JOURNAL OF HEPATOLOGY

Current epidemiology of cholangiocarcinoma in Western countries

Mathew Vithayathil, Shahid A. Khan*

Keywords: cholangiocarcinoma; intrahepatic; extrahepatic; age-standardised mortality.

Received 17 May 2022; received in revised form 9 July 2022; accepted 18 July 2022; available online 14 August 2022

Liver Unit, Division of Digestive Diseases, Imperial College London and Imperial College Healthcare NHS Trust, United Kingdom

* Corresponding author. Address: Division of Digestive Diseases, Imperial College London, London, United Kingdom. Tel: +44 (0)20 3312 6254.

E-mail address: shahid.khan@imperial.ac.uk (S.A. Khan).

https://doi.org/10.1016/j.jhep.2022.07.022

Summary

Cholangiocarcinomas are cancers arising from bile ducts, either found within the liver (intrahepatic) or outside the liver (extrahepatic). In Western countries, deaths due to intrahepatic cancers are rising at a higher rate than deaths due to extrahepatic cancers. This may be due to rising cases of liver disease and misclassification of the different cancer types.

Key point

Mortality rates for intrahepatic cholangiocarcinoma are greater than for extrahepatic cholangiocarcinoma for most Western countries, based on the current classification of cancers.

Epidemiology of cholangiocarcinoma

Cholangiocarcinoma (CCA) encompasses a rare group of primary neoplasms arising from the biliary tree.[1] CCAs have traditionally been classified as intrahepatic (iCCA) or extrahepatic (eCCA) based on their anatomical origin within the biliary tree. eCCAs can be further sub-classified into perihilar (pCCA) and distal (dCCA), based on their location relative to the cystic duct[2,3] (Fig. 1). iCCAs are the second most common cause of primary liver cancer, after hepatocellular carcinoma.[1,4] pCCAs account for up to 60% of all CCAs, with iCCAs accounting for less than 10% of primary biliary tree tumours.[5,6] iCCA and eCCA show distinct epidemiological, clinical, molecular and genetic characteristics.[7–10] Resection is the mainstay of curative treatment for both iCCA and eCCA, with anatomical location influencing the surgical techniques employed.[11] Locoregional and, in particular, systemic therapy play a significant role in both curative and palliative cohorts, with precision strategies based on DNA profiling increasingly utilised for both iCCA and eCCA.[12,13]

Previous studies have demonstrated the distinct, worldwide, epidemiological trends in iCCA and eCCA.[14–17] These distinct epidemiological profiles reflect specific risk factors, treatment options and previous misclassification of tumours.[4,7–9,18] Herein, we examine the most recent trends in iCCA and eCCA mortality in Western countries and review the key factors which may be underlying these trends.

Mortality data acquisition

Mortality data for males and females for iCCA and eCCA were obtained from the World Health Organisation (WHO) Mortality Database[19] using the International Classification of Disease 10th Revision (ICD-10) codes 22.1 and 24.0. Mortality data for males and females from individual countries were included for the years 2008, 2010, 2012, 2014, 2016 and 2018 where available. Western countries with consistent reporting of annual mortality rates were included: European Union (EU) (Austria, Belgium, Croatia, Czech Republic, Denmark, France, Germany, Hungary, Ireland, Italy, Latvia, Lithuania, Malta, Netherlands, Poland, Portugal, Romania, Slovakia, Spain and Sweden); Non-EU Europe (Norway, Switzerland, the UK); North America (Canada and the USA); and Oceania (Australia and New Zealand). Age-stratified population data (for age strata: 0-4, 5-9, 10-14, 15-19, 20-24, 25-29, 30-34, 35-39, 40-44, 45-49, 50-54, 55-59, 60-64, 65-69, 70-74, 75-79, 80-84, 85-89, 90-94, 95+) were obtained from the census data for Canada[20] and the USA,[21] and the WHO mortality database for all other countries.[19] The age-standardised mortality rate (ASMR) per 100,000 people was calculated for each year for individual countries using the WHO standard population.[22] Average annual percentage change (AAPC) was calculated for each country for iCCA and eCCA. iCCA:eCCA ratio was calculated for all countries for 2018 where available. For countries where 2018 mortality data were unavailable, 2016 mortality data were used.

Current trends in mortality

The annual male and female ASMRs for iCCA in individual Western countries between 2008 and 2018 are shown in Table 1. In Europe, the highest most recent mortality rates were seen in Malta, Ireland and Spain for males and Ireland, the UK and Switzerland for females, with Romania, Hungary and Poland reporting the lowest rates for both sexes. Canada and Australia had higher mortality rates in males and females compared to the USA and New Zealand, respectively. 53.8% of countries had male mortality rates greater than 1 in 100,000, which increased to 71.4% of countries in 2018. Similarly, the proportion of countries with female mortality rates greater than 1 in 100,000 increased from 26.9% to 66.7% between 2008 and 2018. 2018 mortality rates were greater than 2 in 100,000 in

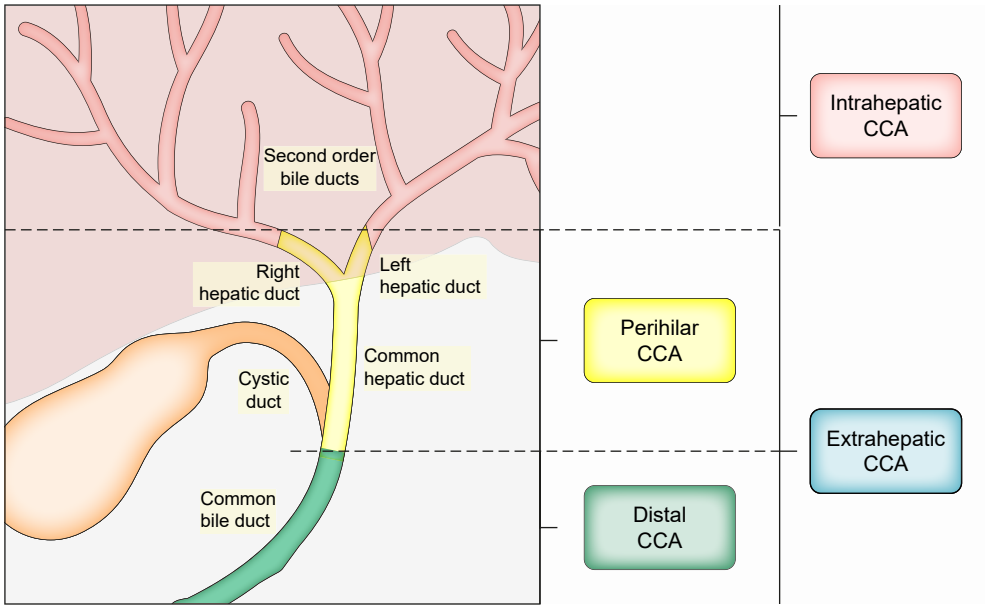

Fig. 1. Classification of cholangiocarcinoma based on anatomical location in the biliary tract. CCA, cholangiocarcinoma.

