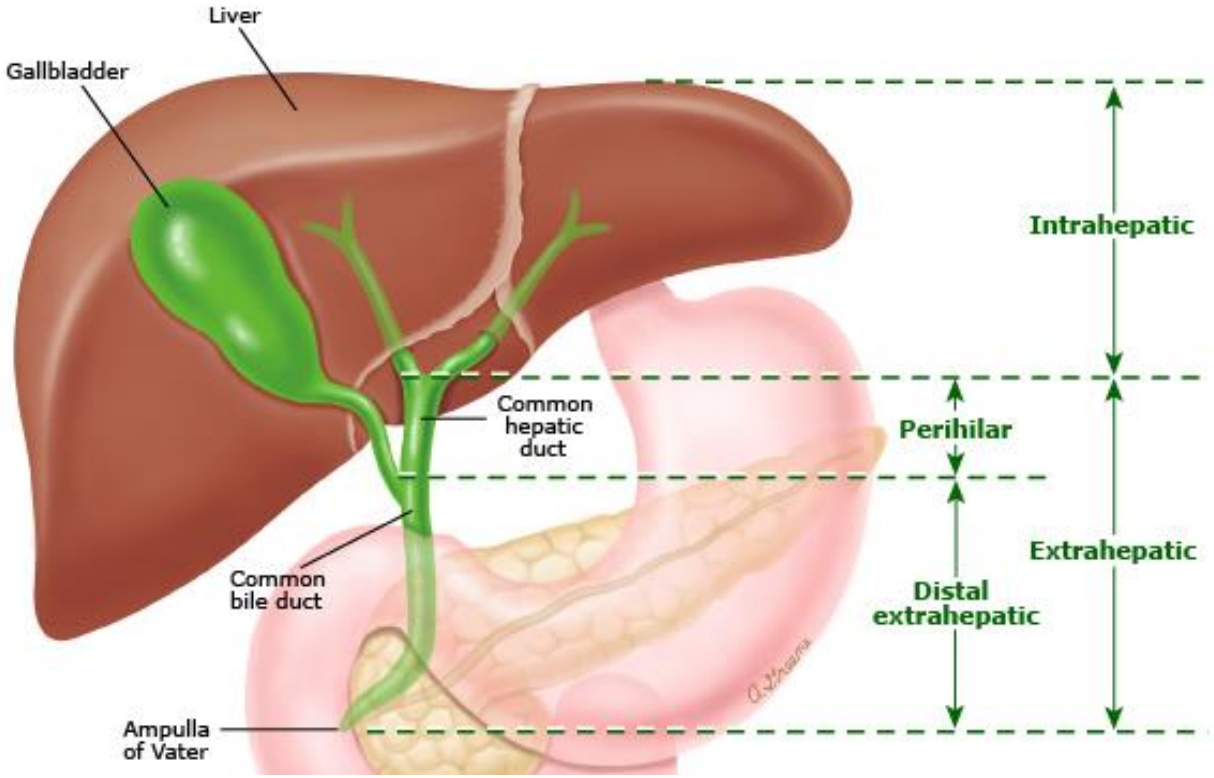
Biliary cancer



Bible class 24.03.2021

Stefan Christen

Incidence gallblader cancer

Gallbladder cancer is distinct from cholangiocarcinoma in epidemiology, pathobiology, clinical presentation and management

- 1-2:100’000 (USA)
-Higher in Korea, Japan, Eastern Europe, Spain, South America
- Female>male
- Older Age
-Shorter median survival than CCC

Risk factors gallblader cancer

- Chronic inflammation
- Cholecystolithiasis
- Porcellain gallblader (7-15%)
- Anomalous pancreaticobiliary junction
- Primary sclerosing cholangitis
- Inflammatory bowel disease
- Salmonella infection
- Polyps > 1 cm and/or PSC with any polyp

Incidence/Facts CCC

- Second most common primary hepatic malignancy after hepatocellular carcinoma
- approximately 15% of all primary liver tumours and 3% of gastrointestinal cancers
- 0.3–6 per 100,000 per year; mortality 1–6 per 100,000 per year
- >6 per 100,000 in South Korea, China and Thailand (local RF? genetic predisposition?)

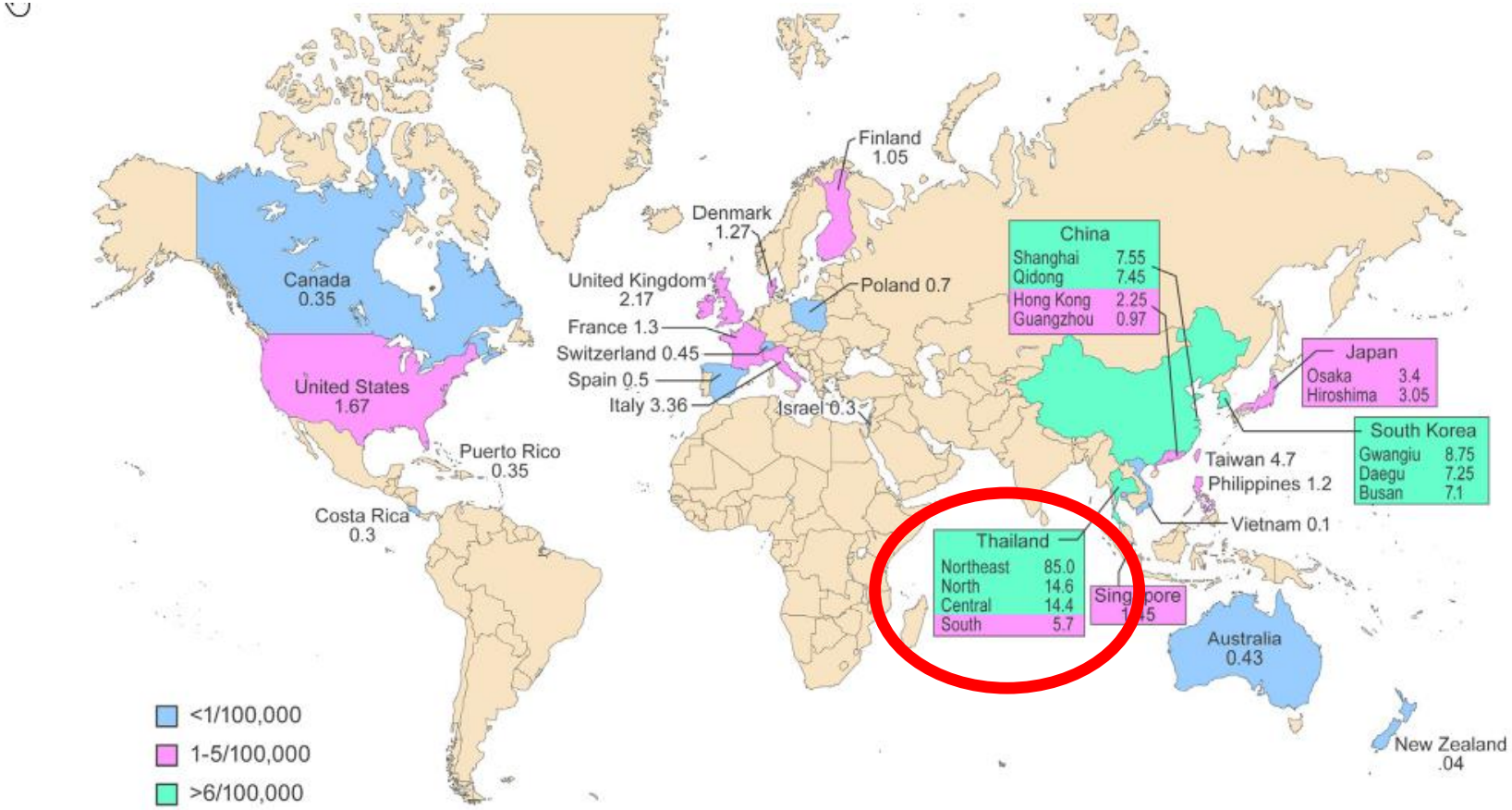


Fig. 1. Incidence of cholangiocarcinoma worldwide where reported.

