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ORIGINAL ARTICLE

Nationwide treatment and outcomes of intrahepatic cholangiocarcinoma

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Abstract

Background: Most data on the treatment and outcomes of intrahepatic cholangiocarcinoma (iCCA) derives from expert centers. This study aimed to investigate the treatment and outcomes of all patients diagnosed with iCCA in a nationwide cohort.

Methods: Data on all patients diagnosed with iCCA between 2010 and 2018 were obtained from the Netherlands Cancer Registry.

Results: In total, 1747 patients diagnosed with iCCA were included. Resection was performed in 292 patients (17%), 548 patients (31%) underwent palliative systemic treatment, and 867 patients (50%) best supportive care (BSC). The OS median and 1-, and 3-year OS were after resection: 37.5 months (31.0–44.0), 79.2%, and 51.6%,; with systemic therapy, 10.0 months (9.2–10.8), 38.4%, and 5.1%, and with BSC 2.2 months (2.0–2.5), 10.4%, and 1.3% respectively. The resection rate for patients who first presented in academic centers was 33% (96/292) compared to 13% (195/1454) in non-academic centers ($P < 0.001$).

Discussion: Half of almost 1750 patients with iCCA over an 8 year period did not receive any treatment with a 1-year OS of 10.4%. Three-year survival was about 50% after resection, while long-term survival was rare after palliative treatment. The resection rate was higher in academic centers compared to non-academic centers.

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Introduction

Intrahepatic cholangiocarcinoma (iCCA) is the second most common primary liver cancer after hepatocellular carcinoma. The origin of iCCA is the epithelium of the bile ducts, proximal to the left and right hepatic ducts. Usually there are either no or non-specific symptoms and consequently these tumours are often large and multifocal at first presentation. Therefore, most patients with iCCA are not eligible for surgical resection.[1,2]

Complete resection is possible in about 20% of patients in the absence of distant metastatic or locally advanced disease. Resection typically involves a major liver resection with substantial postoperative morbidity and mortality, depending on the extent of resection and the performance status of the patient.[3,4] Without treatment, survival is poor with a median overall survival (OS) of 5 months.[5,6] Palliative systemic chemotherapy with gemcitabine and cisplatin has been the standard treatment for advanced iCCA since the completion of the ABC-02 trial in 2010. This can extend median OS to 17 months as shown in a post-hoc analysis specific for the iCCA subgroup, yet survival beyond two years is very rare.[7–11] However, this subgroup analysis of the ABC trials included only 64 patients who received gemcitabine and cisplatin for iCCA. The low incidence of iCCA of around 1–2 per 100.000 in Western countries, has resulted in centralization of care for these patients to a limited number of centers. Consequently, most series are published by expert centers, often focusing on patients who are eligible for surgical resection. Reliable data evaluating the proportion of patients who undergo resection or receive palliative systemic therapy are unavailable. In addition, real-life data on survival outcomes of all patients with iCCA on a nationwide level are limited.

The aim of this study was to describe the treatment and outcomes of all patients with iCCA in the nationwide cancer registry in the Netherlands.

Methods

All patients registered with iCCA in the Netherlands Cancer Registry (NCR) between 2010 and 2018 were included. The definition of iCCA was: a malignant lesion arising from the epithelium of the bile ducts, proximal to the second order bile ducts. Patients were identified for inclusion in the NCR through the Dutch national pathology archives (PALGA) and the hospital discharge register (HDR) and were verified in patient records in all Dutch hospitals by trained registration clerks approximately 9 months after inclusion when further data were gathered and coded. Tumour location and tumour type are coded according to the International Classification of Diseases for Oncology (ICD-O-3) with invasive C22.1 intrahepatic bile duct (adeno)carcinoma selected for this study. The NCR data have a high degree of accuracy.[12] The study protocol was evaluated and approved by the Dutch Hepatocellular & Cholangiocarcinoma Group (DHCG). The Institutional Medical Ethics committee of the Erasmus MC Cancer Center waived the need for ethical approval.