Ireland, Portugal, Spain, Australia, Canada, the UK and Belgium for males, and in Hungary for females. All Western countries showed an increase in iCCA mortality in males over the 10-year period with increasing mortality seen in females in all but 2 countries (Austria and New Zealand). The largest increases in AAPCs were observed in the Eastern European countries of Lithuania, Latvia and Poland for males and in Latvia, Lithuania and Slovakia for females.

ASMRs for males and females with eCCA in Western countries are shown in Table 2. In Europe, Hungary, Austria, Germany and Sweden had the highest most recent mortality rates for both sexes, with Malta, Ireland and the UK reporting the lowest rates. In contrast to iCCA, the USA reported higher mortality rates for eCCA than Canada, and New Zealand reported higher rates than Australia. Unlike iCCA, no countries had mortality rates for eCCA greater than 1 in 100,000 for either males or females in 2008, rising to only 14.2% and 4.8% of all countries in 2018 for males and females, respectively. No countries had mortality rates greater than 2 in 100,000. Regarding AAPCs, Norway, Spain and Hungary showed the highest positive increase in AAPCs in Europe. In contrast to iCCA, negative AAPCs were observed in several countries, including Denmark, Ireland, Italy, Netherlands, Portugal and the UK for males and Croatia, Denmark, Ireland, Italy, Latvia, Netherlands, Portugal, Slovakia and the UK for females. Canada and Australia showed negative AAPCs compared to positive AAPCs seen in the USA and New Zealand.

Mortality rates for 2018 for iCCA and eCCA in males and females are shown in Figs. 2 and 3, respectively. ASMRs were higher for iCCA compared to eCCA for all countries except Hungary (for both sexes) and Sweden (for females). iCCA:eCCA mortality ratios were greater than 10 for Australia, Ireland, the UK, Canada, Belgium, and Portugal for both sexes and for Spain for males and Norway for females.

Drivers of variation in mortality trends

Based on the most recent WHO mortality data, mortality rates were higher for iCCA than eCCA in the majority of Western countries, with higher ASMRs seen in males compared to females. There has been a general increase in iCCA-related mortality for both sexes over the last decade in all countries. In comparison, eCCA-related mortality increases were modest, with multiple countries showing a decrease in eCCA-related mortality.

Previous studies have demonstrated that mortality rates for iCCA are rising. Taylor-Robinson *et al.* first reported rising mortality rates in the UK.[16] The same authors observed decreasing rates of eCCA-related mortality. These trends have been observed globally in subsequent population studies.[14,15,17] Bertuccio *et al.* observed rising global mortality rates for iCCA between 1995 and 2016, with rates for eCCA remaining stable across the same time period,[17] in line with current trends. There are several drivers underlying the differing trends in iCCA and eCCA, including misclassification of CCAs, varying risk factors, early diagnosis and surveillance, and access to specialist care.

Misclassification and coding

The classification of CCAs has been subject to repeated change. Though the currently accepted subtype classification of CCA is iCCA, pCCA and

Key point

Mortality rates for intrahepatic cholangiocarcinoma are consistently rising across Western countries.

Table 1. Age-standardised (WHO World Standard population) mortality rates for intrahepatic cholangiocarcinoma (ICD-10 code 22.1) per 100,000 person-years for male and females from Western countries.

	Male							Female						
	2008	2010	2012	2014	2016	2018	AAPC %	2008	2010	2012	2014	2016	2018	AAPC %
Europe														
EU														
Austria	1.76	2.15	1.66	1.99	1.81	1.94	1.73	1.15	1.30	1.41	1.47	0.89	1.00	-0.09
Belgium	1.20	1.61	1.37	1.63	2.01	2.00	6.16	0.92	1.16	1.13	1.23	1.03	1.29	4.15
Croatia	1.23	1.20	1.52	1.11	1.29		1.69	0.57	0.40	0.68	1.10	0.67		7.71
Czech Republic	0.50	0.67	0.54	0.80	0.68	0.89	7.93	0.31	0.43	0.46	0.53	0.59	0.65	8.15
Denmark	0.48	0.74	0.80	1.37	1.01	1.01	10.85	0.46	0.96	0.91	1.12	1.02	1.15	13.10
France	1.62	1.82	2.02	2.06			4.26	1.04	1.10	1.19	1.20			2.49
Germany	1.27	1.38	1.26	1.39	1.47	1.51	1.85	0.91	1.02	0.94	0.87	1.02	1.16	2.79
Hungary	0.34	0.26	0.59	0.60	0.67	0.53	9.61	0.20	0.29	0.24	0.47	0.42	0.44	11.43
Ireland	1.93		1.84			2.67	4.02	1.62		1.74			2.66	6.05
Italy	0.89	1.06	1.20	1.20	1.32		5.26	0.68	0.68	0.84	0.83	0.88		3.64
Latvia	0.26	0.51	0.86	1.11	1.15	0.98	18.14	0.06	0.34	0.70	0.52	0.48	1.01	64.69
Lithuania	0.36	0.65	0.98	0.68	1.68	1.53	23.74	0.24	0.51	0.85	0.74	1.15	0.80	18.87
Malta	2.17	2.57	1.89	2.32	3.87		10.17	0.65	0.38	1.29	1.04	0.48		15.18
Netherlands	0.65	0.89	1.24	1.23	1.55	1.24	8.23	0.58	0.65	0.92	1.00	1.25	1.31	9.13
Poland	0.09	0.14	0.22	0.26	0.32	0.34	16.01	0.11	0.13	0.17	0.19	0.19	0.26	9.59
Portugal	0.94	1.40	1.38	2.08	2.40	2.58	12.19	0.60	0.87	0.70	1.12	1.27	1.20	9.24
Romania	0.28	0.39	0.49	0.46	0.57	0.67	10.12	0.17	0.19	0.26	0.31	0.38	0.45	10.88
Slovakia		0.52	0.71	1.04	0.87	0.86	8.31		0.33	0.28	0.55	0.59	0.91	17.66
Spain	1.53	1.79	1.99	2.04		2.40	4.86	1.02	1.13	1.14	1.21		1.31	2.58
Sweden	0.58	0.68	0.75	0.98	0.84	1.11	7.70	0.45	0.64	0.79	0.70	0.63	0.71	5.59
Non-EU														
UK	1.41	1.51	1.73	1.87	1.93	2.03	3.83	1.30	1.44	1.67	1.73	1.86	1.91	4.05
Norway	0.86	1.01	1.19	1.36	1.57		8.10	0.94	1.00	1.29	1.01	1.13		3.22
Switzerland	1.50	1.37	1.38		1.62	1.58	5.17	0.99	1.06	1.25		1.04	1.44	6.78
North America														
Canada	1.36	1.43	1.75	1.79	1.87	2.05	4.41	1.02	1.20	1.45	1.56	1.61	1.66	5.25
USA	1.06	1.12	1.20	1.26	1.37	1.48	3.44	0.77	0.88	0.97	0.97	1.10	1.17	4.34
Oceania														
Australia	1.53	1.76	1.71	1.97	2.13	2.20	3.86	1.25	1.25	1.50	1.67	1.66	1.76	3.66
New Zealand	1.11	1.03	1.10		1.36		2.96	0.86	0.95	1.24		0.55		-1.75

