Intrahepatic cholangiocarcinoma, its variants, and its precursor lesions

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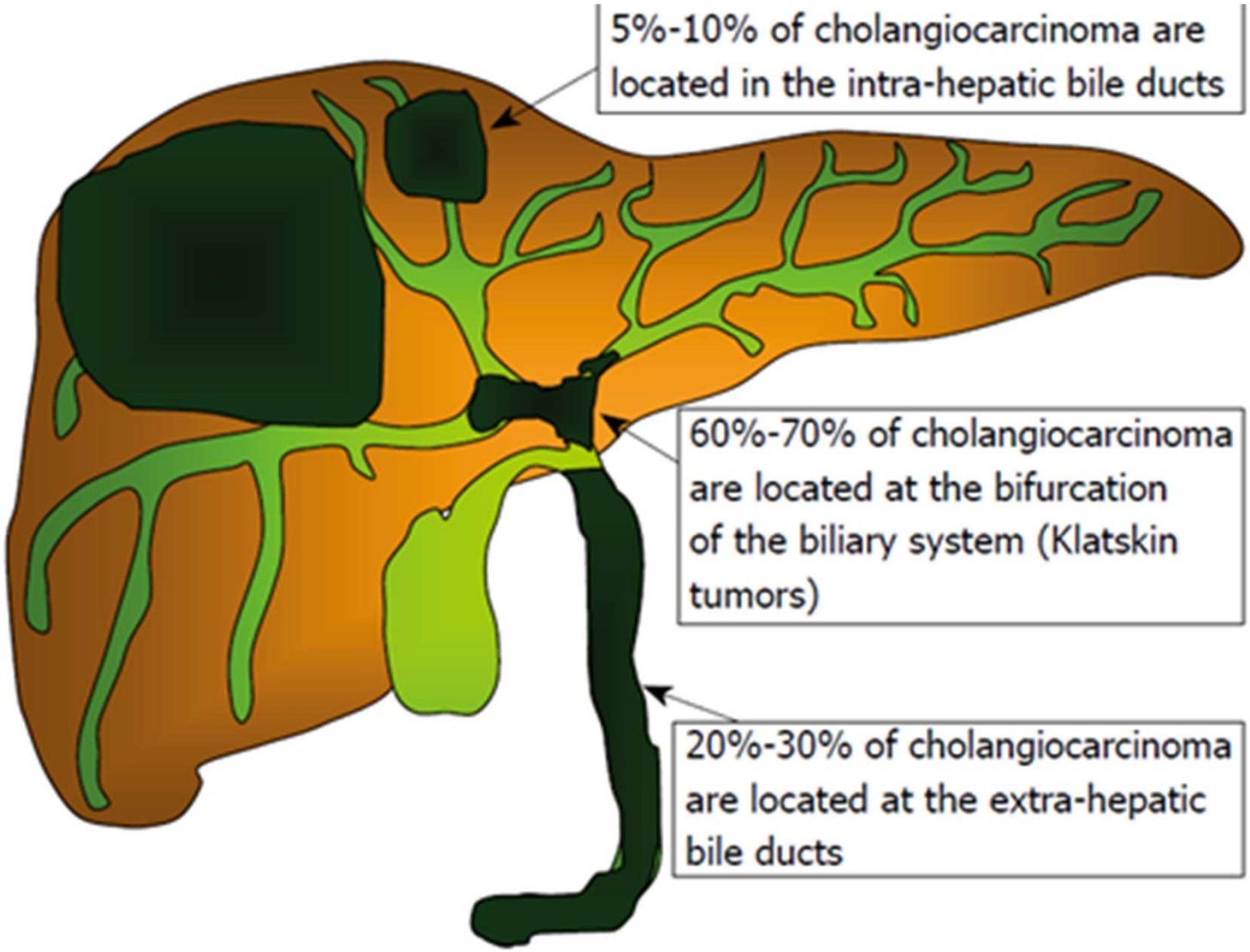
Cholangiocarcinoma

- Intrahepatic cholangiocarcinoma
- Perihilar cholangiocarcinoma (Klatskin tumour)
- Distal cholangiocarcinoma

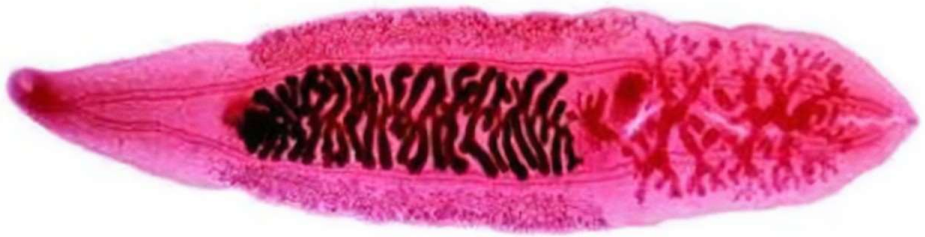

5%-10% of cholangiocarcinoma are located in the intra-hepatic bile ducts
60%-70% of cholangiocarcinoma are located at the bifurcation of the biliary system (Klatskin tumors)
20%-30% of cholangiocarcinoma are located at the extra-hepatic bile ducts

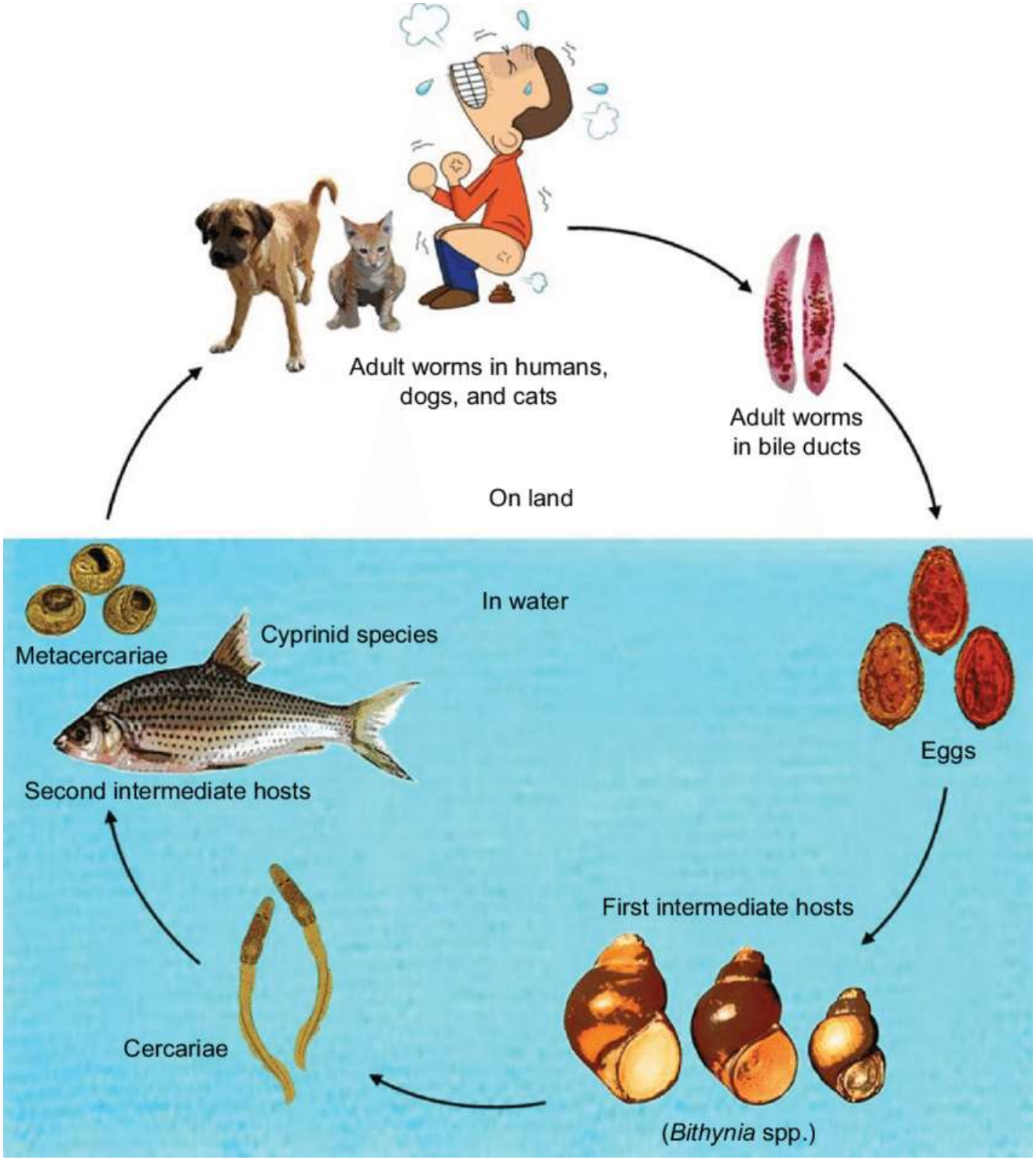
Intrahepatic cholangiocarcinoma

- 10-15% of primary liver malignancies
- General incidence: 1/100.000 people/year
- Proposed risk factors: choledochal cyst, anatomical anomalies, primary sclerosing cholangitis, chronic B or C viral hepatitis, non-alcoholic fatty liver disease, Lynch syndrome
- Higher incidence: South Korea (>Clonorchis sinensis) and Thailand (>Opistorchis viverrini)

