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The clinical presentation and prognostic factors for intrahepatic and extrahepatic cholangiocarcinoma in a tertiary care centre

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SUMMARY

Background
The incidence of cholangiocarcinoma is rising. Accurate predictors of survival at diagnosis are not well defined.

Aim
To clarify the clinical presentation and prognostic factors of intrahepatic cholangiocarcinoma and extrahepatic cholangiocarcinoma in a contemporary cohort of patients.

Methods
Records for consecutive patients at the University of Michigan hospital diagnosed with cholangiocarcinoma between January 2003 and April 2008 were reviewed.

Results
In all, 136 patients had cholangiocarcinoma (79 intra- and 57 extrahepatic cholangiocarcinoma). Median survival was 27.3 months–25.8 months for intrahepatic cholangiocarcinoma and 30.3 months for extrahepatic cholangiocarcinoma. Independent predictors of mortality at presentation on multivariate analysis were elevated bilirubin level (HR 1.04, 95%CI 1.01–1.07), CA 19-9 levels >100 U/mL (HR 1.90, 95%CI 1.17–3.08) and stage of disease (HR 1.51, 95%CI 1.16–1.96). After adjusting for baseline prognostic factors, surgical therapy was associated with improved survival (HR 0.48; 95% CI 0.26–0.88). There were no significant differences regarding clinical presentation, disease stage ($P = 0.98$), and survival ($P = 0.51$) between intra- and extrahepatic cholangiocarcinoma.

Conclusions
Survival for cholangiocarcinoma remains poor with no significant difference in outcomes between intra- and extrahepatic cholangiocarcinoma. Stage of disease, bilirubin level and CA 19-9 level are important prognostic factors at presentation. Surgical therapy provides similar efficacy for both tumours when adjusted for other prognostic variables.

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INTRODUCTION

Cholangiocarcinoma (CCA), the second most common primary hepatic malignancy, accounts for approximately 3% of all gastrointestinal cancers.[1] It can arise anywhere along the biliary tract and has been classified into intrahepatic cholangiocarcinoma (ICC) and extrahepatic cholangiocarcinoma (ECC) based on its anatomic location. ICC tumours occur proximal to the bifurcation of the right and left hepatic ducts and are confined to the liver. ECC tumours are further divided into perihilar CCA, located at the bifurcation of the hepatic ducts, and distal CCA. Perihilar tumours account for 50–60% of all CCA, while ICC (10%) and distal tumours (30–40%) occur less frequently.[2] ICC and ECC vary not only in location but also in epidemiology, clinical presentation, prognosis and treatment options.[3]

The worldwide incidence of CCA has been growing, largely because of an increasing incidence of ICC, while the incidence of ECC is decreasing.[4] The aetiology for the rising incidence of ICC remains unclear, particularly given that only 10% of all CCA cases are associated with a recognized risk factor such as primary sclerosing cholangitis (PSC), choledochal cysts, cirrhosis and infestation with liver flukes.[5] Although analysis of the Surveillance, Epidemiology and End Results (SEER) database suggested that underlying cirrhosis was the risk factor most strongly associated with ICC when compared with randomly selected Medicare patients without a history of cancer (OR 27.2, 95% CI 19.9–37.1),[6] this epidemiologic information is difficult to interpret as many perihilar tumours were incorrectly classified as ICC.[7, 8]

For reasons of the frequent presentation of CCA with advanced stages, prognosis continues to be poor. The primary potential curative therapy is surgical resection, which results in a median survival of 15–40 months and 5-year survival rates of 9–50%.[9, 10] More recently, liver transplantation has been shown to be associated with favourable outcomes in highly selected patients with ECC, but confirmatory studies are necessary.[11] Unfortunately, surgical therapy is feasible only in a minority of cases.[12] In patients with unresectable tumours, optimal supportive care only provides a median survival of <1 year.[13] Most studies on prognostic factors for patients with CCA have focused on patients undergoing surgical resection.[14–16] Only a few reports involving a small number of patients have evaluated prognostic factors in unselected patients with CCA with very little stratification of ICC vs. ECC.[17, 18] The aims of our study were to (i) clarify the presenting symptoms, treatment options, and factors affecting outcomes of CCA and (ii) compare these findings between patients with ICC and ECC in a contemporary consecutive series of patients evaluated at a single liver referral centre in the United States.

