Original Article

Epidemiology, survival and new treatment modalities for intrahepatic cholangiocarcinoma

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Background: Intrahepatic cholangiocarcinoma (iCCA) is a rare biliary tract cancer with increasing incidence and poor survival rates. This study aims to evaluate the incidence and survival trends of iCCA patients over 20 years using a national cancer database, and assess the temporal association between survival and landmark clinical trials.

Methods: Data was extracted from the Surveillance, Epidemiology, and End Results (SEER) database. Age-adjusted incidence rates (AAIRs) were calculated from 2000 to 2020. Overall survival was analyzed based on diagnosis time and disease stage. Subgroup analysis was performed for patients diagnosed between 2015 and 2020. Landmark clinical trials were reviewed to determine temporal changes in survival.

Results: In this analysis of 28,918 iCCA patients, the AAIR increased from 0.49 per 100,000 in 2000 to 1.38 in 2020 [annual percent change (APC) 6.94, 95% confidence interval (CI): 6.32 to 7.56], with a notable decline from 2019 to 2020. Incidence rates overall displayed an uptrend course across subgroups divided by sex, race, age, and disease stage. The age-adjusted median overall survival (mOS) improved from 5.28 months in 2000 to 9.3 months in 2013, then stabilized between 8.0–9.0 months after 2013. Using 2010 as a cutoff, when the ABC-02 trial was published, the decade-based mOS increased from 6.55 months in 2000–2010 to 9.06 months in 2010–2020. During 2015–2020, the overall mOS was 8.8 months, with mOS of 24.3, 12.1, and 5.4 months for local, regional, and distant stages, respectively.

Conclusions: The study indicates a steady rise in iCCA incidence since 2000 across all subgroups. Survival rates improved since 2000 but stabilized after 2013, following the ABC-02 trial publication in 2010. The impact of more recent clinical trials on survival rates requires further analysis in the coming years.

Keywords: Intrahepatic cholangiocarcinoma (iCCA); epidemiology; survival trend

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Introduction

Intrahepatic cholangiocarcinoma (iCCA) ranks as the second most prevalent primary liver tumor, following hepatocellular carcinoma (1). Originating from the epithelial cells within the intrahepatic bile ducts, iCCA is associated with a variety of factors such as inflammatory bowel disease, bile duct congenital abnormalities, primary sclerosing cholangitis, tobacco use, cirrhosis, obesity, hepatic viral infections, and parasites (2,3). Unlike perihilar and extrahepatic cholangiocarcinoma, patients with iCCA often lack early-stage symptoms, which frequently manifest in advanced or metastatic stages beyond the criteria of surgical resection, leading to a notably bleak prognosis with a median overall survival (mOS) of only 8 months and 5-year overall survival (OS) of 9% (4).

Treatment of iCCA requires a multidisciplinary approach. If localized and technically feasible, surgical resection is the main treatment approach. However, because of their often-challenging locations and diagnosis at advanced stages, surgical resection is only feasible in 20–30% of newly diagnosed iCCA (5). Unfortunately, despite curative resection, the 5-year survival rate remains as high as 20–35% (6). For unresectable iCCA, the ABC-02 trial in 2010 set the first-line treatment standard using gemcitabine and cisplatin (7). Later, in 2022, the TOPAZ-1 trial showed that incorporating durvalumab into the doublet chemotherapy could notably extend survival (8). This has since been adopted as the contemporary standard of care for the first-line treatment of patients with unresectable biliary tract cancers. More recently, genomic profiling has highlighted targeted treatment options for iCCA, especially in tumors with microsatellite instability-high (MSI-H), FGFR2 fusion (found in 15% of patients), BRAF mutation (seen in 5% of patients), and IDH1 mutation (present in 15% of patients) (9-14).

Considering the changing treatment paradigm of iCCA in the last decade, the primary goal of the present study is to evaluate the trend of iCCA incidence and survival since the beginning of this century from a population perspective. Further, temporal changes in survival are evaluated based on the publication of landmark trials, followed by a discussion of more recently published and ongoing clinical trials. Last but not least, an updated survival outcome using recent data after 2015 is provided, which may serve as a reference of comparison for future clinical trials. We present this article in accordance with the STROBE reporting checklist (available at https://jgo.amegroups.com/article/view/10.21037/jgo-24-165/rc).

Highlight box

Key findings

- The study reveals a significant increase in intrahepatic cholangiocarcinoma (iCCA) incidence from 2000 to 2020, along with improved overall survival rates that peaked in 2013 and then stabilized.

What is known and what is new?

- iCCA is a rare biliary tract cancer with historically poor survival rates, and clinical trials have influenced treatment approaches.
- This 20-year analysis provides precise data on the increasing incidence of iCCA across various subgroups, quantifies survival improvements over time, and demonstrates a plateau in survival rates after 2013, while also suggesting a temporal association between survival trends and landmark clinical trials.

What is the implication, and what should change now?