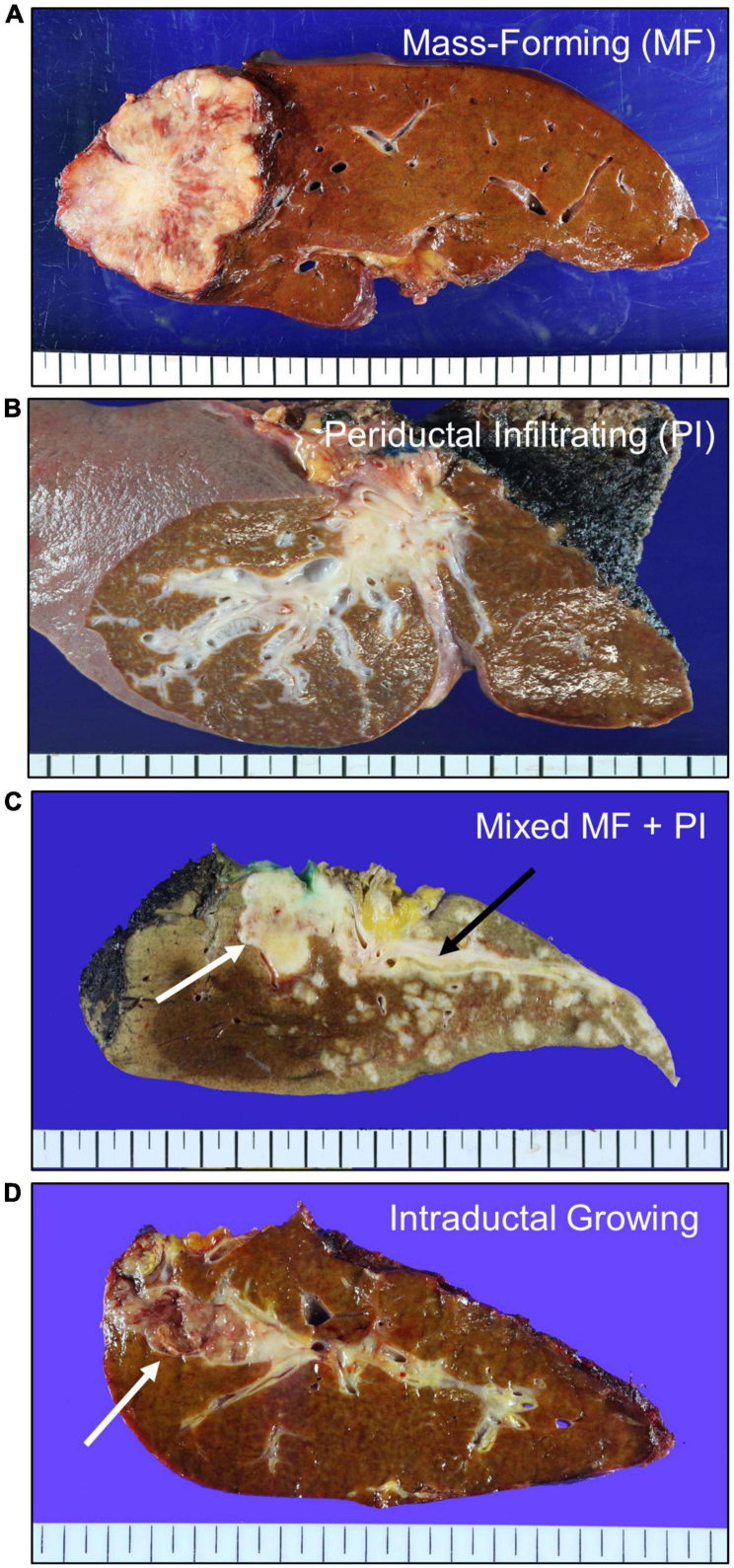
Clonorchis sinensis

Opistorchis viverrini





Hughes T, *Int J Gen Med* 2017



Chung T, *Front Med (Lausanne)* 2022

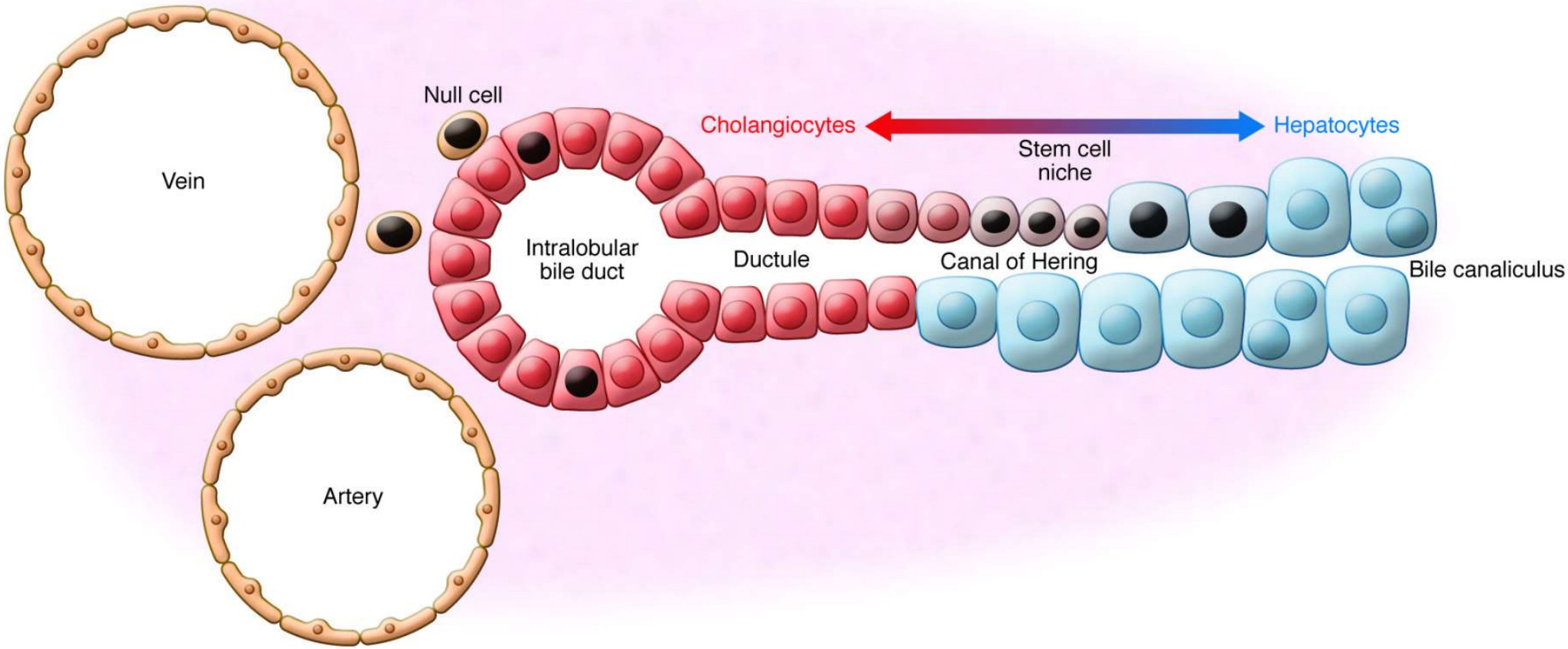
Intrahepatic cholangiocarcinoma (iCCA)

Small duct type

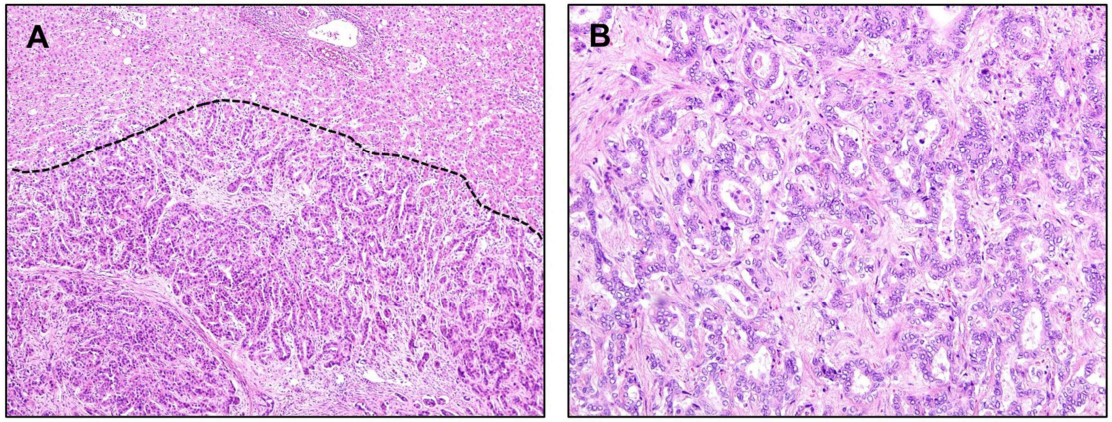
- Peripheral, ductular or cholangiolar type (synonyms)
- 36-84% of iCCA cases
- Background: often chronic hepatitis B or C, alcoholic hepatitis, non-alcoholic steatohepatitis
- Origin: canals of Hering, cuboidal cholangiocytes, interlobular bile ducts

Large duct type

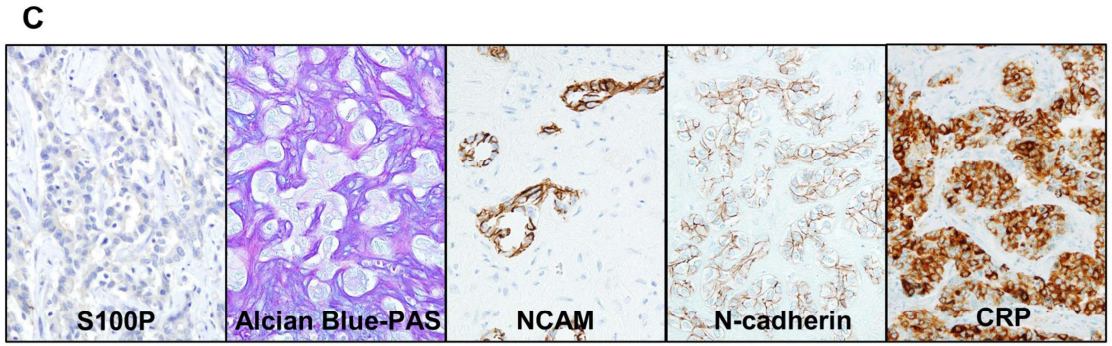
- Bile duct type of perihilar type (synonyms)
- 8-60% of iCCA cases
- Background: often chronic bile duct injury due to hepatolithiasis, parasites or primary sclerosing cholangitis
- Origin: columnar biliary epithelium, peribiliary glands around them