Northeastern Thailand, high incidence of hepatobiliary flukes (Opisthorchis viverrini and Clonorchis sinensis)

EASL Guidelines 2014

Incidence/Facts CCC

- Incidence iCCC raising, incidence pCCC falling
  - Age-adjusted incidence rates of iCCA in the US increased by 165% from 0.3 per 100,000 in 1975–1979 to 0.9 per 100,000 in 1995–1999
  - In Italy iCCA mortality rates increased from 0.2 to 5.9 per million between 1980 and 2003 and in Germany iCCA mortality more than tripled between 1998 and 2008

- both sexes, with a slight male predominance

- usually asymptomatic in early stages and, therefore, often diagnosed when the disease is already in advanced stages

- mixed HCC–CCC tumours are a rare type of liver malignancy sharing features of both iCCC and HCC and presenting an aggressive disease course and poor prognosis

- prognosis has not improved substantially in the past decade, with 5-year survival 7–20%

Risk factors CCC

- Most without riskfactor

- Choledochal cysts (especially type 1 and 4), caroli disease, anomalous pancreaticobiliary junction

- Liver flukes

- primary sclerosing cholangitis (PSC)

-hepatolithiasis and toxins (chronic biliary inflammation and increased cellular)

- iCCC

- Cirrhosis, HCV, HBV, alcohol, obesity, NAFLD, tobacco, diabetes

Clinical italien Guidelines 2020 Risk Factros

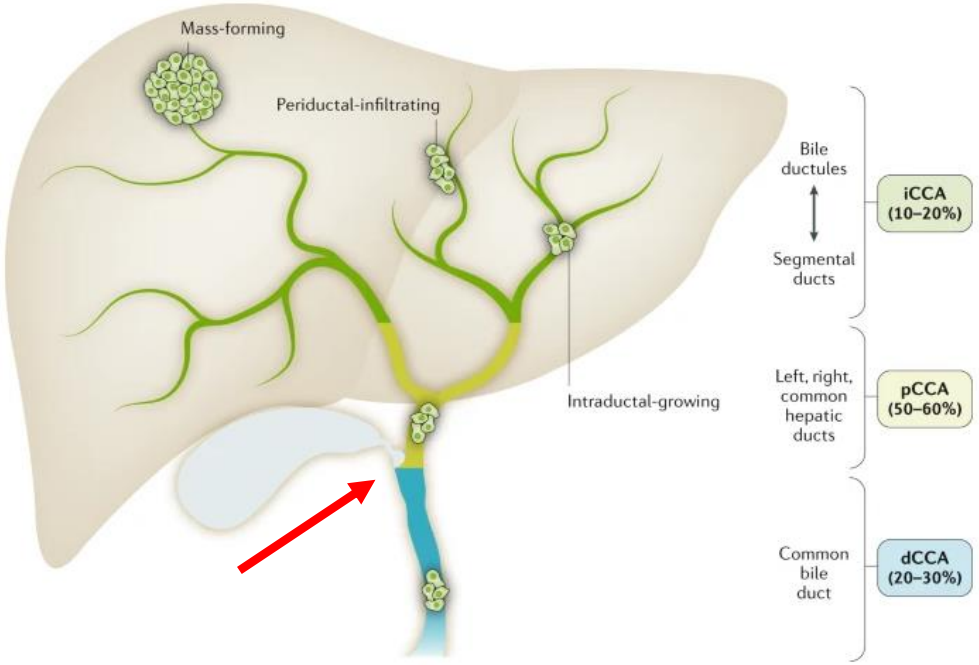
Table 3
Risk factors* for intrahepatic and extrahepatic cholangiocarcinoma.

Risk factor	OR (95% CI) Intrahepatic	Extrahepatic
Choledochal cyst	26.71 (15.80, 45.16)	34.94 (24.36, 50.12)
PSC	21.52 (7.21, 26.90)	40.80 (34.96, 47.60)
Choledocholithiasis	10.08 (5.50, 18.49)	18.58 (11.07, 31.18)
Cirrhosis	15.32 (9.33, 25.15)	3.82 (2.58, 5.65)
Chronic Pancreatitis	6.61 (5.21, 8.40)	2.66 (1.72, 4.10)
Cholelithiasis	3.38 (1.93, 5.92)	5.92 (3.09, 11.32)
HBV	4.57 (3.43, 6.09)	2.11 (1.64, 2.73)
HCV	4.28 (2.98, 6.16)	1.98 (1.33, 2.94)
Alcohol	3.15 (2.24, 4.41)	1.75 (1.20, 2.55)
NAFLD	2.22 (1.52, 3.24)	1.55 (1.03, 2.33)
Cholecystolithiasis	1.75 (0.97, 3.16)	2.94 (2.10, 4.11)
IBD	2.68 (1.79, 4.01)	2.37 (1.34, 4.22)
T2DM	1.73 (1.47, 2.04)	1.50 (1.31, 1.71)
Cigarette Smoking	1.25 (1.05, 1.49)	1.69 (1.28, 2.22)
Hypertension	1.10 (0.89, 1.37)	1.21 (0.77, 1.90)
Obesity	1.14 (0.93, 1.39)	1.20 (0.84, 1.70)

Abbreviations: PSC, Primary Sclerosing Cholangitis; NAFLD, Non Alcolic Fatty Liver Disease; IBD, Inflammatory Bowel Diseases; T2DM, type 2 diabetes mellitus.
Data obtained from ref# 1, 3, 6, 7, 63-65.

Classification

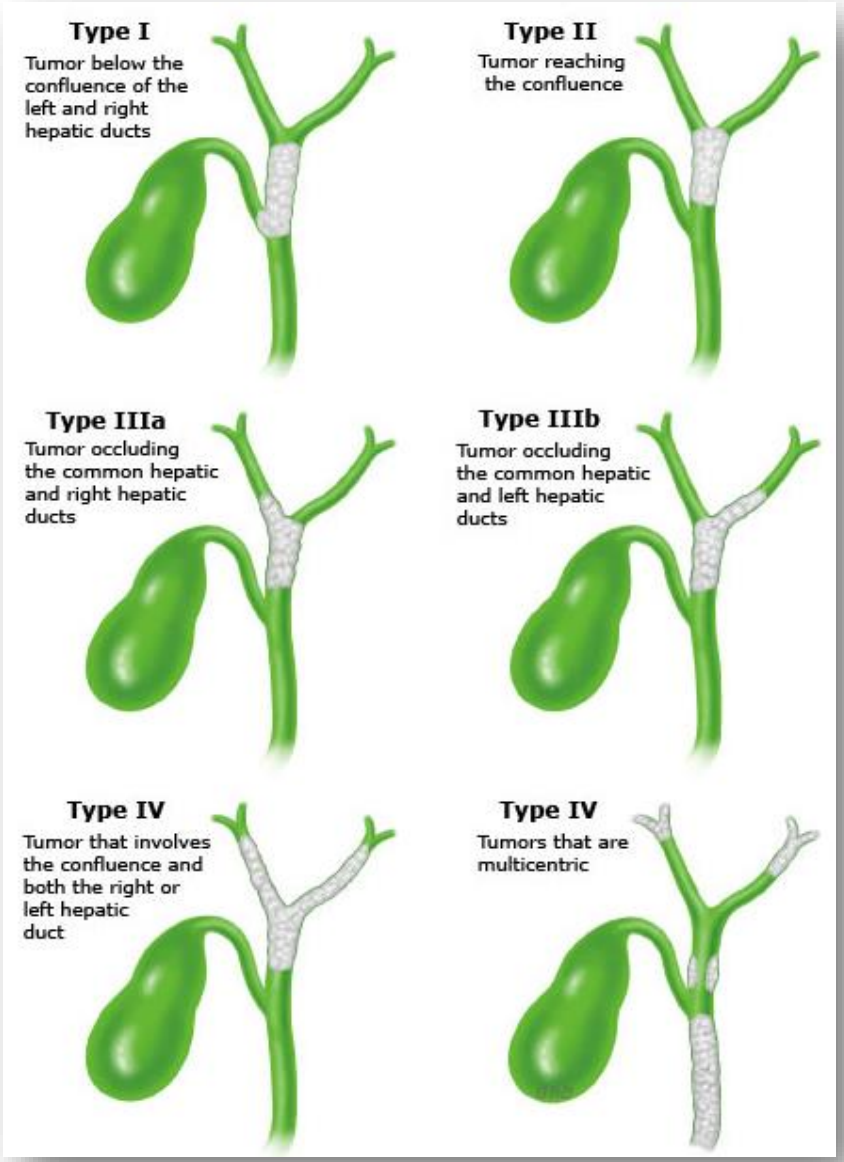
- CCA is best classified anatomically
  - intrahepatic (iCCA)
  - perihilar (pCCA): tumors above the cystic duct up to the second biliary branches
  - distal (dCCA) CCA



- The terms Klatskin and extrahepatic are discouraged (EASL)

- Histologically, the vast majority of pCCA and dCCA are mucin- secreting adenocarcinomas rich in desmoplastic stroma, while iCCA is a more heterogeneous tumor (sometimes overlapping with HCC)

