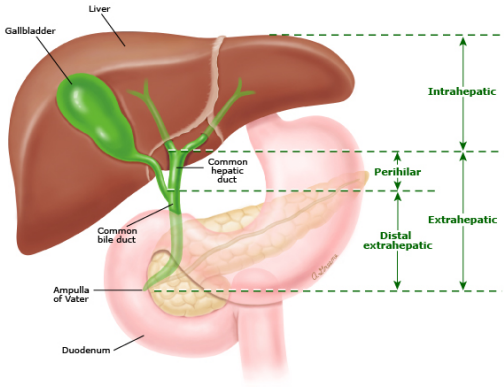
CHOLANGIOCARCINOMA

General Overview

- Rare cancer, and often diagnosed in advanced stage. Usually adenocarcinoma. Subclassified:
  - Intrahepatic CCA (iCCA) 10%
  - Extrahepatic : Perihilar (pCCA) 50%
  - Extrahepatic: Distal (dCCA) 40%
- Risk factors: PSC, fibro polycystic liver disease, hepatolithiasis, cirrhosis and hepatotropic viruses, obesity, alcohol
- Linked with genetic disorders: Lynch, BRCA-associated protein-1 BAP1 tumor predisposition syndrome, biliary papillomatosis
- Clinical symptoms: abdominal pain, weight loss, fever, biliary obstruction: jaundice, pruritus, clay-colored stools, dark urine



Staging (AJCC Version 8) and Prognosis

- Diagnosis: CT, MRI, ERCP (or MRCP), tumormarkers (CA19-9 and CEA), viral serology, IgG4
- Prognostic factors: margin status, vascular invasion and lymph node metastases

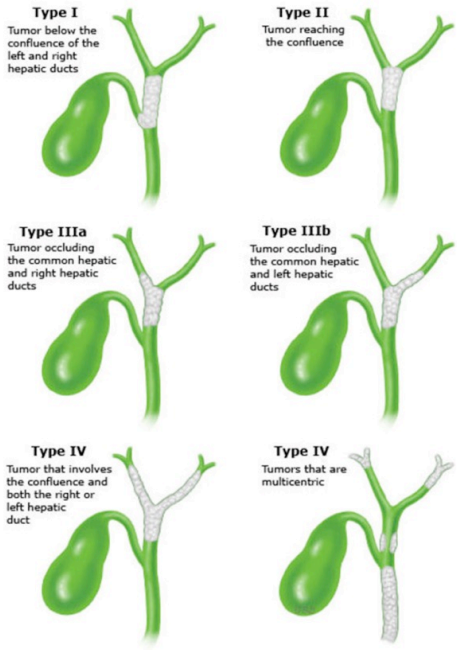
Perihilar CCA

Primary Tumor (T)	Regional Lymph Nodes (N)	Distant Metastasis (M)
Tx: Primary tumor cannot be assessed **T0**: No evidence of primary tumor **Tis**: Ca in situ, high grade dysplasia **T1**: Tumor confined to the bile duct, with extension up to the muscle layer or fibrous tissue **T2**: tumor invades: **T2a**: beyond the wall of the bile duct **T2b**: adjacent hepatic parenchyma **T3**: Tumor invades unilateral branches of the portal vein or hepatic artery **T4**: tumor >4 cm in greatest dim **T4**: Tumor invades the main portal vein or its branches bilaterally, or the common hepatic artery; or unilateral second-order biliary radicals with contralateral portal vein or hepatic artery involvement	**Nx**: LN cannot be assessed **N0**: no regional LN **N1**: M+ in 1-3 LN involving hilar, cystic duct, common bile duct, hepatic artery, posterior pancreatoduodenal and portal vein LN **N2**: M+ in 4 or more LN	**M0**: no distant M **M1**: distant M

Bismuth-Corlette classification for pCCA:

- Type I: Tumors below the confluence of the left and right hepatic ducts
- Type II: Tumors reaching the confluence
- Type IIIa: Tumors occluding the common hepatic duct and the right hepatic duct
- Type IIIb: Tumors occluding the common hepatic duct and the left hepatic duct
- Type IV: Tumors that are multicentric, or that involve the confluence and both the right or left hepatic duct