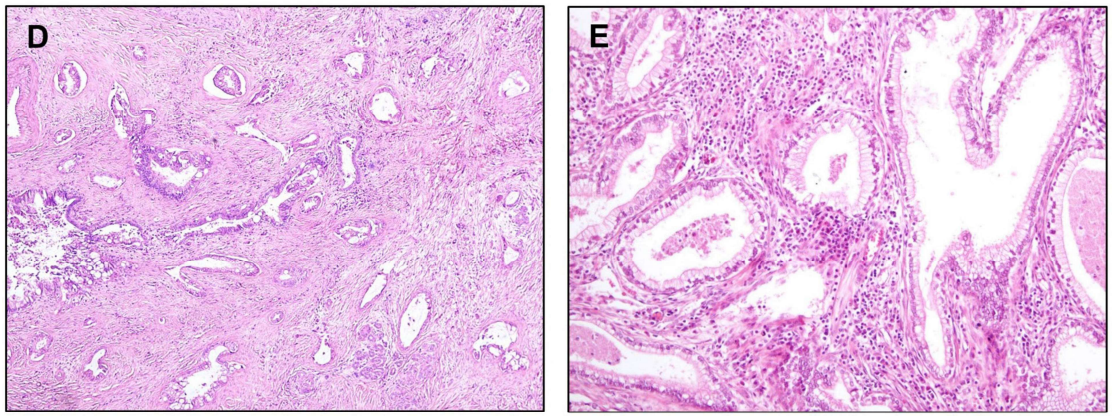


Cordes C, *J Clin Invest* 2013

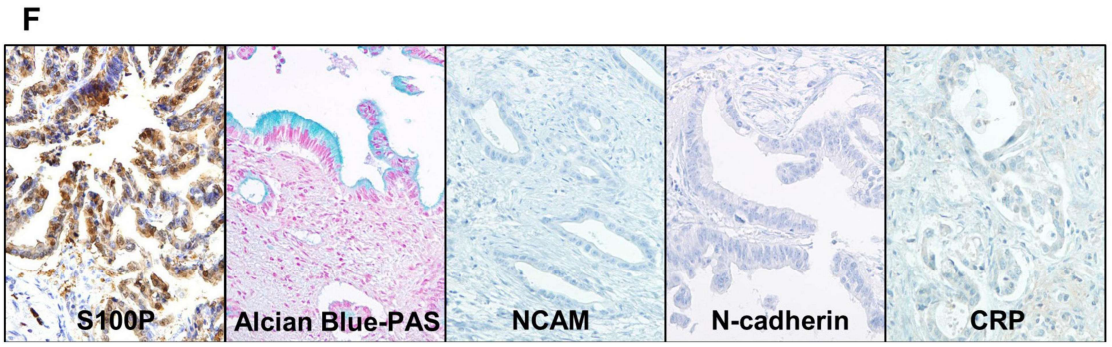


A, B and C: small duct type

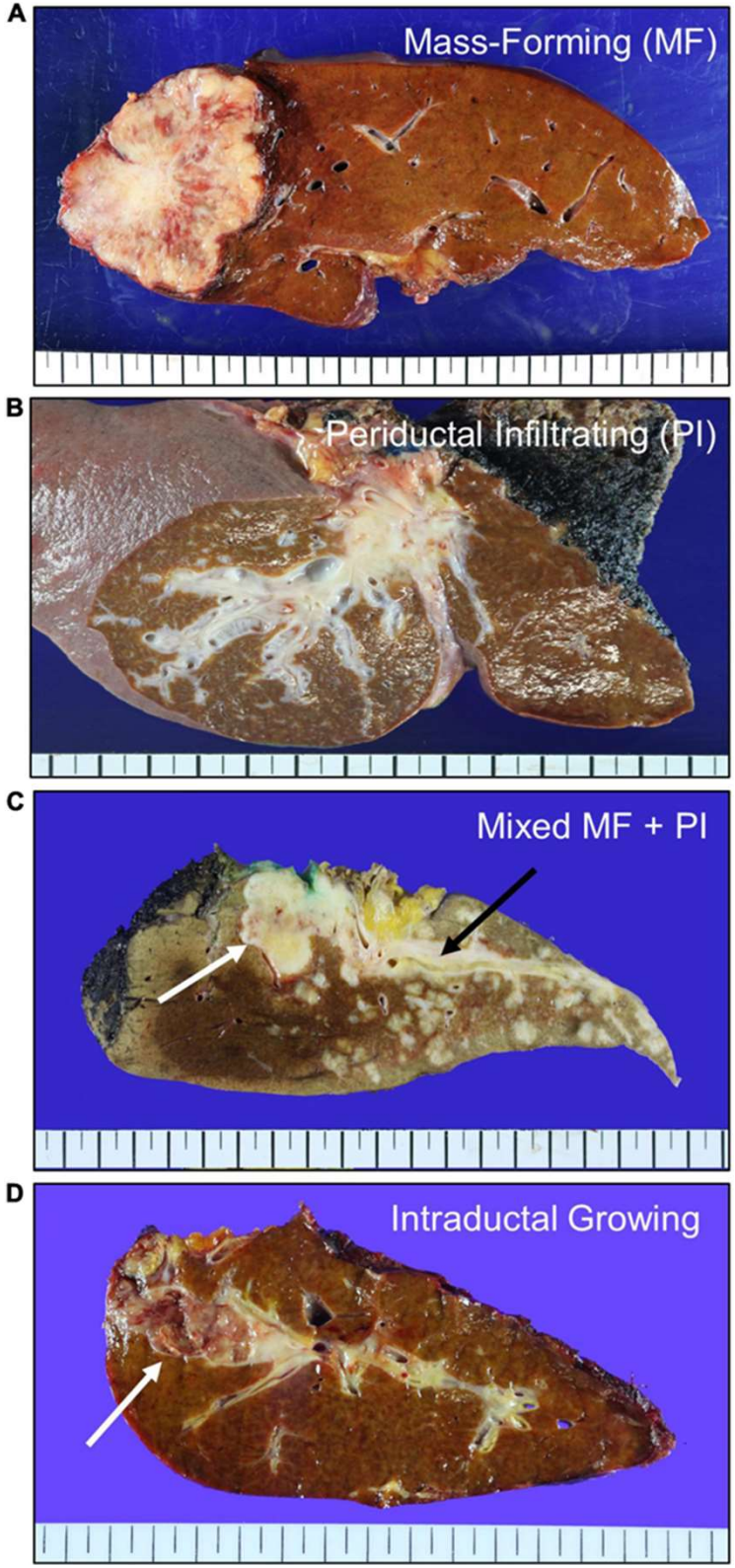




D, E and F: large duct type



Chung T, *Front Med (Lausanne)* 2022



> Small duct and large duct types

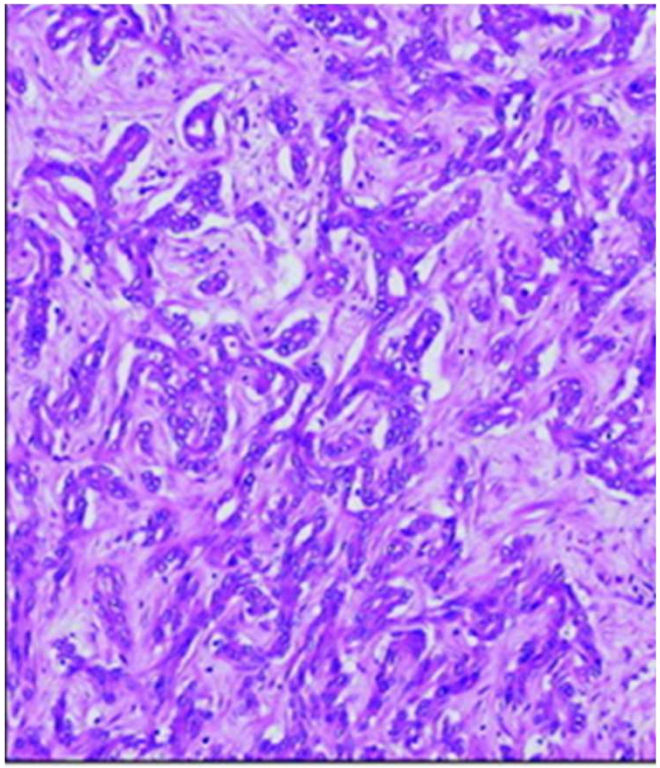
> Exclusively large duct type

Chung T, *Front Med (Lausanne)* 2022

Variants of intrahepatic cholangiocarcinoma

- Cholangiolocarcinoma
- Intrahepatic cholangiocarcinoma with ductal plate malformation pattern
- Adenosquamous carcinoma/squamous carcinoma
- Mucinous carcinoma/signet ring cell carcinoma
- Clear cell carcinoma
- Mucoepidermoid carcinoma
- Lymphoepithelioma-like carcinoma
- Sarcomatous intrahepatic carcinoma