- The rising incidence of iCCA and stagnating survival rates necessitate urgent action. Priorities should include enhancing early detection, developing more effective treatments (especially for advanced cases), expanding precision medicine approaches, and fostering collaborative research. Addressing coronavirus disease 2019 (COVID-19)-related diagnostic delays and refining disease classification are also crucial to improve outcomes for this growing patient population.

Methods

Data source

Data were obtained and calculated using SEER*Stat software, version 8.4.0.1 (National Cancer Institute) from 22 SEER registries (November 2023 submission) (15). Microscopically confirmed cases of iCCA were identified using International Classification of Disease for Oncology 3rd edition (16) (Hist/behav: '8160/3: Cholangiocarcinoma'; Primary Site: 'C22.0-Liver', 'C22.1-Intrahepatic bile duct'; Diagnostic Confirmation: 'Microscopically confirmed'). The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

Statistical analysis

Incidence rates for 2000–2020 were age-standardized to the 2000 US population in 5-year age groups. Incidence was further stratified based on age groups (49 and under, 50–74, and ≥75 years), race (White, Black, Asian and Pacific Islander, American Indian/Alaskan), sex (male and

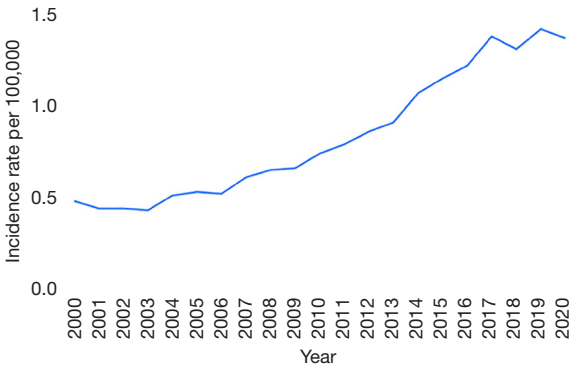

Figure 1 Age adjusted annual incidence rate.

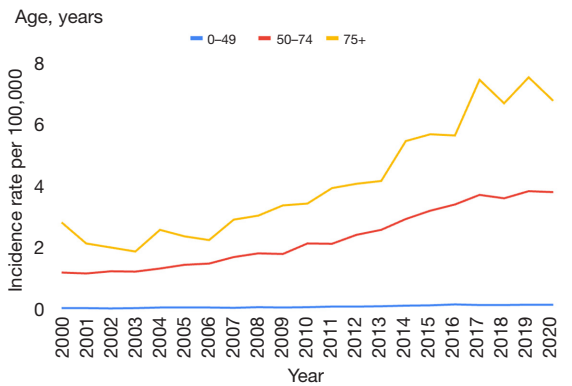

Figure 2 Age adjusted annual incidence rate based on age.

female), and disease stage (localized, regional, and distant). Disease stage was grouped based on SEER criteria, which was available after 2004. The annual percent change (APC) with 95% confidence interval (CI) and P value was used to characterize incidence trends, which was calculated from the underlying rates using the Joinpoint Trend Analysis Software, version 5.0.2 (17).

Survival rates reported in the SEER database are age-adjusted to the 2000 US standard population. Cancer-specific survival rates were calculated to provide updated information, survival among patients diagnosed after 2015 was calculated, reported as mOS, and OS at 1-, 3-, and 5-year.

Literature review was performed using PubMed and Google Scholar to determine clinical trials in iCCA and potential temporal association. The only landmark trial within the study time frame of SEER database was the ABC-02 trial, which was published in 2010. Therefore, OS subgroup analysis was performed using 2010 as cutoff. Ongoing clinical trials were identified on https://clinicaltrials.gov/.

Data were collected and analyzed from May to July 2023. Incidence and survival were reported with 95% CI. Two-sided P<0.05 was considered as statistically significant difference.

Results

A total of 28,918 patients with iCCA were identified from 2000 to 2020 (Female: n=14,063 (48.6%); male: n=14,855 (51.4%). The number of patients diagnosed in the time frame of 2000–2004, 2005–2010, 2010–2014, and 2015–2020 were 3,061 (10.6%), 5,506 (19.0%), 5,978 (20.7%), and 14,373 (49.7%). The majority of patients were 50–74 years at the time of diagnosis (n=18,836, 65.1%), followed by patients >75 years (n=7,457, 25.8%), with patients <49 years being the least (n=7,457, 25.8%). Most patients were white (n=23,363, 80.8%), followed by Asian or Pacific Islander (n=2,644, 9.1%) and Black (n=2,637, 9.1%); only 150 patients (0.52%) were American Indian/Alaska Natives; race was unknown among 123 (0.43%) patients. Excluding 4,348 patients (15.0%) with unknown staging, 36.9% patients had distant disease at the time of diagnosis (n=10,681), whereas local and regional disease were 24.5% (n=7,079) and 23.6% (n=6,810), respectively.

Incidence

The age-adjusted incidence rate (AAIR) showed a continuous uptrending course from 2000 through 2017, and experienced two drops in 2018 and 2020 (*Figure 1*).