Patient characteristics included in the NCR were: age, gender, socioeconomic status, and previous diagnosis of a malignancy. Socioeconomic state was coded by linking the patients' postal code at the time of diagnosis to data from the Netherlands Institute for Social Research. The socioeconomic score was based on income, employment, and education, and scores were divided into the tertiles low, middle, and high. 'High' indicated higher income, employment, and/or education. All malignancies except for basal cell carcinoma were defined as a previous malignancy. Tumour characteristics were cTNM stage (UICC-TNM) and the location of metastases (ICD-O-3), using the 7th edition up to 2016 and 8th edition since 2017. Treatment was characterized as surgical resection, (any) palliative systemic therapy, non-surgical local therapy, and best supportive care (BSC) (e.g. no surgery, palliative systemic therapy or non-surgical local therapy). Patients who had unresectable tumours at surgical exploration were classified according to the care received after surgical exploration (i.e. palliative systemic therapy or BSC). Major hepatectomy was defined as resection of 3 or more Couinaud liver segments. The hospital of first diagnosis was defined as the type of hospital at which the patient first presented and was diagnosed (regular, teaching, or academic hospital), irrespective of the hospital in which the patient underwent treatment. The Netherlands has eight academic hospitals. Teaching hospitals are the Dutch non-academic teaching hospitals. The remaining hospitals were defined as regular. Follow-up and survival data were collected by annual linkage of the NCR with the Dutch civil municipal registry and was last updated on February 1st 2019. Survival was defined as the time between diagnosis and death or last follow-up (February 1st 2019).

Statistical analysis

Annual incidence rates for the period 2010–2018 were calculated as number of new cases per 100,000 person-years, age-standardized to the European standard population (ESP, 1976). The analyses included the treatment characteristics and the associated outcomes. Differences in treatment outcomes for older patients (70 years or older), and differences in outcomes according to the hospital of first diagnosis. Categorical variables were presented as numbers with percentages and differences between variables were tested using either Fisher's exact or chi-square tests. Continuous variables were presented as median with interquartile-range (IQR) and differences were tested using Kruskal–Wallis tests. Survival and follow-up data were presented as medians with 95% confidence intervals (95%CI). Survival curves were generated according to the Kaplan–Meier methods and differences between groups were tested using log-rank tests. Uni- and multivariable analysis were performed using binary logistic regression analysis. The odds ratios were reported with their 95% CI. Statistical analyses were performed using SPSS

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Version 26 (IBM, Chicago, IL) and figures were generated using Graphpad Prism (Graphpad Inc, La Jolla, CA).

Results

In the study period 1763 patients were diagnosed with iCCA. Seven patients did not have any follow-up data and were excluded. Nine patients who underwent liver transplantation were excluded from the general analyses. The remaining 1747 were included in the analyses. The incidence of iCCA increased from 0.54 per 100.000 persons per year in 2010 to 1.53 in 2018.

Baseline characteristics and treatment

Baseline characteristics are shown in Table 1. Median age at diagnosis was 68 (59–75) years, 44% was aged 70 or older, and 40% of all patients presented with metastatic disease. The most common metastatic sites at presentation were lung (33%, n = 233), peritoneal (32%, n = 222), and/or extra regional intra-abdominal lymph nodes (27%, n = 191).

BSC was given in 867 patients (50%) and 548 (31%) patients were treated with (palliative) systemic therapy. Surgical resection was performed in 292 (17%) patients. Thirty-five patients (2%) underwent non-surgical local therapy, which included trans-arterial chemo-embolization in 10 patients (29%), radio-frequency or microwave ablation in 5 patients (14%), trans-arterial radio-embolization in 4 patients (11%), photodynamic therapy in one patient (3%), stereotactic radiotherapy in one patient (3%), and an unspecified local treatment in 14 patients (40%). None of these patients underwent systemic therapy before non-surgical local therapy. For the remaining five patients the treatment was missing. Baseline characteristics for patient who underwent BSC, palliative systemic therapy, and surgical resection are shown in Table 1, and for all groups including the 35 patients with non-surgical local therapy in Table S1. During

Table 1 Baseline characteristics

	Total[a] = 1747	BSC N = 867	ST N = 548	Resection N = 292	P-value
Age, *median (IQR)*	68 (59–75)	71 (64–79)	63 (55–70)	66 (57–72)	<0.001
70 years or older, n (%)	762 (44)	505 (58)	139 (25)	101 (35)	<0.001
Female sex, n (%)	891 (51)	443 (51)	279 (51)	148 (51)	0.991
Socioeconomic state, n (%)					0.057
Low	569 (33)	309 (36)	155 (28)	90 (31)	
Middle	674 (39)	322 (37)	222 (41)	114 (39)	
High	504 (29)	236 (27)	171 (31)	88 (30)	
Inclusion year, n (%)					0.943
2010–2012	334 (19)	158 (18)	105 (19)	54 (18)	
2013–2015	630 (36)	311 (36)	198 (36)	111 (38)	
2016–2018	783 (45)	398 (46)	245 (45)	127 (44)	
cT, n (%)					<0.001
1	289 (17)	105 (12)	41 (7)	138 (47)	
2	774 (44)	380 (44)	308 (56)	70 (24)	
3	150 (9)	81 (9)	48 (9)	18 (6)	
4	100 (6)	54 (6)	40 (7)	5 (2)	
X	434 (25)	247 (29)	111 (20)	61 (21)	
cN, n (%)					<0.001
0	766 (44)	338 (39)	184 (34)	224 (77)	
1	705 (40)	360 (42)	291 (53)	44 (15)	
X	276 (16)	169 (19)	73 (13)	34 (8)	
Metastases, n (%)	696 (40)	400 (46)	287 (52)	5 (2)	<0.001
Hospital of diagnosis, n (%)					<0.001
Regular	616 (35)	295 (34)	241 (44)	69 (24)[b]	
Teaching	838 (48)	456 (53)	235 (43)	126 (43)	
Academic	292 (17)	116 (13)	72 (13)	96 (33)	