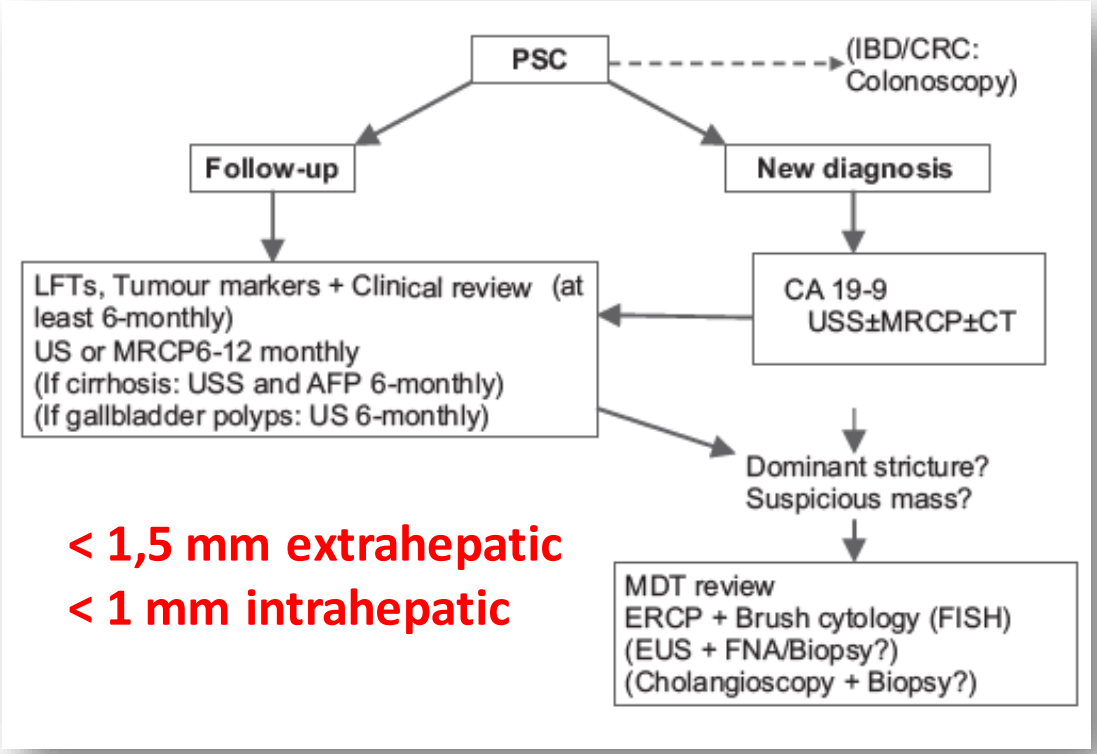
Bismuth-Corlette Classification

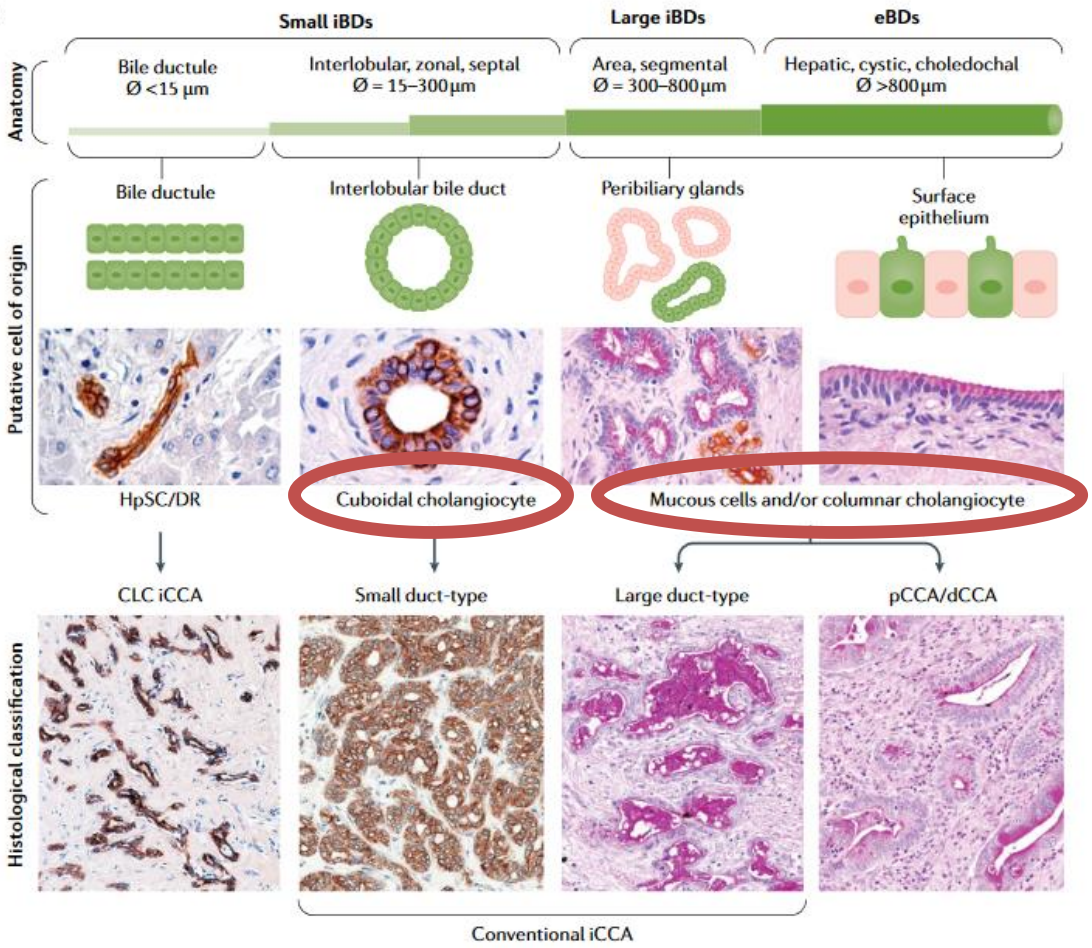


Risk of CCC in PSC

- Incidence 0.6-1.5/y
- Life- time risk of up to 20%
- 50% diagnosed within the first 2 years

Screening algorithm





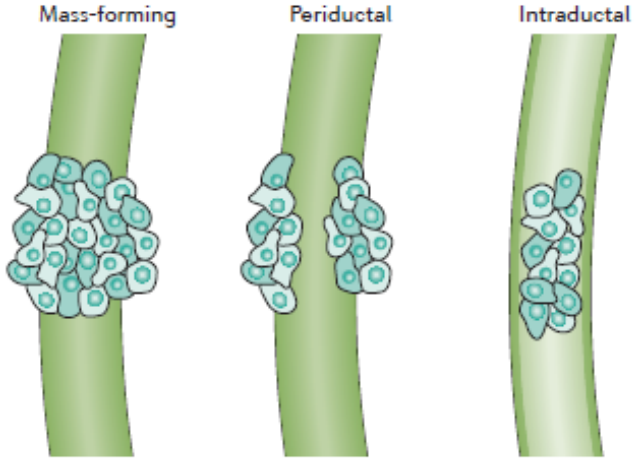


Fig. 3 | **Histological classification and putative cells of origin in cholangiocarcinoma.** Based on the duct size, the intrahepatic biliary tree can be further subdivided into small and large intrahepatic bile ducts (iBDs). Small iBDs are lined by small cuboidal cholangiocytes whereas columnar and mucous cholangiocytes line large iBDs. Typically, large iBDs contain peribiliary glands within their wall. The extrahepatic biliary tree shares anatomical features with large iBDs. Histological cholangiocarcinoma (CCA) variants reflect the phenotype of the involved duct and the putative cell of origin. Conventional intrahepatic CCA (iCCA) has two main variants: small duct-type iCCA arises in small iBDs with cuboidal cholangiocytes representing the putative cell of origin, and large duct-type iCCA involves large iBDs and is considered to be derived from columnar cholangiocytes and peribiliary glands (seromucous glands; mucous acini are shown in light pink, serous acini are shown in green). Cholangiolocarcinoma (CLC) is a frequent histological variant of iCCA and its phenotype suggests the origin from bile ductules or ductular reaction (DR) that occurs in chronic liver diseases. The vast majority of perihilar CCA (pCCA) and distal CCA (dCCA) are considered to originate from the lining epithelium and peribiliary glands. This histological subtyping underlies distinct clinicopathological and molecular features as summarized in TABLE 2. eBD, extrahepatic bile duct; HpSC, human pluripotent stem cell.

Table 2 | **Clinicopathological and molecular features of cholangiocarcinoma**

CCA type	Gross pattern	Precancerous lesion	Underlying disease	Tissue markers[a]	Frequent mutations
iCCA — CLC	Mass-forming	None	Viral, cirrhosis	NCAM	*IDH1/2*, *FGFR2* fusions, *BAP1*, *BRAF*, *ARID1A*, *KRAS*, *TP53*, *SMAD4* Increased *IDH1* and *TP53*
iCCA — small duct type	Mass-forming	None	Viral, cirrhosis	NCAM, N-cadherin, SMAD4, BAP1^{loss}	*IDH1/2*, *FGFR2* fusions, *BAP1*, *BRAF*, *ARID1A*, *KRAS*, *TP53*, *SMAD4* Increased *IDH1/2*, *FGFR2* fusion
iCCA — large duct type	Periductal infiltrating (±mass-forming) or intraductal growing	Biliary epithelial neoplasia, IPNB, ITPN, mucinous cystic neoplasm	Primary sclerosing cholangitis, liver flukes	Mucin[b], MUC5AC, MUC6, S100P, SMAD4^{loss}, BAP1	*IDH1/2*, *FGFR2* fusions, *BAP1*, *BRAF*, *ARID1A*, *KRAS*, *TP53*, *SMAD4* Increased *KRAS* and *TP53*
pCCA–dCCA	Periductal infiltrating or intraductal growing	Biliary epithelial neoplasia, IPNB, ITPN, mucinous cystic neoplasm	Primary sclerosing cholangitis, liver flukes	Mucin[b], MUC5AC, MUC6, S100P, SMAD4^{loss}, BAP1	*KRAS*, *TP53*, *SMAD4*, *ERBB3*, *PRKACA–PRKACB* fusions, *ELF3*

CCA, cholangiocarcinoma; CLC, cholangiolocarcinoma; dCCA, distal cholangiocarcinoma; iCCA, intrahepatic cholangiocarcinoma; IPNB, intraductal papillary neoplasm of the bile duct; ITPN, intraductal tubulopapillary neoplasm; pCCA, perihilar cholangiocarcinoma. [a]Markers from single-centre experience; international criteria and consensus on a definite panel of markers are still needed. [b]Mucin refers to histomorphological stains periodic acid–Schiff (PAS) or Alcian PAS.

Clinical features?