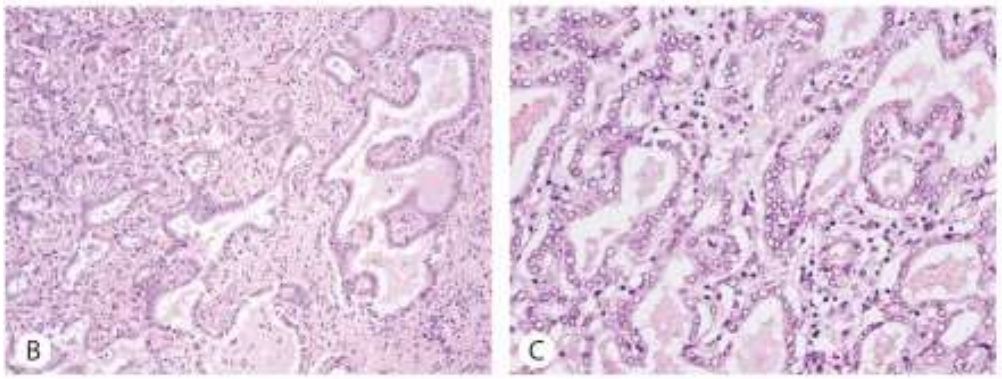
Cholangiolocarcinoma



- Belongs to the small duct type
- iCCA with more than 80% of tumour area showing cholangiolocellular differentiation
- Excellent outcome

Komuta M, *Hepatology* 2008

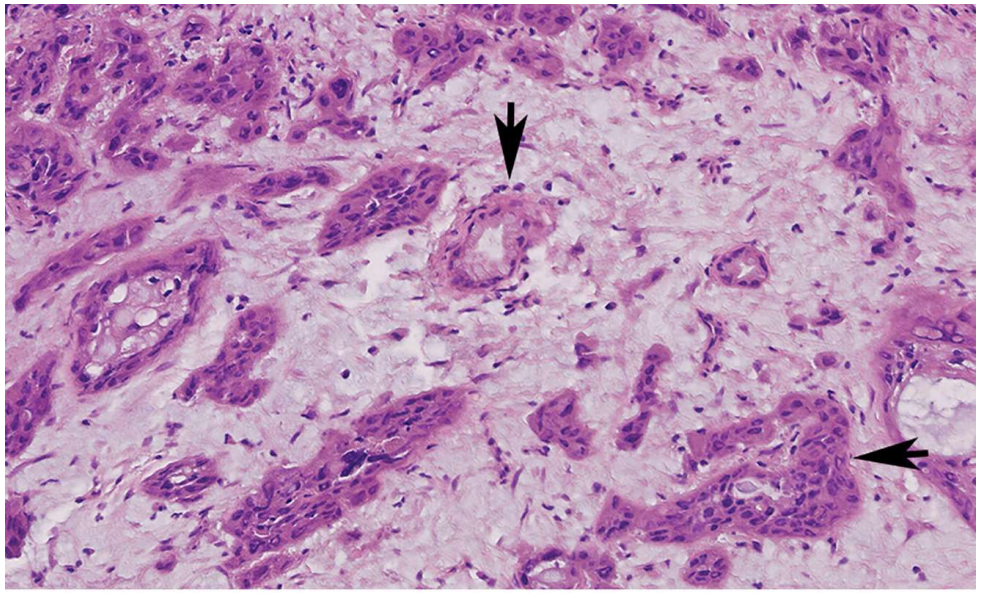
Intrahepatic cholangiocarcinoma with ductal plate malformation pattern



- Ductal plates: pathologically existing embryonic bile duct structures
- 3% of iCCA cases
- Survival better than that of conventional small duct ICC

Choe JY, *Clin Mol Hepatol* 2014

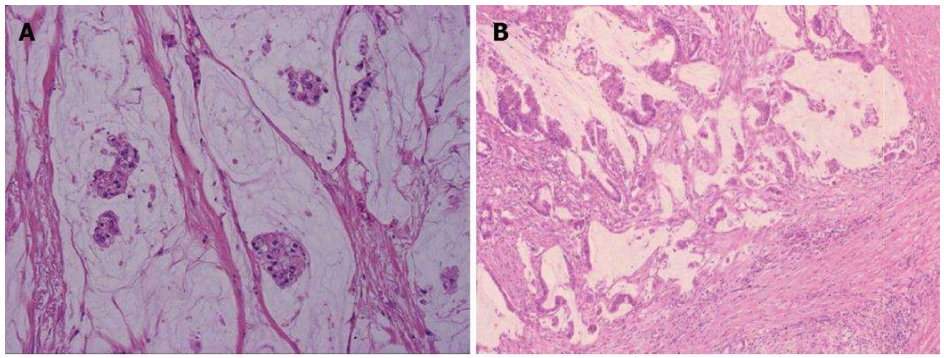
Adenosquamous carcinoma/ squamous carcinoma



- Correlated with chronic cholangitis caused by liver flukes or hepatolithiasis
- Poor prognosis, median survival 6 months

Gou Q, *Front Oncol* 2021

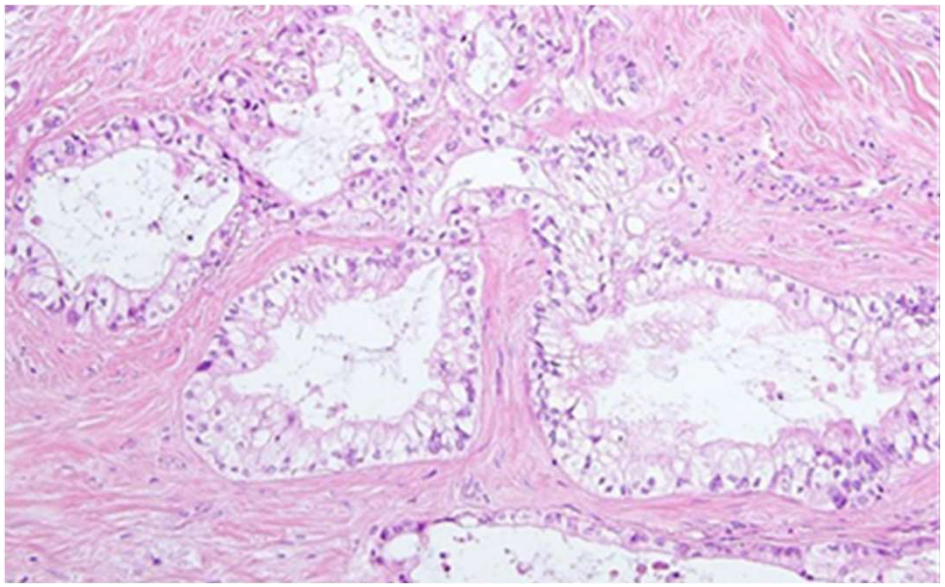
Mucinous carcinoma/ signet ring cell carcinoma



- Belongs to large duct type iCCA
- By convention at least 50% of tumour volume
- Usually due to malignant transformation of intraductal papillary neoplasm of the bile duct (IPNB)

Nakanuma Y, *World J Hepatol* 2010

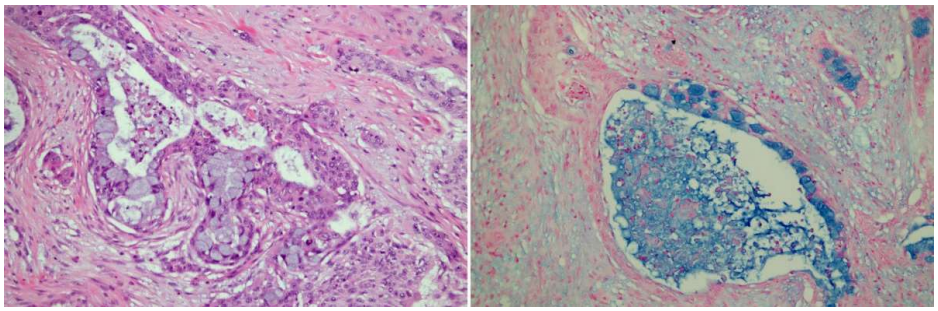
Clear cell carcinoma



- Bulky cytoplasm clearing
- Eccentrically located nuclei
- Glandular and/or trabecular growth patterns
- DD: HCC with clear cell change, metastatic clear cell carcinoma of the kidney, metastasis of other GI tract tumours

Chung T, *Front Med (Lausanne)* 2022

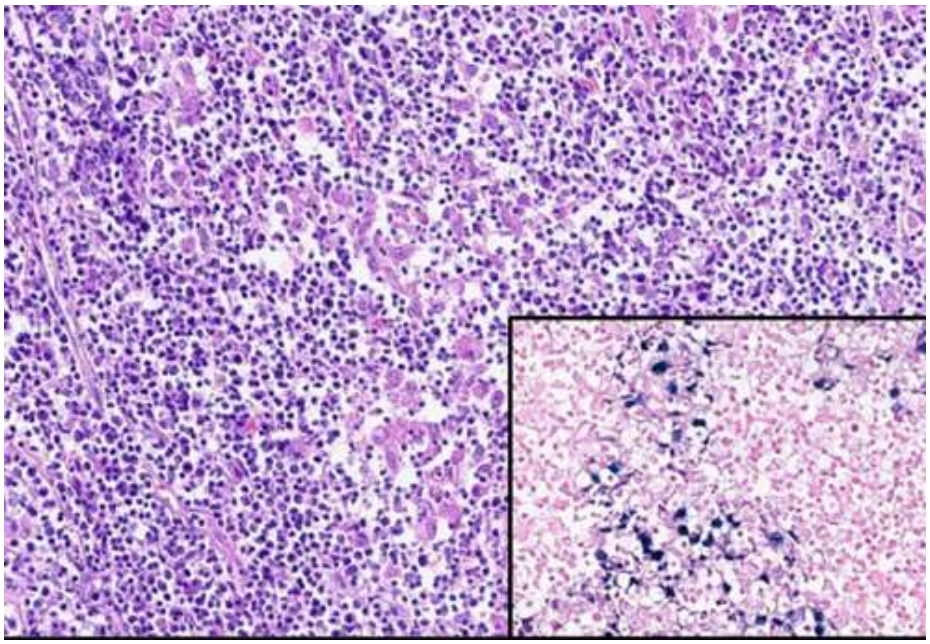
Mucoepidermoid carcinoma



- Mixture of epidermoid/squamous and mucin-secreting elements
- Only a few case reports
- Poor prognosis