PATIENTS AND METHODS

Study population

We retrospectively reviewed records for consecutive adult patients at the University of Michigan Medical Center who had cytological or histopathological diagnosis of CCA between January 2003 and April 2008. Patients were initially identified using ICD-9 codes for CCA (155.1 and 156.1). Patients were excluded if the suspected CCA was discovered to be ampullary, gallbladder, or pancreatic adenocarcinoma. Patients without imaging studies were excluded given that tumour characteristics could not otherwise be adequately determined. All cases of CCA were defined as ICC or ECC according to the primary tumour location. This study was approved by the Institutional Review Board of the University of Michigan.

Data collection

Patient demographics, clinical history, laboratory data and imaging results were obtained through review of computerized medical records. Age, gender, race, lifetime alcohol history and lifetime smoking history were recorded. Alcohol use was quantified as greater or less than 80 g of ethanol per day and tobacco use was quantified as greater or less than 20 pack-years based on estimates from the medical records.[19] Past medical history including any history of gallstones, liver disease including PSC and diabetes was determined by review of clinical notes. Laboratory data including platelets, albumin, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, bilirubin, international normalized ratio, alpha-fetoprotein (AFP), carcinoembryonic antigen (CEA) and cancer antigen 19-9 (CA 19-9) at the time of initial diagnosis were included in our analysis. AFP levels were also categorized as greater or less than 8 ng/mL, the upper limit of normal for our hospital laboratory. Tumour characteristics were determined by imaging studies (CT, MRI or MRCP/ERCP), which were interpreted by

radiologists at our institution. Tumour characteristics of interest included the CCA subtype, number of lesions, tumour diameter, lymph node involvement, vascular involvement, presence of extrahepatic metastases, and stage of the tumour at diagnosis. Vascular involvement was a broad category that was further categorized as bland thrombus, vascular encasement, or vascular invasion based on the interpretation of available imaging studies. Tumours distal to the bifurcation of the right and left hepatic ducts were defined as ECC, whereas tumours proximal to the bifurcation were defined as ICC. Subtypes for ECC included distal, middle and hilar tumours while subtypes for ICC included intraductal, infiltrating, mass forming, and mass forming + infiltrative. Staging of each lesion was based on the American Joint Committee on Cancer system of Tumor, Node, Metastasis (TNM) for CCA.[20] Each patient's clinical course including mode of diagnosis, treatments received, and survival through 31 December 2008 was recorded. Survival status of patients not currently followed up or those patients known to have died was verified through the Social Security Death Index. Patient treatment was categorized as the best supportive care, chemotherapy, radiation therapy, chemotherapy plus radiation therapy, resection and resection with adjuvant chemotherapy.

Statistical analysis

All data values were expressed as median (range) unless otherwise stated. The demographic features, tumour characteristics, treatments and survival were compared between patients diagnosed with ICC and ECC. Chi-squared tests were used for categorical variables and t tests were used for continuous variables. The Scheffé method was used to adjust significance levels in all linear regression analyses to account for multiple comparisons. Survival curves were generated utilizing Kaplan-Meier plots and compared using log rank test. Cox multivariate regression analysis was performed to determine factors associated with survival. All data analysis was performed using SPSS 15 (SPSS Inc., Chicago, IL, USA).

RESULTS

Patient characteristics

Between January 2003 and April 2008, 131 patients had cytological or histological confirmation of the diagnosis of CCA in our institution. Five additional patients were included in whom histology could not be obtained, but clinical suspicion for CCA was sufficiently high to make a presumptive diagnosis using a combination of CT, MRI and ERCP. There were 79 (58.1%) patients diagnosed with ICC and 57 (41.9%) patients diagnosed with ECC (Table 1). The median age of the patients was 65 years (range 26–95). More than 90% (n = 126) of patients were Caucasian and 57% (n = 78) were men. There was no significant difference in the demographic features of patients with ICC and ECC.