Gallblader carcinoma
- Often advanced stage => general symptoms
- If jaundice => bad prognostic sign (OS 6 mt)

iCCC
- General symptoms

eCCC
- Painless jaundice
- cholangitis uncommon without instrumentation

Laboratory parameters

CA 19-9

- Sensitivity of 40-70%, specificity of 50-80% (similar to CEA)
- Elevated: biliary obstruction, pancreatic + gastric malignancy, severe liver injury
- Not produced by 10% of people

AFP

- If possible iCCC

EASL: Serological tumor markers such as CA19-9 are insensitive for the diagnosis, but may be of prognostic significance

"CA 19-9 values greater than 100 U/ml were associated with worse recurrence-free survival after surgical resection"

How to get tissue

Direct techniques

Brushing during ERCP

-Sensitivity 40-70%

Cholangioscopy with biopsy

- Sensitivity > 90%

Transperitoneal techniques

EUS with FNA (seeding 1:10’000 – 40’000)

Percutaneous biopsy

Is tissue always required before surgery?

No!

- ERCP/PTCD only if need for interventions
- EUS (with FNP) only after surgical consultation
  (no FNP if possible OLT for perihilar CCC!)
- GI-endoscopy if diagnosis of iCCC is unclear to exclude esophageal, gastric and colon cancer

=> First surgical consultation

Differential diagnosis

IgG 4 associated cholangiopathy

- More often middle aged men
- 92% with autoimmune pancreatitis
- 74% elevated IgG4
- Treated with steroids

Metastatic adenocarcinoma from extrahepatic primary tumors

- The histological appearance of iCCA is similar to lung, pancreas, esophagus and stomach
- The differentiation of iCCA from metastatic adenocarcinoma often cannot be made on histological examination

Staging

CT chest/abdomen/pelvis

Abdominal MRI also possible

MRCP if jaundice (not invasive)

ERC +- Cholangioscopy

Staging laparascopy may be considered
(10-20% patients with peritoneal involvement, 50% lymph node positive)

TNM Classification

Table 1. The AJCC/UICC staging of cholangiocarcinoma and gallbladder cancer [21]

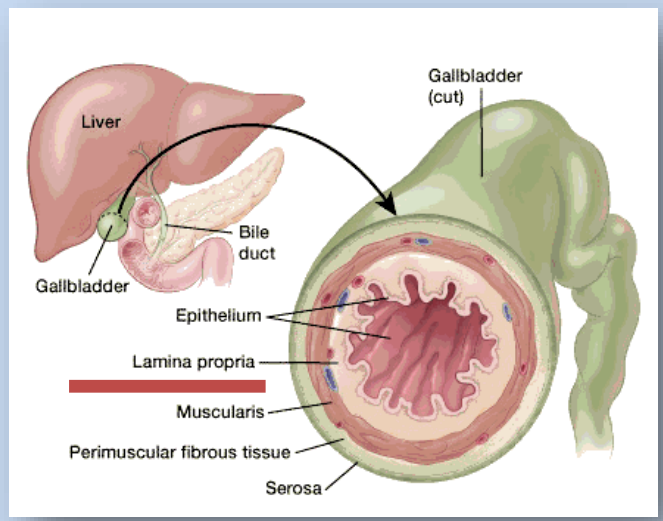
Cholangiocarcinoma						Gallbladder cancer	
Cholangiocarcinoma - intrahepatic		Cholangiocarcinoma - perihilar		Cholangiocarcinoma - distal		Gallbladder cancer	
Primary tumour (T)		Primary tumour (T)		Primary tumour (T)		Primary tumour (T)	
TX	Primary tumour cannot be assessed	TX	Primary tumour cannot be assessed	TX	Primary tumour cannot be assessed	TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour	T0	No evidence of primary tumour	T0	No evidence of primary tumour	T0	No evidence of primary tumour
Tis	Carcinoma *in situ* (intraductal tumour)	Tis	Carcinoma *in situ*	Tis	Carcinoma *in situ*	Tis	Carcinoma *in situ*
T1	Solitary tumour without vascular invasion	T1	Tumour confined to the bile duct, with extension up to the muscle layer or fibrous tissue	T1	Tumour confined to the bile duct histologically	T1	Tumour invades the lamina propria or muscular layer
T2a	Solitary tumour with vascular invasion	T2a	Tumour invades beyond the wall of the bile duct to the surrounding adipose tissue	T2	Tumour invades beyond the wall of the bile duct	T1a	Tumour invades the lamina propria
T2b	Multiple tumours, with or without vascular invasion	T2b	Tumour invades the adjacent hepatic parenchyma	T3	Tumour invades the gallbladder, pancreas, duodenum or other adjacent organs without involvement of the coeliac axis, or the superior mesenteric artery	T1b	Tumour invades the muscular layer
T3	Tumour perforating the visceral peritoneum or involving the local extrahepatic structures by direct invasion	T3	Tumour invades unilateral branches of the portal vein or the hepatic artery	T4	Tumour involves the coeliac axis, or the superior mesenteric artery	T2	Tumour invades the perimuscular connective tissue; no extension beyond the serosa or into the liver
T4	Tumour with periductal invasion	T4	Tumour invades the main portal vein or its branches bilaterally; or the common hepatic			T3	Tumour perforates the serosa (visceral peritoneum) and/or directly invades the liver

TNM Classification

Table 1. The AJCC/UICC staging of cholangiocarcinoma and gallbladder cancer [21]

Cholangiocarcinoma						Gallbladder cancer	
Cholangiocarcinoma - intrahepatic		Cholangiocarcinoma - perihilar		Cholangiocarcinoma - distal		Gallbladder cancer	
Primary tumour (T)		Primary tumour (T)		Primary tumour (T)		Primary tumour (T)	
			artery; or the second-order biliary radicals bilaterally; or unilateral second-order biliary radicals with contralateral portal vein or hepatic artery involvement				and/or one other adjacent organ or structure, such as the stomach, duodenum, colon, pancreas, omentum or extrahepatic bile ducts
						T4	Tumour invades the main portal vein or the hepatic artery or invades two or more extrahepatic organs or structures
Regional lymph nodes (N)		Regional lymph nodes (N)		Regional lymph nodes (N)		Regional lymph nodes (N)	
NX	Regional lymph nodes cannot be assessed	NX	Regional lymph nodes cannot be assessed	NX	Regional lymph nodes cannot be assessed	NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis	N0	No regional lymph node metastasis	N0	No regional lymph node metastasis	N0	No regional lymph node metastasis
N1	Regional lymph node metastasis present	N1	Regional lymph node metastasis (including nodes along the cystic duct, common bile duct, hepatic artery and portal vein)	N1	Regional lymph node metastasis	N1	Metastases to nodes along the cystic duct, common bile duct, hepatic artery and/or portal vein
		N2	Metastasis to periaortic, pericaval, superior mesenteric artery and/or coeliac artery lymph nodes			N2	Metastases to periaortic, pericaval, superior mesenteric artery and/or coeliac artery lymph nodes
Distant metastasis (M)		Distant metastasis (M)		Distant metastasis (M)		Distant metastasis (M)	
M0	No distant metastasis	M0	No distant metastasis	M0	No distant metastasis	M0	No distant metastasis
M1		M1	Distant metastasis	M1	Distant metastasis	M1	Distant metastasis

Therapy of gallbladder cancers



Surgery! Curative

- CHE for T1a cancers
- CHE with limited hepatic resection and portal lymphadenectomy => tertiary center!

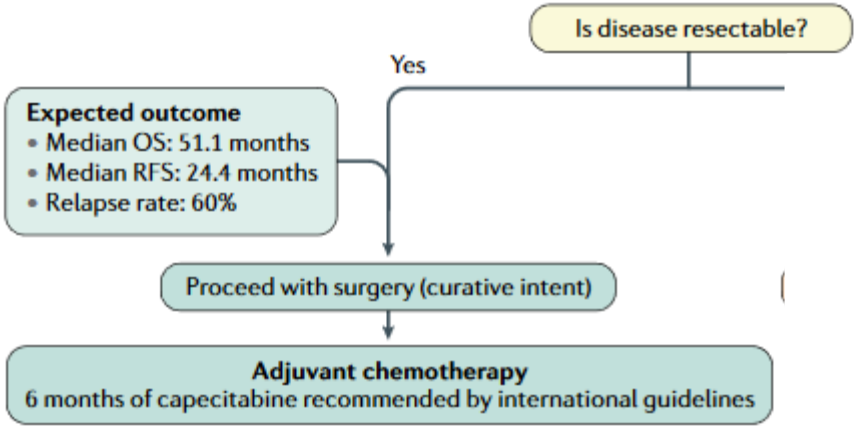
What is usually not resectable?