Guo XQ, *Diagn Pathol* 2014

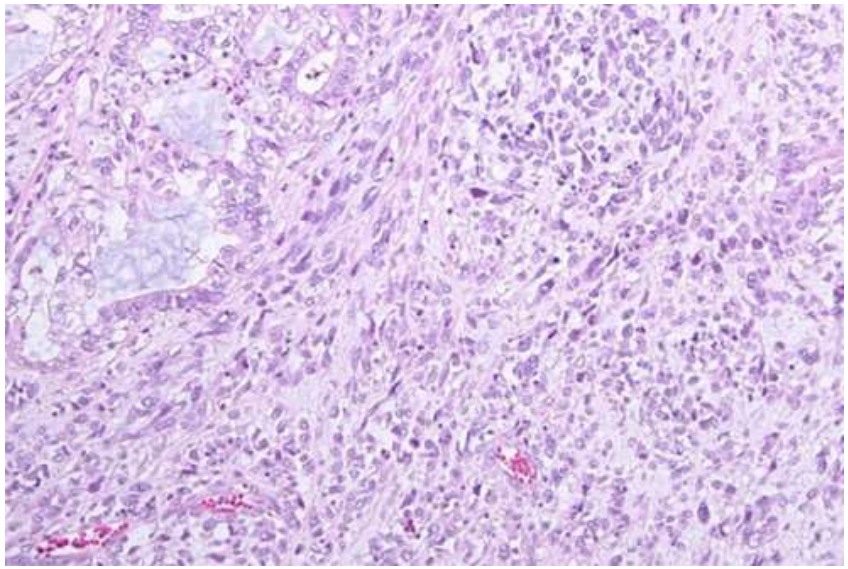
Lymphoepithelioma-like carcinoma



- Dense lymphoid stroma
- Undifferentiated or gland-forming tumour cells
- Almost all cases are Epstein-Barr encoded small RNA (EBER) positive
- Usually favourable outcome

Chung T, *Front Med (Lausanne)* 2022

Sarcomatous iCCA



- Mixed features of conventional iCCA and undifferentiated components with spindle cell features
- Sarcomatoid component often negative for epithelial markers
- Worse prognosis than conventional iCCA

Chung T, *Front Med (Lausanne)* 2022

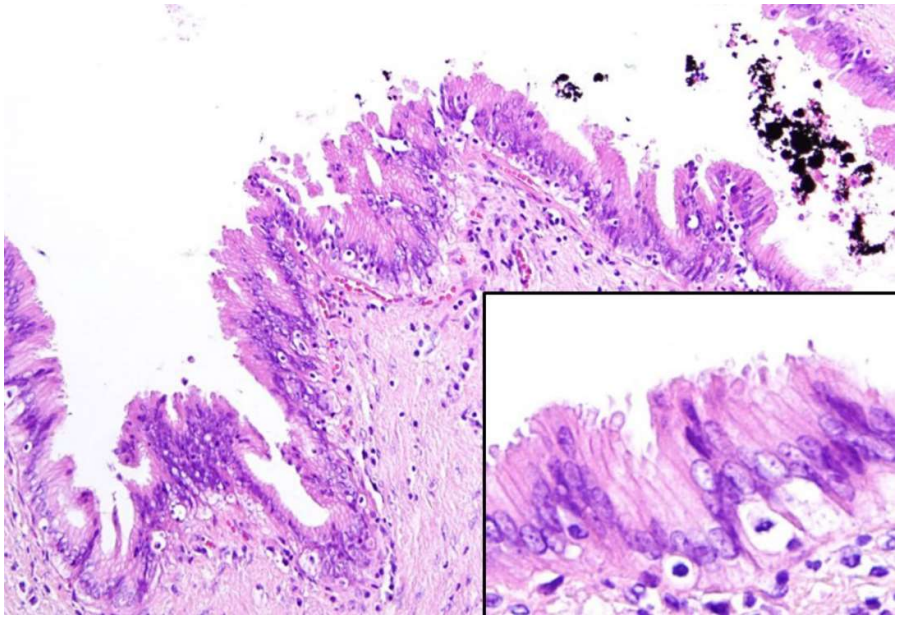
Precursor lesions of iCCA

- Biliary intraepithelial neoplasia (BilIN)
  - Low-grade BilIn
  - High-grade BilIn
- Intraductal papillary neoplasm of the bile duct (IPNB)
  - Low-grade IPNB
  - High-grade IPNB

Biliary intraepithelial neoplasia (BilIN)

- Often accompanying large duct type iCCA, but not small duct type
- Invisible upon gross examination (or associated with subtle mucosal thickening)

Low-grade BilIN



- Mild cytoarchitectural atypia (flat pseudopapillary and/or micropapillary growth)
- Hyperchromatic nuclei
- Increase nuclear-cytoplasmic ratio
- Nuclear polarity is preserved
- p53 usually negative
- p16 relatively preserved

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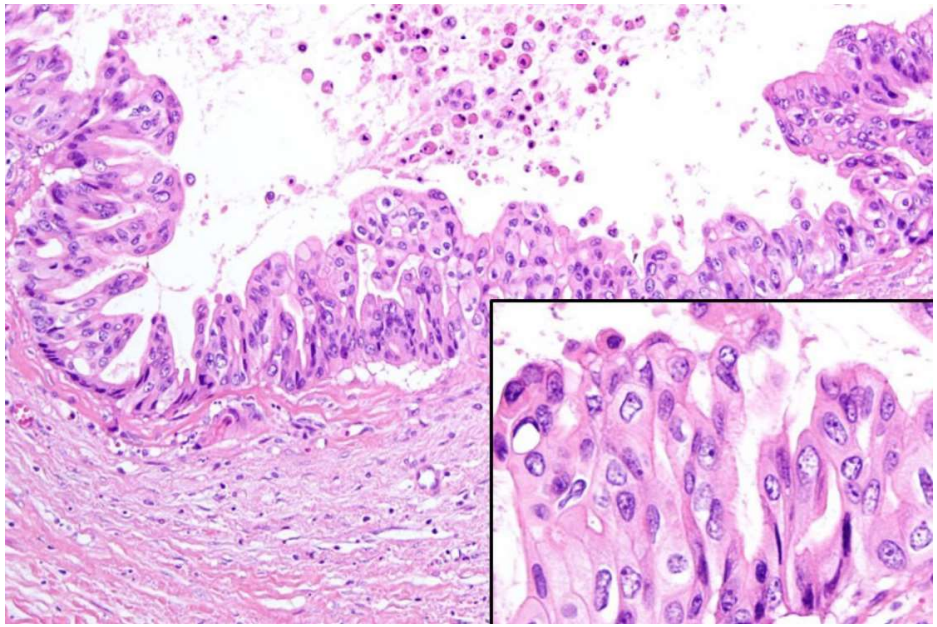
High-grade BilIN