The AAIR per 100,000 was 0.49 (95% CI: 0.45–0.53) in 2000, 1.39 (95% CI: 1.33–1.44) in 2017, 1.32 (95% CI: 1.26–1.37) in 2018, 1.43 (95% CI: 1.38–1.49) in 2019, and 1.38 (95% CI: 1.32–1.43) in 2020. The APC was 6.94 (95% CI: 6.32–7.56).

The incidence rate from 2000 to 2020 stratified by age group, sex, race and ethnicity and stage are shown in *Figures 2-5*.

The AAIR per 100,000 for age below 50 years is leveling around 0.08–0.19, with APC of 5.44 (95% CI: 4.76–6.12) from 2004 to 2000. The incidence rate increased in both the 50–74 years (from 1.23 per 100,000 in 2000 to 0.19 per 100,000 in 2020) and older than 75 years groups (from 2.85 per 100,000 in 2000 to 6.78 per 100,000 in 2020). In the 50–74 years group, APC was 7.00 (95% CI: 6.46–7.55). In the older than 75 years group, APC was 7.28 (95% CI:

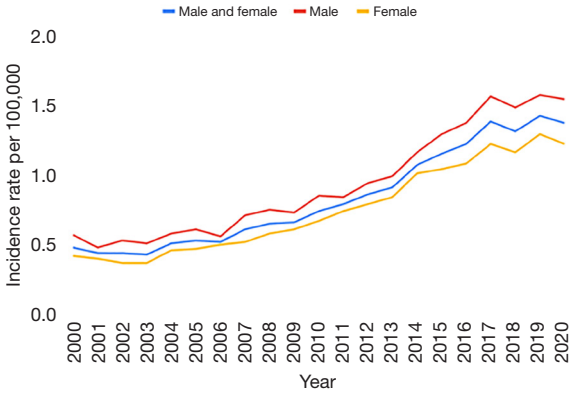

Figure 3 Age adjusted annual incidence rate based on sex. Male and female APC =6.94 (95% CI: 6.32–7.56), male APC =6.83 (95% CI: 6.15–7.52), female APC =6.98 (95% CI: 6.35–7.62). APC, annual percentage change; CI, confidence interval.

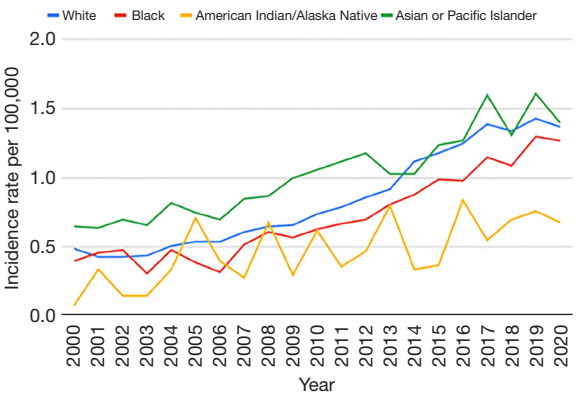

Figure 4 Age-adjusted incidence rate (AAIR) based on race and ethnicity.

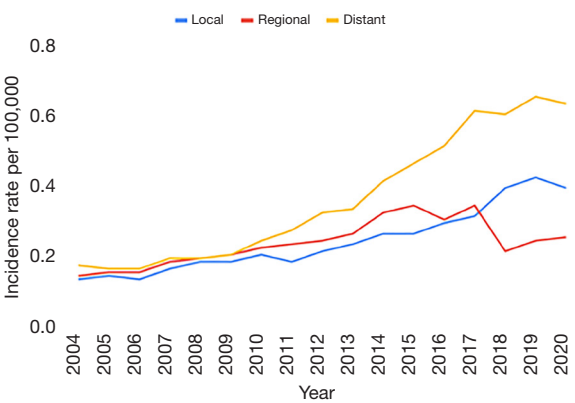

Figure 5 Age-adjusted incidence rate based on stage.

6.22–8.36). The increased incidence rate was observed in both sex groups, with male consistently higher than female. In male, the incidence increased from 0.58 per 100,000 in 2000 to 1.55 per 100,000 in 2020 with an APC of 6.83 (95% CI: 6.15–7.52). In female, the incidence increased from 0.43 per 100,000 in 2000 to 1.23 per 100,000 in 2020 with an APC of 6.98 (95% CI: 6.35–7.62). The incidence rates also increased among all race group during the study period. In white, the APC was 7.10 (95% CI: 6.41–7.79). The APC in Black was 7.04 (95% CI: 6.07–8.03). The APC in American Indian/Alaska native was 4.95 (95% CI: 1.73–8.27). In Asian /Pacific Islanders, the APC was 4.67 (95% CI: 3.84–5.51). Asian or Pacific islander have the highest incidence rate (1.40 per 100,000 in 2020), followed by White (1.37 per 100,000 in 2020), with the lowest among American Indian/Alaska native (0.68 per 100,000 in 2020). The incidence among Blacks in 2020 was 1.27 per 100,000.