[a] Including the 35 patients who underwent non-surgical local therapy.
[b] Missing for 1 patient who underwent resection. Abbreviations: BSC; best supportive care, ST; systemic therapy.

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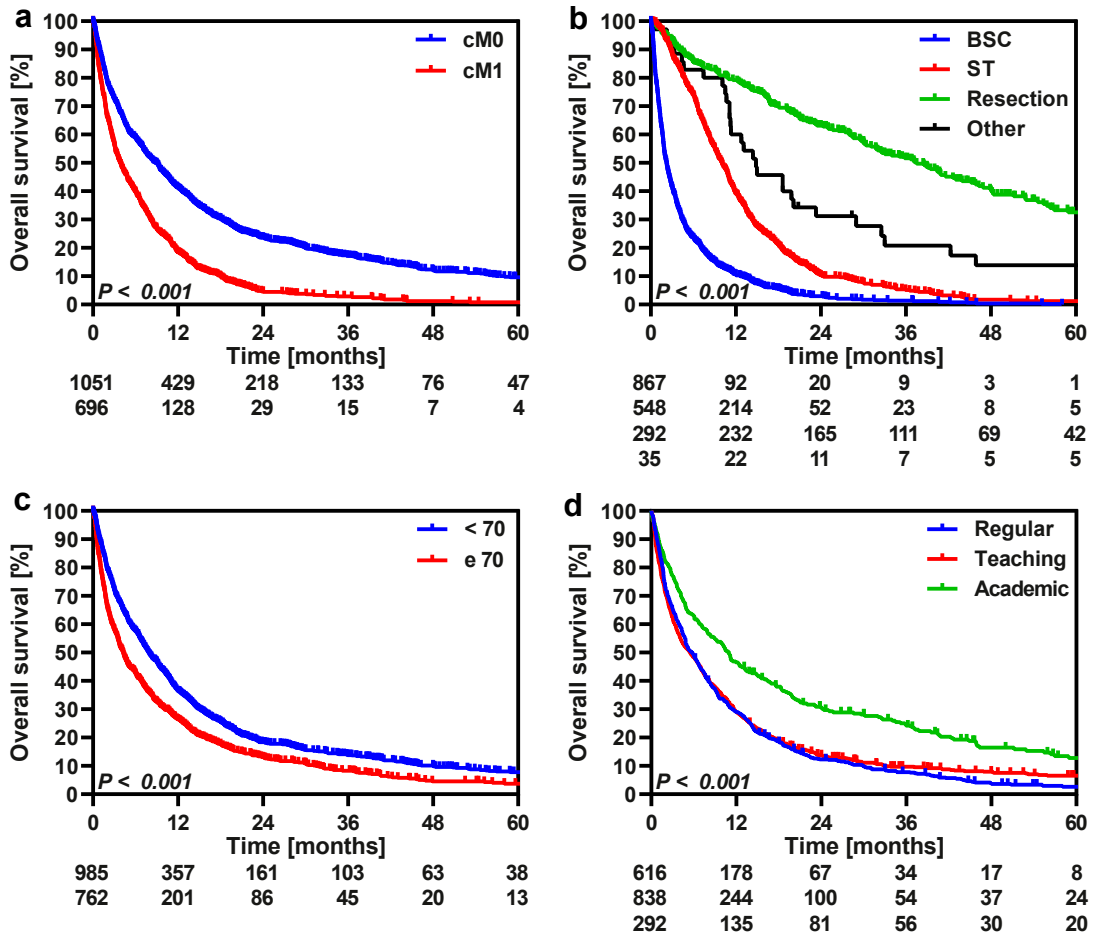

Figure 1 Overall survival in all patients diagnosed with iCCA according to (a) metastases, (b) treatment, (c) age, and (d) the hospital of first diagnosis. Curves were generated using the Kaplan–Meier method and below the graph are the numbers at risk. Groups were compared using log-rank tests. Abbreviations: BSC; best supportive care, ST; systemic therapy

the 9-year study period, the proportion of patients who underwent surgical resection and systemic therapy remained stable.