AAPC, average annual percentage change.

dCCA,[23,24] pCCAs currently do not have a separate ICD-10 code. pCCAs account for up to 60% of all CCAs,[5,6] and misclassification of these malignancies has been demonstrated to greatly influence the accuracy of reported iCCA and eCCA mortality rates. The second edition International Classification of Diseases for Oncology (ICD-O-2) previously assigned pCCA a histological code assigned to the iCCA rather than the eCCA grouping.[25] Though the more recent third edition (ICD-O-3) established in 2013[26] allows assignment of pCCA to either iCCA or eCCA, different countries adopt classifications at different time points.[27] A retrospective review of the US Surveillance, Epidemiology and End Results (SEER) database demonstrated that a change from the ICD-O-2 classification of pCCAs to the ICD-O-3 classification resulted in a decreasing trend in iCCA and an increasing trend in eCCA incidence.[27] ICD-O-2 classifications from the SEER database resulted in 91% of pCCAs being incorrectly classified as iCCAs, leading to a 13% overestimation of iCCA incidence and a 15% underestimation of eCCA incidence.[4] The impact of misclassification on our epidemiological understanding of CCAs has been demonstrated in further studies,[18,28,29] and the rising iCCA and declining eCCA mortality rates in the West may be reflective of this misclassification.

In a recent study from the UK, original clinical notes of cases coded as hepatobiliary carcinoma using WHO ICD-10 criteria (C22.1/Intrahepatic Bile Duct carcinoma, C24.0/Extrahepatic Bile Duct carcinoma, C23X/Malignant Neoplasm Gall Bladder, C22.0/Malignant Neoplasm Liver Cell Carcinoma) at 3 independent UK regional hepatopancreatobiliary centres over a 2-year period were reviewed by independent clinicians.[18] The agreed final diagnosis was compared to the originally allocated ICD-10 code. Of all the cases originally coded as C22.1/iCCA, only 43% were deemed to be true iCCA and thus coded correctly, while 34% cases were actually pCCA. Furthermore, 92% all pCCA cases were incorrectly coded as iCCA.[18] Given all countries use the same coding system with its inherent errors, and show similar trends, this systemic error may well be occurring on a large scale. Future epidemiological studies where more accurate classifications are adopted universally may highlight different trends in CCA subtypes. It is also

Table 2. Age-standardised (WHO World Standard population) mortality rates for extrahepatic cholangiocarcinoma (ICD-10 code 24.0) per 100,000 person-years for male and females from Western countries.

	Male							Female						
	2008	2010	2012	2014	2016	2018	AAPC %	2008	2010	2012	2014	2016	2018	AAPC %
Europe														
EU														
Austria	0.84	0.90	0.74	0.73	1.03	1.21	4.64	0.67	0.61	0.56	0.66	0.75	0.67	0.45
Belgium	0.08	0.18	0.14	0.12	0.15	0.10	9.09	0.05	0.11	0.06	0.07	0.04	0.08	13.78
Croatia	0.40	0.57	0.74	0.77	0.75		9.07	0.49	0.51	0.48	0.48	0.44		-1.22
Czech Republic	0.44	0.64	0.41	0.76	0.60	0.63	8.08	0.47	0.53	0.28	0.45	0.41	0.45	2.63
Denmark	0.21	0.18	0.14	0.09	0.16	0.11	-2.74	0.35	0.31	0.35	0.13	0.23	0.18	-0.72
France	0.08	0.08	0.07	0.09			1.79	0.05	0.06	0.05	0.06			4.53
Germany	0.46	0.59	0.79	1.00	1.01	1.15	10.44	0.34	0.46	0.65	0.74	0.78	0.78	9.39
Hungary	0.30	0.34	0.42	1.61	1.69	1.77	32.96	0.31	0.31	0.32	1.09	1.13	1.24	25.92
Ireland	0.15		0.16			0.07	-4.27	0.19		0.21			0.03	-7.54
Italy	0.30	0.28	0.22	0.22	0.22		-3.64	0.17	0.19	0.14	0.14	0.13		-2.33
Latvia	0.61	0.14	0.47	0.58	0.55	0.20	10.98	0.34	0.33	0.22	0.40	0.22	0.16	-2.83
Lithuania	0.40	0.16	0.35	0.42	0.23	0.42	11.52	0.30	0.24	0.30	0.12	0.16	0.20	0.45
Malta	0.32	0.60	0.26				7.71							
Netherlands	0.50	0.37	0.44	0.59	0.38	0.34	-2.03	0.42	0.33	0.33	0.46	0.43	0.32	-1.49
Poland	0.15	0.14	0.20	0.16	0.13	0.15	1.13	0.13	0.15	0.14	0.13	0.11	0.13	0.57
Portugal	0.76	0.49	0.69	0.10	0.15	0.16	-2.21	0.45	0.44	0.29	0.12	0.10	0.09	-12.52
Romania	0.35	0.38	0.38	0.38	0.38	0.39	0.92	0.17	0.28	0.23	0.26	0.31	0.21	4.32
Slovakia		0.24	0.27	0.36	0.57	0.48	10.96		0.32	0.32	0.33	0.26	0.29	-0.94
Spain	0.05	0.07	0.07	0.21	0.22	0.16	21.86	0.04	0.03	0.04	0.10		0.14	26.15
Sweden	0.66	0.46	0.67	0.80	0.83	0.81	3.49	0.83	0.80	0.66	0.73	0.85	0.81	0.21
Non-EU														
UK	0.06	0.07	0.08	0.05	0.07	0.05	-0.75	0.04	0.05	0.03	0.04	0.04	0.04	-0.60
Norway	0.08	0.14	0.03	0.08	0.16		32.02	0.08	0.11	0.02	0.07	0.09		27.39
Switzerland	0.33	0.31	0.49		0.37	0.43	0.82	0.22	0.35	0.35		0.28	0.38	2.87
North America														
Canada	0.09	0.08	0.09	0.08	0.09	0.07	-1.63	0.11	0.09	0.07	0.06	0.06	0.07	-3.52
USA	0.14	0.14	0.13	0.14	0.16	0.18	2.65	0.11	0.09	0.09	0.10	0.12	0.14	2.83
Oceania														
Australia	0.12	0.12	0.09	0.04	0.04	0.04	-7.04	0.09	0.12	0.08	0.03	0.05	0.01	-5.86
New Zealand	0.33	0.31	0.21		0.34		3.02	0.21	0.16	0.09		0.18		4.64

AAPC, average annual percentage change.

important to encourage adoption of the next version of ICD (ICD-11) which will, for the first time, have a unique code for pCCA.

