including surgical interventions, such as palliative bypass). Categories for patients with metastatic disease were: A) resection of the primary tumour and/or metastatic site(s) (location unknown), B) resection of the primary tumour combined with chemo(radio)therapy, C) chemotherapy alone, D) radiotherapy alone, and E) no (anti-cancer) treatment. One patient with no information on treatment was excluded.

OS was defined as time from date of diagnosis to date of death from any cause and censored at February 1st, 2019 or last follow-up date in case of emigration. Information on vital status was obtained through annual linkage of the NCR with the Municipal Administrative Database.

To evaluate trends in treatment and OS, four seven-year time periods of diagnosis were defined: 1989–1995, 1996–2002, 2003–2009 and 2010–2016.

Statistics

Annual incidence rates for the period 1989–2016 were calculated as number of new cases per 100,000 person-years, overall and stratified by sex. The incidence rates were age-standardised to the European standard population (ESP) from 1976 and to the revised ESP (RESP) from 2013. Change in incidence in 1989–2016 was evaluated by calculating the estimated annual percentage change (EAPC). Trends in treatment over time were analysed, stratified by metastatic disease status using Chi-square test for trend. OS was calculated with the Kaplan-Meier method for the total study population and stratified by metastatic disease status and by resection

within the group of patients with non-metastatic disease, using log rank tests for trend to compare OS between periods of diagnosis. Multivariable Cox-regression analyses to assess the effect of period of diagnosis on OS were performed with and without treatment modality in all patients and in non-metastatic disease, adjusted for age, differentiation grade and TNM-stage. Variables with a p-value <0.10 in the univariable regression analyses were selected for the multivariable regression analyses. In case of multicollinearity, the most relevant parameter to represent a certain variable family was selected based on the -2log likelihood. A p-value <0.05 was considered to be statistically significant. Data were analysed using IBM SPSS Statistics for Windows, version 25 (IBM Corp., Armong, NY, USA).

Results

Of the 3840 patients included, median age at diagnosis was 72 years [IQR 63–79] and 55.0% of the patients were male (Table 1). The majority of the ampullary cancer cases were pathologically confirmed (89%). In total, 87.1% of the patients had non-metastatic disease, 12.1% had metastatic disease and in 0.9% (n = 33) data were lacking. The median follow-up at last follow-up was 12.3 years.

Incidence rate

The incidence increased from 0.59 per 100,000 in 1989–1995 to 0.68 per 100,000 in 2010–2016. The overall incidence rate (ESR) was 0.66 per 100,000 between 1989 and 2016, with an estimated annual percentage of change (EAPC) of +0.63% (95% CI: 0.39–0.88) from 1989 to 2016 (ESP-based, p = 0.02, Fig. 1). The RESP-based incidence increased with a similar EAPC of +0.61 (Supplementary Fig. A1). The increase in incidence was smaller in males than in females, with an EAPC of respectively +0.47% (ESP-based, p = 0.13) and +0.68% (ESP-based, p = 0.04).

Trends in treatment

Of patients with non-metastatic disease (M0), the proportion of patients who underwent resection of the primary tumour without (neo-)adjuvant therapy increased over time from 49.5% in 1989–1995 to 63.9% in 2010–2016 (p < 0.001, Fig. 2A). Resection plus (neo-) adjuvant chemo(radio)therapy increased from 3.2% in 1989–1995 to 7.9% in 2010–2016 (p < 0.001). The majority of the resected patients underwent a pancreatoduodenectomy and only a small proportion underwent endoscopic (n = 17) or surgical local (n = 22) resection (Supplementary Table A4). Within the group of (neo-)adjuvant therapy plus resection (n = 157), 0.6% (n = 1) received neoadjuvant radiotherapy, 75.8% received adjuvant chemotherapy, 3.1% adjuvant radiotherapy, and 20.3% adjuvant chemoradiotherapy between 1989 and 2016. No patients received neoadjuvant chemotherapy. Only few patients with non-metastatic disease received chemotherapy, radiotherapy, or chemoradiotherapy without resection of the primary

Table 1
Patient and tumour characteristics of patients diagnosed with ampullary cancer in the Netherlands in 1989–2016.

