What we need to know about cholangiocarcinoma

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7th DICE Masterclass
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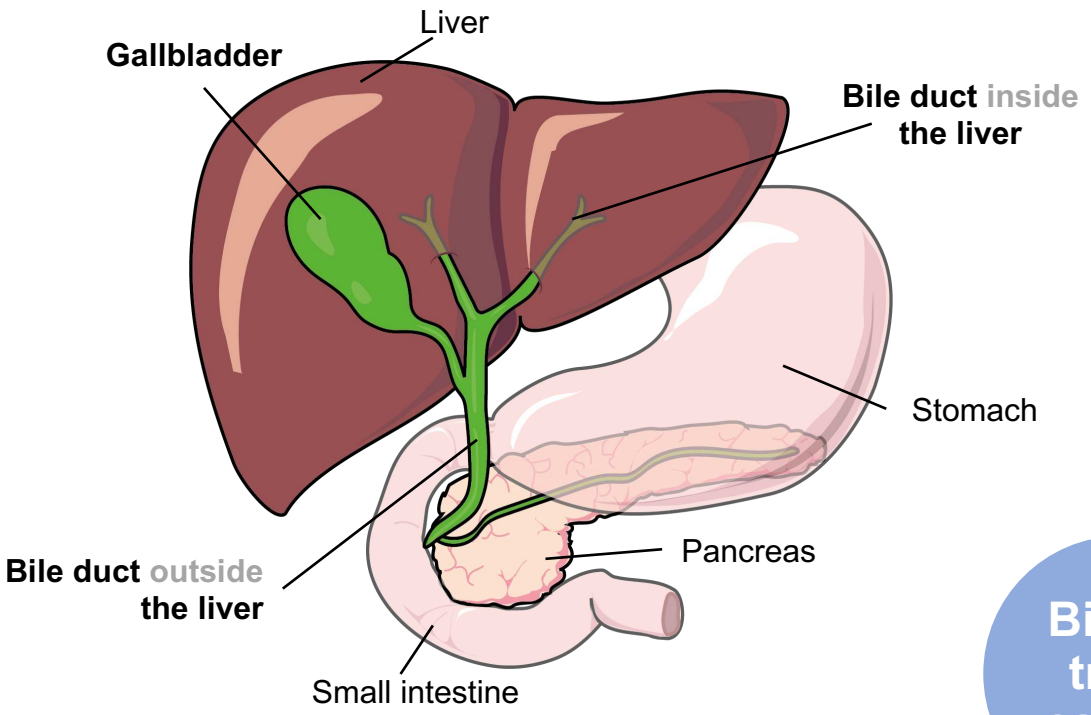
What is cholangiocarcinoma

What is biliary tract cancer?



Biliary tract cancer includes cancers of the bile duct, also known as cholangiocarcinoma, and the gallbladder

- The **biliary tract** moves bile from the liver to the small intestine, where it helps to digest the fats in food
  - It includes the **gallbladder** (where bile is stored), and the **bile ducts** (thin tubes that carry the bile)

Biliary tract cancer

- **Gallbladder cancer**
- **Bile duct cancer (cholangiocarcinoma)**
  - ***Intrahepatic*** **bile duct cancers start in the ducts inside the liver**
  - ***Extrahepatic*** **bile duct cancers start in the ducts outside the liver**

Source: NCCN Guidelines for Patients. Gallbladder and Bile Duct Cancers 2021, available at https://www.nccn.org/patients/guidelines/content/PDF/gallandbile-hp-patient.pdf, accessed 15 Jun 2022

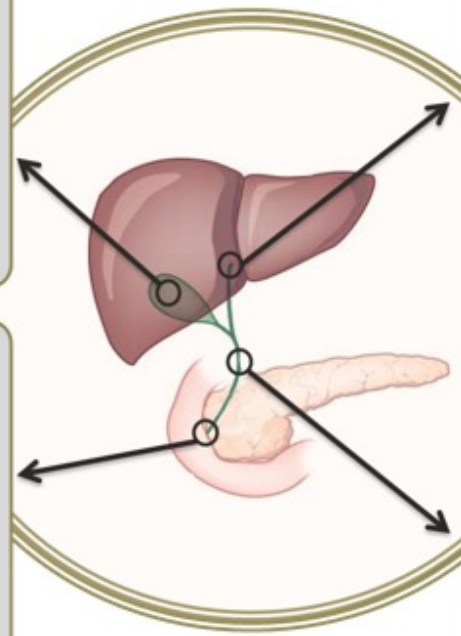
Biliary tract cancer is an heterogeneous disease

Gallbladder Cancer

- **Females** > males
- Adenocarcinoma
- Risk factors: **gallstones**, gallbladder polyps, chronic infections, drugs (methyl-dopa), obesity, diabetes
- Typically presented as **incidental finding** following cholecystectomy (localised stage) of with abdominal **pain** (advanced stage)
- **Adjuvant** chemotherapy (capecitabine-based)
- Palliative chemotherapy: **cisplatin/gemcitabine**
- No widely accepted second-line palliative chemotherapy
- No role for radioembolisation
- Molecular characteristics: TP53 mutation (47.1-59%); **ERBB2/3 amplification** (9.8-19%); CDKN2A/B loss (5.9-19%); ARID1A mutation (13%); KRAS mutation (4-13%); PIK3CA mutation (5.9-12.5%); NRAS mutation (6.3%); BRAF mutation (1-5.9%)