Distant metastases

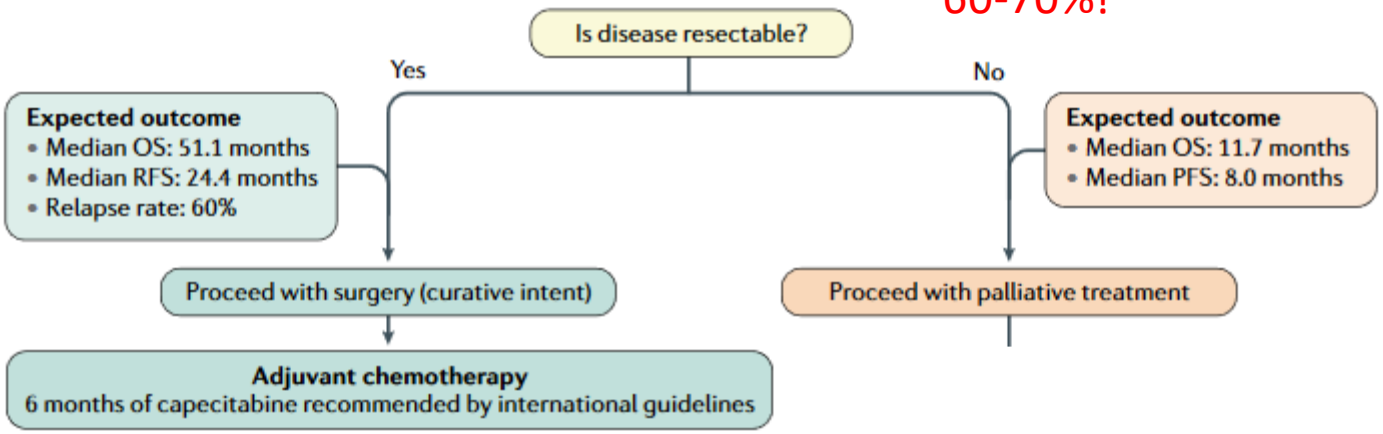
Lymph node metastases beyond the porta hepatis

Extensive involvement of the porta hepatis

borderline resectable disease->Neoadjuvant chemotherapy


Is disease resectable?
Yes
Expected outcome
• Median OS: 51.1 months
• Median RFS: 24.4 months
• Relapse rate: 60%
Proceed with surgery (curative intent)
Adjuvant chemotherapy
6 months of capecitabine recommended by international guidelines

60-70%!


Is disease resectable?
Yes
No
Expected outcome
• Median OS: 51.1 months
• Median RFS: 24.4 months
• Relapse rate: 60%
Expected outcome
• Median OS: 11.7 months
• Median PFS: 8.0 months
Proceed with surgery (curative intent)
Proceed with palliative treatment
Adjuvant chemotherapy
6 months of capecitabine recommended by international guidelines

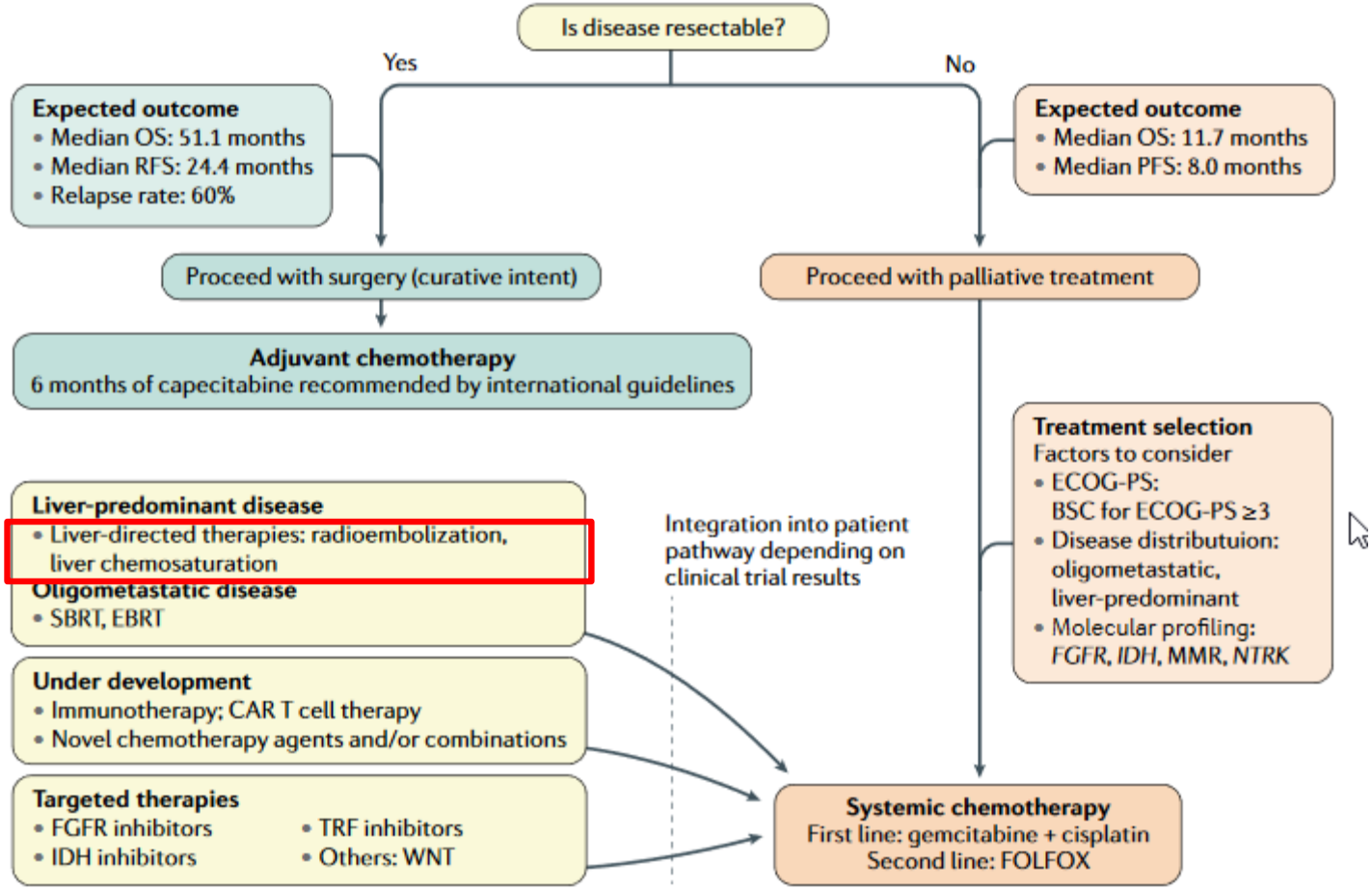


Fig. 7 | **Current decisions and management of patients with cholangiocarcinoma.** Flow chart of the presentation, management and outcome of patients with cholangiocarcinoma (CCA) according to current formal guidelines (Supplementary Table 1). BSC, best supportive care; CAR, chimeric antigen receptor; EBRT, external beam radiation therapy; ECOG-PS, Eastern Cooperative Oncology Group Performance Status; FOLFOX, folinic acid, 5-fluorouracil and oxaliplatin; MMR, DNA mismatch repair; OS, overall survival; PFS, progression-free survival; RFS, relapse-free survival; SBRT, stereotactic body radiation therapy.

Chemoresistence

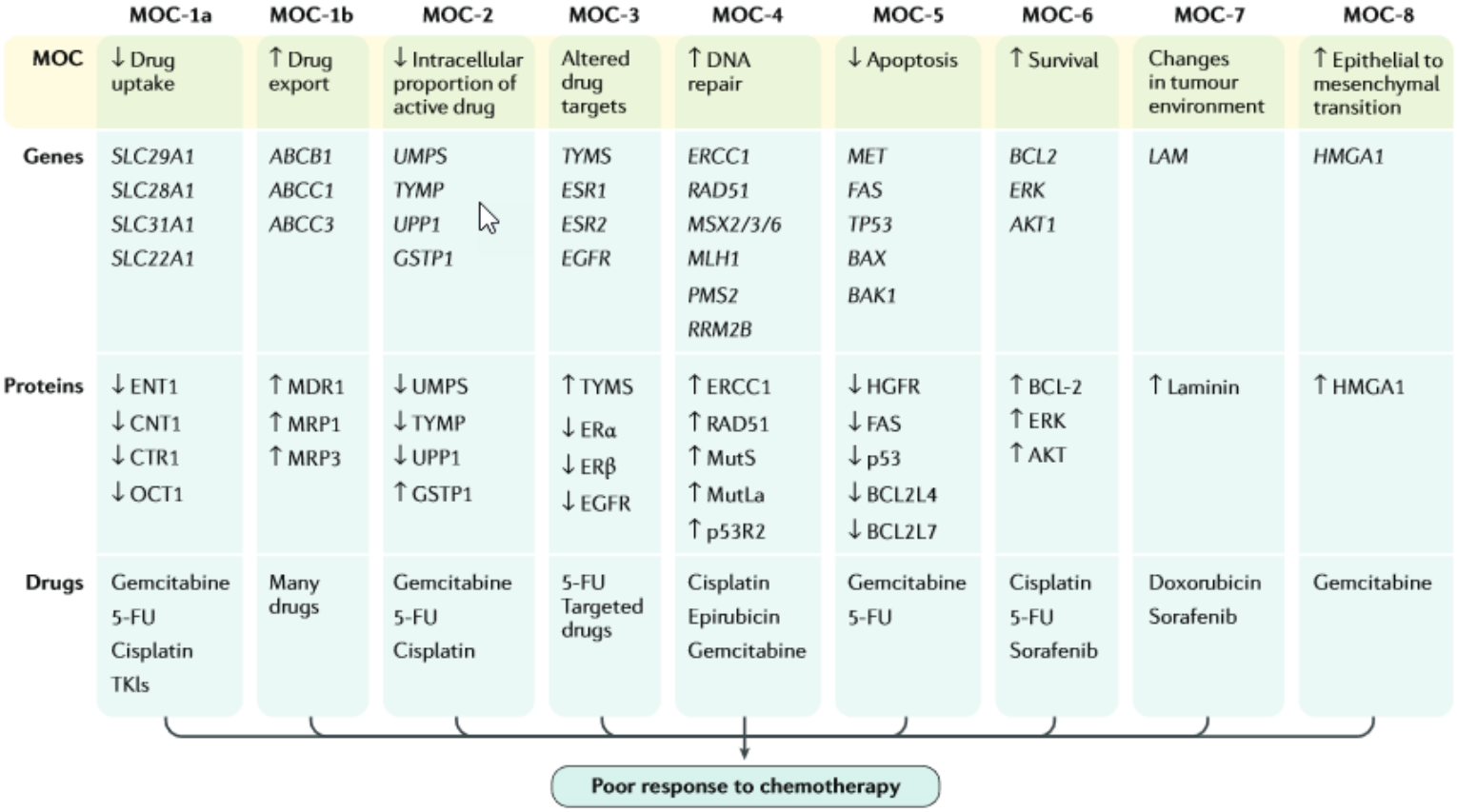


Fig. 8 | **Mechanisms of chemoresistance in cholangiocarcinoma.** Relevant genes and proteins involved in each type of mechanism of chemoresistance (MOC-1 to MOC-7) in cholangiocarcinoma (CCA) are shown, either because they are upregulated or downregulated or their function is enhanced or impaired. Drugs whose efficacy is affected by these changes in the resistome are shown. 5-FU, 5-fluorouracil; TKI, tyrosine-kinase inhibitor.