	Total (n = 3840)		1989–1995 (n = 785)		1996–2002 (n = 834)		2003–2009 (n = 1061)		2010–2016 (n = 1160)		p-value
	N	%	N	%	N	%	N	%	N	%	
Sex											0.405
Male	2113	55	420	54	445	53	598	56	650	56	
Female	1727	45	365	47	389	47	463	44	510	44	
Age (median [IQR])	72 [63–79]		72 [63–80]		72 [63–79]		72 [62–79]		72 [64–79]		–
Age (categorical)											*0.033*
<65 years	1096	29	230	29	246	30	328	31	292	25	
65–75 years	1350	35	269	34	279	34	352	33	450	39	
≥75 years	1394	36	286	36	309	37	381	36	418	36	
T-classification[a]											*<0.001*
T1	948	25	224	29	240	29	277	26	207	18	
T2	719	19	120	15	121	15	199	19	279	24	
T3	835	22	153	20	202	24	216	20	264	23	
T4	224	6	0	0	0	0	83	8	141	12	
Unknown	1114	37	288	32	271	27	286	23	269	29	
N-classification[a]											*<0.001*
N0	1760	46	298	38	336	40	562	53	564	49	
N1	1108	29	147	19	195	23	296	28	470	41	
Nx	740	19	224	29	236	28	166	16	114	10	
Unknown	232	6	116	15	67	8	37	4	12	1	
M-classification											*<0.001*
M0	3344	87	709	90	735	88	913	86	987	85	
M1	463	12	56	71	88	11	146	14	173	15	
Unknown	33	1	20	3	11	1	2	0	0	0	
TNM stage											*<0.001*
Stage I	1195	31	261	33	274	33	345	33	315	27	
Stage II	1145	30	212	27	258	31	298	28	377	33	
Stage III	201	5	0	0	0	0	72	7	129	11	
M0 NOS	803	21	236	30	203	24	198	19	166	14	
Stage IV	463	12	56	7	88	11	146	14	173	15	
Unknown	33	1	20	3	11	1	2	0	0	0	
Grade											0.152
Well differentiated	321	8	84	11	73	9	72	7	92	8	
Moderately differentiated	1244	32	244	31	287	34	340	32	373	32	
Poorly differentiated	755	20	151	19	164	20	205	19	235	20	
Unknown[b]	1520	40	306	39	310	37	444	42	460	40	

NOS, not otherwise specified; IQR, interquartile range.
[a] Classification based on pathological classification, supplemented with clinical classification and extent of disease respectively.
[b] Grade of differentiation is unknown because this is not reported in the pathological specimen, or because the patient had no pathological diagnosis.

