

# PRACTICAL INSIGHTS FOR EARLY DIAGNOSIS AND MANAGEMENT OF BILIARY TRACT CANCERS

## Biliary Tract Cancer: Early Signs, Risk Factors, Key Factors for Diagnosis, and Prevention Strategies

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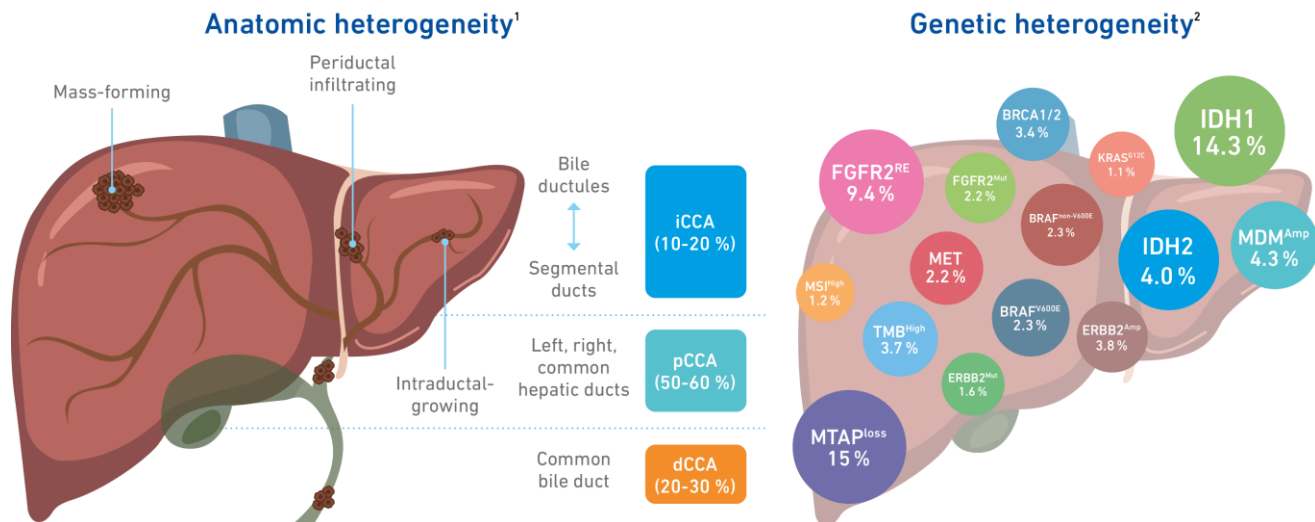
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M-ES-ONC-2500074

# Biliary Tract Cancers: A Heterogeneous Disease Entity



**dCCA:** distal cholangiocarcinoma; **iCCA:** intrahepatic cholangiocarcinoma; **pCCA:** perihilar cholangiocarcinoma; **IDH1:** Isocitrate Dehydrogenase 1; **IDH2:** Isocitrate Dehydrogenase 2; **FGFR2:** Fibroblast Growth Factor Receptor 2; **MSI:** Microsatellite Instability; **BRCA 1/2:** Breast Cancer Gene; **KRAS:** Kirsten Rat Sarcoma virus; **MET:** Mesenchymal-Epithelial Transition; **ERBB2:** Erb-B2 Receptor Tyrosine Kinase 2; **TMB:** Tumor Mutational Burden; **MTAP:** Methylthioadenosine Phosphorylase; **MDM<sup>Amp</sup>:** Mouse Double Minute 2 amplification