Risk factors and mutational biology

Though misclassification of CCAs may account for some of the divergence of iCCA and eCCA mortality trends, the underlying aetiology and risk factors for the different subtypes could be contributory. iCCA and eCCA have common and differing risk factors. Liver flukes are an established risk factor for both iCCA and eCCA in Eastern Asia.[30] Primary sclerosing cholangitis (PSC) is a strong risk factor for both iCCA and eCCA and affected patients represent a high-risk cohort.[7] In Western countries, risk factors associated with chronic liver disease including viral hepatitis, alcohol consumption and non-alcoholic fatty liver disease are all associated with iCCA but not eCCA.[31] In contrast, biliary diseases (including gallstone disease) are more strongly associated with eCCA.[7,32] The rising trend in iCCA-related mortality could be reflective of increasing rates of chronic liver disease, in particular non-alcoholic fatty liver disease and alcohol-related liver disease.[33] By contrast, the increasing application of biliary interventions, such as cholecystectomy for gallstone disease,[34–36] may be leading to a reduction in the risk of eCCA.

Though there are established risk factors for CCA, the majority of cases are sporadic, with no identified cause. Though some genetic polymorphisms have been linked to CCA, no genome-wide association studies have been conducted.[37] Carcinogenesis is mediated by the interaction between multiple cellular processes, involving pro-inflammatory cytokines, bile acids, aberrant activation of cell signalling receptors and increased cell proliferation.[37,38] Though activation of pathways such as *RAS-MAPK* are common to CCA subtypes, there is heterogeneity in other signalling protein expression. In iCCA, identification of aberrant expression of key proteins (including IDH [isocitrate dehydrogenase] and FGFR2 [fibroblast growth factor receptor 2]) has led to the development of novel targeted therapies.[38] Conversely, pCCA and dCCA demonstrate higher frequencies of mutations in *KRAS*, *TP53* and *ELF3* mutations.[37] This variation in underlying mutational biology may contribute to the disparity in mortality trends between subtypes. Further understanding of these

Key point

Mortality rates for extrahepatic cholangiocarcinoma show a more modest rise compared to intrahepatic cholangiocarcinoma, with a decrease observed in many Western countries.

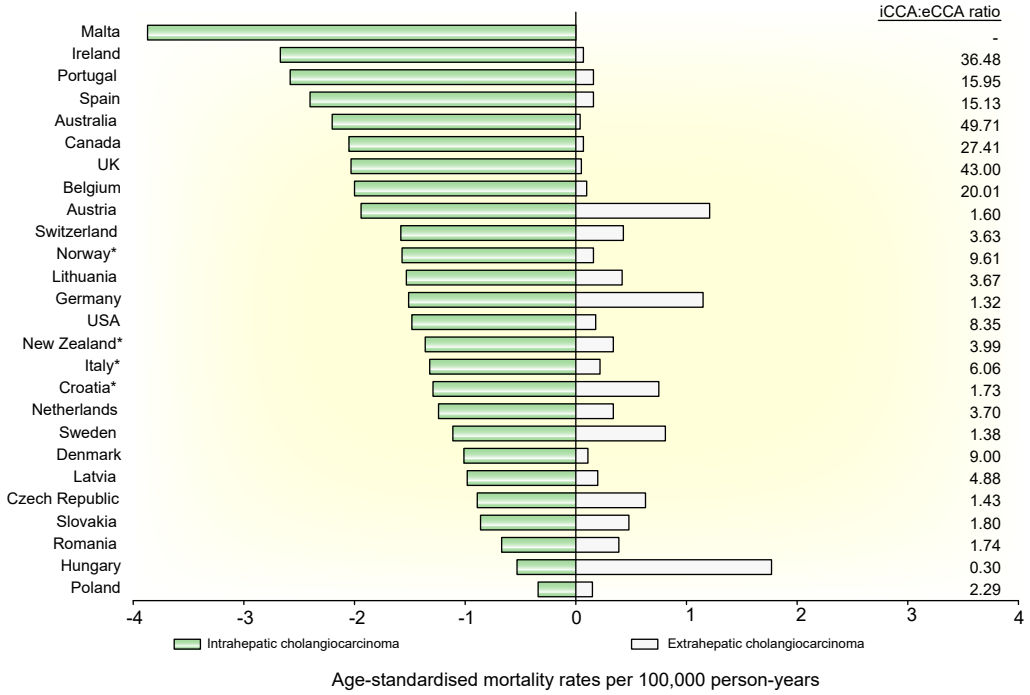

Fig. 2. Age-standardised mortality rates for intrahepatic and extrahepatic cholangiocarcinoma per 100,000 person-years for males from Western countries for 2018.* *2016 Age-standardised mortality rates reported for Croatia, Italy, Norway and New Zealand.

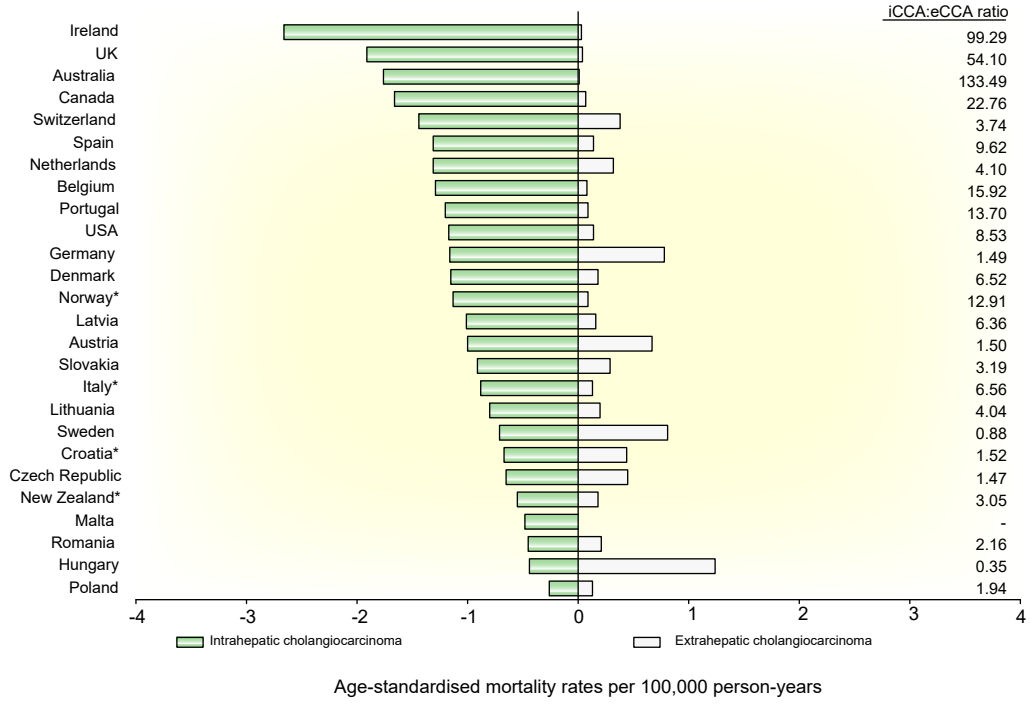

Fig. 3. Age-standardised mortality rates for intrahepatic and extrahepatic cholangiocarcinoma per 100,000 person-years for females from Western countries for 2018.* *2016 Age-standardised mortality rates reported for Croatia, Italy, Norway and New Zealand.

pathways and identification of actionable mutations will help to guide the development of targeted therapies with the potential to improve patient survival.