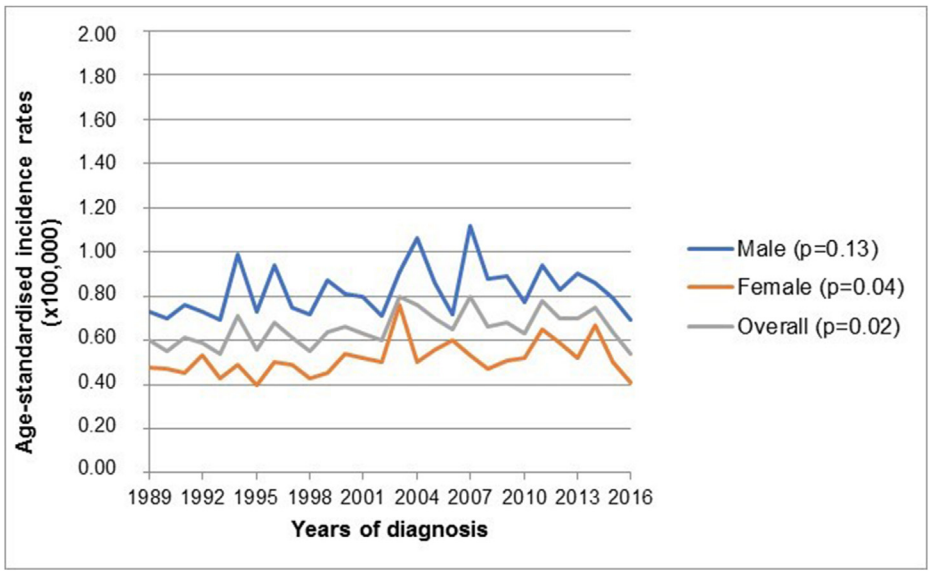

Fig. 1. Age-standardised incidence rates of ampullary cancer in the Netherlands between 1989 and 2016 based on the European standard population (p-value indicates significance of estimated annual percentage of change).

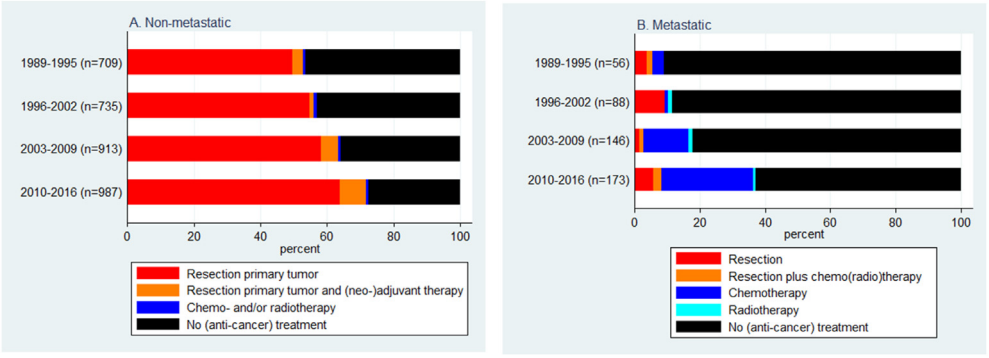

Fig. 2. Treatment of patients with (A) non-metastatic and (B) metastatic ampullary cancer in the Netherlands between 1989 and 2016.

tumour (n = 27, 0.8% of all M0). Patients receiving no (anti-tumour) treatment decreased over time from 46.4% in 1989–1995 to 27.5% in 2010–2016 (p < 0.001).

For patients with metastatic disease, chemotherapy use increased from 3.6% (n = 2) in 1989–1995 to 28.3% (n = 49) in 2010–2016 (p < 0.001), while radiotherapy use remained nihil over time with none in 1989–1995 and 0.6% (n = 1) in 2010–2016 (p = 0.91), Fig. 2B).

Trends in overall survival

Median OS of the total population was 16.1 months (95% CI 15.2–17.1) and increased over time from 14.2 months (95% CI 12.0–16.3) in 1989–1995 to 18.3 months (95% CI 16.4–20.2; p < 0.001) in 2010–2016 (Fig. 3A). Regardless of the period of diagnosis, median OS decreased with a more advanced TNM-stage (Supplementary Fig. A2).

In non-metastatic disease, 1- and 5-year OS increased from 58.3% (95% CI 54.6–61.9) and 19.8% (95% CI 16.9–22.8) in 1989–1995 to 67.3% (95% CI 64.3–70.2) and 29.1% (95% CI 26.0–32.1) in 2010–2016, respectively (logrank p < 0.001, data not shown). Patients with non-metastatic disease who underwent resection had better OS compared to patients with non-metastatic disease without resection, a 5-year OS of 39.3% (95% CI 36.4–32.3) and 3.0% (95% CI 0.0–6.1) respectively (Fig. 3B and C). In patients who also received (neo-)adjuvant therapy, the 5-year OS was 28.5% (95% CI 21.3–35.7). Multivariable Cox regression analyses showed that patient age, T- and N-classification and differentiation grade were prognostic factors for OS in non-metastatic ampullary cancer (Supplementary Table A5). In patients with metastatic disease, the median OS (95%) was 4.4 months (3.6–5.1) in 1989–1995 and 5.9 months (4.7–7.1) in 2010–2016 (logrank p = 0.06, Fig. 3D).