Update: December 2024



Distal CCA

Primary Tumor (T)	Regional Lymph Nodes (N)	Distant Metastasis (M)
Tx: Primary tumor cannot be assessed **Tis**: Ca in situ, high grade dysplasia **T1:** tumor invades the bile duct wall with a depth < 5mm **T2**: tumor invades the bile duct wall with a depth 5-12 mm **T3**: tumor invades the bile duct wall with a depth > 12 mm **T4**: Tumor involves the celiac axis, superior mesenteric artery and/or common hepatic artery	**Nx**: LN cannot be assessed **N0**: no regional LN **N1**: M+ in 1-3 reg LN **N2**: M+ in 4 or more reg LN	**M0**: no distant M **M1**: distant M

Intrahepatic CCA

Primary Tumor (T)	Regional Lymph Nodes (N)	Distant Metastasis (M)
Tx: Primary tumor cannot be assessed **T0**: No evidence of primary tumor **Tis:** Carcinoma in situ (intraductal tumor) **T1:** solitary tumor without vascular invasion: T1a: tumor ≤5 cm, T1b: tumor >5cm **T2**:Solitary tumor with intrahepatic vascular invasion or multiple tumors, with or without vascular invasion **T3**: Tumor perforating the visceral peritoneum **T4**: Tumor involving local extrahepatic structures by direct invasion	**Nx**: LN cannot be assessed **N0**: no regional LN **N1**: M+ in reg LN	**M0**: no distant M **M1**: distant M

Staging

pCCA		dCCA		iCCA	
Stage	**TNM**	**Stage**	**TNM**	**Stage**	**TNM**
I	T1 N0 M0	I	T1 N0 M0	IA	T1a N0 M0
II	T2 a-b N0 M0	IIA	T1 N1 M0 T2 N0 M0	IB	T1b N0 M0
IIIA	T3 N0 M0	IIB	T2 N1 M0	II	T2 N0 M0
IIIB	T4 N0 M0		T3 N0 M0		
IIIC	Any T N1 M0		T3 N1 M0		
IVA	Any T N2 M0	IIIA	T1 N2 M0	IIIA	T3 N0 M0
IVB	Any T any N M1		T2 N2 M0 T3 N2 M0		
		IIIB	T4 N0 M0 T4 N1 M0 T4 N2 M1	IIIB	T4 N1 M0 Any T, N1 M0
		IV	Any T Any N M1	IV	Any T any N M1

Treatment

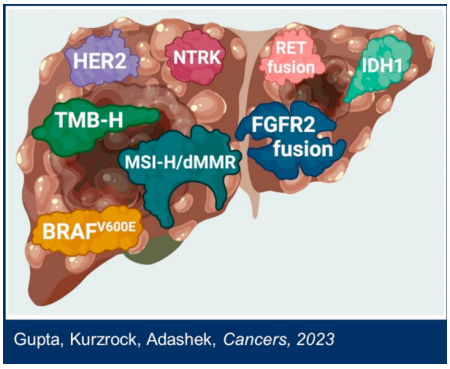
Primary surgery depends on the localization of the disease and extent of local tumor invasion.

Resectable disease

- Surgical resection (R0)
- Role of adjuvant therapy:
    - Three negative RCT evaluating adjuvant gemcitabine-oxaliplatin (PRODIGE12), gemcitabine (BCAT) and capecitabine (BILCAP). No difference in OS for the ITT population
    - BILCAP: in the per-protocol analysis adjuvant capecitabine for a period of 6 months (8 cycles) following curative resection showed a benefit from adjuvant capecitabine when compared with observation alone, in terms of OS (HR 0.71) (mOS 53 m vs 36m)
    - Conclusion: adjuvant capecitabine can be considered after resection when risk factors such as nodal positive disease are present.
- CCA with microscopic positive surgical margins (R1) has to be discussed in MDT. The role of chemoradiotherapy is unclear
- **Follow up:** Every 3-6 months in the first 2 years. Every 6-12 months up to 5 years.