ICC

- **Males** > females
- Adenocarcinoma
- Risk factors: bile duct morphological anomalies, **primary sclerosing cholangitis**, hepatitis, Lynch syndrome, *Opistorchis viverrini* , Lynch syndrome, obesity, diabetes
- Typically presented with **obstructive jaundice**
- **Adjuvant** chemotherapy (capecitabine-based)
- Palliative chemotherapy: **cisplatin/gemcitabine**
- No widely accepted second-line palliative chemotherapy
- **Radioembolisation** may be an option for liver-predominant disease
- Molecular characteristics: **FGFR1-3 fusions** (11-45%), TP53 mutation (2.5-44.4%), **IDH1/2 mutation** (4.9-36%), **ARID1A mutations** (6.9-36%), CDKN2A/B loss (5.6-25.9%), PTEN mutation (0.6-11%), PIK3CA mutations (3-9%), BRAF mutations (3-7.1%), ERBB3 amplification (7%), MET amplification (2-7%)



Ampullary Cancer

- **Males** > females
- Adenocarcinoma
- Risk factors: **polypoid syndromes** (Lynch syndrome, familial adenomatous polyposis), **inflammatory bowel disease**
- Typically presented with **obstructive jaundice** (+/- PEI)
- **Adjuvant** chemotherapy (gemcitabine-based)
- Palliative chemotherapy: **cisplatin/gemcitabine**. **5-FU based** first-line treatment has also been suggested due to similarities with small bowel adenocarcinoma
- No widely accepted second-line palliative chemotherapy
- No role for radioembolisation
- Molecular characteristics: TP53 mutation (41-53%), **MET amplification** (39%), PIK3CA mutation (38%), WNT pathway mutation (38%), KRAS mutation (35%), CDKN2A/B loss (19%), **ERBB2/3 amplification** (13-17%)

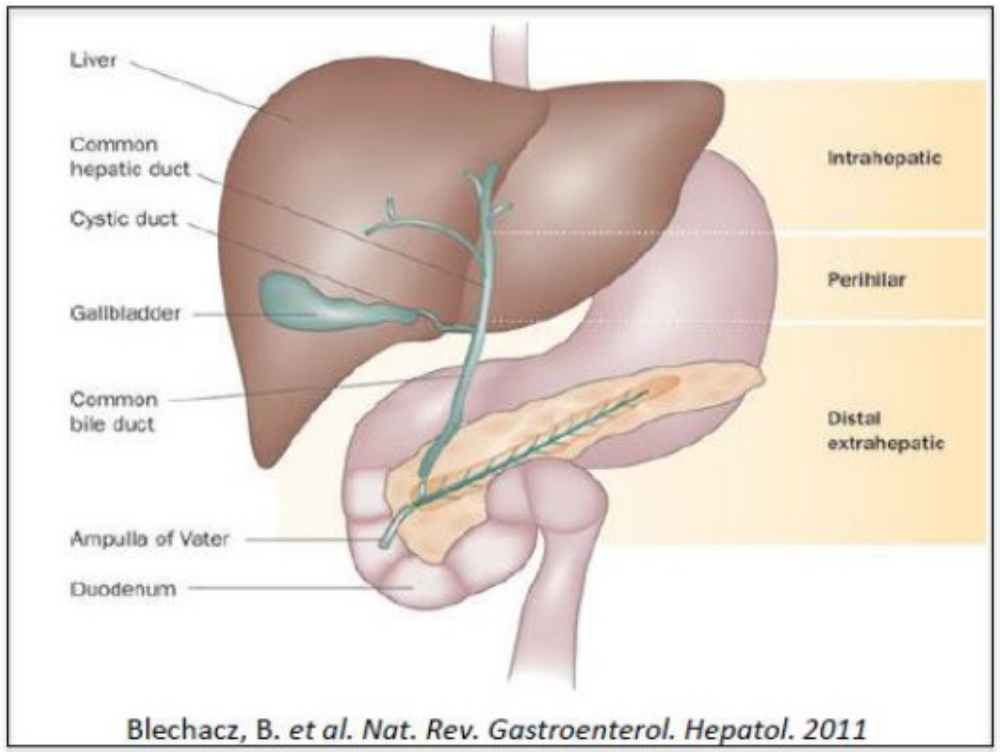
ECC (hilar/distal)