Overall survival

Median follow-up of surviving patients was 56.7 (48.3–65.1) months. The median OS in the overall cohort was 6.2 (5.6–6.8) months. Median OS was 8.8 (7.8–9.9) months in non-metastatic patients, compared to 3.8 (3.2–4.4) months in patients with metastatic disease ($P < 0.001$, Fig. 1A). Median OS in patients with known multifocal liver-only disease was 5.0 (3.7–6.3) months.

Surgical resection was associated with a median OS of 37.5 (31.0–44.0) months, with survival rates at 1, 3, and 5 years of 79.2% (73.9–83.0), 51.6% (45.5–58.0) and 32.6% (26.2–39.1), respectively (Fig. 1B). The 35 patients who underwent local treatment other than resection survived for a median 14.9 (9.2–20.5) months, with 1-, 3-, and 5-year survival rates of 60.0% (42.1–73.9), 20.8% (8.6–36.0), and 13.9% (4.6–28.2), respectively. Systemic treatment was associated with a median OS of 10.0 (9.2–10.8) months, with 1-, 3-, and 5-year survival rates of 38.4% (24.5–43.4), 5.1% (3.8–7.4), and 1.2% (0.5–2.7) respectively.

For patients with non-metastatic disease who did not undergo resection, median OS with systemic therapy was 10.9 (9.8–12.0) months and 8.8 (7.9–9.7) months for those with metastatic disease ($P = 0.032$). 1-, 3- and 5-year survival in these patients was 50.0% (42.5–58.0), 6.1% (1.3–9.3), 0.8% (0.1–3.8) and 34.1% (29.4–41.9), 4.8% (2.2–6.7), 1.5% (0.5–3.4) respectively. In patients with multifocal liver-only disease receiving systemic therapy (n = 102), median OS was 9.5 (8.3–10.7) months. Survival at 1, 3, and 5 years for these patients was 36.2 (26.9–45.6), 3.5% (0.8–9.4), and, 3.5% (0.8–9.4).

For patients who underwent BSC, the median OS was 2.2 (2.0–2.5) months, with 1-, 3-, and 5-year survival rates of 10.4% (8.2–12.7), 1.3% (0.2–2.5), and 0.0% (0.0–0.0), respectively. The reasons why patients underwent BSC were patient condition (n = 138, 16%), refusal of treatment (n = 126, 15%), rapid progression (n = 94, 20%), comorbidity (n = 29, 3%), and

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advanced age (n = 8, 1%). Reasons were unkown or unspecified in the remaining 472 patients.

Surgical treatment

In total, 383 patients underwent surgical exploration of whom 292 (76%) underwent a surgical resection. The procedures included 76 minor hepatectomies (26%), 206 major hepatectomies (72%) and 10 unspecified resections (3%). Negative resection margins were confirmed in 192 patients (67%). Postoperative 90-day mortality for all 292 resections was 12% (34/292). The 90-day mortality was 5% after minor hepatectomy (4/76) and 14% after major hepatectomy (29/206). Out of all procedures, 239 (82%) were performed at academic centers, 43 (15%) at non-academic centers, and 10 (3%) at hospitals outside of the Netherlands. In academic centers, 175 (73%) procedures were major liver resections and in non-academic centers 23 (53%) procedures (P = 0.001). The 90-day mortality rate was similar with 12% (28/239) in academic and 14% (6/43) in non-academic centers (P = 0.618).

Impact of age on treatment and outcomes

Out of the 1747 patients, 985 (56%) were younger than 70 years old at presentation and 762 (54%) were 70 years or older. Treatment differed according to these age-groups with a resection rate of 19% (191/985) in the younger group and 13% (101/762) in the older group. The use of systemic therapy did also depend on age, where 42% of patients (409/985) were treated with systemic therapy in the younger and 18% (139/762) in the older group. In the older group 66% of patients (504/762) got BSC, compared to 33% (363/762) in the younger group ($P < 0.001$). Median OS in the older group was 4.2 (3.6–4.8) months compared to 7.8 (6.9–8.6) months in the younger group ($P < 0.001$, Fig. 1C). In the younger patient group, 90-day mortality after major liver resection was 11% (16/141), and 20% (13/65) in the older group ($P = 0.097$).