Based on stage, distant and local disease had the steepest uptrending incidence rate, from 0.18 per 100,000 in 2004 to 0.64 per 100,000 in 2020. The incidence of localized disease also increased from 0.14 per 100,000 in 2004 to 0.40 per 100,000 in 2020. By comparison the incidence rate of regional disease increased from 2004 (0.15 per 100,000) till 2015 (0.35 per 100,000), plateauing until 2017 (0.35 per 100,000) and then trended downwards (0.26 per 100,000 in 2020). The APC of localized, regional, and distant diseases were 7.59 (95% CI: 6.74–8.44), 3.72 (95% CI: 1.53–5.95), and 10.49 (95% CI: 9.34–11.66). Distant disease has the highest incidence rate consistently throughout the study period.

Survival

Between 2000 and 2013, there was a gradual increase in the cancer-specific mOS from 5.28 months in 2000 to 9.3 months by 2013. After 2013, the mOS remained relatively consistent, fluctuating between 8 and 9 until 2017. The 1-, 3-, and 5-year OS rates during this period were 40.20%, 16.30%, and 10.60%, respectively (*Figure 6*).

In 2010, the ABC-02 trial marked gemcitabine and cisplatin as the standard treatment for unresectable cholangiocarcinoma. From 2000 to 2010, the mOS was 6.55 months with 1-, 3-, and 5-year OS rates of 35.80%, 14.6%, and 9.6%, respectively. In contrast, in the later decade from 2010 to 2020, the mOS was 9.06 months with 1-, 3-, and 5-year OS rates of 42.2%, 17.10%, and 10.90%, respectively. Notably, the 1-, 3-, and 5-year OS of patients

diagnosed between 2010–2020 appeared to be higher than those diagnosed between 2000–2010 (*Table 1*).

Updated OS of patients diagnosed from 2015 to 2020

The overall mOS of patients diagnosed after 2015 was 8.8 months. The OS rates at 1-year, 3-year, and 5-year were 42.5%, 17.5%, and 11.1%, respectively. Stratified according to disease stage, patients with localized iCCA demonstrated mOS of 24.3 months and 1-, 3-, and 5-year OS rates of 67.1%, 39.6%, and 28.2%, respectively.

Patients with regional disease had an mOS of 12.1 months and corresponding OS rates of 50.3%, 21.0%, and 12.1% for 1-, 3-, and 5-year.

Patients diagnosed with distant disease presented a shorter mOS of 5.4 months and disheartening OS rates of 27.3%, 6.0%, and 3.0% for 1-, 3-, and 5-years, respectively (*Table 2*).

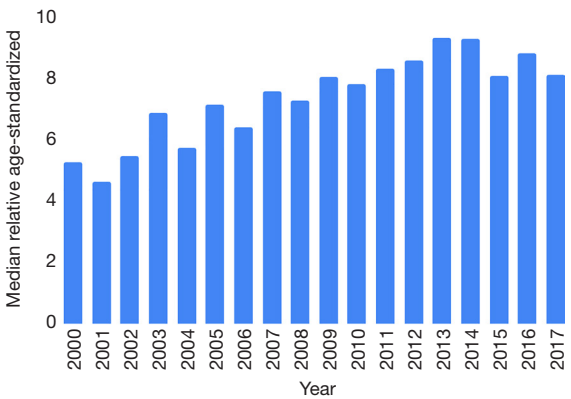

Figure 6 Cancer specific age adjusted median overall survival.

Table 1 mOS, 1-, 3-, and 5-year OS for 2000–2020, 2000–2010 and 2010–2020

Survival	2000–2020	2000–2010	2010–2020
mOS (months)	8.17	6.55	9.06
1-year OS	40.20%	35.80%	42.20%
3-year OS	16.30%	14.60%	17.10%
5-year OS	10.60%	9.60%	10.90%

mOS, median overall survival; OS, overall survival.

Approved treatments and ongoing trials

The majority of Food and Drug Administration (FDA) approved iCCA treatments were greenlit after 2019, suggesting a potential impact on iCCA's future survival rates that are not captured by the current SEER database. Ongoing clinical trials related to iCCA have also been compiled for forthcoming insights (*Tables 3*,*4*).

In 2010, gemcitabine and cisplatin became the first-line regimen for advanced biliary cancers, following the phase III ABC-02 trial (7). This trial compared gemcitabine, both solo and in combination with cisplatin, among 410 patients. The combined treatment showed an mOS of 11.7 months, surpassing the 8.3 months with gemcitabine alone (HR, 0.70; P=0.002). Both groups had comparable side effects.

In 2019, capecitabine was approved for post-surgery use in biliary tract patients based on the BILCAP study (18). Here, post-resection patients were assigned to capecitabine (1,250 mg/m^2 daily) or observation. The mOS was 51 months for capecitabine versus 36 months for observation (HR 0.8, P=0.097). When considering only protocol-adherent patients, the mOS was 25.9 months with capecitabine compared to 17.4 months in the observation group.