- **Males** > females
- Adenocarcinoma
- Risk factors: bile duct morphological anomalies, **primary sclerosing cholangitis** , gallstones, Lynch syndrome, *Opistorchis viverrini* , Lynch syndrome, obesity, diabetes
- Typically presented with **obstructive jaundice**
- **Adjuvant** chemotherapy (capecitabine-based)
- Palliative chemotherapy: **cisplatin/gemcitabine**
- No widely accepted second-line palliative chemotherapy
- No role for radioembolisation
- Molecular characteristics: KRAS mutation (8.3-42%), TP53 mutation (40%), SMAD4 mutation (21%), CDKN2A/B loss (17%), **ERBB2/3 amplification** (11-17%), **ARID1A mutations** (12%), IDH1/2 mutation (0-7.4%), PIK3CA mutation (7%), MET mutation (3.7%), BRAF mutations (3%), MET amplification (1%)

Lamarca A, et al. *Current Med Chem.* 2018

Cholangiocarcinoma
Overview

- Cholangiocarcinoma can be divided in three groups on the basis of the anatomical location: intrahepatic, perihiliar and distal[1]
- Intrahepatic cholangiocarcinoma (iCCA) arises from the small bile ducts within the liver and forms classic mass lesions in 85% of cases[2]
- Typically, iCCA has a poor prognosis, resection being the main treatment option in 30-40% of cases[3]
- At more advanced stages, chemotherapy regimens are standard of practice (i.e., cisplatin plus gemcitabine)[4]



Blechacz, B. *et al. Nat. Rev. Gastroenterol. Hepatol. 2011*

Intrahepatic 25%
Extrahepatic 75%

Cholangiocarcinoma: Epidemiology

Epidemiology of liver cancer

- Liver cancer is the sixth most common cancer globally, 2nd cause of cancer-related mortality[1].
- Hepatocellular carcinoma (HCC) is the most common type of liver cancer, whereas **cholangiocarcinoma (iCCA) accounts for 10% of cases**
- Over 850,000 new cases of liver cancer are diagnosed worldwide each year,[1] including
  - Eastern Asia: 470,000[1] ,Japan: 39,000[1], Europe: 58,000[1], US: 21,000[1]
- The incidence of iCCA is increasing globally

1.International Agency for Cancer Research. Globocan 2008. Available at: http://www-dep.iarc.fr. September 2, 2010. 2. Bosch XF, et al. Clin Liver Dis. 2005;9:191-21