Better OS among all patients was observed after adjusting for period of diagnosis, age, sex, T- and N-classification and differentiation grade for patients diagnosed in 2003–2009 (HR = 0.88, p = 0.020), and 2010–2016 (HR = 0.80, p < 0.001) when compared with 1989–1995 (Table 2). After including treatment in the multivariable model, the period effects (expressed as HRs) on OS decreased and were no longer statistically significant.

Discussion

This population-based study showed an increase in the incidence, resection rate and use of adjuvant therapy. Most importantly, 5-year OS improved from 19.8% in 1989–1995 to 29.1% in 2010–2016. In metastatic disease, chemotherapy was administered

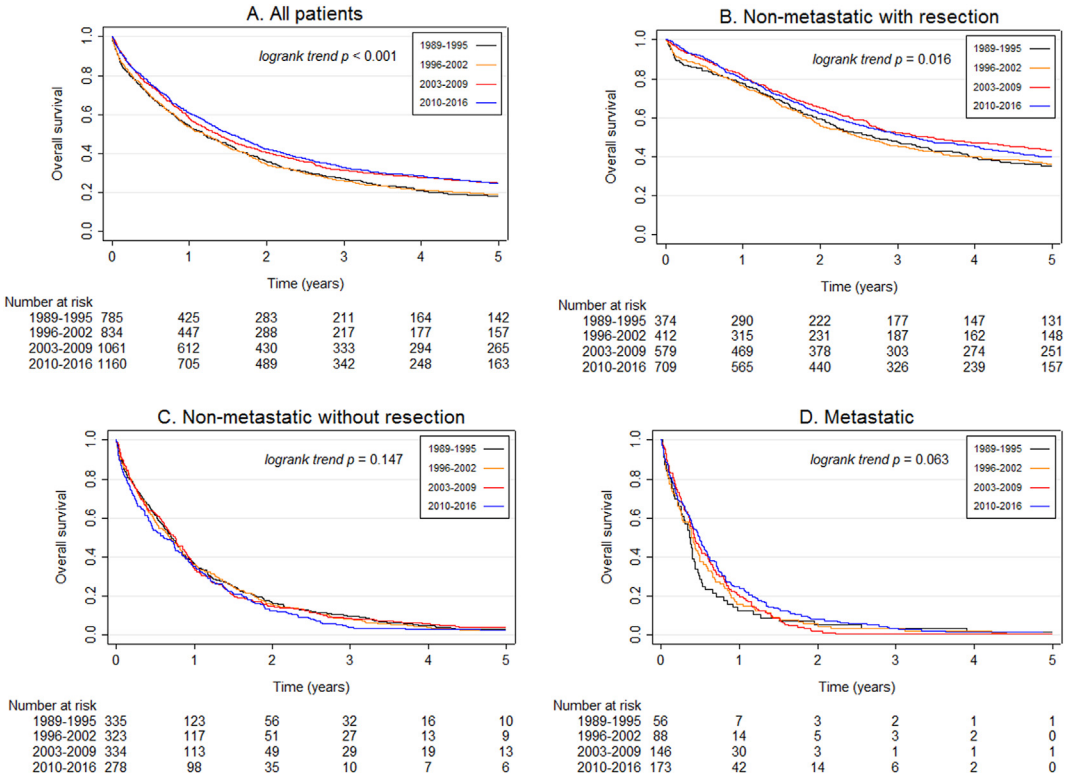

Fig. 3. Overall survival by period of diagnosis of (A) all, (B) non-metastatic resected, (C) non-metastatic non-resected, and (D) metastatic patients diagnosed with ampullary cancer in the Netherlands between 1989 and 2016.

more often over time, but without any clinically relevant or statistically significant impact on OS. The multivariable analysis in all patients showed that the change in administered therapies could explain the improved OS over time.