In 2020, pemigatinib was approved for FGFR fusion-positive iCCA, stemming from the FIGHT-202 trial (19). With a median follow-up of 17.8 months, 38 patients (35.5% with FGFR2 fusions or rearrangements) exhibited an objective response, including three complete and 35 partial responses.

In 2021, infigratinib, targeting FGFR fusion, was

Table 2 mOS, 1-, 3-, and 5-year OS for 2015–2020, and subgroup analysis based on stage

Survival	Diagnosis 2015+	Local	Regional	Distant
mOS (months)	8.8	24.31	12.13	5.4
1-year OS	42.50%	67.10%	50.30%	27.30%
3-year OS	17.50%	39.60%	21.00%	6.00%
5-year OS	11.10%	28.20%	12.10%	3.00%

mOS, median overall survival; OS, overall survival.

Table 3 FDA-approved therapies for iCCA since 2010 and a brief summary of pivotal trials leading to corresponding FDA approval

Therapy	FDA approval year	Dose	Comparator	Trial name	Study phase	Primary endpoint	Statistically significant OS benefit	Indication or line of treatment	Statistically and clinically significant outcomes from trials
Gemcitabine plus cisplatin	2010	Cisplatin, 25 mg/m^2 followed by gemcitabine 1,000 mg/m^2, each administered on days 1 and 8, every 3 weeks for eight cycles	Gemcitabine alone	ABC-02	Phase 2	OS	Yes	First line for previously untreated unresectable or metastatic or recurrent disease	mOS was 11.7 months with cisplatin-gemcitabine *vs.* 8.1 months with gemcitabine group
Capecitabine	2019	1,250 mg/m^2 bid on days 1–14 of a 21-day cycle, for eight cycles	Observation	BILCAP	Phase 3	OS	No	First line for resected BTC	mOS was 51.1 months with capecitabine *vs.* 36.4 months with observation in the intention to treat analysis
Pemigatinib	2020	13.5 mg once daily	NA	FIGHT-202	Phase 2	ORR	NA	Second line	35.5% ORR with FGFR2 fusions or rearrangements
Infigratinib	2021	125 mg oral once daily	NA	NA	Phase 2	ORR	NA	Second line	23.1 ORR
Ivosidenib	2021	500 mg, once daily	Placebo	ClarIDHy	Phase 3	PFS	Yes	Second line	mOS was 10.3 months with ivosidenib *vs.* 5.1 months with placebo with crossover allowed
FU/LV liposomal irinotecan	2021	LV, 400 mg/m^2, bolus and FU, 2,400 mg/m^2, for a 46-hour infusion intravenously every 2 weeks with nal-IRI, 70 mg/m^2	FU/LV alone	NIFTY	Phase 2b	PFS	NA	Second line	PFS was 4.2 months with nal-IRI plus FU/LV *vs.* 1.7 months with FU/LV alone
Durvalumab plus gemcitabine and cisplatin	2022	Durvalumab, 1,500 mg day 1 of each cycle, gemcitabine 1,000 mg/m^2, cisplatin 25 mg/m^2, day 1 and 8 of each cycle	Placebo plus gemcitabine and cisplatin	TOPAZ-1	Phase 3	OS	Yes	First line for previously untreated unresectable or metastatic or recurrent disease	HR for OS was 0.8, P=0.021. 24-month OS was 24.9% with durvalumab and 10.4% with placebo
Dabrafenib plus trametinib	2022	Dabrafenib 150 mg twice daily and oral trametinib 2 mg once daily	NA	ROAR basket	Phase 2	ORR	NA	Second line	ORR was 51%

FDA, Food and Drug Administration; iCCA, intrahepatic cholangiocarcinoma; OS, overall survival; mOS, median overall survival rate; BTC, biliary tract cancer; ORR, objective or overall response rate; HR, hazard ratio; PFS, progression-free survival; NA, not applicable; FU, fluorouracil; LV, leucovorin; nal-IRI, nanoliposomal irinotecan.

Table 4 Registered ongoing phase 3 trials or completed trials without results posted for iCCA