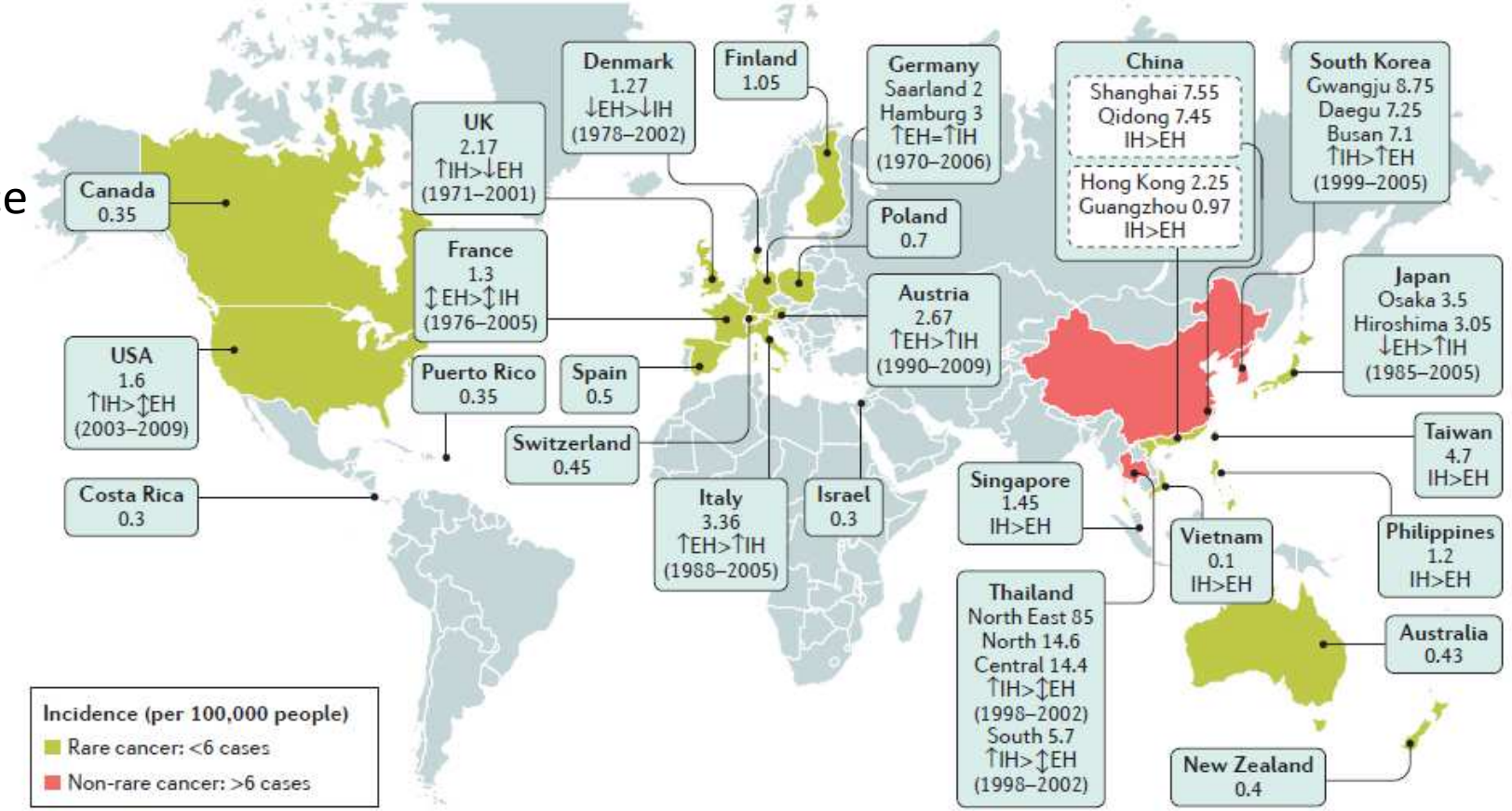
Cholangiocarcinoma: Epidemiology

- Rare cancers[1–3]
  - Incidence: <6/100,000

  In western countries.
  - Endemis zones incidence

  Is 40 times higher.
- Incidence increasing[1–3]
  - iCCA
- Poor prognosis[1–3]
  - 5-year OS (<20%)
  - Late diagnosis
    - 70% advanced stages
  - High relapse rate

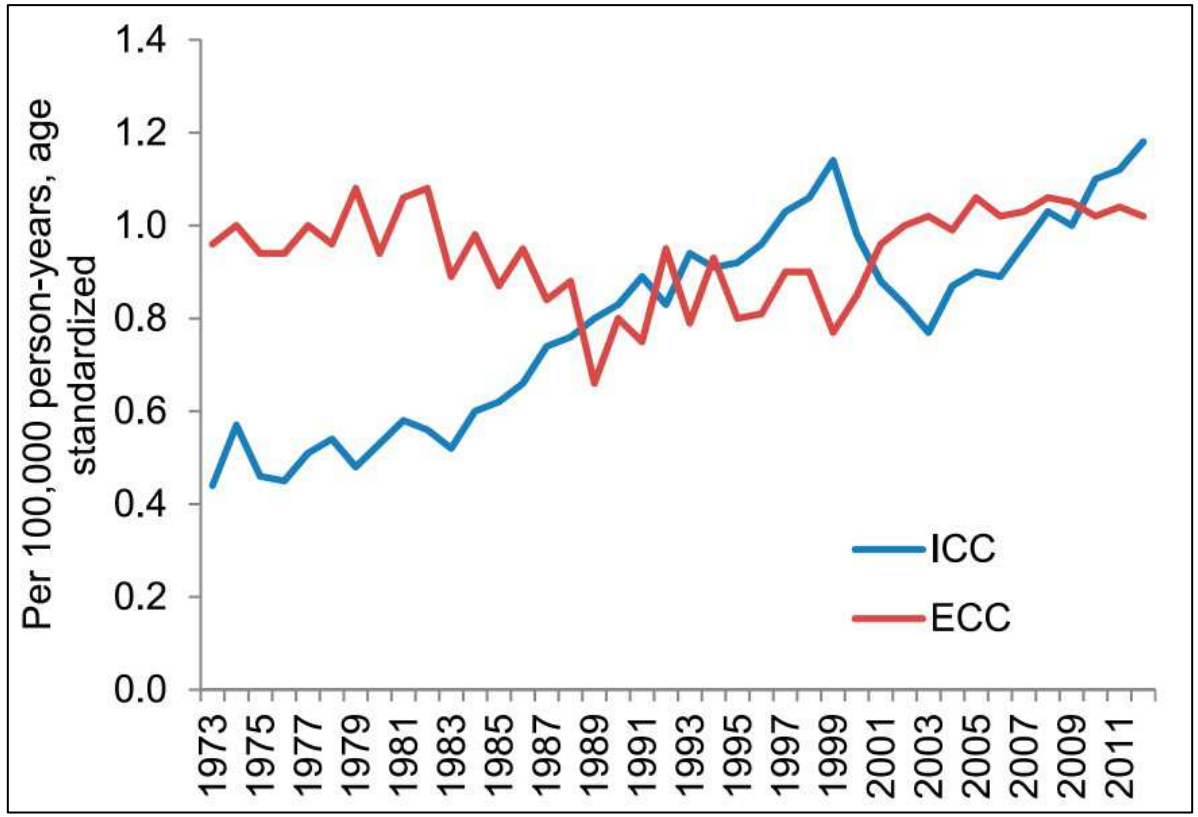
Global incidence rates of CCA[1]



CCA, cholangiocarcinoma; EH, extrahepatic; iCCA, intrahepatic CCA; IH, intrahepatic; OS, overall survival.

1. Bañales JM, et al. *Nat Rev Gastroenterol Hepatol*. 2016;13:261–80; 2. DeOliveira ML, et al. *Ann Surg.* 2007;245:755–62;
3. Valle JW, et al. *Ann Oncol.* 2016;27:v28–37.