Surgery for CCC

iCCC
⇒ Resection of the involved segments

dCCC
⇒ Pancreatoduodenectomy/bile duct excision

Mid duct CCC (type I/II pCCC)
⇒Rarely only bile duct excision

pCCC III/IV
⇒ Major hepatectomy/caudate lobectomy/bile duct excision

⇒Only 30-40% are eligible for resection

What if the future liver remnant is to low?

- FLR of approximately 25% after resection is enough if the liver function is normal
- In case of hepatic dysfunction or earlier liver injury (eg, due to chemotherapy) FLR of approximately 40% is recommended
- FLR to body weight ratio should be greater than 0.5 (healty liver)

If FLR < 30-40%

$\Rightarrow$ Contralateral portal vein embolisation and ipsilateral biliary drainage

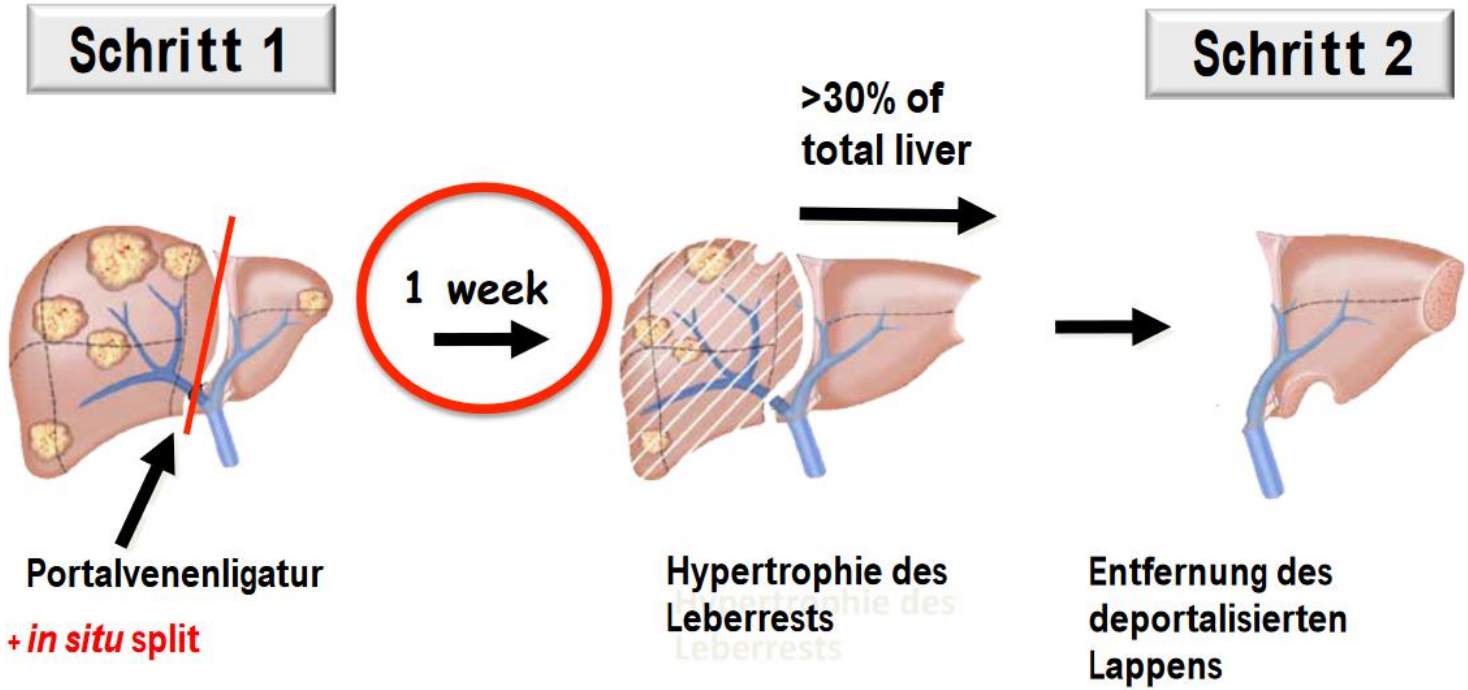
If FLR after portal vein embolisation < 20% or degree of hypertrophy < 5%

$\Rightarrow$ High risk for surgery

ALLPS

- faster hypertrophy than portal vein embolisation (1-2W vs 6-8W)

Was ist “ALPPS”?



Associating Liver Partition and Portal Vein Ligation for Staged Hepatectomy

Clavien Ann Surg 2012

Role of liver transplantation

Highly selected patients with locally unresectable disease, recourence up to 50%

After neoadjuvant radiochemotherapy

Patients with underlying liver disease mainly PSC

a multi centre retrospective study in 216 patients with early-stage, unresectable pCCA treated with neoadjuvant chemoradiotherapy followed by liver transplantation in 12 centres in the USA demonstrated 5- year disease-free survival of 65%

Indication for drainage before surgery

Absolute indications for biliary drainage

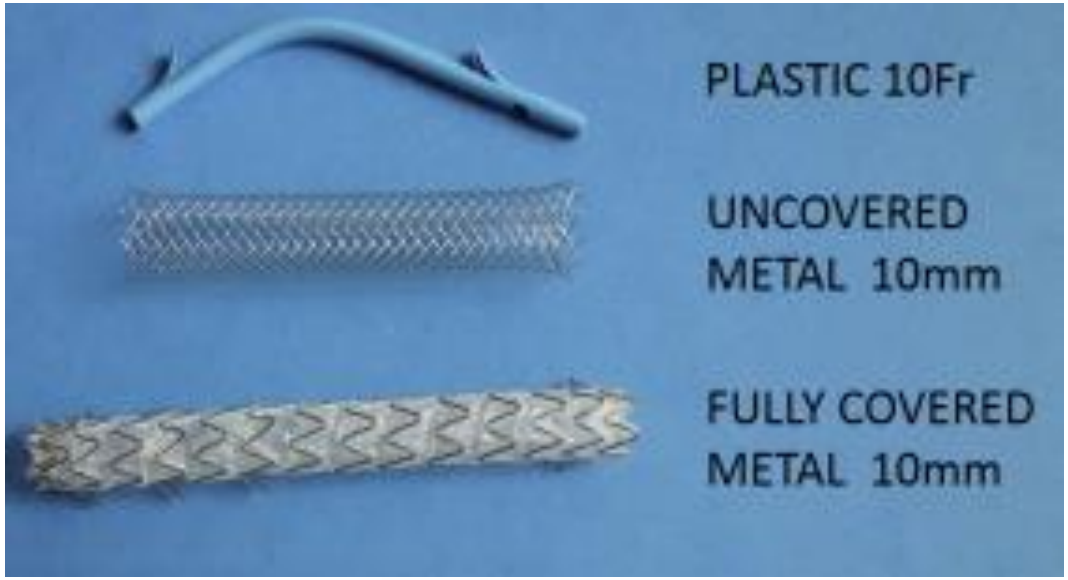
- cholangitis or sepsis originating from the biliary tract (rare)
- intractable pruritus
- long-lasting or severe jaundice (total bilirubin > 250 mmol/l)
- patients eligible for neoadjuvant chemotherapy or preoperative procedures such as portal embolization

Otherwise routine biliary drainage does not improve morbidity or mortality of patients with resected pCCA.