Locally advanced unresectable /metastatic disease

- Molecular Testing: IDH1 mutation (25% iCCA), FGFR2 fusions (10-16% iCCA), MSI-H, NTRK IHC (optional: HER2 amplification (11-20% pCCA/dCCA), BRAF mutation (1-5%), KRAS G12C (1%)).



- 1st line treatment
  - standard option: cisplatin-gemcitabine plus durvalumab (TOPAZ-1 trial)
  - Alternative: cisplatin-gemcitabine plus pembrolizumab (Keynote 966 trial)
  - Difference in maintenance schedule for TOPAZ-1 and Keynote 966 trial

	TOPAZ -1 (Cis/Gem + Durva vs Cis Gem)	KEYNOTE- 966 (Cis/Gem + Pembro vs Cis Gem)
Number of patients	685	1069
Overall Survival	12.8 m vs 11.5 m **HR 0.80** (0.66-0.97)	12.7 m vs 10.9 m **HR 0.83** (0.72-0.95)
24-month OS	**24.9 % vs 10.4%**	**26% vs 19% (calculated)**
Progression free survival	7.2 m vs 5.7 m HR 0.75 (0.63-0.89)	6.5 m vs 5.6 m HR 0.86 (NS)
Objective response rate	26.7% vs 18.7% (OR 1.6)	Similar between arms
Grade 3 AEs	**75.7% vs 77.8%**	**69% vs 70%**
HRQoL	No deterioration	No deterioration

Maintenance schedule

Up to 8 cycles Gem/cis + Durva
Maintenance: durva mono

Up to 8 cycles Gem/cis + Pem
Maintenance: gem until PD, Pem for up to 2 years

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  - Consider oxaliplatin if cisplatin is contraindicated;
  - Gemcitabine monotherapy for patients with ECOG PS 2.

- 2nd line treatment (ECOG PS 0-2)
  - FOLFOX (ABC-06 trial) or CAPOX
  - Alternative: Naliri + 5FU (NIFTY phase 2 trial)
  - Molecular targeted therapy:
    - MSI-H: pembrolizumab (reimbursement after at least 1 line)
    - IDH-1 mutations (R132): ivosidenib (reimbursement after at least 1 line)
    - FGFR2 fusions: pemigatinib (reimbursement after at least 1 line) / futigatinib (no reimbursement)
    - NTRK fusions: entrectinib or larotrectinib.
    - RET fusions: selpercatinib (no reimbursement)
    - BRAF V600 mutations: dabrafenib plus trametinib (no reimbursement)

  - Subsequent-Line Therapy: FOLFIRI, Regorafenib (REACHIN phase 2 trial, not reimbursed in Belgium)

References

1) BILCAP trial: Primrose JN, et al. Lancet Oncol 2019;20(5):663 ; Bridgewater J, et al JCO 2022;40(18):2048
2) TOPAZ-1 trial: Oh DY, et al. Lancet Gastroenterol Hepatol 2024;9(8):694
3) KEYNOTE 966: Kelley RK, et al. Lancet 2023;401(10391):1853
4) ABC-06 trial: Lamarca A, et al. Lancet Oncol 2021;22(5):690
5) NIFTY trial: Yoo C, et al. Lancet Oncol 2021;22(11):1560
6) REACHIN trial: Demols A, et al. Ann Oncol 2023;31(9):1169
7) ClarIDHy trial (ivosidenib): Zhu AX et al JAMA oncol 2021;7(11):1669
8) Fight202 trial (pemigatinib): Abou-Alfa GK et al. Lancet Oncol 2020;21(5):671

Update: December 2024

What's new ?

- HER2 positive biliary tumors (amplification or overexpression)
  - 5 – 20% of cases
  - Pertuzumab plus trastuzumab (Javle et al Lancet oncol 2021): 23% RR
  - Neratinib (HER2 mutations) (Harding et al Nat Comm): 16% RR
  - Trastuzumab plus tucatinib (SGNTUC-019) (Nakamura Y et al JCO 2023): 47% RR
  - Trastuzumab deruxtecan (Ohba A et al JCO 2024): 36% RR
  - Zanidatamab (Herizon-BTC-01) (Harding JJ et al Lancet Oncol 2023): 41% RR