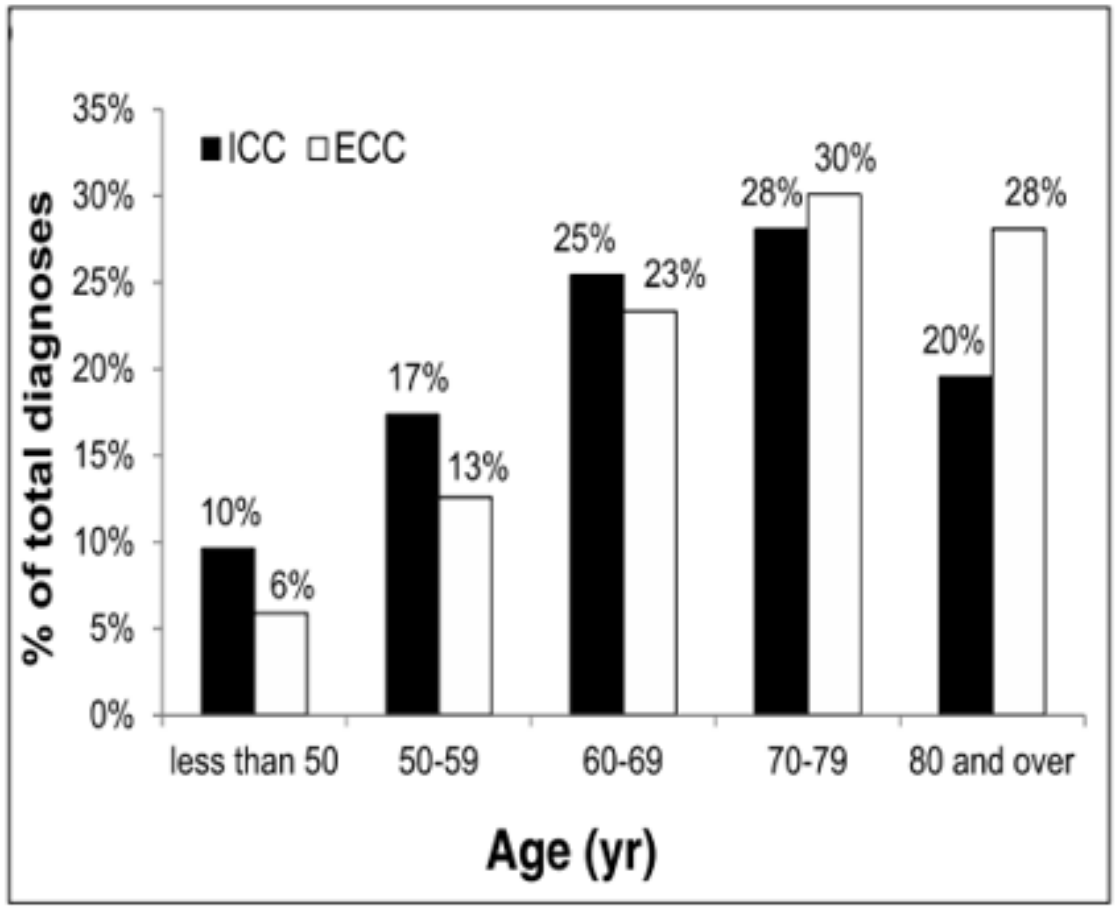
Cholangiocarcinoma: Epidemiology



- Recent epidemiological reports indicate an increasing worldwide incidence of intrahepatic CCA but a decreasing incidence of extrahepatic CCA
- ICCA in USA, UK from 0.1/100.000 is rising to 0.6/100.000 over the past 30 years

- Saha SK. et al. The Oncologist 2016;21:594–599

Cholangiocarcinoma: Epidemiology



CCA mainly occur not earlier than in the fourth decade of life and rather in men than in women

- Saha SK. et al. The Oncologist 2016;21:594–599

Cholangiocarcinoma: Symptoms

What are the symptoms of biliary tract cancers?

Most symptoms of gallbladder cancer are more likely to be from other causes, such as gallstones or liver disease[1]

Bile duct cancer does not usually cause symptoms until later in the disease, when the bile ducts become blocked[2]

Common symptoms include[1,2]:

- Jaundice (yellow eyes or skin)
- Dark urine
- Light coloured / greasy stools
- Pain below the ribs on the right side
- Fever, chills
- Itching
- Nausea, loss of appetite, weight loss

Referral

If a patient presents to their doctor with any of the above symptoms, they may be referred to a specialist in digestive diseases (gastroenterologist)[3]

Sources: 1. American Cancer Society Signs and Symptoms of Gallbladder Cancer, available at https://www.cancer.org/cancer/gallbladder-cancer/detection-diagnosis-staging/signs-and-symptoms.html, accessed 15 Jun 2022; 2. American Cancer Society Signs and Symptoms of Bile Duct Cancer, available at https://www.cancer.org/cancer/bile-duct-cancer/detection-diagnosis-staging/signs-symptoms.html, accessed 15 Jun 2022; 3. Mayo Clinic. Cholangiocarcinoma (bile duct cancer), available at https://www.mayoclinic.org/diseases-conditions/cholangiocarcinoma/symptoms-causes/syc-20352408, accessed 15 June 2022.