Therapy type	Study drug	Dose	Comparator	Trial name/NCT no.	Study phase	Primary endpoint	Indication or line of treatment	Status
Targeted therapy	Ivosidenib	500 mg qd	NA	ProvIDHe	Phase 3	Number of AE	IDH-1 inhibitor. Second line or beyond	Recruiting
	Tinengotinib	8 mg qd or 10 mg qd	Physician's choice	FIRST-308	Phase 3	Incidence, duration, and severity of AEs, PFS	Aurora A or B kinase inhibitor. Third line or beyond	Not yet recruiting
	Pemigatinib	13.5 mg qd	Gemcitabine and cisplatin	FIGHT-302	Phase 3	PFS	FGFR2 fusion inhibitor. Frist line	Recruiting
	Bortezomib	Unknown	Supportive care	NCT03345303	Phase 3	ORR	Proteasome inhibitor. Second line for PTEN mutation/deletion	Unknown status
	Futibatinib	20 mg qd, oral, every 21 days	Gemcitabine-cisplatin	FOENIX-CCA3	Phase 3	PFS	Pan-FGFR inhibitor. First line treatment for advanced iCCA	Active, not recruiting
Local regional therapy	Hepatic arterial infusion chemotherapy (HAIC) with FOLFOX	Unknown	Gemcitabine and cisplatin	NCT04961970	Phase 3	OS	First line for unresectable iCCA	Recruiting
	Y-90 followed by cisplatin-gemcitabine	Cisplatin 25 mg/m^2, gemcitabine 1,000 mg/m^2	Gemcitabine and cisplatin alone	SIRCCA	Phase 3	Survival at 18 months	First line for unresectable iCCA	Completed (No results posted yet)
	Cisplatin/gemcitabine followed by melphalan/HDS	Melphalan/HDS 3.0 mg/kg, cisplatin 25 mg/m^2, gemcitabine 1,000 mg/m^2	Cisplatin and gemcitabine	NCT03086993	Phase 3	OS	First line for unresectable iCCA	Active, not recruiting
Chemotherapy	Gemcitabine and oxaliplatin	Gemcitabine 1,000 mg/m^2, oxaliplatin 100 mg/m^2	Xeloda and oxaliplatin	NCT01470443	Phase 3	PFS	First line for metastatic or unresectable iCCA	Unknown status
	Gemcitabine and cisplatin with nab-paclitaxel	Unknown	Gemcitabine and cisplatin only	NCT03768414	Phase 3	OS	First line for untreated, advanced iCCA	Active, not recruiting
	Perioperative gemcitabine plus cisplatin followed by radical liver resection	Unknown	Immediate radical liver resection alone with or without adjuvant chemotherapy	GAIN	Phase 3	OS	Neoadjuvant for pt with resectable/borderline resectable iCCA	Recruiting
	Oxaliplatin and gemcitabine	Oxaliplatin 85 mg/m^2, gemcitabine 1,000 mg/m^2; every three weeks for 6–8 cycles in total.	Capecitabine	NCT02548195	Phase 3	RFS	Adjuvant setting for resectable iCCA	Unknown
	Gemcitabine/cisplatin capecitabine	Cisplatin 25 mg/m^2, gemcitabine 1,000 mg/m^2	Capecitabine	ACTICCA-1	Phase 3	DFS	Adjuvant setting for resectable iCCA	Active, not recruiting
	Gemcitabine with capecitabine	Gemcitabine 1,000 mg/m^2, capecitabine 1,250 mg/m^2	Capecitabine	AdBTC-1	Phase 3	DFS	Adjuvant setting for resectable iCCA	Recruiting
Immunotherapy	CTX-009 plus paclitaxel	Unknown	Paclitaxel	COMPANION-002	Phase 3	BOR	Second line for unresectable advanced, metastatic or recurrent iCCA	Recruiting
	SMT-NK and pembrolizumab	Pembrolizumab 200 mg, SMT-NK, 3×10^6 cells/kg	Pembrolizumab	NCT05429697	Phase 3	PFS	Second line for unresectable, advanced iCCA	Recruiting
	Pembrolizumab plus gemcitabine and cisplatin	Pembrolizumab, 200 mg, gemcitabine, 1,000 mg/m^2, cisplatin, 25 mg/m^2, q3wks	Gemcitabine and cisplatin alone	Keytruda 966	Phase 3	OS	First line for unresectable, locally advanced or metastatic iCCA	Resulted
	Radiofrequency ablation (RFA) and cytokine-induced killer cells (CIK) transfusion	Unknown	RFA alone	NCT02482454	Phase 3	RFS	First line for unresectable iCCA	Active, not recruiting
	Lenvatinib, tislelizumab combined with gemcitabine and cisplatin	Unknown	Gemcitabine and cisplatin	GPLET	Phase 3	Objective remission rate	First line for advanced iCAA	Not yet recruiting
	Toripalimab plus lenvatinib and gemcitabine and oxaliplatin or gemcitabine and cisplatin	Toripalimab, 240 mg, lenvatinib, 8 mg orally (po) once daily (qd), oxaliplatin, 85 mg/m^2 IV, gemcitabine, 1 g/m^2 IV, cisplatin 25 mg/m^2 IV	Intravenous placebo, oral placebo and gemcitabine and cisplatin or gemcitabine and oxaliplatin	NCT05342194	Phase 3	OS	First-line for patients with Unresectable Advanced iCCA	Not yet recruiting
	Gemcitabine, oxaliplatin, lenvatinib and toripalimab prior to surgery, plus capecitabine post-surgery	Oxaliplatin 85 mg/m^2, gemcitabine 1 g/m^2, lenvatinib 8 mg/d, toripalimab 240 mg q3wks, capecitabine 2,500 mg/m^2	Capecitabine post-surgery only	NCT04669496	Phase 3	EFS	Neoadjuvant	Recruiting
Antiparasite	Anlotinib hydrochloride + levamisole	Levamisole, 150 mg/d, po, anlotinib hydrochloride 12 mg/d, po	Anlotinib hydrochloride	TAICC	Phase 3	PFS	Second line for unresectable or recurrent iCCA	Unknown
High dose radiation therapy	High rose radiation therapy plus gemcitabine and cisplatin	52.5–60 Gy/25 fractions to the gross disease and 45 Gy/25 fractions to suspected microscopic disease	Gemcitabine and cisplatin alone	NCT02773485	Phase 3	OS	First line for unresectable nonmetastatic iCCA	Recruiting