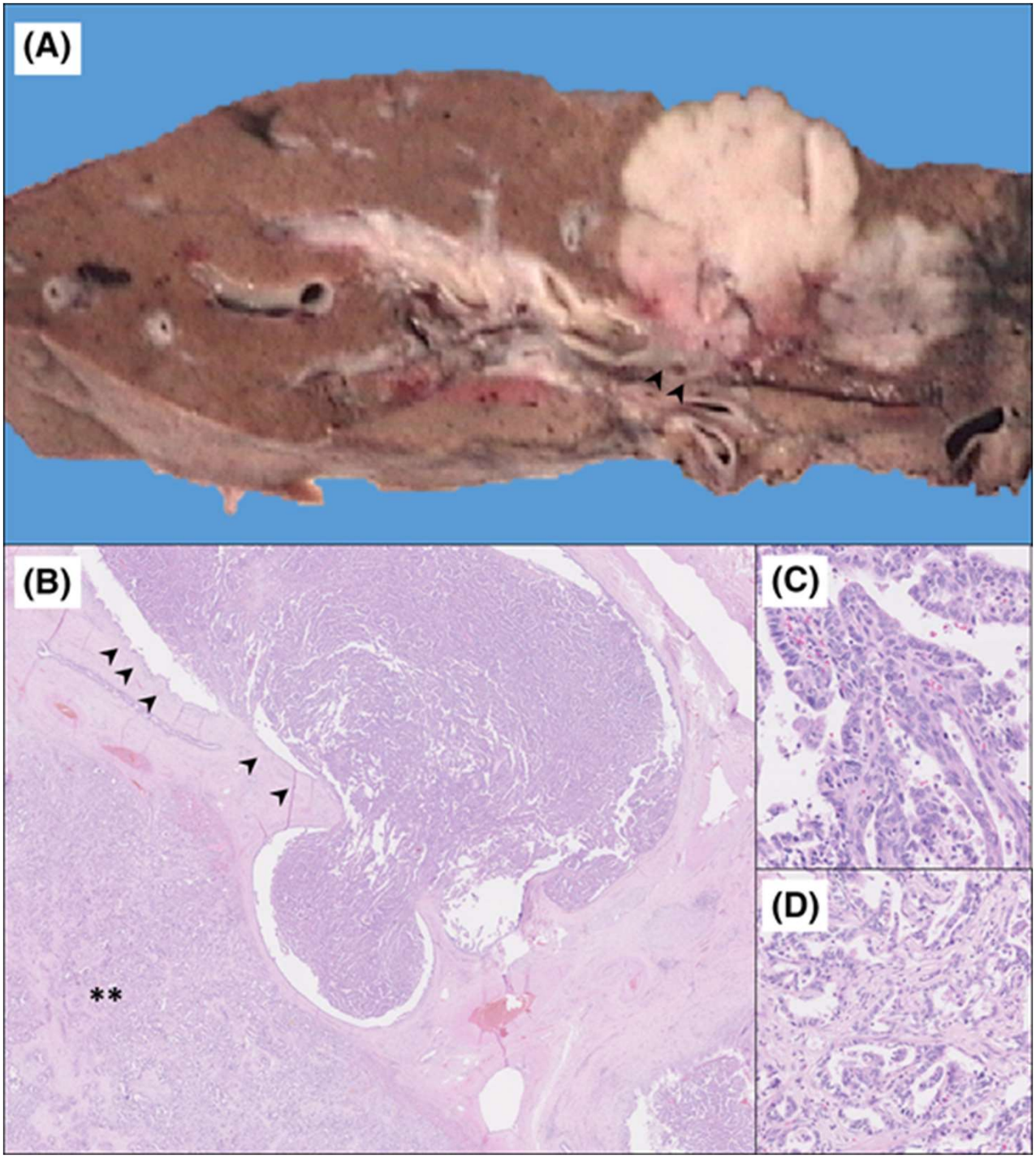


- Moderate to severe cytoarchitectural atypia (more complex patterns, compete loss of polarity, marked nuclear atypia)
- Frequent mitosis
- p53 often overexpressed
- p16 decreased

Chung T, *Front Med (Lausanne)* 2022

Intraductal papillary neoplasm of the bile duct (IPNB)

- Grossly visible premalignant neoplasm
- Intraductal papillary or villous growth of biliary-type epithelium
- Four subtypes: pancreatobiliary, intestinal, gastric and oncocytic
- When invasive carcinoma develops in this lesion, it should be diagnosed as IPNB with associated invasive carcinoma



Verset L, *Liver Int* 2019

Intraductal papillary neoplasm of the bile duct (IPNB)

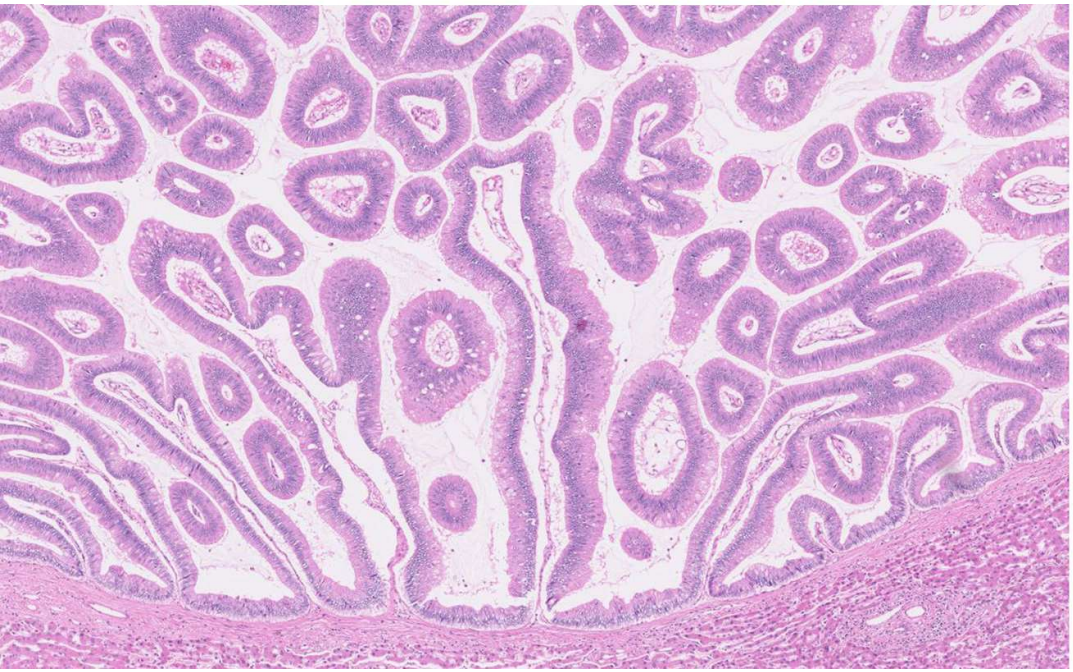
Type 1

- More homogeneous appearance
- Regular villous, papillary or tubular structures
- Usually low-grade dysplasia
- Frequently mucin overproduction
- Stromal invasion uncommon
- Most common in intrahepatic bile ducts
- Higher mutation rates of *KRAS*, *GNAS* and *RNF43*

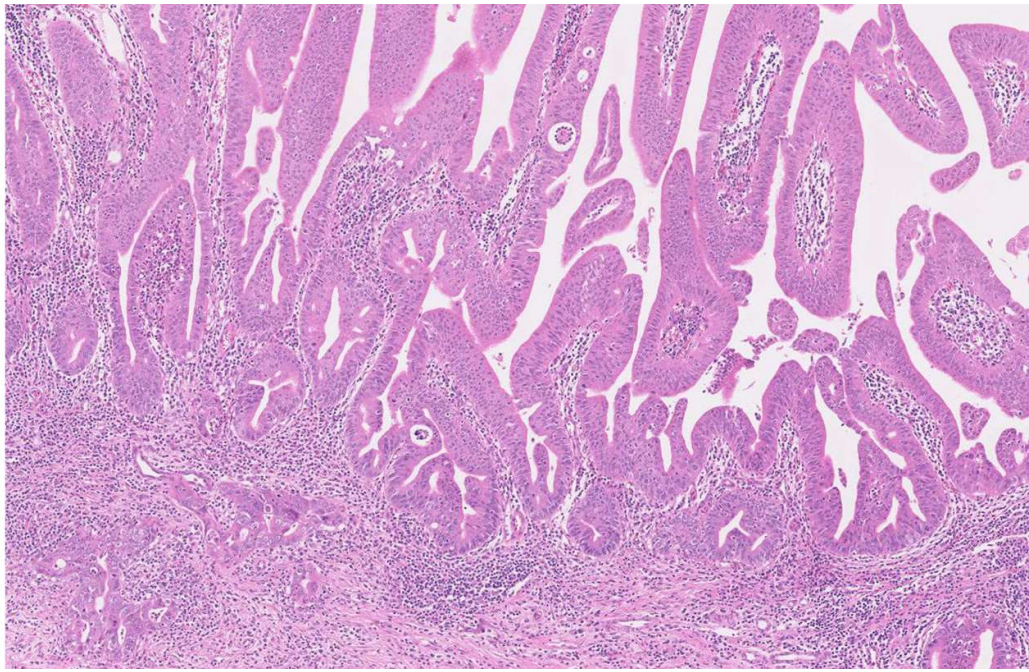
Type 2

- Heterogeneous appearance
- Irregular villous, papillary or tubular structures
- Usually high-grade dysplasia
- Rarely mucin overproduction
- Stromal invasion more common
- Arises throughout the biliary tree
- Higher mutation rates of *TP53* and *SMAD4*