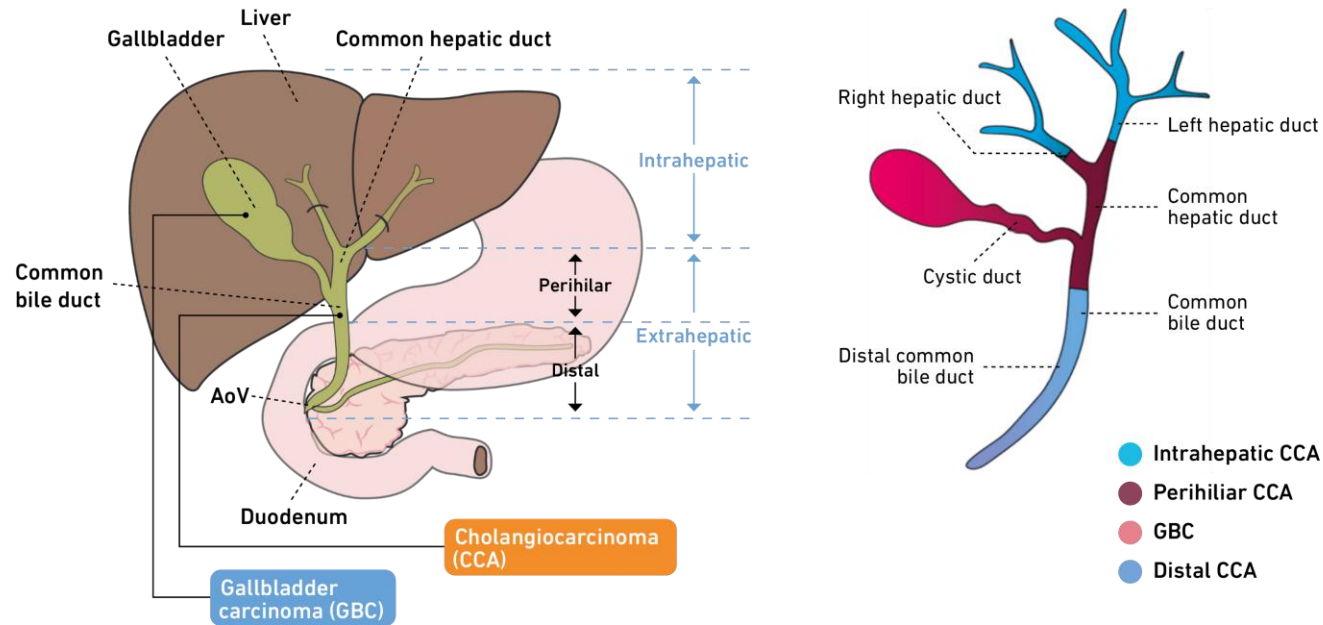
1. Banales JM, et al. Nat Rev Gastroenterol Hepatol. 2020;17:557-588. 2. Modified from Kendre G, et al. J Hepatol. 2023;78:614-626.

# Biliary Tract Cancers (BTC): Basic Epidemiology and Clinical Relevance

- BTC is a group of heterogenous neoplasms arising in the epithelium of the bile ducts.
- BTC accounts for around 1 % of all new cancer cases and 3-5 % of all gastrointestinal cancers worldwide.
  - ✓ Marked geographic variation in incidence, highest rates in Southeast Asia and parts of Latin America.
- BTCs are highly lethal malignancies with five-year survival rates <20-15 %.
- Most cases are diagnosed at advance stage (60-70 %).

Lamarca A et al. Cancer Treat Rev. 2018;70:168-177; Bridgewater JA et al. Am Soc Clin Oncol Educ Book. 2016;35:e194-203.

# BTC Classification: Anatomic Heterogeneity



Adapted from: Valle JW, Kelley RK, Nervi B, Oh DY, Zhu AX. Biliary tract cancer. Lancet. 2021 Jan 30;397(10272):428-444. doi: 10.1016/S0140-6736(21)00153-7.

# BTC Early Signs and Symptoms

## Clinical presentation of CCA

- Early-stage CCA may only manifest as mild changes in serum liver function tests.
- Patients with iCCA present with non-specific symptoms (fever, weight loss and/or abdominal pain) and as a result are more likely to present with advanced disease.
- iCCA may also present as an incidental hepatic lesion in asymptomatic patients, when imaging is obtained as part of the workup for other conditions.
- Patients with eCCA are more likely to present with jaundice followed by evidence of a biliary obstruction or abnormality on subsequent imaging.

## Clinical presentation of GBC

- Often diagnosed at an advanced stage.
- Mimics that of biliary colic or chronic cholecystitis.
- Other possible clinical presentations include a suspicious mass, biliary tract obstruction with jaundice or chronic right upper quadrant abdominal pain (advanced stage).
- Typically presents as an incidental finding following surgical removal of the gallbladder (cholecystectomy).

**BTC:** Biliary Tract Cancer; **CCA:** cholangiocarcinoma; **iCCA:** intrahepatic cholangiocarcinoma; **eCCA:** extrahepatic cholangiocarcinoma.

Vogel A. Biliary tract cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. Ann Oncol. 2023 Feb;34(2):127-140. doi: 10.1016/j.annonc.2022.10.506. Banales JM. Cholangiocarcinoma 2020: the next horizon in mechanisms and management. Nat Rev Gastroenterol Hepatol. 2020 Sep;17(9):557-588. doi: 10.1038/s41575-020-0310-z. NCCN Guidelines Biliary Tract Cancers 2025 Version 2.2025 - 2 July, 2025. Access 29 August 2025: [https://www.nccn.org/professionals/physician\\_gls/pdf/btc.pdf](https://www.nccn.org/professionals/physician_gls/pdf/btc.pdf).