Laboratory values upon presentation were most notable for a difference in bilirubin levels between patients with ECC and those with ICC. The median bilirubin level was 9.4 mg/dL in those with ECC compared with a median bilirubin level of 1.0 in those with ICC ($P < 0.01$). The median CA 19-9 level of 140 U/mL (range 2–170 716) was not significantly different between patients with ICC and those with ECC ($P = 0.58$). CA 19-9 levels were >100 U/mL in 38 patients (54.3%) with ICC and 29 patients (60.4%) with ECC ($P = 0.51$). CEA levels were not significantly different between patients with ICC and those with ECC ($P = 0.62$), with a median level of 2.1 ng/mL in the entire cohort.

Chronic liver disease was found in 14.7% of all patients, including 10 patients with cirrhosis and 10 patients with PSC. There was a trend towards a higher prevalence of underlying liver disease in patients with ICC (17.8%) compared with patients with ECC (10.5%), although this was not statistically significant ($P = 0.24$).

Tumour characteristics

Nearly three-fourths of patients with ECC (n = 44) presented with hilar tumours, with only 22.8% (n = 13) of patients having nonhilar tumours. The median tumour diameter was 6.3 cm (range 1–20) for all patients (Table 1). Patients with ICC had larger tumours than those with ECC, with a median tumour diameter of 7.6 cm vs. 3.0 cm, ($P < 0.01$). Approximately 55% (n = 82) of patients had lymph node involvement and nearly 20% (n = 28) had extrahepatic metastases at diagnosis. Majority of patients had vascular encasement (n = 51) with true invasion suspected in only 18% (n = 24) of patients. Less than 20% (n = 23) of patients were diagnosed with stage I disease with nearly 65% (n = 87) of all patients being diagnosed

Table 1. Patient and tumour characteristics of patients with cholangiocarcinoma

Variable	Overall (n = 136)	ECC (n = 57)	ICC (n = 79)	P-value
Age (years)*	65 (40–83)	66 (45–79)	64 (41–83)	0.45
Gender (% males)	57.4	61.4	54.4	0.42
Race (% Caucasian)	92.7	91.2	93.7	0.24
Liver disease (%)	14.7	10.5	17.8	0.24
PSC (%)	7.4	5.3	8.9	
Hepatitis C (%)	7.4	5.3	8.9	
Gallstones (%)	34.6	52.6	21.5	<0.01
Alcohol >80 g/day (%)	23.5	24.6	22.8	0.81
Tobacco >20 pack-year (%)	40.4	38.6	41.8	0.71
Bilirubin (mg/dL)*	2.2 (0.3–29.1)	9.4 (0.6–23)	1.0 (0.3–22.3)	<0.01
Bilirubin >3 mg/dL (%)	48.5	70.4	33.3	<0.01
Bilirubin >10 mg/dL (%)	32.8	45.6	23.4	<0.01
Platelets (K/mm^3)*	265 (103–507)	274 (176–49)	254 (104–493)	0.70
Albumin (g/dL)*	3.6 (2.1–4.6)	3.6 (2.6–4.3)	3.7 (2.5–4.6)	0.19
INR*	1.0 (0.9–1.7)	1.0 (0.9–1.4)	1.0 (0.9–1.7)	0.40
AFP (ng/mL)*	3.5 (1.0–42.4)	1.8 (1.3–2.0)	3.7 (1–42.4)	0.36
CEA (ng/mL)*	2.1 (0.6–161)	2.2 (1.0–95.8)	2.1 (0.7–30)	0.62
CA 19-9 (U/mL)*	140 (2.2–68 730)	253 (7–20 358)	124 (6.5–68 730)	0.58
CA 19-9 >40 U/mL (%)	71.2	75.0	68.6	0.53
CA 19-9 >100 U/mL (%)	56.8	60.4	54.3	0.51
Number of lesions (n)*	1.0 (1–10)	1.0 (1–5)	1.0 (1–5)	0.23
Maximum diameter (cm)*	6.3 (1.5–13)	3.0 (1.5–6.8)	7.6 (3.0–13)	<0.001
Abdominal lymph nodes (%)	56.9	58.9	62.0	0.72
Vascular involvement (%)	56.3	53.6	58.2	0.59
Vascular invasion (%)	17.8	12.5	21.5	0.18
Vascular encasement (%)	37.8	37.5	38.0	0.96
Extrahepatic metastases (%)	20.7	28.6	15.2	0.06
Stage, n (%)				
I	23 (17.0)	6 (10.7)	17 (21.5)	0.98
II	25 (18.5)	22 (39.3)	3 (3.8)	
III	59 (43.7)	12 (21.4)	47 (59.5)	
IV	28 (20.7)	16 (28.6)	12 (15.9)	