Early diagnosis and surveillance

CCAs are mainly asymptomatic, with diagnosis usually made at more advanced stages. Less than one-third of cases have single lesions less than 3 cm at diagnosis, with regional lymph node invasion present in almost half of patients and distant metastases present in a quarter.[39] As a consequence, curative resection is possible in less than 30% of patients.[40] Early diagnosis is important for early intervention and improving patient survival. pCCAs and dCCAs appear to be detected at earlier stages, while patients with iCCA tend to present with multiple, larger and more poorly differentiated lesions at diagnosis.[39] This is due to extrahepatic lesions causing biliary obstruction and hence earlier clinical presentation compared to iCCAs. This earlier clinical presentation may contribute to the divergent trends in mortality rates between iCCA and eCCA subtypes; efforts to increase the rates of early detection could lead to significant survival improvements.

PSC is an autoimmune disorder characterised by inflammation and stricturing of intra- and extrahepatic bile ducts.[41] The underlying mechanisms behind PSC remain poorly understood and there are currently no effective disease-modifying therapies. Patients with PSC are at high risk (up to 600-fold greater than the general population) of developing CCA.[42] Data from the US SEER database demonstrated autoimmune cholangitis was associated with a significantly increased risk of both iCCA (odds ratio [OR] 21.52; 95% CI 7.21-26.90) and eCCA (OR 40.80; 95% CI 34.96-47.60).[7] Data on 2,234 patients with CCA from 11 countries in the European Network for the Study of Cholangiocarcinoma demonstrate that PSC is more strongly associated with pCCA than with iCCA or eCCA, based on the current classification systems.[39]

Given the elevated risk of CCA in patients with PSC, surveillance has been advocated in this cohort. However, there is a paucity of studies demonstrating the effectiveness of biomarker- and imaging-based surveillance in reducing CCA-related mortality. However, 3 retrospective studies provide evidence for the potential survival benefit of CCA imaging surveillance in PSC.[43–45] A study of 830 patients with PSC from the Mayo Clinic reported that patients who underwent imaging surveillance had significantly increased overall survival if diagnosed with CCA compared to those in whom surveillance was not performed (hazard ratio 0.22, 95% CI 0.12-0.41; p <0.001).[44] Similarly, yearly imaging was associated with a 2-fold reduction in hepatopancreatobiliary cancers in patients with PSC and concurrent inflammatory bowel disease.[45] Bergquist *et al.* assessed the effects of imaging surveillance strategies in 27 centres from 12 Western countries.[43] The authors found scheduled imaging surveillance was associated with a lower risk of overall mortality (hazard ratio 0.61; 95% CI 0.47-0.80) and improved survival after CCA diagnosis compared to no scheduled imaging. Though these studies are suggestive of regular surveillance improving CCA outcomes, due to the retrospective design they are limited by selection bias, lead-time bias and the potential for confounder factors. Serum biomarkers carcinoembryonic antigen and carbohydrate antigen 19-9 (CA19-9) are associated with CCAs.[46] However, the clinical performance of these biomarkers for detecting early CCA is inconsistent, with the sensitivity of CA19-9 varying between 68%-97%[47–50] and that of carcinoembryonic antigen between 63.3-68.6%.[49,51] However, these markers are also elevated in other diseases, including biliary obstruction and acute cholangitis,[52,53] and like imaging-based strategies there is limited prospective evidence demonstrating their role in surveillance in patients with PSC. There is a need for high-quality prospective randomised studies to assess both the clinical and economic effectiveness of different surveillance strategies. However, given patients with PSC often require imaging due to cholestasis and infection during their natural disease course, conducting any potential prospective longitudinal studies is challenging.

Due to the lack of robust prospective evidence, currently there is no internationally agreed standard for screening for CCA. According to the recommendations of the American College of Gastroenterology, clinicians can consider screening for CCA with regular cross-sectional imaging (ultrasound or MRI) with serial CA19-9 every 6-12 months.[54] Both the American Association for the Study of Liver Diseases[55] and the European Association for the Study of Liver[56] guidelines state there is insufficient evidence to formally recommend regular biochemical or radiological screening, but that it should be used if there is a clinical deterioration in patients with PSC. This lack of consensus guidance means there is a wide variation in surveillance strategies in clinical practice. A retrospective study including 2,975 patients with PSC from 10 European countries, the USA and Canada showed there was a wide variation of surveillance strategies adopted within centres both within the same and across different countries.[43] There was further variation in the choice of surveillance, with ultrasound, MRI, CA19-9 and endoscopic retrograde cholangiopancreatography all being employed based on local centre protocols. This lack of standardisation in surveillance could potentially contribute to the variation of CCA trends in different countries; more in-depth studies looking at national surveillance strategies are needed.

Key point

Inaccurate coding, the misclassification of perihilar cholangiocarcinoma, subtype-specific risk factors and variations in national surveillance and cancer treatment may contribute to the divergence in observed mortality rates.

Key point

Future epidemiological studies where more accurate classifications are adopted universally may highlight different trends in cholangiocarcinoma subtypes.

Access to specialist care

There are multiple treatment strategies available for CCAs dependent on cancer stage. For localised disease, curative resection is the gold standard for iCCA and eCCA. For iCCA lesions, hepatectomy with neoadjuvant chemotherapy is associated with improved survival,[57] whilst pCCA and dCCA may require more extensive hepatopancreatobiliary resection.[58,59] Promising outcomes have been achieved with liver transplantation in patients with pCCA[60,61] or iCCA[62] and localised disease, but its application is limited by organ availability. As mentioned, curative resection is possible in less than 30% of patients,[40] hence, non-curative management with biliary intervention and medical pharmacotherapy is the mainstay of treatment. Combination systemic chemotherapy with cisplatin and gemcitabine is associated with improved survival in patients with unresectable disease.[39,63] The advent of DNA profiling has identified targetable somatic mutations and the development of precision-based cancer pharmacotherapy, such as the FDA-approved fibroblast growth factor receptor antagonist pemigatinib for unresectable iCCA.[12,64] Furthermore, the advent and efficacy of immunotherapy in multiple cancer types has spurred clinical interest in CCA.[65]

These different treatment modalities are delivered by highly specialised secondary and tertiary care centres. Treatment in specialist high-volume centres is associated with improved survival in general cancer care.[66,67] These findings are replicated in CCA: surgical resection in academic centres is associated with significantly increased overall survival and R0 resection margins[68,69]; furthermore, non-curative chemotherapy for patients with CCA is associated with increased overall survival when delivered in referral centres.[70] There is large intra- and inter-country variation in access to specialist cancer services, which is influenced by public policies and national health systems.[71] This inequality in access may partly account for the variation in CCA mortality rates observed between countries, and focused studies at the local and national levels are needed to examine the magnitude of this effect.