Cholangiocarcinoma: Risk Factors

Epidemiology and Risk factors

- Significant geographical and ethnic variation in the epidemiology of IHCC. The incidence is the highest in the Southeast of Asia (Thailand).
- Western countries: The vast majority of IHCC is sporadic.
- Risk factors: Cirrhosis, chronic hepatitis B and C, obesity, diabetes, and OH.
- Other: Primary sclerosing cholangitis, biliary duct cysts, hepatolithiasis, and hepatobiliary flukes.

Moeini et al, Clin Cancer Res 2015

Cholangiocarcinoma:
How is diagnosis established

How are biliary tract cancers diagnosed?

Specialists may use different types of tests and exams to accurately diagnose biliary tract cancer

History and physical exam

Blood tests

Imaging tests and endoscopy

Biopsy

Biomarker and genetic tests

Diagnosis

The diagnosis includes the **subtype** of cancer, **where** it is located, if it has **spread** and any known relevant **mutations**

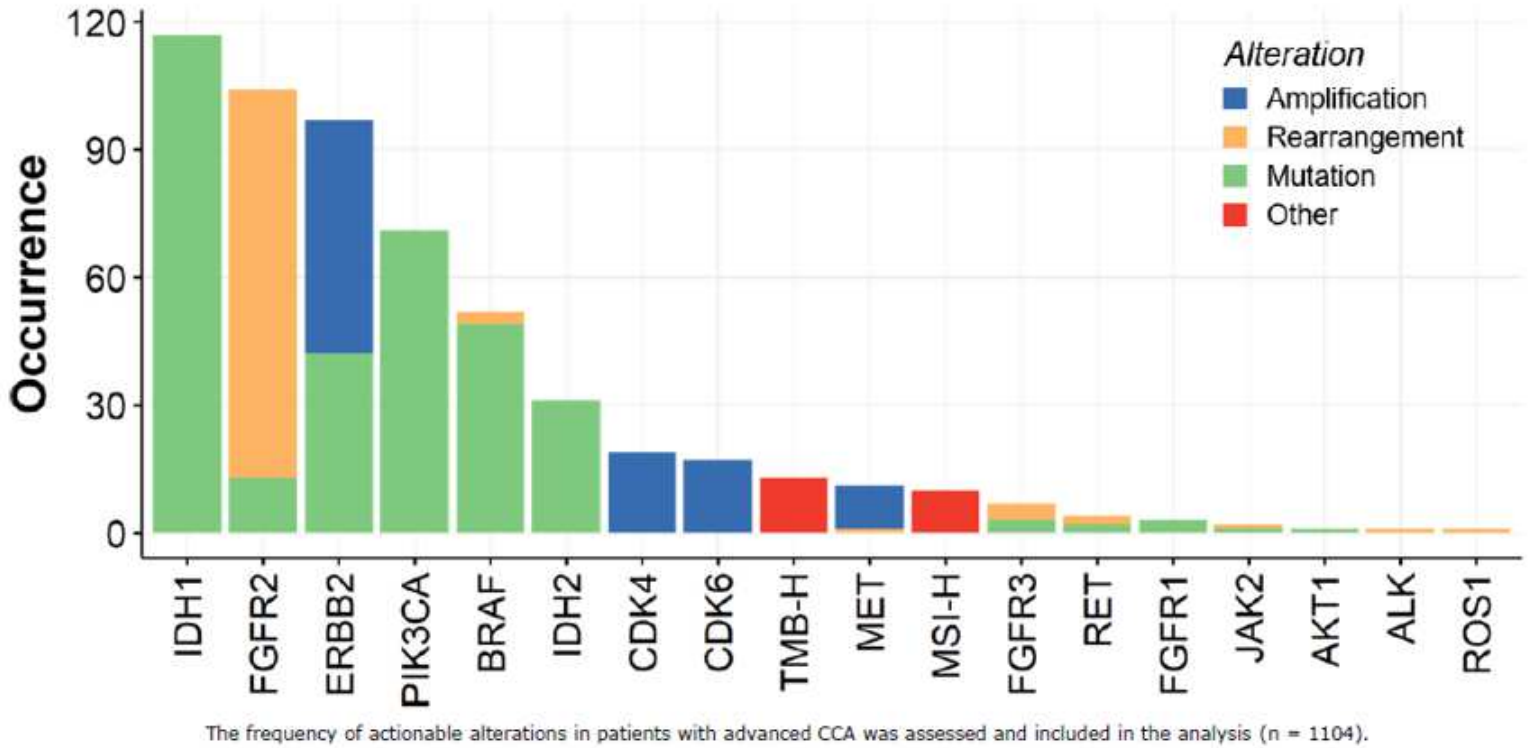
Source: NCCN Guidelines for Patients. Gallbladder and Bile Duct Cancers 2021, available at https://www.nccn.org/patients/guidelines/content/PDF/gallandbile-hp-patient.pdf, accessed 15 Jun 2022.