INR, international normalized ratio; AFP, alpha-fetoprotein; CEA, carcinoembryonic antigen; CA 19-9, cancer antigen 19-9; ECC, extrahepatic cholangiocarcinoma; ICC, intrahepatic cholangiocarcinoma; PSC, primary sclerosing cholangitis.
* Expressed as median (interquartile range).

with stage III or IV disease. There was no significant difference in the stage of disease at the time of diagnosis between patients with ICC and patients with ECC (P = 0.98).

Treatment

The treatments given to patients are described in Table 2. Approximately half (n = 64) of all patients received some combination of chemotherapy and radiation. In total, 39 (29%) patients were treated with surgical resection, of which 24 (30%) patients had ICC and 15 (26%) had ECC. There were 24% (n = 32) of patients who were treated with best supportive care. There was no statistically significant difference between treatment regimens for the patients with ICC and those with ECC, although we may have been underpowered to detect a difference, given limited numbers in each subgroup (P = 0.27).

Predictors of survival at time of diagnosis

The median survival of the 136 patients after diagnosis was 27.3 months (range 0.5–312.6) with a 71% 1-year survival and 42% 3-year survival (Figure 1). There was no significant difference in the median survival

Table 2. Type of treatment received according to type of cholangiocarcinoma [*n*(%)]

Treatment type	Overall (n = 136)	ECC (n = 57)*	ICC (n = 79)
Best supportive care	32 (23.7)	16 (28.6)	16 (20.2)
Chemotherapy	17 (12.6)	5 (8.9)	12 (15.2)
Radiation Therapy	7 (5.2)	4 (7.1)	3 (3.8)
Chemotherapy + radiation	40 (29.6)	16 (28.6)	24 (30.4)
Resection	23 (17.0)	6 (10.7)	17 (21.5)
Resection + adjuvant therapy	16 (11.9)	9 (16.1)	7 (8.9)

ECC, extrahepatic cholangiocarcinoma; ICC, intrahepatic cholangiocarcinoma.
* One patient with ECC was lost to follow-up and treatment received in this case is unknown.

between patients with ICC (25.8 months) and those with ECC (30.3 months) (P = 0.51). On univariate analysis, CA 19-9 levels (P < 0.01), CEA levels (P = 0.03), bilirubin levels (P < 0.01), albumin (P < 0.01), platelet count (P < 0.01), number of lesions (P < 0.01), tumour size (P = 0.03), lymph node involvement (P < 0.01), metastatic disease (P < 0.01) and overall tumour stage (P < 0.01) were predictors of survival (Table 2). On multivariate analysis, independent predictors of worse survival at the time of diagnosis included bilirubin level (HR 1.04; 95% CI 1.01–1.07), CA 19-9 levels >100 U/mL (HR 1.90; 95% CI 1.17–3.08) and overall stage of disease (HR 1.51; 95% CI 1.16–1.96) (Table 3).