Hospital of diagnosis

The hospital of first presentation was a regular hospital in 616 patients (35%), a teaching hospital in 838 patients (46%) and an academic center in 292 patients (17%). The type of hospital of diagnosis was missing in 11 patients. Patients who first presented in regular hospitals underwent resection in 11%, compared to 15% in teaching hospitals and 33% (96/292) in academic centers ($P < 0.001$). At multivariable analysis, the higher resection rate in academic centers was upheld (Table 2). For patients who first presented at a regular hospital, the median OS of was 5.7 (4.9–6.4) versus 5.5 (4.6–6.4) months at a teaching hospital ($P = 0.450$). Those who first presented in academic centers had a median OS of 10.6 (8.3–12.9) months ($P < 0.001$, Fig. 1D).

Discussion

This nationwide study on 1747 patients diagnosed with iCCA showed a resection rate of 17%, treatment with palliative systemic therapy was given in 31% of patients and BSC in 50%. Resection was associated with a median OS of 37.5 months and a 12% 90-day mortality rate. Palliative systemic therapy resulted in a median OS of 11.9 months and a 3-year OS of 5.1%. BSC resulted in a median OS of 2.2 months with a 3-year survival rate of 1.3%. The resection rate for patients who first presented in academic centers was 33% compared to 13% in non-academic centers. Patients aged 70 or older were less likely to undergo resection (13 versus 19%) and palliative systemic therapy (18 versus 42%).

Few population-based studies have reported on the resection rate of intrahepatic cholangiocarcinoma. An analysis on 3756 patients from the national cancer institute in the United States up to 2003 reported a resection rate of 12%.[13] A subsequent series on 27,120 patients from the same database from 2004 to 2015 reported a 22% resection rate.[14] The resection rate of 17% in this study was similar. Most other studies are smaller single center series and reported on the resection rate in patients at a surgical department. These resection rates are 32–54% and are most likely an overestimation of population-based resection rates.[15–18]

Median OS after surgical resection for iCCA ranges in the literature from 33 to 39 months, which is in line with the 37.5 in this nationwide cohort.[19–21] The postoperative mortality in the present nationwide study was 12%, which is comparable to the high end of the 5–12% mortality range reported in the literature.[21–23] Postoperative mortality after liver resection for iCCA is much higher compared to other indications, because of underlying liver disease, the extent of liver resection (mostly major or extended), and the need for hepaticojejunostomy in about 15% of cases. Moreover, nationwide outcomes are typically worse than

Table 2 Treatment of patients with intrahepatic cholangiocarcinoma according to the hospital of first diagnosis

	Regular N = 616	Teaching N = 838	Academic N = 292	P-value
Best supportive care	295 (48)	456 (54)	116 (40)	0.025
Systemic therapy	241 (39)	235 (28)	72 (25)	<0.001
Resection	69 (11)	126 (15)	96 (33)	<0.001
Other local treatment	9 (1)	18 (2)	8 (3)	0.403
Unknown	2 (0)	3 (0)	–	0.994

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those from expert centers. For example, 90-day mortality after liver resection in a large German study of 2519 patients was 14%.[3] The risk of surgery should be balanced with the oncological benefit, especially in elderly or frail patients.

Survival in patients who did not undergo surgical resection is poor, with median OS under 12 months after palliative systemic therapy. A subgroup analysis of the ABC trials found a median OS of 17 months for patients with advanced iCCA treated with gemcitabine and cisplatin.[11] The median OS of the present study was lower, most likely due to the unselected nationwide cohort, compared to somewhat strict inclusion criteria of the ABC trial (e.g. bilirubin level below 1.5 times the upper limit).[9,11] A previous study found that only about 54% of patients treated with gemcitabine with cisplatin for advanced iCCA fulfilled inclusion criteria of the ABC trials.[24] In recent years, immunotherapy has emerged as treatment option for iCCA in addition to chemotherapy. Addition of durvalumab to chemotherapy in advanced biliary tract cancer showed increased response rates. The increase in OS was limited and future studies should address the place of immunotherapy in the treatment of iCCA.[25,26]

Most patients with iCCA, in particular in the absence of extrahepatic disease, die from progressive disease in the liver with segmental biliary obstruction and liver failure. Local treatment may control hepatic disease and prevent biliary obstruction and liver failure.[27] In the present study, only 2% received local treatment other than resection. They had a much better median OS compared to patients who only received palliative systemic chemotherapy. However, this is probably at least partly due to selection bias.