Conclusion

iCCA-related mortality has increased consistently across Western countries over the last decade. Mortality rates for eCCA have increased more slowly. These differences may reflect the different genetic and environmental drivers of the cancer subtypes, as well as variations in disease surveillance, early diagnosis and management in different countries. Further epidemiological studies looking at regional variations within countries and more accurate coding and sub-classification of CCAs are crucial to monitor and better understand the underlying factors driving mortality trends over time.

Abbreviations

AAPC, average annual percentage change; ASMR, age-standardised mortality rate; CCA, cholangiocarcinoma; eCCA, extrahepatic cholangiocarcinoma; iCCA, intrahepatic cholangiocarcinoma; ICD, International Classification of Disease; ICD-O, International Classification of Diseases for Oncology; PSC, primary sclerosing cholangitis; SEER, Surveillance, Epidemiology and End Results; WHO, World Health Organisation.

Financial support

No financial support was given for completion of the manuscript.

Conflict of interest

The authors have no conflicts of interests or disclosures.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

SK and MV conceived the article structure, drafted the manuscript and reviewed and approved the final version of the manuscript.

Data availability statement

All data is available upon request from the corresponding author.

Acknowledgments

We are grateful for support from the UK National Institutes for Health Research (NIHR) Biomedical Facilities at Imperial College London.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2022.07.022.

References

[1] Khan SA, Tavolari S, Brandi G. Cholangiocarcinoma: epidemiology and risk factors. Liver Int 2019;39:19–31. https://doi.org/10.1111/liv.14095.

[2] Blechacz B, Komuta M, Roskams T, Gores GJ. Clinical diagnosis and staging of cholangiocarcinoma. Nat Rev Gastroenterol Hepatol 2011;8:512–522. https://doi.org/10.1038/nrgastro.2011.131.

[3] Rizvi S, Gores GJ. Pathogenesis, diagnosis, and management of cholangiocarcinoma. Gastroenterology 2013;145:1215–1229. https://doi.org/10.1053/j.gastro.2013.10.013.

[4] Welzel TM, McGlynn KA, Hsing AW, O'Brien TR, Pfeiffer RM. Impact of classification of hilar cholangiocarcinomas (Klatskin tumors) on the incidence of intra- and extrahepatic cholangiocarcinoma in the United States. J Natl Cancer Inst 2006;98:873–875. https://doi.org/10.1093/jnci/djj234.