Actionable alterations in advanced cholangiocarcinoma

Biomarker and genetic tests

Comprehensive genomic profiling in FIGHT-202 trial:

42.9% of patients had at least one alteration for which a targeted agent



The frequency of actionable alterations in patients with advanced CCA was assessed and included in the analysis (n = 1104).

TP53 (38.1%), *CDKN2A/B* (28.8%), *KRAS* (21.9%), *ARID1A* (15.7%), *SMAD4* (11.3%), *BAP1* (10.6%), *IDH1* (10.5%), *PBRM1* (10.0 %), *FGFR2* (9.4%), *ERBB2* (7.6%), *PIK3CA* (7.0%), *MDM2/FRS2* (5.8%), and *BRAF* (4.7%)

Silverman et al, presented in ASCO 2019 (abstr 4080)

Cholangiocarcinoma: Treatment options and outlook

How to define localised cholangiocarcinoma tumours?

Oncologist

Nutritionist

Nurses

Pathologist

Radiologist

Surgeons

Owing to the difficulty of relying on strict criteria of resectability, it should be recommended that
ALL localized CCA with no metastases are discussed by a multidisciplinary board in a high-volume centre

NCCN Guidelines. Pancreatic Adenocarcinoma. Version 1.2020. Available at https://www.nccn.org/professionals/physician_gls/PDF/pancreatic.pdf (Accessed March 2020)

PDAC, pancreatic ductal adenocarcinoma

Why is the prognosis so poor for biliary tract cancers?

Surgery offers patients with resectable disease their best chance for cure[1]

Only approximately
20–30%
of biliary tract cancers are considered resectable at diagnosis[2]

At least
2/3
of cancers recur within 5 years of surgery[2]

Even in resectable intrahepatic bile duct cancer, patients live only 1–2.5 years[1]

Many patients relapse **within 6 months** of surgery

Few patients with very early relapse live **beyond 5 years**[1]

Adjuvant capecitabine is recommended

Sources: 1. Tsilimigras DI, et al. *JAMA Surg* 2020;155:823-831; 2. Belkouz A et al. *Crit Rev Oncol Hematol* 2020;151:102975.

BTC Patient Journey – Current Management of Advanced Disease

ADVANCED DISEASE

RESPONSE

Cis-gem for 8 cycles

Cis-gem until progression

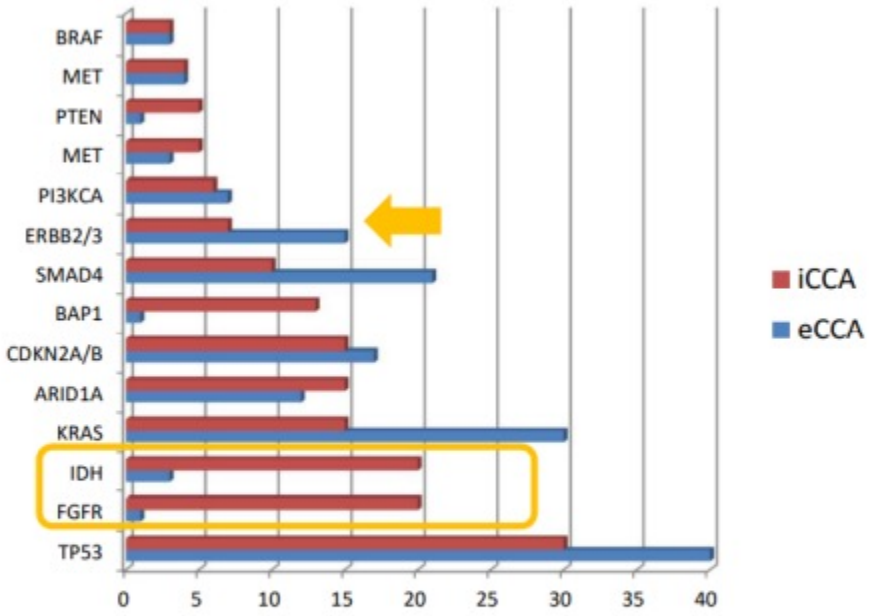
Local treatment

Embolisation	Radiation	Hepatic artery infusion chemotherapy	Ablation
• Transarterial embolisation • Selective internal radiotherapy/ transarterial radioembolisation • Transarterial chemoembolisation	• External beam radiotherapy • Stereotactic body radiotherapy • Proton beam therapy • Selective internal radiotherapy/transarterial radioembolisation	**HAIC** involves placement of an arterial catheter attached to an infusion pump, enabling chemotherapeutic agents to be given directly to the tumour;[1] the hepatic artery supplies most GBCs, and HAI allows the liver to remove the ct agent before it reaches other parts of the body[2]	• Microwave ablation • Electroporation • Radiofrequency ablation • Photodynamic therapy