Patients with a CA 19-9 level over 100 U/mL had a median survival of 18.2 months and a 3-year survival rate of 26%, which was significantly lower than the median survival of 42.9 months and a 3-year survival of 58% in patients with CA 19-9 levels <100 U/mL (P < 0.01; Figure 2). Higher bilirubin levels upon presentation were also significantly associated with worse survival (P = 0.02). Patient with a bilirubin level below 3 mg/dL had a median survival of 37.7 months and a three-year survival of 53%, compared with a median survival of 20.2 months and a 3-year survival of 29% in those with bilirubin levels >3 mg/dL (P < 0.01; Figure 2).

Exploratory multivariate analysis was performed to look for possible differences in prognostic factors between patients with ICC and those with ECC, although we had limited power for this post-hoc subset analysis. For patients with ICC, bilirubin (P < 0.01) and CA 19-9 (P = 0.04) remained significant predictors of survival, while overall stage of disease had a trend towards significance (P = 0.06). There were no other significant prognostic factors on multivariate analysis.

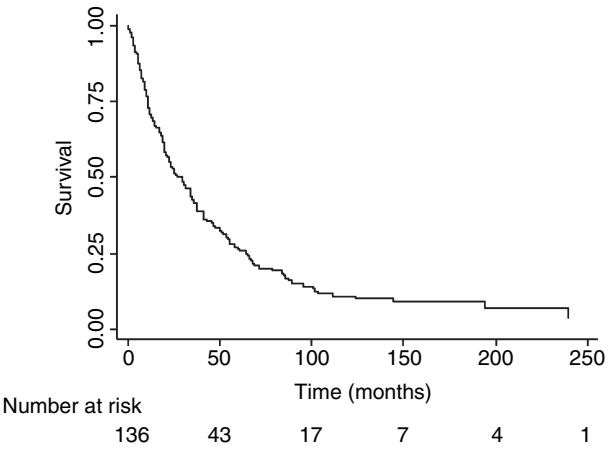


Figure 1. Overall survival of patients with cholangiocarcinoma. Patients with cholangiocarcinoma had a 71% 1-year survival and 42% 3-year survival. There was no difference in survival between patients with intrahepatic cholangiocarcinoma and those with extrahepatic cholangiocarcinoma.

For patients with ECC, stage of disease (P < 0.01) remained significant, while CA 19-9 (P = 0.07) and bilirubin (P = 0.07) had a trend towards significance. On multivariate analysis, age (HR 1.04, 95% CI 1.00–1.08, P = 0.04) and CEA (HR 1.01; 95% CI 1.00–1.02, P < 0.01) were also significant prognostic factors for ECC. No further prognostic factors were identified for patients with ICC.

Impact of surgical treatment

After adjusting for prognostic factors prior to their treatment, surgical resection was independently correlated with a decrease in mortality (HR 0.48; 95% CI

Table 3. Univariate and multivariate analysis of predictors of survival in patients with cholangiocarcinoma

	Univariate analysis			Multivariate analysis		
Variable	Hazard ratio	95% CI	Significance	Hazard Ratio	95% CI	Significance
Age	1.01	0.99–1.03	0.18			
Gender	0.95	0.66–1.36	0.77			
Race	0.51	0.71–1.43	0.98			
Lifetime alcohol history	1.67	0.42–1.01	0.06			
Lifetime smoking history	1.71	0.61–1.26	0.47			
Gallstones	0.73	0.89–1.88	0.18			
Underlying liver disease	0.73	0.77–2.15	0.33			
Diabetes	0.99	0.69–1.63	0.79			
CA 19-9 >100 U/mL	2.12	1.43–3.16	<0.001	1.90	1.17–3.08	.009
CEA >2 ng/mL	1.56	1.05–2.33	0.03			
Albumin	0.57	0.43–0.75	<0.001			
AST	1.00	1.00–1.00	0.49			
Total bilirubin	1.46	1.16–1.80	0.005	1.04	1.16–1.96	.015
Platelet count	1.00	1.00–1.00	0.009			
Number of lesions	1.69	1.21–2.35	0.002			
Tumour size >5 cm	1.50	1.04–2.17	0.03			
Lymph node involvement	1.64	1.13–2.38	0.009			
Vascular involvement	1.35	0.94–1.94	0.11			
Extrahepatic metastasis	2.92	1.87–4.57	<0.001			
Stage of disease	1.61	1.31–1.99	<0.001	1.51	1.16–1.96	.002
ECC vs. ICC	1.12	0.79–1.62	0.51			

AST, aspartate aminotransferase; CEA, carcinoembryonic antigen; ECC, extrahepatic cholangiocarcinoma; ICC, intrahepatic cholangiocarcinoma.