Type 1

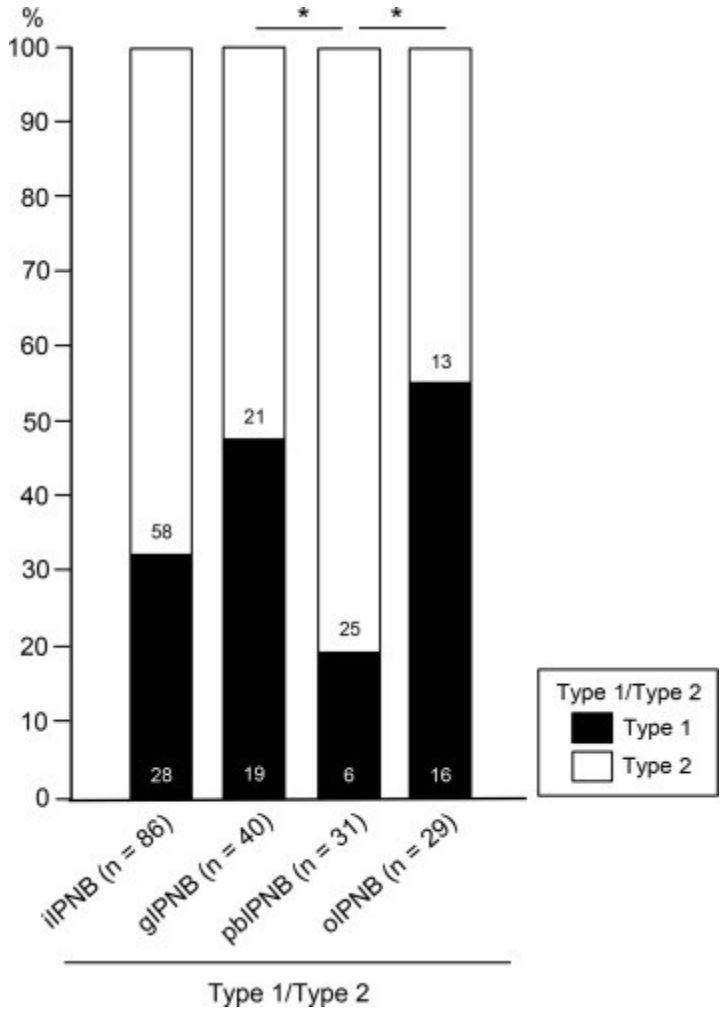


Type 2



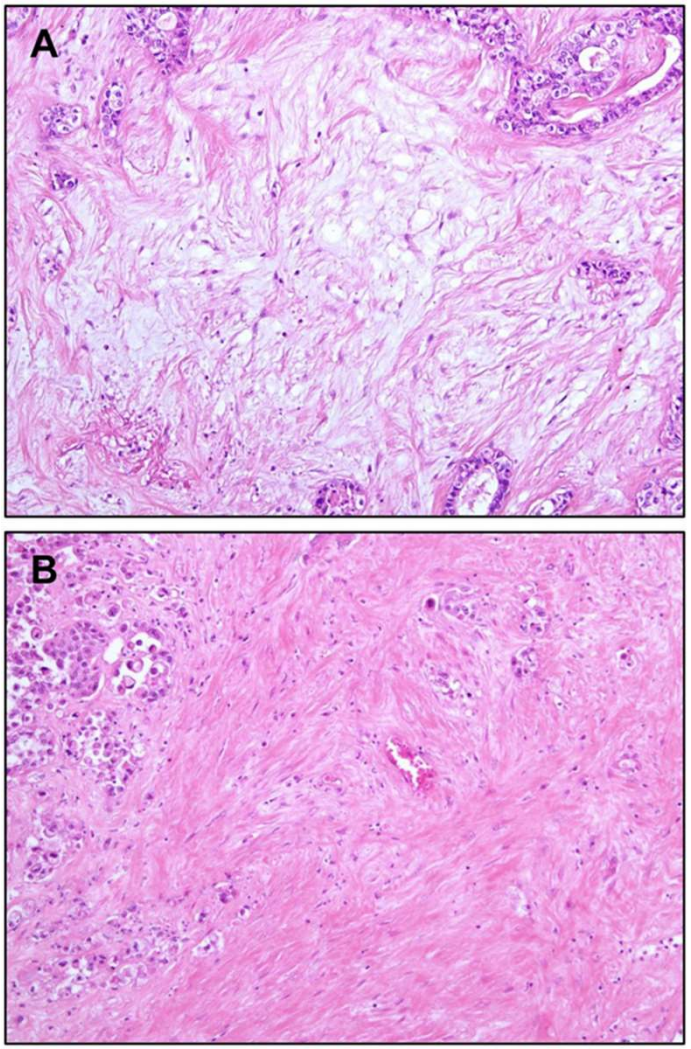
Nakanuma Y, *Hum Pathol* 2021

Proportion of types 1 and 2 in the four subtypes



Nakanuma Y, *Hum Pathol* 2021

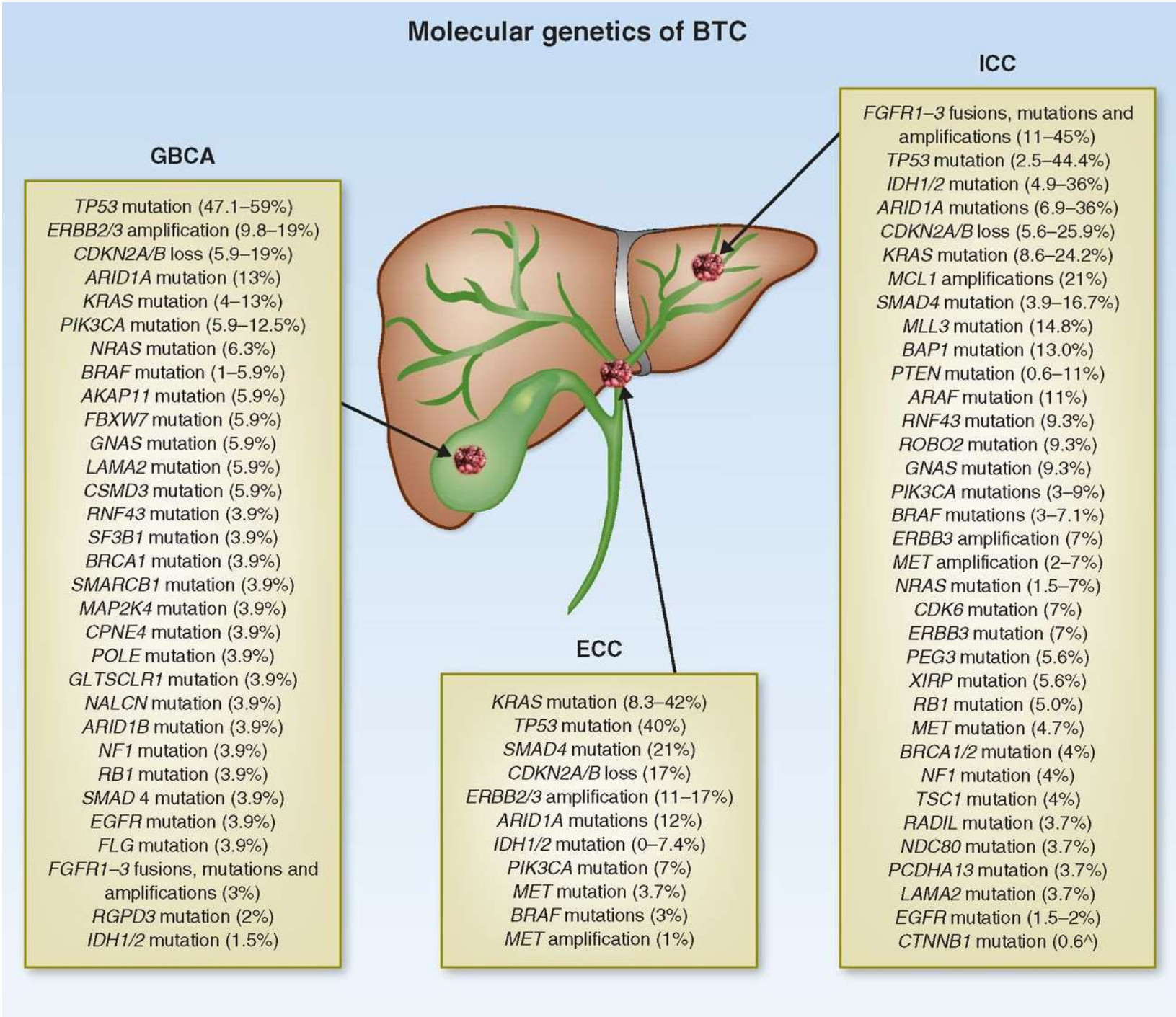
Immature versus mature stroma in intrahepatic cholangiocarcinoma



> Immature stroma; poorer prognosis

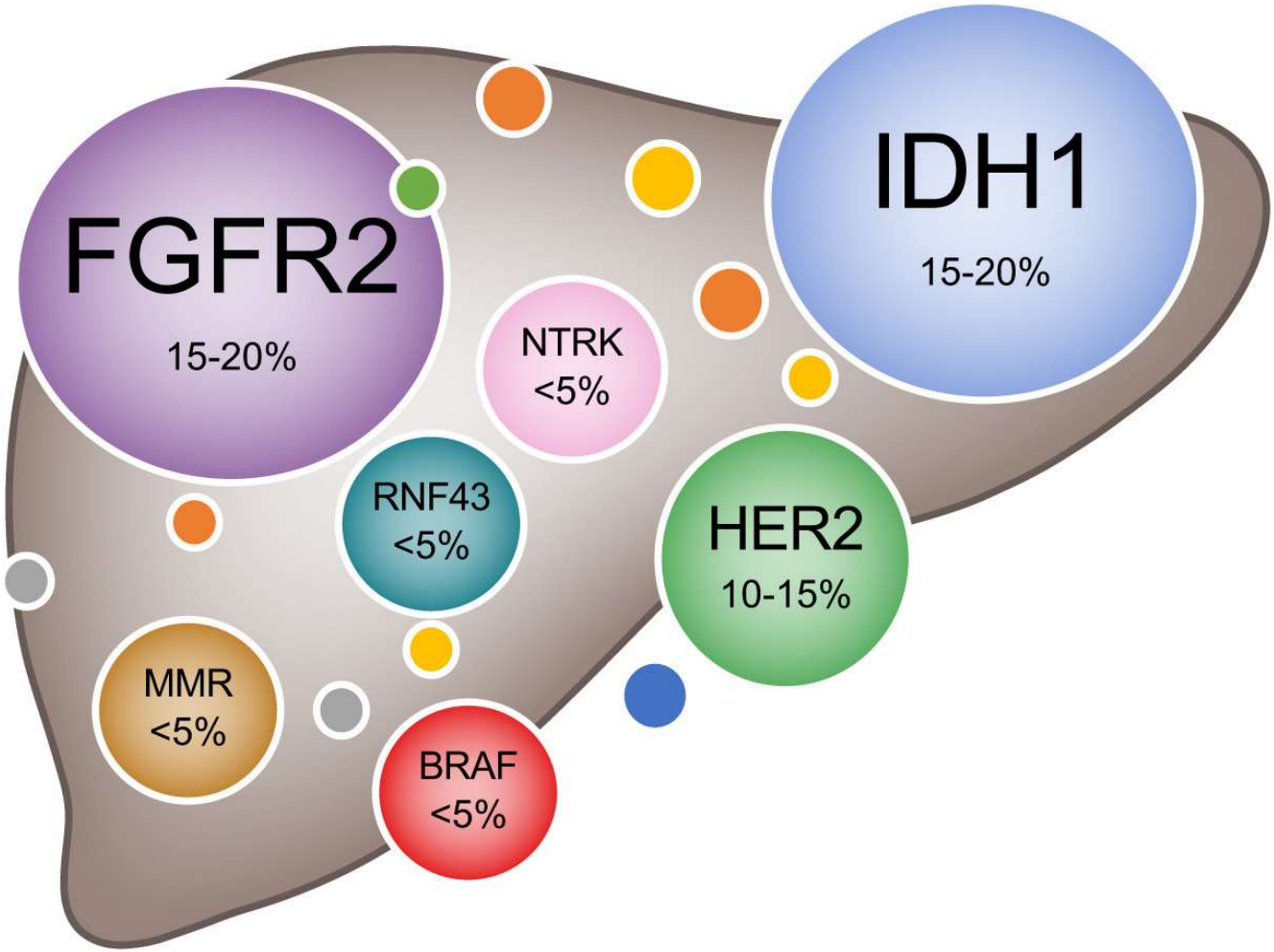
> Mature stroma; better prognosis

Zhang XF, *Hum Pathol* 2017
Kojima S, *Anticancer Res* 2020
Chung T, *Front Oncol* 2022