[5] Nakeeb A, Pitt HA, Sohn TA, Coleman J, Abrams RA, Piantadosi S, et al. Cholangiocarcinoma. A spectrum of intrahepatic, perihilar, and distal tumors. Ann Surg 1996;224:463–473. https://doi.org/10.1097/00000658-199610000-00005. ; discussion 473-5.
[6] DeOliveira ML, Cunningham SC, Cameron JL, Kamangar F, Winter JM, Lillemoe KD, et al. Cholangiocarcinoma: thirty-one-year experience with 564 patients at a single institution. Ann Surg 2007;245:755–762. https://doi.org/10.1097/01.sla.0000251366.62632.d3.
[7] Petrick JL, Yang B, Altekruse SF, Van Dyke AL, Koshiol J, Graubard BI, et al. Risk factors for intrahepatic and extrahepatic cholangiocarcinoma in the United States: a population-based study in SEER-Medicare. PLoS One 2017;12:e0186643. https://doi.org/10.1371/journal.pone.0186643.
[8] Tyson GL, El-Serag HB. Risk factors for cholangiocarcinoma. Hepatology 2011;54:173–184. https://doi.org/10.1002/hep.24351.
[9] Cardinale V, Semeraro R, Torrice A, Gatto M, Napoli C, Bragazzi MC, et al. Intra-hepatic and extra-hepatic cholangiocarcinoma: new insight into epidemiology and risk factors. World J Gastrointest Oncol 2010;2:407–416. https://doi.org/10.4251/wjgo.v2.i11.407.
[10] Vij M, Puri Y, Rammohan A, Gowripriya G, Rajalingam R, Kaliamoorthy I, et al. Pathological, molecular, and clinical characteristics of cholangiocarcinoma: a comprehensive review. World J Gastrointest Oncol 2022;14:607–627. https://doi.org/10.4251/wjgo.v14.i3.607.
[11] Sano T, Shimizu Y, Senda Y, Kinoshita T, Nimura Y. Assessing resectability in cholangiocarcinoma. Hepatic Oncol 2014;1:39–51. https://doi.org/10.2217/hep.13.6.
[12] Vithayathil M, Bridegwater J, Khan SA. Medical therapies for intra-hepatic cholangiocarcinoma. J Hepatol 2021;75:981–983. https://doi.org/10.1016/J.JHEP.2021.04.004.
[13] Manne A, Woods E, Tsung A, Mittra A. Biliary tract cancers: treatment updates and future directions in the era of precision medicine and immuno-oncology. Front Oncol 2021;11:768009. https://doi.org/10.3389/fonc.2021.768009.
[14] Patel T. Worldwide trends in mortality from biliary tract malignancies. BMC Cancer 2002;2:10. https://doi.org/10.1186/1471-2407-2-10.
[15] Khan SA, Taylor-Robinson SD, Toledano MB, Beck A, Elliott P, Thomas HC. Changing international trends in mortality rates for liver, biliary and pancreatic tumours. J Hepatol 2002;37:806–813. https://doi.org/10.1016/s0168-8278(02)00297-0.
[16] Taylor-Robinson SD, Toledano MB, Arora S, Keegan TJ, Hargreaves S, Beck A, et al. Increase in mortality rates from intrahepatic cholangiocarcinoma in England and Wales 1968-1998. Gut 2001;48:816–820. https://doi.org/10.1136/gut.48.6.816.
[17] Bertuccio P, Malvezzi M, Carioli G, Hashim D, Boffetta P, El-Serag HB, et al. Global trends in mortality from intrahepatic and extrahepatic cholangiocarcinoma. J Hepatol 2019;71:104–114. https://doi.org/10.1016/j.jhep.2019.03.013.
[18] Selvadurai S, Mann K, Mithra S, Bridgewater J, Malik H, Khan SA. Cholangiocarcinoma miscoding in hepatobiliary centres. Eur J Surg Oncol 2021;47:635–639. https://doi.org/10.1016/j.ejso.2020.09.039.
[19] WHO. World Health Organization (WHO). Mortality Database Health statistics and information systems. 2019. https://www.who.int/healthinfo/statistics/mortality_rawdata/en/. [Accessed 2 March 2022].
[20] Canada S. Census of Population n.d. https://www12.statcan.gc.ca/census-recensement/index-eng.cfm?MM=1 (accessed March 22, 2022).
[21] Bureau USC. U.S. Census Bureau, Current Population Survey, Annual Social and Economic Supplement n.d. https://www.census.gov/data/datasets/time-series/demo/cps/cps-asec.html (accessed March 22, 2022).
[22] Ahmad OB, Boschi-pinto C, Lopez AD. Age standardization of rates: a new WHO standard. GPE Discuss Pap Ser 2001.
[23] Banales JM, Cardinale V, Carpino G, Marzioni M, Andersen JB, Invernizzi P, et al. Expert consensus document: cholangiocarcinoma: current knowledge and future perspectives consensus statement from the European Network for the Study of Cholangiocarcinoma (ENS-CCA). Nat Rev Gastroenterol Hepatol 2016;13:261–280. https://doi.org/10.1038/nrgastro.2016.51.
[24] Bridgewater J, Galle PR, Khan SA, Llovet JM, Park J-W, Patel T, et al. Guidelines for the diagnosis and management of intrahepatic cholangiocarcinoma. J Hepatol 2014;60:1268–1289. https://doi.org/10.1016/j.jhep.2014.01.021.
[25] World Health Organization. International classification of diseases for oncology. Second edition 1990.
[26] Organization WH. International classification of diseases for oncology. Third Edition 2013.
[27] Khan SA, Emadossadaty S, Ladep NG, Thomas HC, Elliott P, Taylor-Robinson SD, et al. Rising trends in cholangiocarcinoma: is the ICD classification system misleading us? J Hepatol 2012;56:848–854. https://doi.org/10.1016/j.jhep.2011.11.015.
[28] Tyson GL, Ilyas JA, Duan Z, Green LK, Younes M, El-Serag HB, et al. Secular trends in the incidence of cholangiocarcinoma in the USA and the impact of misclassification. Dig Dis Sci 2014;59:3103–3110. https://doi.org/10.1007/s10620-014-3276-2.
[29] Walter D, Ferstl P, Waidmann O, Trojan J, Hartmann S, Schnitzbauer AA, et al. Cholangiocarcinoma in Germany: epidemiologic trends and impact of misclassification. Liver Int 2019;39:316–323. https://doi.org/10.1111/liv.13954.
[30] Sripa B, Kaewkes S, Sithithaworn P, Mairiang E, Laha T, Smout M, et al. Liver fluke induces cholangiocarcinoma. PLoS Med 2007;4:e201. https://doi.org/10.1371/journal.pmed.0040201.
31 El-Serag HB, Engels EA, Landgren O, Chiao E, Henderson L, Amaratunge HC, et al. Risk of hepatobiliary and pancreatic cancers after hepatitis C virus infection: a population-based study of U.S. veterans. Hepatology 2009;49:116–123. https://doi.org/10.1002/hep.22606.
32 Schottenfeld D, Beebe-Dimmer J. Chronic inflammation: a common and important factor in the pathogenesis of neoplasia. CA Cancer J Clin n.d.;56:69–83. https://doi.org/10.3322/canjclin.56.2.69.
33 Pimpin L, Cortez-Pinto H, Negro F, Corbould E, Lazarus JV, Webber L, et al. Burden of liver disease in Europe: epidemiology and analysis of risk factors to identify prevention policies. J Hepatol 2018;69:718–735. https://doi.org/10.1016/j.jhep.2018.05.011.
34 Bray F, Balcaen T, Baro E, Gandon A, Ficheur G, Chazard E. Increased incidence of cholecystectomy related to gallbladder disease in France: analysis of 807,307 cholecystectomy procedures over a period of seven years. J Visc Surg 2019;156:209–215. https://doi.org/10.1016/j.jviscsurg.2018.12.003.
35 Lunevicius R, Nzenwa IC, Mesri M. A nationwide analysis of gallbladder surgery in England between 2000 and 2019. Surgery 2022;171:276–284. https://doi.org/10.1016/j.surg.2021.10.025.
36 Mollah T, Christie H, Chia M, Modak P, Joshi K, Soni T, et al. Gallbladder-associated hospital admission and cholecystectomy rates across Australia and Aotearoa New Zealand (2004-2019): are we over-intervening? Ann Hepato-Biliary-Pancreatic Surg 2022. https://doi.org/10.14701/ahbps.22-007.
37 Banales JM, Marin JJG, Lamarca A, Rodrigues PM, Khan SA, Roberts LR, et al. Cholangiocarcinoma 2020: the next horizon in mechanisms and management. Nat Rev Gastroenterol Hepatol 2020. https://doi.org/10.1038/s41575-020-0310-z.
38 Vithayathil M, Bridegwater J, Khan SA. Medical therapies for intra-hepatic cholangiocarcinoma. J Hepatol 2021;75:981–983. https://doi.org/10.1016/j.jhep.2021.04.004.
39 Izquierdo-Sanchez L, Lamarca A, La Casta A, Buettner S, Utpatel K, Klümpen H-J, et al. Cholangiocarcinoma landscape in Europe: diagnostic, prognostic and therapeutic insights from the ENSCCA Registry. J Hepatol 2022;76:1109–1121. https://doi.org/10.1016/j.jhep.2021.12.010.
40 van Vugt JLA, Gaspersz MP, Coelen RJS, Vugts J, Labeur TA, de Jonge J, et al. The prognostic value of portal vein and hepatic artery involvement in patients with perihilar cholangiocarcinoma. HPB (Oxford) 2018;20:83–92. https://doi.org/10.1016/j.hpb.2017.08.025.
41 Karlsen TH, Folseraas T, Thorburn D, Vesterhus M. Primary sclerosing cholangitis - a comprehensive review. J Hepatol 2017;67:1298–1323. https://doi.org/10.1016/j.jhep.2017.07.022.
42 Bergquist A, Ekbom A, Olsson R, Kornfeldt D, Lööf L, Danielsson A, et al. Hepatic and extrahepatic malignancies in primary sclerosing cholangitis. J Hepatol 2002;36:321–327. https://doi.org/10.1016/s0168-8278(01)00288-4.
43 Bergquist A, Weismüller TJ, Levy C, Rupp C, Joshi D, Nayagam JS, et al. Impact on follow-up strategies in patients with primary sclerosing cholangitis. Liver Int 2022. https://doi.org/10.1111/liv.15286.
44 Ali AH, Tabibian JH, Nasser-Ghodsi N, Lennon RJ, DeLeon T, Borad MJ, et al. Surveillance for hepatobiliary cancers in patients with primary sclerosing cholangitis. Hepatology 2018;67:2338–2351. https://doi.org/10.1002/hep.29730.
45 Trivedi PJ, Crothers H, Mytton J, Bosch S, Iqbal T, Ferguson J, et al. Effects of primary sclerosing cholangitis on risks of cancer and death in people with inflammatory bowel disease, based on sex, race, and age. Gastroenterology 2020;159:915–928. https://doi.org/10.1053/j.gastro.2020.05.049.
46 Macias RIR, Kornek M, Rodrigues PM, Paiva NA, Castro RE, Urban S, et al. Diagnostic and prognostic biomarkers in cholangiocarcinoma. Liver Int 2019;39(Suppl 1):108–122. https://doi.org/10.1111/liv.14090.

47 Hultcrantz R, Olsson R, Danielsson A, Järnerot G, Lööf L, Ryden BO, et al. A 3-year prospective study on serum tumor markers used for detecting cholangiocarcinoma in patients with primary sclerosing cholangitis. J Hepatol 1999;30:669–673. https://doi.org/10.1016/s0168-8278(99)80198-6.