In the present study, the incidence rates were higher compared with the ESR in England in 1998–2007 [7]. Better diagnostic modalities over time and distinguishing ampullary cancer from other periampullary cancers more often probably explain the increase over time in the present study (+0.63%) [6,7].

Approximately 4% of all patients with non-metastatic disease in 1989–2016 received adjuvant chemo- and/or radiotherapy in the current study. This is lower than the 8.9% observed in France in 1976–2009 but appears to be in line with recommendations in the guidelines to limit the use to study treatments [5]. Also in the most recent time periods, patients with non-metastatic disease received adjuvant therapy less often (5.1% and 7.9% in 2003–2009 and 2010–2016, respectively) compared with a population-based study from the USA presenting an increase in use of adjuvant chemotherapy in resected ampullary cancer patients from 29% in 2004–2006 to 46% in 2010–2012 [22]. Higher rates of adjuvant chemo(radio)therapy in ampullary cancer were also reported in retrospective single centre studies in the USA in 1977–2016 [29–32]. Due to the small number of patients treated with surgery plus adjuvant therapy and the risk of confounding by indication, the benefit of adjuvant therapy on OS could not be assessed in this study. In a population-based study in the USA an improvement in survival (2004–2012) was seen in patients with surgically resected ampullary cancer, together with an increased use of adjuvant chemo(radio)therapy. The improved OS could mirror this increased use, but no analyses were done to confirm this association and the impact of other factors on OS [22]. Randomized controlled trials on adjuvant therapy, in which only limited numbers of patients with ampullary cancers are enrolled, report mixed results [13,17,18]. Regarding neoadjuvant therapy in ampullary cancer, only retrospective studies are available [33–35]. Therefore, the value of both neoadjuvant and adjuvant therapy in patients with ampullary cancer remains unknown and subject to further prospective studies. To obtain highest level of evidence on the efficacy of (neo) adjuvant therapy in patients with ampullary cancer in specific, a multi-centre prospective randomized controlled trial is needed. The provided results will contribute to evidence-based adaptations in international guidelines.

The multivariable analysis performed in all patients showed that the higher use of surgery (with or without (neo)adjuvant therapy) explained most of the improved OS over time. However, other factors might also explain the improved OS. First, a more accurate diagnosis of ampullary cancer, as diagnostic modalities got better over time, could have resulted in a better distinction between periampullary cancers. As the prognosis of ampullary cancer is better, compared with the periampullary cancers, a more homogeneous group results in a higher OS [2,22,36]. Second, advancement of both surgical techniques and postoperative support itself over time may have led to an increase in OS [37,38]. Third, improved surgical care and more expertise due to centralization and a minimal hospital volume requirement of pancreatic surgery, which was initiated in the 2000s and officially regulated from 2013 and onwards, might explain the improved outcome [39]. The effect of stage migration on OS is believed to be small as the increase in OS in patients with metastatic disease was not statistically significant over time.

The reported OS for the total population in the current study with one out of five patients alive after five years is comparable with the 27.7% and 20.8% in previously reported data from cohorts of France (1976–2009) and England (1998–2007), respectively [5,7]. On the contrary, the 5-year OS in patients with non-metastatic disease in the present study was lower compared to

Table 2
Uni- and multivariable analysis for overall survival of patients with ampullary cancer with and without including treatment.