-> Not routinely recommendend,

-> Risk of complications and bacterial translocation with cholangitis

Biliary stents



Liegedauer

3 Mt

>6 Mt

bis 6 Mt

Biliary stents

Surgery or unclear diagnosis/resectability

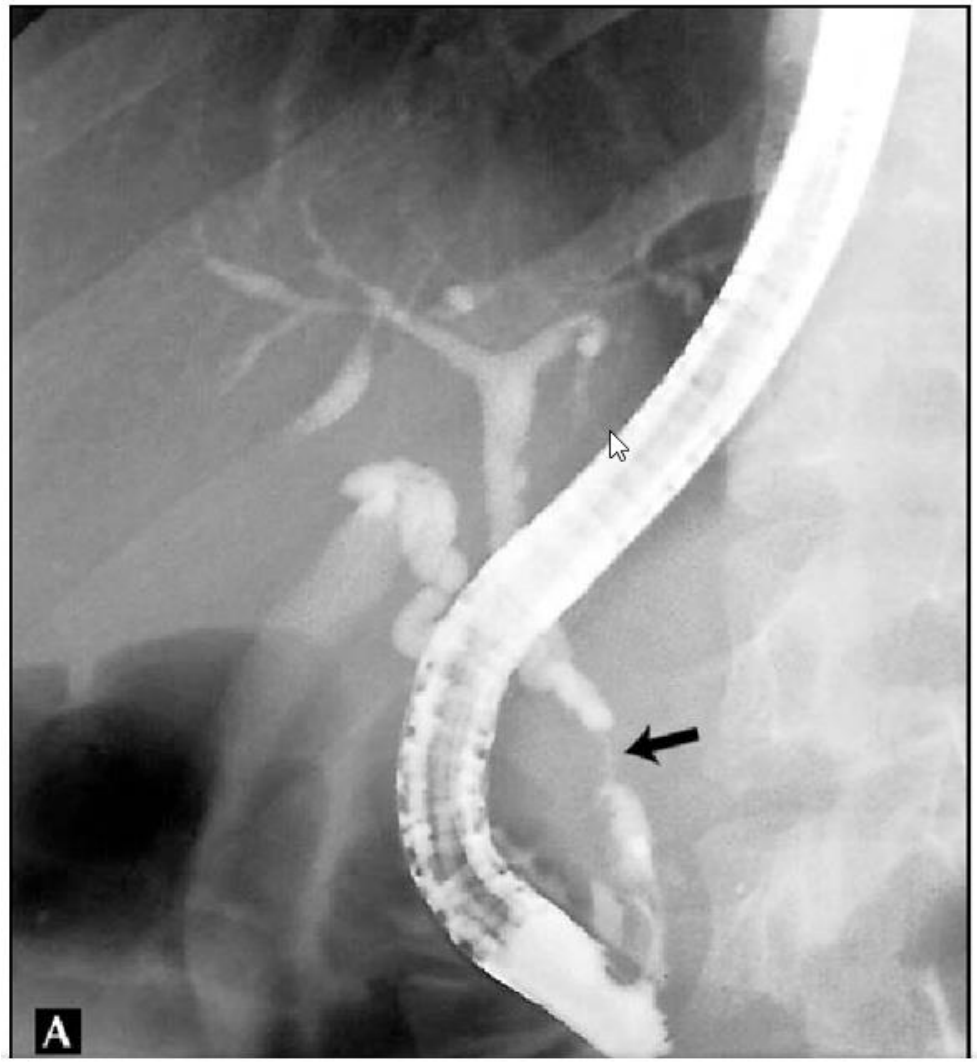
$\Rightarrow$ plastic stent

Survival < 4 months

$\Rightarrow$ Usually plastic stent

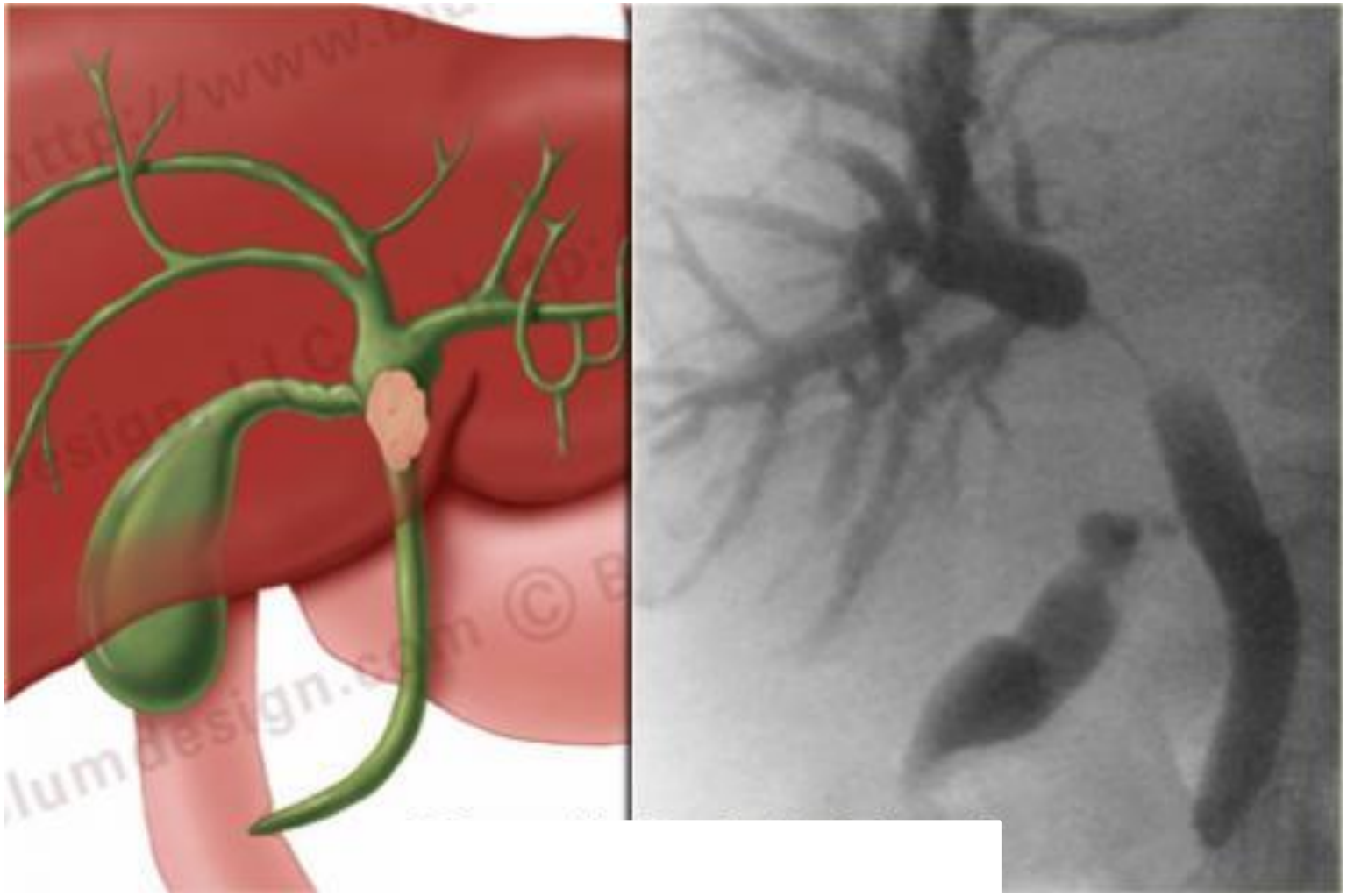
Otherwise SEMS possible

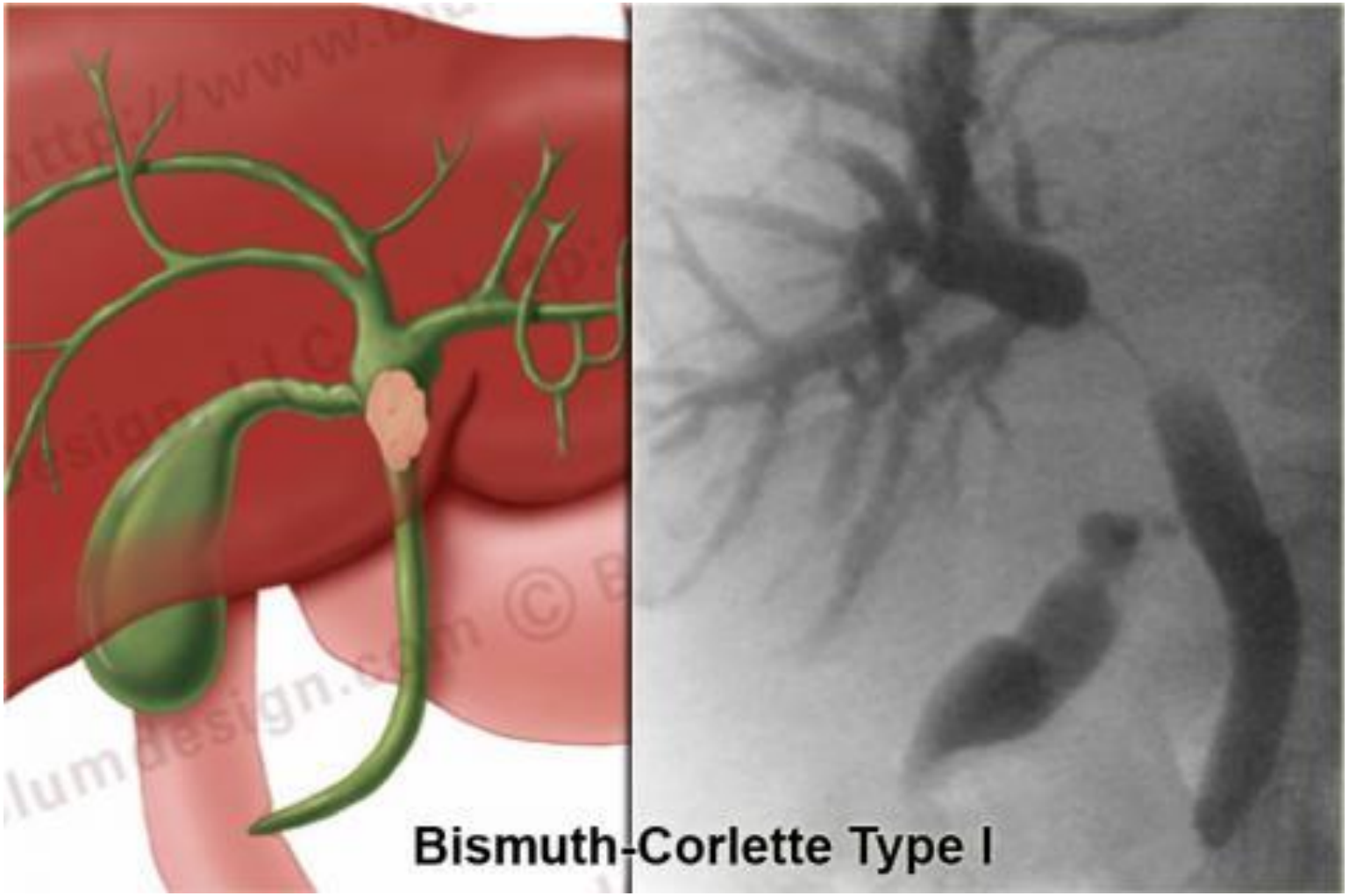
- Covered SEMS => more dislocation
- Uncovered SEMS => more tumor ingrowth