48 Torzilli G, Makuuchi M, Ferrero A, Takayama T, Hui A-M, Abe H, *et al.* Accuracy of the preoperative determination of tumor markers in the differentiation of liver mass lesions in surgical patients. Hepatogastroenterology n.d.;49:740–745.

49 Qin X-L, Wang Z-R, Shi J-S, Lu M, Wang L, He Q-R. Utility of serum CA19-9 in diagnosis of cholangiocarcinoma: in comparison with CEA. World J Gastroenterol 2004;10:427–432. https://doi.org/10.3748/wjg.v10.i3.427.

50 Caturelli E, Bisceglia M, Villani MR, de Maio G, Siena DA. CA 19-9 production by a cystadenoma with mesenchymal stroma of the common hepatic duct: a case report. Liver 1998;18:221–224. https://doi.org/10.1111/j.1600-0676.1998.tb00155.x.

51 Kau SY, Shyr YM, Su CH, Wu CW, Lui WY. Diagnostic and prognostic values of CA 19-9 and CEA in periampullary cancers. J Am Coll Surg 1999;188:415–420. https://doi.org/10.1016/s1072-7515(98)00326-3.

52 Ker CG, Chen JS, Lee KT, Sheen PC, Wu CC. Assessment of serum and bile levels of CA19-9 and CA125 in cholangitis and bile duct carcinoma. J Gastroenterol Hepatol n.d.;6:505–508. https://doi.org/10.1111/j.1440-1746.1991.tb00896.x.

53 Shiozawa K, Ishii K, Mori T, Takamura N, Ikehara T, Shinohara M, et al. Heterochronous development of intrahepatic cholangiocellular carcinoma following hepatocellular carcinoma in a hepatitis B virus carrier. Intern Med 2001;40:624–630. https://doi.org/10.2169/internalmedicine.40.624.

54 Lindor KD, Kowdley KV, Harrison ME, American College of Gastroenterology. ACG clinical guideline: primary sclerosing cholangitis. Am J Gastroenterol 2015;110:646–659. https://doi.org/10.1038/ajg.2015.112. ; quiz 660.

55 Chapman R, Fevery J, Kalloo A, Nagorney DM, Boberg KM, Shneider B, et al. Diagnosis and management of primary sclerosing cholangitis. Hepatology 2010;51:660–678. https://doi.org/10.1002/hep.23294.

56 European Association for the Study of the Liver. EASL Clinical Practice Guidelines: management of cholestatic liver diseases. J Hepatol 2009;51:237–267. https://doi.org/10.1016/j.jhep.2009.04.009.

57 Primrose JN, Fox RP, Palmer DH, Malik HZ, Prasad R, Mirza D, et al. Capecitabine compared with observation in resected biliary tract cancer (BILCAP): a randomised, controlled, multicentre, phase 3 study. Lancet Oncol 2019. https://doi.org/10.1016/S1470-2045(18)30915-X.

58 Valle JW, Borbath I, Khan SA, Huguet F, Gruenberger T, Arnold D, et al. Biliary cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol Off J Eur Soc Med Oncol 2016;27:v28–v37. https://doi.org/10.1093/annonc/mdw324.

59 de Jong MC, Marques H, Clary BM, Bauer TW, Marsh JW, Ribero D, et al. The impact of portal vein resection on outcomes for hilar cholangiocarcinoma: a multi-institutional analysis of 305 cases. Cancer 2012;118:4737–4747. https://doi.org/10.1002/cncr.27492.

60 Murad SD, Kim WR, Therneau T, Gores GJ, Rosen CB, Martenson JA, et al. Predictors of pretransplant dropout and posttransplant recurrence in patients with perihilar cholangiocarcinoma. Hepatology 2012;56:972–981. https://doi.org/10.1002/hep.25629.

61 Darwish Murad S, Kim WR, Harnois DM, Douglas DD, Burton J, Kulik LM, et al. Efficacy of neoadjuvant chemoradiation, followed by liver transplantation, for perihilar cholangiocarcinoma at 12 US centers. Gastroenterology 2012;143:88–98.e3. https://doi.org/10.1053/j.gastro.2012.04.008. ; quiz e14.

62 Sapisochin G, Facciuto M, Rubbia-Brandt L, Marti J, Mehta N, Yao FY, et al. Liver transplantation for "very early" intrahepatic cholangiocarcinoma: international retrospective study supporting a prospective assessment. Hepatology 2016;64:1178–1188. https://doi.org/10.1002/hep.28744.

63 Valle J, Wasan H, Palmer DH, Cunningham D, Anthoney A, Maraveyas A, et al. Cisplatin plus gemcitabine versus gemcitabine for biliary tract cancer. N Engl J Med 2010;362:1273–1281. https://doi.org/10.1056/NEJMoa0908721.

64 Abou-Alfa GK, Sahai V, Hollebecque A, Vaccaro G, Melisi D, Al-Rajabi R, et al. Pemigatinib for previously treated, locally advanced or metastatic cholangiocarcinoma: a multicentre, open-label, phase 2 study. Lancet Oncol 2020. https://doi.org/10.1016/S1470-2045(20)30109-1.

65 Le DT, Uram JN, Wang H, Bartlett BR, Kemberling H, Eyring AD, et al. PD-1 blockade in tumors with mismatch-repair deficiency. N Engl J Med 2015. https://doi.org/10.1056/nejmoa1500596.

66 Birkmeyer JD, Siewers AE, Finlayson EVA, Stukel TA, Lucas FL, Batista I, et al. Hospital volume and surgical mortality in the United States. N Engl J Med 2002;346:1128–1137. https://doi.org/10.1056/NEJMsa012337.

67 Stitzenberg KB, Sigurdson ER, Egleston BL, Starkey RB, Meropol NJ. Centralization of cancer surgery: implications for patient access to optimal care. J Clin Oncol 2009;27:4671–4678. https://doi.org/10.1200/JCO.2008.20.1715.

68 Lee GC, Gamblin TC, Fong ZV, Ferrone CR, Goyal L, Lillemoe KD, et al. Facility type is associated with margin status and overall survival of patients with resected intrahepatic cholangiocarcinoma. Ann Surg Oncol 2019;26:4091–4099. https://doi.org/10.1245/s10434-019-07657-5.

69 Wu L, Tsilimigras DI, Paredes AZ, Mehta R, Hyer JM, Merath K, et al. 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 2019;43:1777–1787. https://doi.org/10.1007/s00268-019-04966-4.

70 Sutton TL, Walker BS, Nabavizadeh N, Grossberg A, Thomas CR, Lopez CD, et al. Geographic disparities in referral rates and oncologic outcomes of intrahepatic cholangiocarcinoma: a population-based study. Ann Surg Oncol 2021;28:8152–8159. https://doi.org/10.1245/s10434-021-10650-6.

71 Prager GW, Braga S, Bystricky B, Qvortrup C, Criscitiello C, Esin E, et al. Global cancer control: responding to the growing burden, rising costs and inequalities in access. ESMO Open 2018;3:e000285. https://doi.org/10.1136/esmoopen-2017-000285.