	N	Median survival in months (95%CI)	Univariable analysis		Multivariable analysis (without treatment)		Multivariable analysis (with treatment)	
			HR (95%CI)	p-value	HR (95%CI)	p-value	HR (95%CI)	p-value
Period of diagnosis								
1989–1995	785	14.2 (12.0–16.3)	Ref.		Ref.		Ref.	
1996–2002	834	14.4 (12.5–16.4)	0.99 (0.90–1.10)	0.863	0.98 (0.88–1.08)	0.674	1.01 (0.92–1.12)	0.807
2003–2009	1061	16.4 (15.5–18.3)	0.85 (0.77–0.94)	0.001	0.88 (0.80–0.98)	0.020	0.94 (0.85–1.05)	0.261
2010–2016	1160	18.3 (16.4–20.2)	0.81 (0.74–0.90)	*<0.001*	0.80 (0.72–0.90)	<0.001	0.94 (0.84–1.05)	0.288
Age								
<65 years	1096	26.5 (23.7–29.3)	Ref.		Ref.		Ref.	
65–75 years	1350	17.6 (15.8–19.5)	1.39 (1.27–1.52)	*<0.001*	1.36 (1.24–1.48)	*<0.001*	1.27 (1.16–1.39)	*<0.001*
≥75 years	1394	10.1 (9.2–10.9)	2.35 (2.15–2.57)	*<0.001*	1.92 (1.73–2.12)	*<0.001*	1.34 (1.20–1.49)	*<0.001*
Sex								
Men	2113	16.2 (14.9–175)	Ref.		not included		not included	
Women	1727	15.8 (14.4–17.3)	0.99 (0.93–1.06)	0.785				
Differentiation grade								
Good	321	32.9 (26.4–39.4)	Ref.		Ref.		Ref.	
Moderate	1244	26.9 (24.2–29.6)	1.04 (0.91–1.19)	0.591	1.02 (0.89–1.17)	0.763	1.05 (0.92–1.21)	0.456
Poor or undifferentiated	755	13.3 (11.7–14.8)	1.61 (1.39–1.86)	*<0.001*	1.43 (1.23–1.65)	<0.001	1.40 (1.21–1.63)	*<0.001*
Unknown	1520	10.2 (9.4–11.0)	1.96 (1.72–2.24)	*<0.001*	1.30 (1.13–1.50)	<0.001	0.97 (0.84–1.12)	0.719
T-classification[b]								
T1	948	26.4 (23.1–29.6)	Ref.		Ref.		Ref.	
T2	719	33.0 (28.0–37.9)	0.86 (0.77–0.97)	*0.010*	0.91 (0.81–1.02)	0.120	1.04 (0.92–1.16)	0.559
T3	835	19.5 (17.4–21.6)	1.30 (1.17–1.43)	*<0.001*	1.26 (1.13 (1.40)	*<0.001*	1.47 (1.32–1.65)	*<0.001*
T4	224	15.6 (13.4–17.8)	1.56 (1.33–1.83)	*<0.001*	1.49 (1.26–1.77)	*<0.001*	1.68 (1.41–2.00)	*<0.001*
Unknown	1114	6.8 (6.1–7.6)	3.31 (3.01–3.65)	*<0.001*	1.95 (1.74–2.18)	*<0.001*	1.19 (1.06–1.33)	*0.002*
N-classification[b]								
N0	1760	26.6 (24.0–29.3)	Ref.		Ref.		Ref.	
N1	1108	17.5 (16.3–18.8)	1.48 (1.36–1.61)	*<0.001*	1.50 (1.37–1.64)	*<0.001*	1.67 (1.53–1.83)	*<0.001*
Nx	740	6.51 (5.61–7.41)	2.67 (2.43–2.92)	*<0.001*	1.49 (1.34–1.66)	*<0.001*	1.26 (1.14–1.40)	*<0.001*
Unknown	232	4.67 (3.64–5.69)	3.72 (3.23–4.29)	*<0.001*	1.20 (1.01–1.43)	*0.042*	1.25 (1.05–1.49)	*0.014*
M-classification								
M0	3344	19.5 (18.3–20.6)	Ref.		Ref.		Ref.	
M1	463	5.1 (4.6–5.6)	3.22 (2.91–3.57)	*<0.001*	2.46 (2.20–2.75)	*<0.001*	1.74 (1.55–1.96)	*<0.001*
Unknown[a]	33	0 (0.0–0.0)	5.14 (3.64–7.25)	*<0.001*	2.72 (1.87–3.95)	*<0.001*	1.40–2.96)	*<0.001*
Treatment								
No (anti-tumour) treatment	1632	6.6 (6.0–7.2)	Ref.		not included		Ref.	
Resection primary tumour	1940	35.8 (32.3–39.4)	0.23 (0.21–0.25)	*<0.001*			0.23 (0.20–0.26)	*<0.001*
Resection + chemo- and/or radiotherapy	164	30.0 (24.7–35.3)	0.28 (0.23–0.33)	*<0.001*			0.22 (0.18–0.27)	*<0.001*
Chemo- and/or radiotherapy	104	10.3 (8.4–12.0)	0.80 (0.66–0.98)	*0.030*			0.59 (0.48–0.73)	*<0.001*