0.26–0.88). Patients who underwent surgical resection had a median survival of 65.6 months and a 3-year survival of 74%, compared with a median survival of 20.2 months and a 3-year survival of 29% in patients who received nonsurgical therapy (Figure 3). Adjuvant chemoradiation (n = 16) provided no additional survival benefit to surgical resection (HR 1.19; 95% CI 0.57–2.47). The prognostic significance of positive surgical margins was not examined given that only five of the 36 patients undergoing resection had positive margins. Patients receiving chemoradiation had a median survival of 29.3 months and a 36% 3-year survival. Patients receiving best supportive care only had a median survival of 9.3 months and a 3-year survival rate of 12.5%.

DISCUSSION

Our study of 136 consecutive patients is one of the largest contemporary CCA cohorts of patients reported in the US. Less than 20% of all CCA patients were diagnosed with stage I disease and nearly 65% had stage III or IV disease at presentation. Although patients with ICC had significantly larger tumours, there was no significant difference in the stage of disease between the two subgroups. The median survival of our cohort was 27.3 months, with similar survival in patients with ICC and those with ECC.

Only a few previous studies have evaluated survival in a large cohort contrasting ICC and ECC patients. Most published series have reported survival rates for select populations, such as post-operative patients, ICC alone or ECC alone. According to the SEER database, the five-year survival for ECC (15.1% in 1983–1987) is significantly better than that of ICC, which has consistently remained below 5%.[21] In our study, the median survival for patients with ECC was 30.3 months, which was not significantly different from the median survival of 25.8 months in patients with ICC. One possible explanation for the difference