None of the patients in the present study received hepatic artery infusion pump (HAIP) chemotherapy with floxuridine. This is local treatment for unresectable liver-confined iCCA that aims to control the disease in the liver. Three phase II trials investigating this treatment found a median OS of about 25 months and a 3-year OS of about 40%.[28–31] In comparison, the 3-year OS was 5.1% in patients undergoing palliative systemic therapy in this study and 0% in patients with liver-only iCCA in the ABC trials.[11] For multifocal liver-confined iCCA, most guidelines recommend palliative systemic chemotherapy, although a resection is frequently technically feasible. Therefore, local treatments such as resection have been frequently performed in these patients.[7,8,32–34] A recent study compared surgical resection with HAIP chemotherapy for multifocal liver-confined iCCA. The OS curves were similar for both patients with 2 or 3 lesions and 4 or more lesions. However, postoperative mortality was much higher in the resection group compared to the HAIP chemotherapy group. HAIP chemotherapy may be an attractive alternative for patients with multifocal iCCA, especially for patients with a high surgical risk.[35]

The resection rate in this study was dependent on the hospital of first presentation. Resection rate in patients first presenting in academic centers was 33% compared to 13% in patients presenting in non-academic centers. This observation was previously reported for perihilar cholangiocarcinoma, and is the result of not referring patients for evaluation in expert centers who may benefit from a resection.[2,36] Patients may not be referred, because iCCA is frequently confused with metastases of an unknown primary. A recent study on patients referred to a regional multi-disciplinary team on cancer of unknown primary, showed 41% of these patients with liver lesions had radiological criteria of iCCA.[37] Moreover, previous reports found that patients treated at academic centers had a lower postoperative 90-mortality rate, higher R0 margin rate, and better OS.[14,38,39] It is likely that regional collaboration and centralization of treatment for iCCA will improve outcomes.[40]

The study has several limitations, mostly related to the retrospective study design. The Netherlands cancer database collects only a limited dataset on surgical treatment. For instance, the reason for unresectability at laparotomy was not recorded. Also, data on systemic therapy regimens, cycles, toxicity, and performance status are not available. It is possible the differences in resection rates across hospital types are partially attributable to differences in background liver disease. Also, referral patterns and regional multidisciplinary meeting use were not recorded in the dataset. Finally, while the data from the Netherlands Cancer Registry is considered accurate, misclassification of some patients cannot be ruled out. Finally, the nine patients who underwent liver transplantation were excluded since there is no transplant program in the Netherlands for iCCA. Possibly, the tumours in these patients were misclassified.

In conclusion, in this nationwide cohort, prognosis of iCCA is poor. About 50% of patients with iCCA did not receive any treatment with a 1-year OS of 10%. Three-year survival was about 50% after resection, while it was rare after palliative treatment. The resection rate was higher for patients who first presented in academic centers compared to non-academic centers.

Informed consent

Not applicable.

Registry and the registration no. of the study/trial

Not applicable.

Animal studies

Not applicable.

Research involving recombinant DNA

Not applicable.

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Authors' contributions

PBO and BGK came up with the study, all authors performed the analysis and interpretation. All authors drafted and reviewed the manuscript and approved the final version.

Data availability statement

Data available upon request and relevant ethical approval.

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Conflict of interest

None declared.