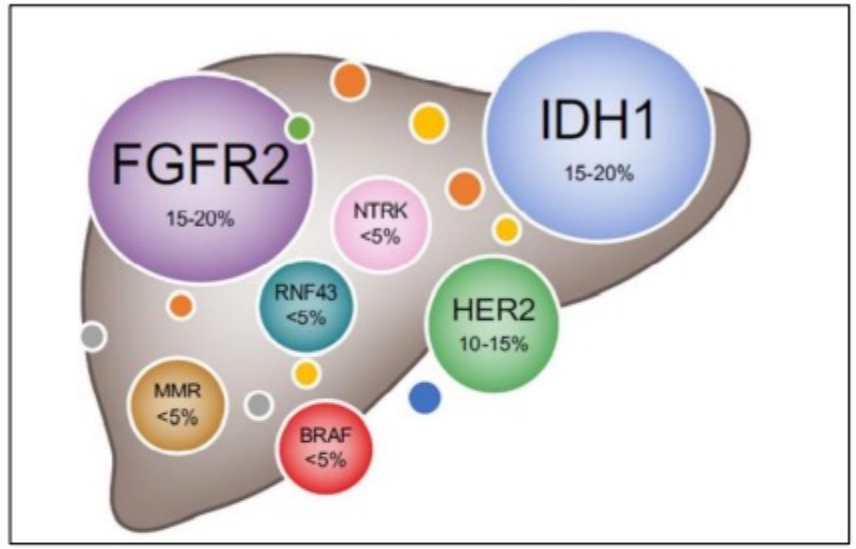
Gómez-España MA, et al. Clin Transl Oncol.2021

1. Labib PL. et al. *Hepat Oncol*. 2017;4:99–109; 2. American Cancer Society. Radiation Therapy for Gallbladder Cancer. Available at https://www.cancer.org/cancer/gallbladder-cancer/treating/radiation.html Accessed October 2020; 3. American Cancer Society. Chemotherapy for Gallbladder Cancer. Available at https://www.cancer.org/cancer/gallbladder-cancer/treating/chemotherapy.html Accessed October 2020

Intrahepatic cholangiocarcinoma: An heterogeneous disease with high rates of targetable alterations



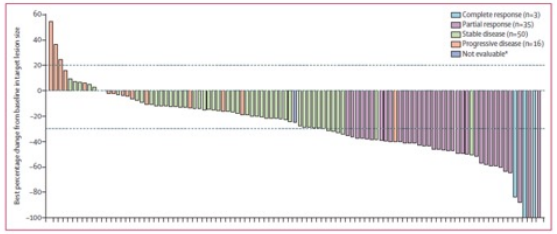
Adapted from Valle JW, et al. *Cancer Disc*. 2017;7:943–62 and Lamarca A, et al. *Current Med Chem*. 2018 (In press); whenever a range was reported, median was plotted



Lamarca et al Journal of Hepatol 2020

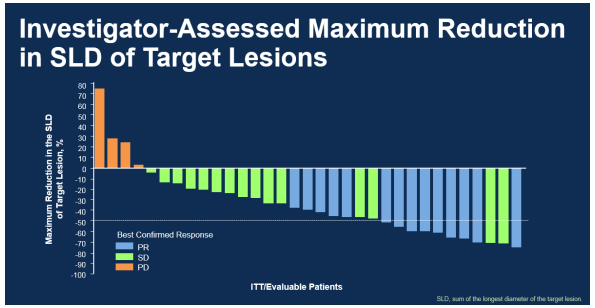
Intrahepatic cholangiocarcinoma: Clinical value of targetable alterations

FDA, EMA approved



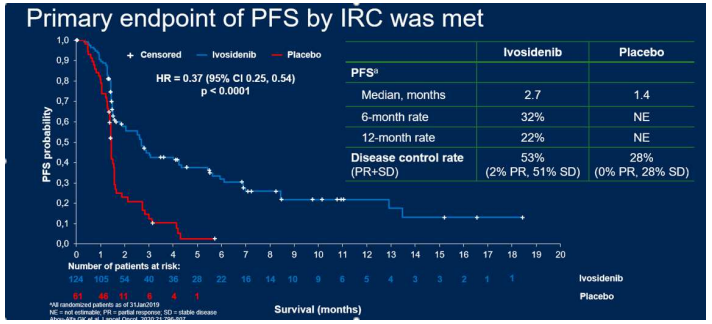
ORR 35.5%, DCR 82%, duration of response 7,5 months
Follow up: 17.8 m
mPFS: 6.9 m
mOS: 21.1 m

Targetable gene	Prevalence, %
FGFR2 (fusions)[1]	10-20
IDH1/2[2]	22-28
BAP1	15 to 25
BRAF V600 (mutation)[3]	5-7



Dabrafenib (BRAF inh) + Trametinib (MEK inh) RR 42%

FDA approved



1- Ghassan K Abou-Alfa et al, Lancet Oncol 2020, 2- Ghassan K Abou-Alfa et al, Lancet Oncol 2020, 3- Wainberg et al, ASCO GI 2019

Take home message

- Cholangiocarcinoma is a tumour that arise from the intrahepatic bile ducts.
- Is a rare tumour in western countries, but endemic in some areas of the world.
- The symptoms at diagnosis are non-specific, the majority of patients are diagnosed in advanced disease.
- Surgery is the curative option, and adjuvant capecitabine.
- In the advanced setting new targeted therapies and treatment options may change the therapeutic armamentarium in this disease.

Thank you for your attention

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