# Risk Factors vary depending on BTC subtype. Cholangiocarcinoma risk factors

## Cholangiocarcinoma (CCA)

### Intrahepatic cholangiocarcinoma (iCCA)

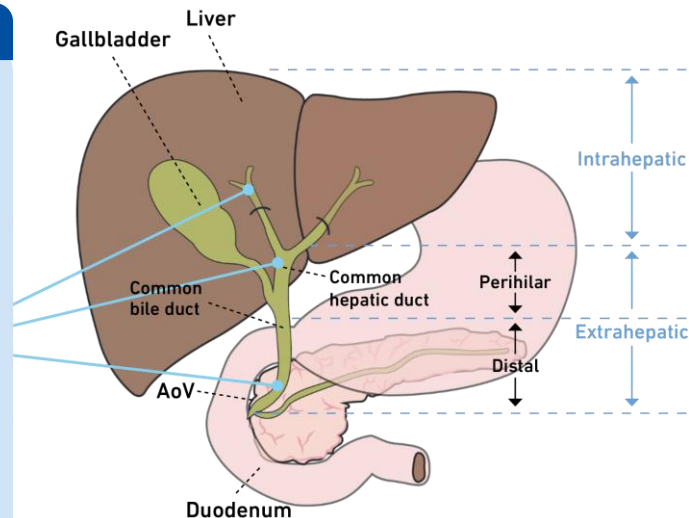
- **Risk factors:** Primary sclerosing cholangitis (PSC, progressive liver or gallbladder disease from bile duct inflammation and scarring), cirrhosis, fluke infection, obesity, diabetes, chronic hepatitis B/C, hepatolithiasis (gallstones in liver bile ducts), Lynch syndrome (a hereditary cancer syndrome), biliary papillomatosis, biliary duct morphologic anomalies.

### Extrahepatic cholangiocarcinoma (eCCA)

- Further subdivided into perihilar (pCCA)\* and distal (dCCA).
- **Risk factors:** PSC, gallstones, Lynch syndrome, fluke infection, bile duct morphological anomalies.

pCCA: perihilar cholangiocarcinoma; dCCA: distal cholangiocarcinoma

Risk factors associated with chronic inflammation present the highest risk for BTC. Up to 15 % of PSC patients may eventually develop BTC.

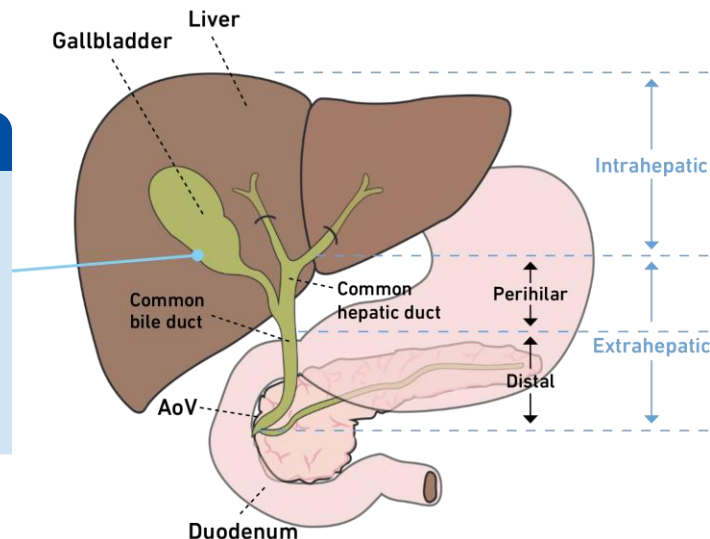


1. Tyson GL. Hepatology. 2011;54:173-184. 2. Hundal R. Clin Epidemiol. 2014; 6:99-109. 3. Welzel TM. Hepatology. 2011;54:463-471. 4. Gatto M. Eur Rev Med Pharmacol Sci. 2010;14:363-367. 5. Khan SA. HPB (Oxford). 2008;10:77-82. 6. Kirstein MM. Visc Med. 2016;32:395-400. 7. Valle JW, et al. Ann Oncol. 2016;27(suppl 5):v28-v37

# Risk Factors vary depending on BTC subtype. Gallbladder cancer risk factors

## Gallbladder carcinoma (GBC)

- **Risk factors:** Gallstones, gallbladder polyps (>10 mm), chronic cholecystitis (gallbladder inflammation, porcelain gallbladder 10-20 %), females, ethnicity, age, *Salmonella typhi* or *Helicobacter bilic* infection, congenital biliary tree malformations, primary sclerosing cholangitis, obesity and diabetes.