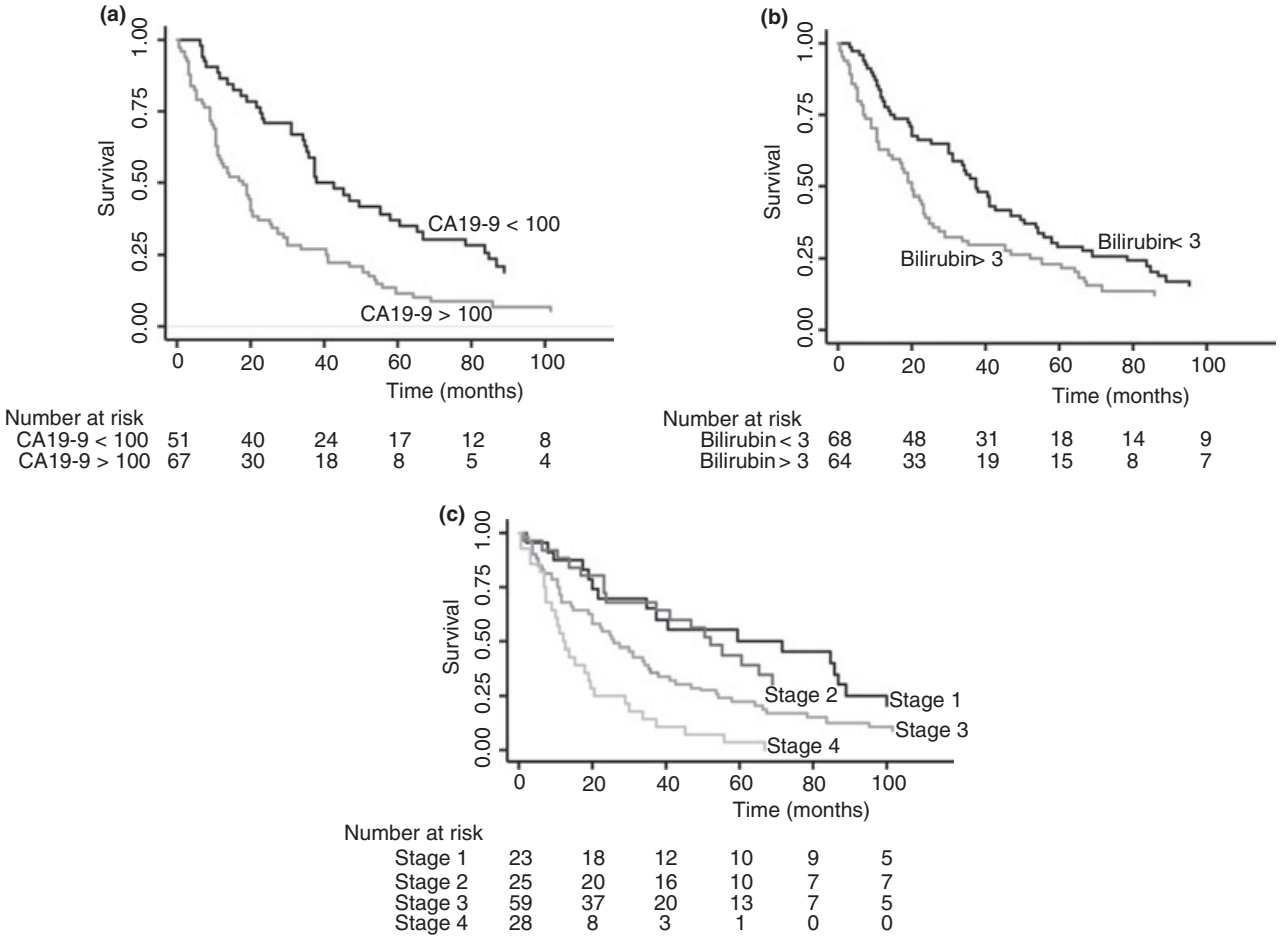
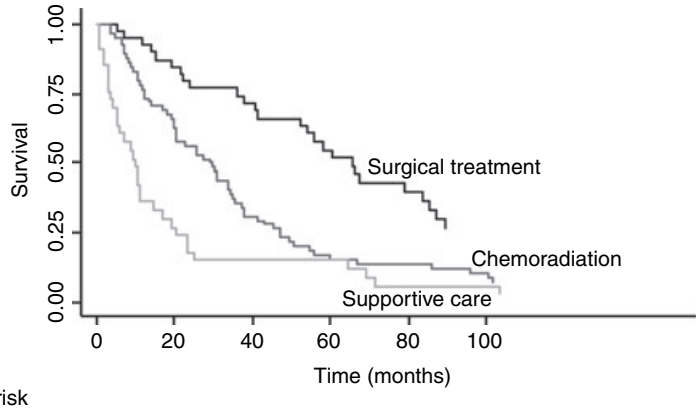


Figure 2. Overall survival in patients with cholangiocarcinoma according to independent predictors of survival at time of diagnosis. (a) Patients with CA 19-9 levels <100 U/mL had a significantly prolonged survival as compared to patients with CA 19-9 levels >100 U/mL. (b) Patients with bilirubin levels <3 mg/dL had significantly better survival compared to patients with bilirubin levels >3 mg/dL. (c) Stage of disease at presentation is an independent predictor of mortality.

between our results and that of the SEER database may be the misclassification of perihilar tumours as ICC in the SEER database.[7, 8] The correct classification of all CCA patients was one of the strengths of our study. Patients with perihilar tumours had a trend towards worse prognosis in our cohort, although this did not reach statistical significance. Given that a majority of ECC are perihilar tumours (75% in our cohort), this could have resulted in dramatic differences in survival data.