iCCA, intrahepatic cholangiocarcinoma; NA, not applicable; IDH-1, isocitrate dehydrogenase 1; BTC, biliary tract cancer; qd, daily; AEs, adverse events; PFS, progression-free survival; ORR, objective response rate; OS, overall survival; RFS, recurrence-free survival; HDS, Hepatic Delivery System; DFS, disease free survival; BOR, best overall response; EFS, event-free survival.

approved based on a phase II study (20). It showed a 23% objective response rate and a median response duration of 5 months in previously treated iCCA patients with FGFR2 fusion.

Ivosidenib, targeting isocitrate dehydrogenase 1 (IDH1), was approved in 2021. IDH1 variants are found in about 20% of iCCA patients. Its approval as a second line iCCA treatment was based on the phase 3 ClarIDHy trial (21). The trial displayed a mOS of 10.3 months with ivosidenib compared to 7.5 months with a placebo. Adjusting for crossover, the placebo's mOS was 5.1 months, marking a significant difference (1-sided P<0.001).

In 2021, based on the phase IIb NIFTY trial (22), the combination of 5FU, LV, and liposomal irinotecan emerged as the standard therapy for metastatic biliary tract cancer patients without actionable somatic tumor mutations. After progressing on gemcitabine and cisplatin, patients received either the combination or just 5FU and LV as a second-line treatment. Those on the 5FU, LV, and liposomal irinotecan regimen had a median progression-free survival (PFS) of 7.1 months, compared to 1.4 months for the latter, with an HR of 0.56 (P=0.0019).

In 2022, durvalumab plus gemcitabine and cisplatin became the preferred standard of care for patients with advanced/metastatic biliary tract cancer. It was based on TOPAZ-1 trial (8), a phase III study that demonstrated the addition of durvalumab to cisplatin-gemcitabine comparing to placebo resulted in a longer mOS of 12.9 (11.6–14.1) months versus 11.3 (10.1–12.5) months, respectively (HR =0.76), together with manageable safety. OS rates for durvalumab plus cisplatin-gemcitabine versus cisplatin-gemcitabine, respectively, were 54.3% versus 47.1% at 12 months, 34.8% versus 24.1% at 18 months and 23.6% versus 11.5% at 24 months.

In 2022, vemurafenib and trametinib, targeting BRAF and MEK respectively, were approved for iCCA patients with the BRAF V600E mutation. This decision stemmed from the phase II ROAR basket study (23), which reported an overall response rate of 53%, a median PFS of 9 months, and an mOS of 13.5 months.

In 2024, a joint analysis of two retrospective cohort studies from France and Italy included patients with FGFR-2 positive iCCA as second- or later-line therapy to assess real-world effectiveness and safety. It revealed an overall response rate of 45.8% and disease control rate of 84.7%, median PFS of 8.7 months, and mOS of 17.1 months (24).

Discussion

There had been a steady increase of iCCA incidence in the United State since the beginning of this century, rising from 0.49 in 2000 to 1.48 per 100,000 persons in 2019. Such uptrend was observed in subgroup analyses in various races, males and females, and different disease stages. Similar trends were observed in epidemiology studies in other parts of the world. In England, the incidence of iCCA increased from approximately 2 per 100,000 in 2001–2003 to 3.5 per 100,000 in 2016–2018 (25). According to the Netherland Cancer Registry, the incidence of ICCA increased from 0.54 per 100,000 in 2010 to 1.53 in 2018 (26). Based on a population-database including 188 registries covering 180.6 million population in China (27), the age-specific incidence of iCCA statistically significantly increased from 2006 to 2015 with an APC of 3.1 (95% CI: 0.2–6.1). The incidence was 2.7 per 100,000 in 2015, accounting for 61,900 Chinese patients with iCCA. Patients older than 65 years demonstrated the steepest increase in iCCA incidence (APC: 3.1%, 95% CI: 0.4–5.9%), similar to the trends among the older age group in the present SEER study.