NOS, not otherwise specified; CI, confidence interval.
[a] 22 of 33 patients classified as unknown stage were diagnosed at autopsy, hence median OS was zero months.
[b] Variables were chosen to avoid multicollinearity between t/n-classification and TNM-stage.

the OS data in the USA (5-year OS from 20% to 50%) between 2004 and 2012 [22]. Possibly this could be explained by the inclusion of patients with unknown clinical or pathological staging, differences in selection of histologic subtypes, and differences in treatment.

Survival of patients with metastatic ampullary cancer in the present study remained poor. Our 1-year OS of 20% is lower compared with the 1-year OS of 44% in France (outcome for the total non-resected group) and approximately 38% in the USA [5,6]. Both the French and American study did not report patient characteristics and treatment modalities in detail hampering objective comparisons. Possibly the current cohort is contaminated with patients with other tumours originating around the pancreatic head as pathological confirmation of the diagnosis is often missing in metastatic disease. Furthermore, the increased use of chemotherapy did not seem to improve OS. This, however, should be interpreted with caution as the analysis was statistically underpowered with no more than 3% of the patients receiving chemotherapy. Although chemotherapy is not recommended in the Dutch guideline, clinicians might decide otherwise and prescribe chemotherapeutic agents approved for pancreatic and/or biliary tract cancer.

The current study has several limitation, inherent to the retrospective study design. First, data such as information on TNM-stage, histological subtype (i.e. pancreatobiliary or intestinal type), time between diagnosis and treatment, the presence of pre-existing comorbidities and recurrences, were partly missing, incomplete or could have been misclassified. Especially data on histological subtype would have been of extra value in survival analyses as these are prognostic factors [3]. Second, risk of residual confounding might explain part of the observed improvement in OS over time. Third, diagnosis of ampullary cancer is difficult, leading to presumed (radiological or histological) misclassification in both surgically and non-surgically treated patients [36,40,41]. It is expected that more patients with ampullary cancer are misclassified as other periampullary cancers than vice-versa, resulting in an underestimation of the true incidence and possibly distorted OS.

In conclusion, this population-based study showed a small increase in incidence and overall survival of patients with non-metastatic ampullary cancer over the last three decades in the Netherlands, among an expansion of applied surgery with and without (neo-)adjuvant chemotherapy in non-metastatic disease. Survival of patients with metastatic disease remained poor, despite higher proportions of patients being treated with chemotherapy in the more recent years.

Declaration of competing interest

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejso.2021.02.028.

CRediT author statement

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Data availability

The data that support the findings of this study are available from the corresponding author upon request.

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