With a poor overall survival in CCA patients, few studies have identified prognostic factors at the time of initial presentation. Hyperbilirubinaemia, elevated CA 19-9, lymph node involvement and extrahepatic metastases are a few of the primary factors that have been previously correlated with poor survival.[14, 16–18, 22, 23] In our cohort, significant prognostic factors at presentation included hyperbilirubinaemia, elevated CA 19-9 levels and overall stage of disease. Patients with CA 19-9 levels >100 U/mL were nearly two times more likely to die than patients with lower CA19-9 levels (HR 1.9; 95% CI 1.17–3.08). Similarly, hyperbilirubinaemia on presentation was an important negative prognostic factor, with a decrease in survival by 4% for every 1 mg/dL increase in bilirubin. Although hyperbilirubinaemia was a poor prognostic factor in both ECC and ICC, the mechanism of hyperbilirubinaemia probably differs between the two groups. Patients with ECC have hyperbilirubinaemia caused by biliary obstruction, which may be relieved with biliary stent placement. In contrast, patients with ICC often have less evidence of biliary obstruction and may have hyperbilirubinaemia related



Number at risk						
Surgical treatment	39	33	26	19	12	8
Chemoradiation	64	41	20	10	9	7
Supportive care	33	9	5	5	2	2

Figure 3. Overall survival in patients with cholangiocarcinoma according to receipt of surgical therapy. Patients who underwent surgical resection had a significantly prolonged survival as compared with patients who received non-surgical therapy.

to underlying hepatic dysfunction. Patient age and CEA levels were also significant prognostic factors in patients with ECC, although this subset analysis was only exploratory in nature and these findings must be confirmed in a larger cohort of ECC patients.

We also confirmed that a more favourable outcome was seen in patients undergoing surgical resection than those receiving nonsurgical treatment options, including chemotherapy and/or radiation therapy. Surgical resection was independently correlated with improved survival even after adjustment for tumour stage on multivariate analysis. Previously reported 5-year survival rates after surgical resection have ranged from 20% to 43%.[10, 24] In our cohort, patients who underwent surgical therapy had a median survival of 65.6 months with a 3-year survival of 74% compared with patients undergoing best supportive care who only had a median survival of 9.3 months and a 12% 3-year survival rate. Although our analysis included current standard of care therapies, recent advances including liver transplantation for early stage tumours and palliative photodynamic therapy for late stage tumours may help improve survival in some patients.[25]

Although this is one of the largest cohorts of patients with CCA outside of the SEER database, we still had a limited number of patients with ICC and ECC, making sub-group analysis difficult and potentially underpowered. It is also important to note that this is a single, tertiary-care institution study, which can introduce a selection bias because of referral patterns and make the results less generalizable. A third limitation of this study is the diagnostic evaluation of patients, the type of imaging tests performed and the quality of the imaging varied among patients. This is particularly true for patients who were initially evaluated at another hospital and then referred to our institution for further care. We attempted to minimize this variability between patients in part by only analysing imaging studies that were interpreted by radiologists at our institution. Another limitation of our study is the retrospective design, which prevented analysis of all previously reported risk factors and prognostic factors. Additional concerns because of the retrospective design of our study include the accuracy of both tumour staging and clinical factors, such as quantification of alcohol and tobacco use by chart review. Finally, the retrospective nature of this study prevents full adjustment for all confounders. Although the stage of disease was adjusted when assessing the prognostic impact of surgical therapy, unmeasured confounders such as co-morbidities that may impact a patient's eligibility for surgery may have been present. Overall, we believe that the limitations of this study are outweighed by its notable strengths including the large size of our cohort, the correct classification of all CCA and diagnostic confirmation of CCA in nearly all cases.

In summary, the prognosis of CCA remains poor with an overall median survival around 27.3 months. A majority of patients present with tumours at an advanced stage of disease when effective therapies are currently not available. Survival is significantly better if CCA is diagnosed at an early stage when surgical resection is possible. Independent predictors of survival in our cohort included stage of disease upon presentation, CA 19-9 levels <100 U/mL, lower bilirubin levels and undergoing surgical therapy. There were no

significant differences between ICC and ECC regarding stage of disease at diagnosis, treatment options and overall survival.

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