References

1. Weber SM, Ribero D, O'Reilly EM, Kokudo N, Miyazaki M, Pawlik TM. (2015) Intrahepatic cholangiocarcinoma: expert consensus statement. *HPB (Oxford)* 17:669–680.
2. Buettner S, van Vugt JL, JN IJ, Groot Koerkamp B. (2017) Intrahepatic cholangiocarcinoma: current perspectives. *OncoTargets Ther* 10: 1131–1142.
3. Filmann N, Walter D, Schadde E, Bruns C, Keck T, Lang H *et al*. (2019) Mortality after liver surgery in Germany. *Br J Surg* 106:1523–1529.
4. Merath K, Chen Q, Bagante F, Alexandrescu S, Marques HP, Aldrighetti L *et al*. (2019) A multi-institutional international analysis of textbook outcomes among patients undergoing curative-intent resection of intrahepatic cholangiocarcinoma. *JAMA Surg* 154e190571.
5. DeOliveira ML, Cunningham SC, Cameron JL, Kamangar F, Winter JM, Lillemoe KD *et al*. (2007) Cholangiocarcinoma: thirty-one-year experience with 564 patients at a single institution. *Ann Surg* 245:755–762.
6. Koch C, Franzke C, Bechstein WO, Schnitzbauer AA, Filmann N, Vogl T *et al*. (2020) Poor prognosis of advanced cholangiocarcinoma: real-world data from a tertiary referral center. *Digestion* 101:458–465.
7. Khan SA, Davidson BR, Goldin RD, Heaton N, Karani J, Pereira SP *et al*. (2012) Guidelines for the diagnosis and treatment of cholangiocarcinoma: an update. *Gut* 61:1657–1669.
8. Valle JW, Borbath I, Khan SA, Huguet F, Gruenberger T, Arnold D *et al*. (2016) Biliary cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 27(suppl 5):v28–v37.
9. Valle J, Wasan H, Palmer DH, Cunningham D, Anthoney A, Maraveyas A *et al*. (2010) Cisplatin plus gemcitabine versus gemcitabine for biliary tract cancer. *N Engl J Med* 362:1273–1281.
10. Valle JW, Furuse J, Jitlal M, Beare S, Mizuno N, Wasan H *et al*. (2014) Cisplatin and gemcitabine for advanced biliary tract cancer: a meta-analysis of two randomised trials. *Ann Oncol* 25:391–398.
11. Lamarca A, Ross P, Wasan HS, Hubner RA, McNamara MG, Lopes A *et al*. (2020) Advanced intrahepatic cholangiocarcinoma: post hoc analysis of the ABC-01, -02, and -03 clinical trials. *J Natl Cancer Inst* 112:200–210.
12. Schouten LJ, Höppener P, van den Brandt PA, Knottnerus JA, Jager JJ. (1993) Completeness of cancer registration in Limburg, The Netherlands. *Int J Epidemiol* 22:369–376.
13. Tan JC, Coburn NG, Baxter NN, Kiss A, Law CH. (2008) Surgical management of intrahepatic cholangiocarcinoma–a population-based study. *Ann Surg Oncol* 15:600–608.
14. Wu L, Tsilimigras DI, Paredes AZ, Mehta R, Hyer JM, Merath K *et al*. (2019) Trends in the incidence, treatment and outcomes of patients with intrahepatic cholangiocarcinoma in the USA: facility type is associated with margin status, use of lymphadenectomy and overall survival. *World J Surg* 43:1777–1787.
15. Lang H, Sotiropoulos GC, Fruhauf NR, Domland M, Paul A, Kind EM *et al*. (2005) Extended hepatectomy for intrahepatic cholangiocellular carcinoma (ICC): when is it worthwhile? Single center experience with 27 resections in 50 patients over a 5-year period. *Ann Surg* 241: 134–143.
16. Lieser MJ, Barry MK, Rowland C, Ilstrup DM, Nagorney DM. (1998) Surgical management of intrahepatic cholangiocarcinoma: a 31-year experience. *J Hepatobiliary Pancreat Surg* 5:41–47.
17. Endo I, Gonen M, Yopp AC, Dalal KM, Zhou Q, Klimstra D *et al*. (2008) Intrahepatic cholangiocarcinoma: rising frequency, improved survival, and determinants of outcome after resection. *Ann Surg* 248:84–96.
18. Nakeeb A, Tran KQ, Black MJ, Erickson BA, Ritch PS, Quebbeman EJ *et al*. (2002) Improved survival in resected biliary malignancies. *Surgery* 132:555–563. discission 63-4.
19. Hyder O, Marques H, Pulitano C, Marsh JW, Alexandrescu S, Bauer TW *et al*. (2014) A nomogram to predict long-term survival after resection for intrahepatic cholangiocarcinoma: an Eastern and Western experience. *JAMA Surg* 149:432–438.
20. Ribero D, Pinna AD, Guglielmi A, Ponti A, Nuzzo G, Giulini SM *et al*. (2012) Surgical approach for long-term survival of patients with intrahepatic cholangiocarcinoma: a multi-institutional analysis of 434 patients. *Arch Surg* 147:1107–1113.
21. Altman AM, Kizy S, Marmor S, Huang JL, Denbo JW, Jensen EH. (2018) Current survival and treatment trends for surgically resected intrahepatic cholangiocarcinoma in the United States. *J Gastrointest Oncol* 9:942–952.
22. Reames BN, Ejaz A, Koerkamp BG, Alexandrescu S, Marques HP, Aldrighetti L *et al*. (2017) Impact of major vascular resection on outcomes and survival in patients with intrahepatic cholangiocarcinoma: a multi-institutional analysis. *J Surg Oncol* 116:133–139.
23. Vitale A, Spolverato G, Bagante F, Gani F, Popescu I, Marques HP *et al*. (2016) A multi-institutional analysis of elderly patients undergoing a liver resection for intrahepatic cholangiocarcinoma. *J Surg Oncol* 113: 420–426.
24. Dierks J, Gaspersz MP, Belkouz A, van Vugt JLA, Coelen RJS, de Groot JWB *et al*. (2018) Translating the ABC-02 trial into daily practice: outcome of palliative treatment in patients with unresectable biliary tract cancer treated with gemcitabine and cisplatin. *Acta Oncol* 57:807–812.
25. Oh DY, Lee KH, Lee DW, Yoon J, Kim TY, Bang JH *et al*. (2022) Gemcitabine and cisplatin plus durvalumab with or without tremelimumab in chemotherapy-naive patients with advanced biliary tract cancer: an open-label, single-centre, phase 2 study. *Lancet Gastroenterol Hepatol* 7:522–532.
26. Uson Junior PLS, Araujo RL. (2022) Immunotherapy in biliary tract cancers: current evidence and future perspectives. *World J Gastrointest Oncol* 14:1446–1455.
27. Yamashita S, Koay EJ, Passot G, Shroff R, Raghav KP, Conrad C *et al*. (2017) Local therapy reduces the risk of liver failure and