While the definite underlying cause behind this such observations remains elusive, several hypotheses have been suggested. On one hand, the escalating incidence can be attributed to increased burden of conditions that predispose patients to iCCA, such as cirrhosis (23), chronic hepatitis B and C (28-31), alcohol consumption (32), diabetes, and obesity (33). In Western countries, the rising prevalence of metabolic syndrome, insulin resistance, and hepatic steatosis (33-35) may cause iCCA through liver inflammation and cirrhosis. Prior study noted a significant association between metabolic syndrome and iCCA (33). While other scholars have voiced concerns that such upticks might be due to diagnostic misclassifications (36-38), changes in the International Classification of Diseases (ICD) over the years may be accountable for the changes in iCCA and extrahepatic biliary disease incidence rates. Furthermore, cancers of unknown origin in the liver are often identified as primary iCCA s, possibly overinflating the incidence (39-42). On the other hand, the stark decline of incidence in 2020 across various demographics could be attributed to coronavirus disease 2019 (COVID-19) pandemic and resulting in decreased iCCA diagnosis, as noted in many other cancer types (43,44). Whether such delayed diagnosis

may lead to increased late-stage diagnoses in the upcoming years and associated increased mortality warrant future studies using updated data in the upcoming years.

Survival outcome of iCCA slowly increased overtime, with mOS increasing from 5 months in 2000 to approximately 9 months in 2017. Based on the most recent data between 2015–2020, the overall mOS was 8.8 months with 1-, 3-, and 5-year OS of 42.5%, 17.5%, and 11.1%, respectively, which were higher than a previous SEER study including patients diagnosed between 2004 and 2015 with an mOS of 7.0 months and 1-, 3-, and 5-year survival rates of 37.1%, 13.3%, and 9.0% (45). Such observation could be attributed to increasing available treatment options. Nonetheless, the prognosis of distant iCCA remains dismal, with a mOS of only 5.4 months, as compared to the 24.3 months among localized iCCA patients. Disease stage related factors such as resectability, liver-only disease, and lymph node invasion have been reported as prognostic factors of OS (46,47). According to the European Network for the Study of Cholangiocarcinoma (ENSCCA) Registry (47), including 24 institutions among 11 European countries, a total of 1,243 patients diagnosed with iCCA from 2010 to 2019 were analyzed. Metastatic disease was an independent factor of OS. Other factors that were not recorded by the SEER database included Eastern Cooperative Oncology Group status and serum carbohydrate antigen 19-9. From the perspective of treatment approach, patients receiving gemcitabine and cisplatin combination demonstrated better survival than gemcitabine-only and best supportive care, whereas R0 resection was associated with better survival than R1 resection.

Despite the incidence of all disease stages trending up, the relative proportion of distant disease was the highest, which might have contributed to the increased mortality of iCCA over time noted in prior literature. According to the World Health Organization (WHO) Mortality Database, the notable improvement in survival rates among patients after 2010 coincide with the landmark ABC-02 trial, reflecting the importance of systemic treatment in prolonging OS. The plateauing of mOS in the more recent years during the study period highlights the need of more effective agents. Nowadays, it has been widely acknowledged that iCCA represents a heterogeneous disease (48), with different targetable genetic mutations. Accordingly, targeted therapies have gained increasing popularity in the last five years, advancing from second-line treatment into neoadjuvant and first-line settings (*Table 4*). Further, locoregional therapies also demonstrated potential benefit in managing unresectable disease, such as transarterial radioembolization (TARE), hepatic artery infusion (HAI), thermal ablation and external beam radiotherapy, with possibilities of prolonging survival and downstage to surgery (49-52). Although immunotherapy on its own has limited success in treating iCCA, combinations with chemotherapy showed promising results such as TOPAZ-1 (8). Targeted therapeutic agents such as toripalimab (53) are being evaluated in phase 3 trials in combination with chemotherapy regimen (*Table 4*). Built upon ABC-02 trial, research delving into cytotoxic regimen demonstrated promising results of adding nab-paclitaxel (54) and S-1 (55). As treatment regimens become more sophisticated in the era of precision medicine, multi-institutional collaboration is crucial for recruiting a homogeneous and large-enough sample size to conduct high quality clinical trials, especially in such rare diseases.

Limitations

The present study should be interpreted with several caveats. Retrospective, population-based study design precludes precise analysis and predisposes to bias. Aforementioned changes in diagnostic criteria and classification may affect reported incidence rates over time. Furthermore, relevant variables, such as detailed treatment regimens and molecular profiles of iCCA tumors, could yield more meaningful results but were not captured. Last but not the least, the majority of newer landmark trials were published after 2020, which were beyond the study period of the most updated SEER database.

Conclusions

This population-based study demonstrates increasing incidence of iCCA in the United States, which warrants attention due to the poor prognosis. Cancer-specific survival has improved but plateaued in late 2010s. In order to further improve OS, enhanced surveillance and screening method, risk factor identification, early intervention, and development of new effective treatment are warranted. As the majority of clinical trials with high level evidence were published after 2020 or currently underway, follow-up analysis in the next five years would be helpful for depicting the effectiveness of these newer treatment agents on a population level.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

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