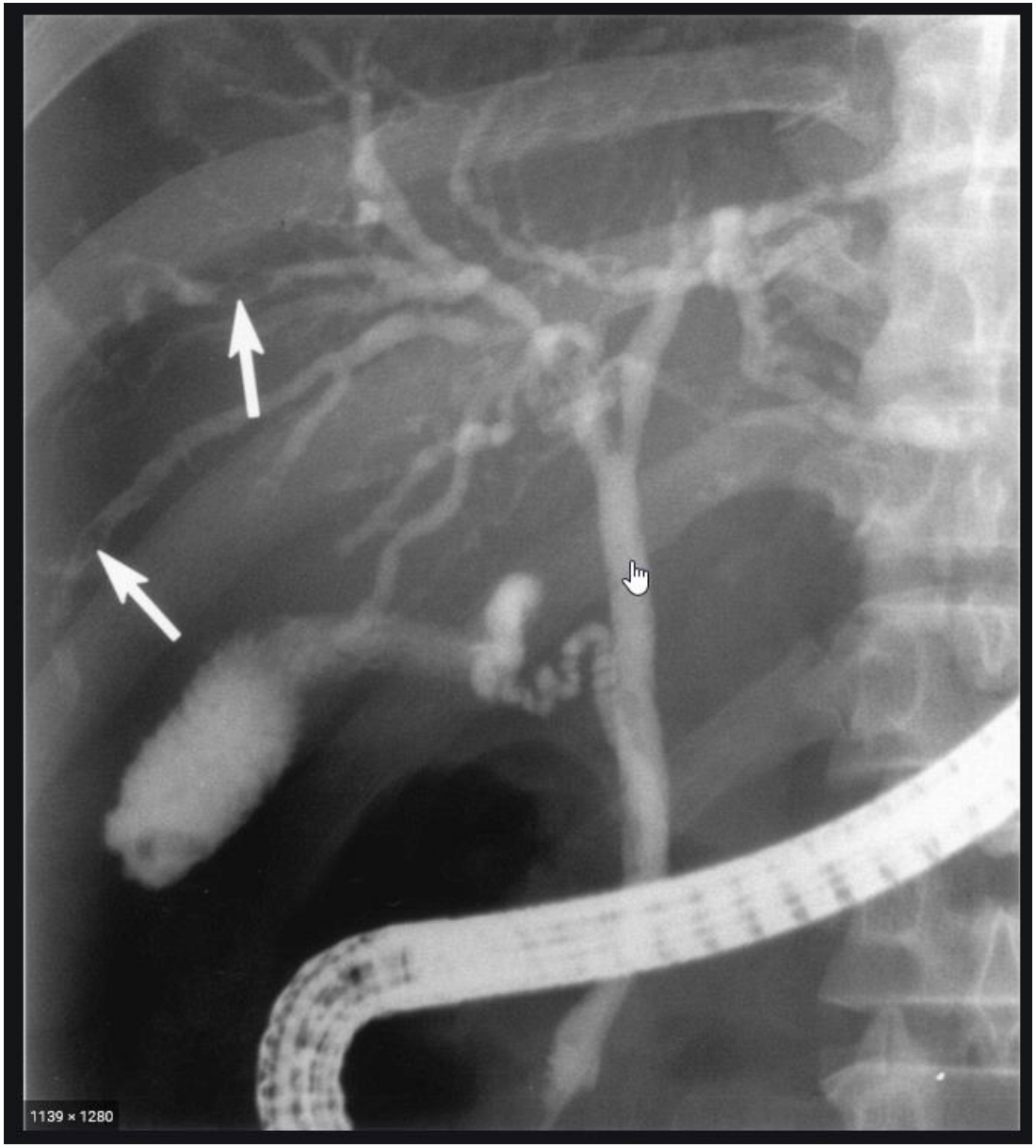


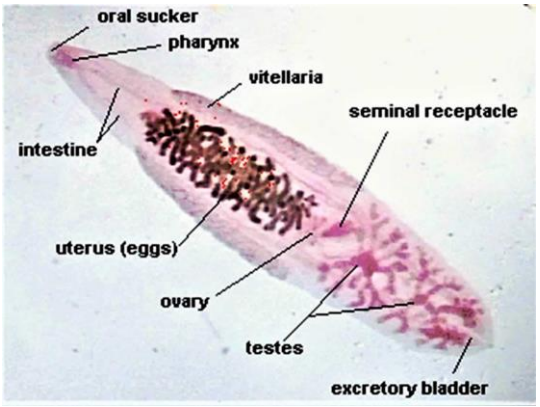
and PSC

distal CCC

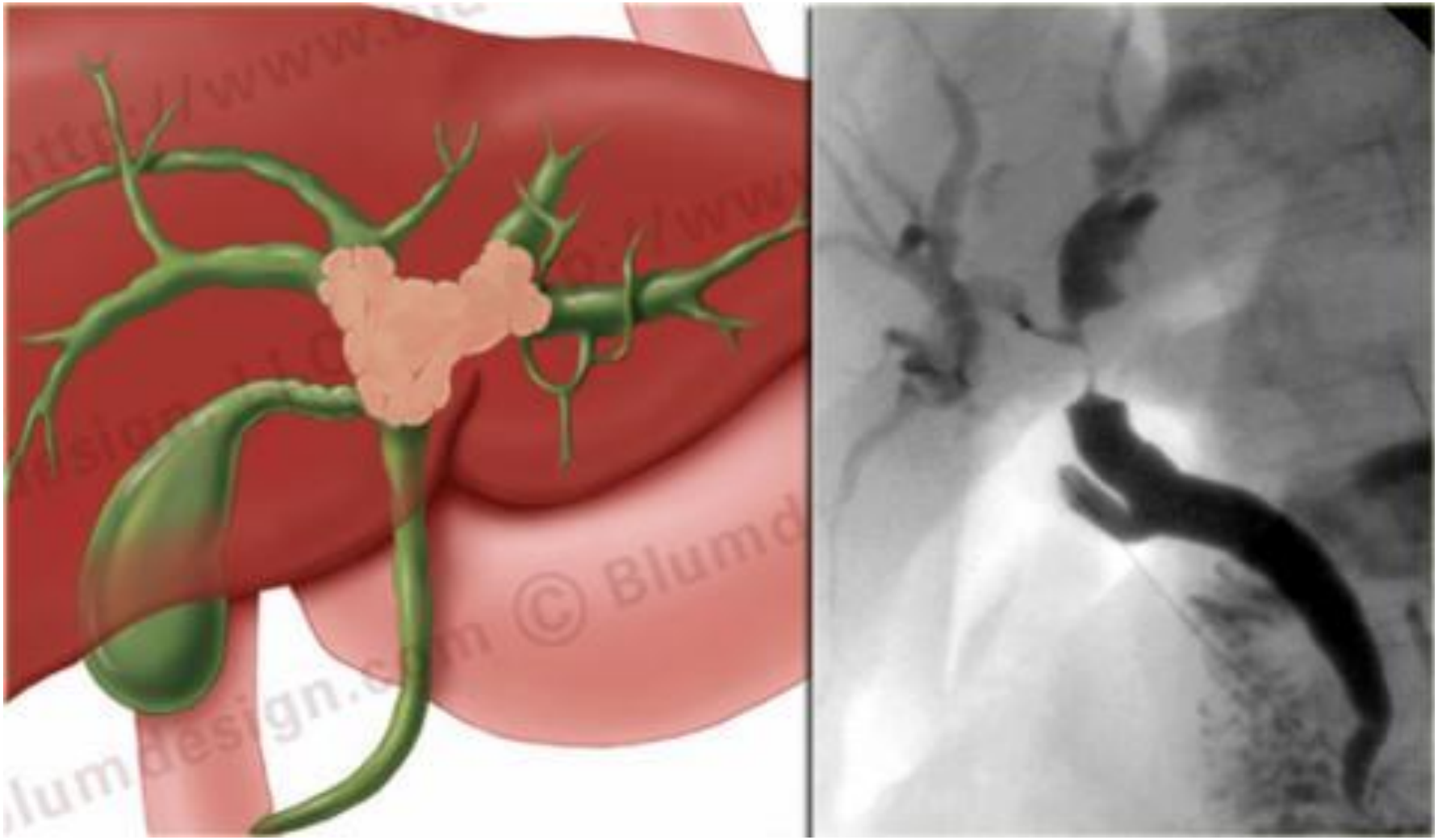



Bismuth-Corlette Type I





clonorchiasis



Klatzkin IV

Summary

Cholangiocarcinoma (CCA) is the second most common primary liver cancer, characterized by a poor prognosis and resistance to chemotherapeutics.

The End