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improves survival in patients with intrahepatic cholangiocarcinoma: a comprehensive analysis of 362 consecutive patients. *Cancer* 123: 1354–1362.

28. Cercek A, Boerner T, Tan BR, Chou JF, Gonen M, Boucher TM *et al*. (2020) Assessment of hepatic arterial infusion of floxuridine in combination with systemic gemcitabine and oxaliplatin in patients with unresectable intrahepatic cholangiocarcinoma: a phase 2 clinical trial. *JAMA Oncol* 6:60–67.

29. Jarnagin WR, Schwartz LH, Gultekin DH, Gonen M, Haviland D, Shia J *et al*. (2009) Regional chemotherapy for unresectable primary liver cancer: results of a phase II clinical trial and assessment of DCE-MRI as a biomarker of survival. *Ann Oncol* 20:1589–1595.

30. Edeline J, Lamarca A, McNamara MG, Jacobs T, Hubner RA, Palmer D *et al*. (2021) Locoregional therapies in patients with intrahepatic cholangiocarcinoma: a systematic review and pooled analysis. *Cancer Treat Rev* 99:102258.

31. Holster JJ, El Hassnaoui M, Franssen S, JNM IJ, de Jonge J, Mostert B *et al*. (2022) Hepatic arterial infusion pump chemotherapy for unresectable intrahepatic cholangiocarcinoma: a systematic review and meta-analysis. *Ann Surg Oncol* 29:5528–5538.

32. Bridgewater J, Galle PR, Khan SA, Llovet JM, Park JW, Patel T *et al*. (2014) Guidelines for the diagnosis and management of intrahepatic cholangiocarcinoma. *J Hepatol* 60:1268–1289.

33. European Association for the Study of the Liver. (2023) Electronic address eee, European association for the study of the L. EASL-ILCA clinical practice guidelines on the management of intrahepatic cholangiocarcinoma. *J Hepatol* 79:181–208.

34. Kubo S, Shinkawa H, Asaoka Y, Ioka T, Igaki H, Izumi N *et al*. (2022) Liver cancer study group of Japan clinical practice guidelines for intrahepatic cholangiocarcinoma. *Liver Cancer* 11:290–314.

35. Franssen S, Soares KC, Jolissaint JS, Tsilimigras DI, Buettner S, Alexandrescu S *et al*. (2022) Comparison of hepatic arterial infusion pump chemotherapy vs resection for patients with multifocal intrahepatic cholangiocarcinoma. *JAMA Surg* 157:590–596.

36. van Keulen AM, Franssen S, van der Geest LG, de Boer MT, Coenraad M, van Driel L *et al*. (2021) Nationwide treatment and outcomes of perihilar cholangiocarcinoma. *Liver Int* 41: 1945–1953.

37. Conway GM A, Smith S, Manoharan P, Mitchell CL, Backen A, Oliveira P *et al*. (2021) 58P - intrahepatic cholangiocarcinoma (iCCA) hidden amongst the unknown: a retrospective analysis of cancer of unknown primary (CUP) cases from a tertiary cancer centre. *Ann Oncol* 32. S376-S38.

38. Kommalapati A, Tella SH, Goyal G, Borad M, Alberts SR, Roberts L *et al*. (2019) Association between treatment facility volume, therapy types and overall survival in patients with intrahepatic cholangiocarcinoma. *HPB (Oxford)* 21:379–386.

39. Lee GC, Gamblin TC, Fong ZV, Ferrone CR, Goyal L, Lillemoe KD *et al*. (2019) Facility type is associated with margin status and overall survival of patients with resected intrahepatic cholangiocarcinoma. *Ann Surg Oncol* 26:4091–4099.

40. Idrees JJ, Merath K, Gani F, Bagante F, Mehta R, Beal E *et al*. (2019) Trends in centralization of surgical care and compliance with National Cancer Center Network guidelines for resected cholangiocarcinoma. *HPB (Oxford)* 21:981–989.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.hpb.2023.06.019.

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