Risk factors associated with chronic inflammation present the highest risk for BTC. Up to 15 % of PSC patients may eventually develop BTC.

1. Tyson GL. Hepatology. 2011;54:173-184. 2. Hundal R. Clin Epidemiol. 2014; 6:99-109. 3. Welzel TM. Hepatology. 2011;54:463-471. 4. Gatto M. Eur Rev Med Pharmacol Sci. 2010;14:363-367. 5. Khan SA. HPB (Oxford). 2008;10:77-82. 6. Kirstein MM. Visc Med. 2016;32:395-400. 7. Valle JW, et al. Ann Oncol. 2016;27(suppl 5):v28-v37

# Current and Potential Prevention Strategies

## Surveillance of high-risk groups

- Regular imaging (ultrasound, MRCP) and serum biomarker monitoring (CA19-9) are recommended in patients with primary sclerosing cholangitis, large gallbladder polyps, or congenital biliary malformations.

## Management of predisposing conditions

- Timely surgical resection of choledochal cysts, endoscopic clearance of hepatolithiasis, and prophylactic cholecystectomy in high-risk gallbladder settings (e.g., porcelain gallbladder, large polyps).

## Infection control

- Reducing liver fluke and Salmonella typhi infections.

## Lifestyle and metabolic health

- Control of obesity, physical activity, diabetes, chronic viral hepatitis or statins use (less robust evidence).

**MRCP:** Magnetic Resonance Cholangiopancreatography

Ellington TD, et al. Incidence and Mortality of Cancers of the Biliary Tract, Gallbladder, and Liver by Sex, Age, Race/Ethnicity, and Stage at Diagnosis: United States, 2013 to 2017. *Cancer Epidemiol Biomarkers Prev.* 2021 Sep;30(9):1607-1614. doi: 10.1158/1055-9965.EPI-21-0265. Liu Z, et al. Statin use and reduced risk of biliary tract cancers in the UK Clinical Practice Research Datalink. *Gut.* 2019 Aug;68(8):1458-1464. doi: 10.1136/gutjnl-2018-317504.

# Initial diagnostic work-up

| Procedure                               | Purpose   |
|---|---|
| Blood tests                             | Assess liver function and the presence of underlying liver or biliary tract disease (viral hepatitis serologies, etc.)  |
| ERCP/PTC ± biopsy (or cholangioscopy)   | Assessment and treatment of biliary obstruction. Obtain tissue for diagnosis, histological classification and NGS   |
| EUS ± biopsy                            | Accurate assessment of: locoregional extension of p/dCCA and GBC, biliary obstruction, hepatic, vascular and lymph node invasion and metastases. Obtain tissue for diagnosis, histological classification and NGS   |
| MRI, including MRCP                     | Accurate assessment of local extension of p/dCCA, including biliary tract and vascular anatomy and identification of hepatic metastases   |
| CT of thorax + abdomen ± pelvis         | Staging of tumour to detect local/distant lymphadenopathy and metastatic disease  |
| PET-CT, if available                    | May allow identification of nodal metastases, distant metastases and disease recurrence   |
| CA 19-9                                 | Non-specific marker can be elevated in other gastrointestinal malignancies and benign conditions (Not diagnostic for BTC). CA 19-9 are associated with poorer prognosis and also useful for assessing response to treatment/follow up. CEA can also be considered |
| Germline testing and genetic counseling | It should be considered in patients with young age at diagnosis, strong personal or family history of cancer or mutations identified during tumor testing that are suspected to be possible germline alterations (i.e. high allelic frequencies)                  |

CT: computed tomography; dCCA: distal cholangiocarcinoma; ERCP: endoscopic retrograde cholangiopancreatography; EUS: endoscopic ultrasonography; GBC: gallbladder carcinoma; MRCP: magnetic resonance cholangiopancreatography; MRI: magnetic resonance imaging; NGS: next-generation sequencing; pCCA: perihilar cholangiocarcinoma; PET: positron emission tomography; PTC: percutaneous transhepatic cholangiography; BTC: Biliary Tract Cancer; CEA: Carcinoembryonic Antigen

Adapted from the ESMO guidelines 2023 & NCCN guidelines v2. 2025.