Valle JW, *Cancer Discov* 2017

Molecular subgroups of intrahepatic cholangiocarcinoma

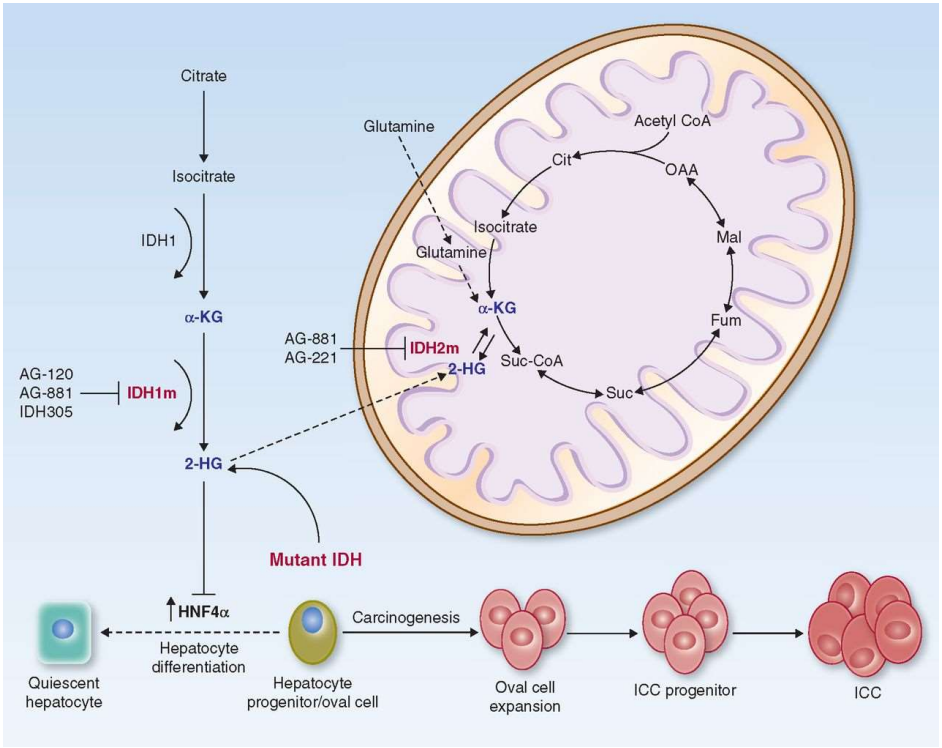


Lamarca A, *J Hepatol* 2020

FGFR2 fusions

- *FGFR2* fusions/rearrangements in 15-20% of intrahepatic cholangiocarcinoma
- Associated with better prognosis
- Tyrosine kinase inhibitors
  - Pemigatinib: oral FGFR 1-3 TK inhibitor
  - Derazantinib: oral pan-TK inhibitor
  - Infigratinib: oral FGFR 1-3 TK inhibitor

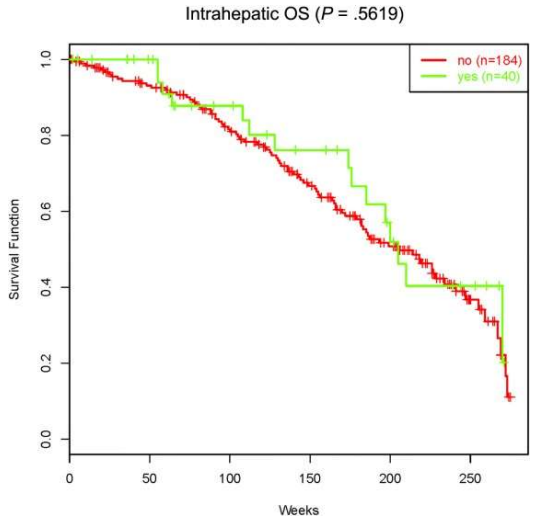
IDH 1 / 2 mutations



IDH : isocitrate dehydrogenase

IDH 1 or 2 mutations in 20% of intrahepatic cholangiocarcinoma

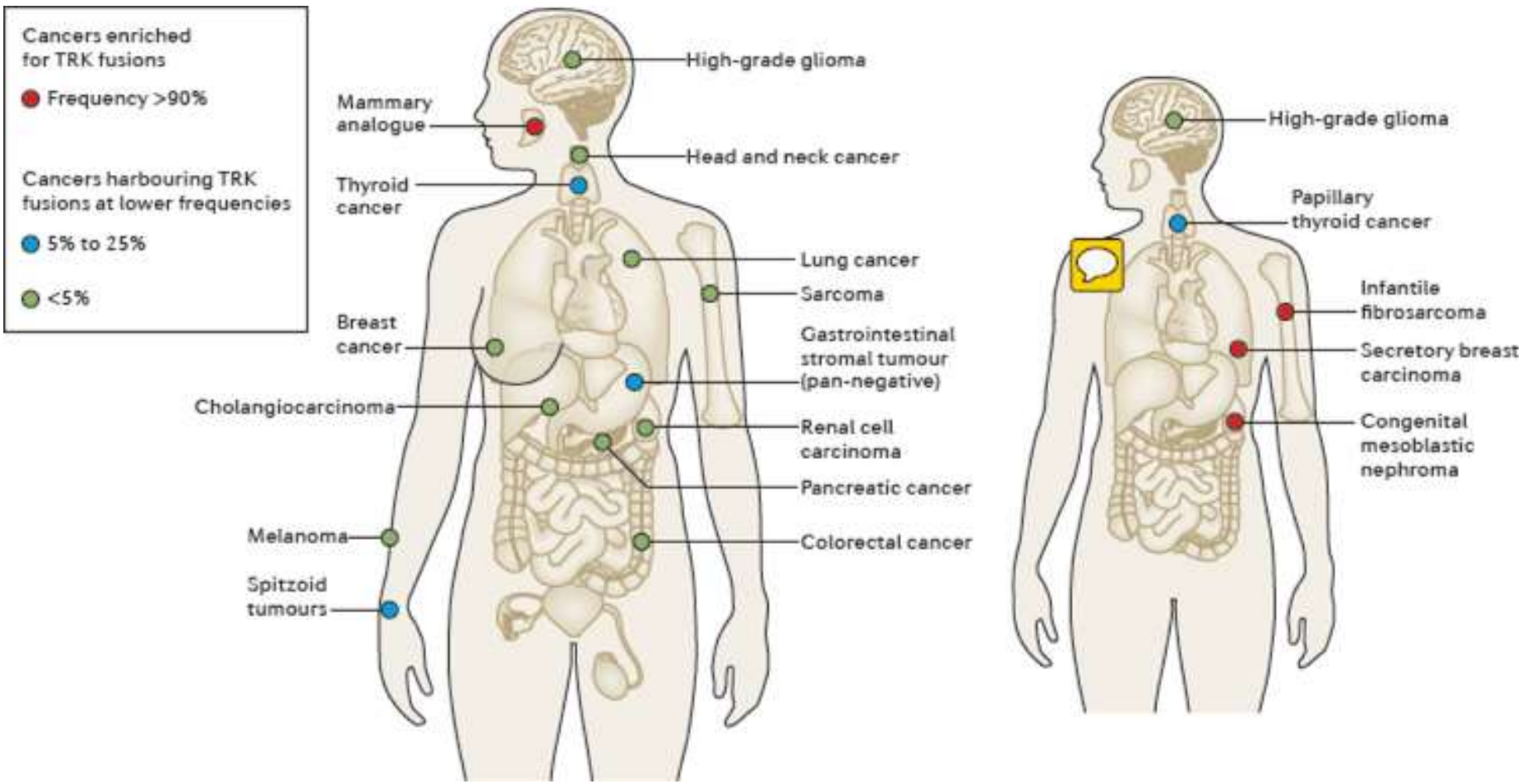
2-hydroglutarate: oncometabolite



IDH 1 mutations have no prognostic value

Ivosidenib: IDH1 inhibitor

Javle M, *Cancer* 2016
Valle JW, *Cancer Discov* 2017



Cocco E, *Nat Rev Clin Oncol* 2018

ESMO recommendations on the standard methods to detect NTRK fusions in daily practice and clinical research.

Marchiò C[1,2], Scaltriti M[3,4], Ladanyi M[3], Iafrate AJ[5,6], Bibeau F[7], Dietel M[8], Hechtman JF[3], Troiani T[9], López-Rios F[10], Douillard JY[11], Andrè F[12], Reis-Filho JS[3].

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10 Pathology & Targeted Therapies Laboratory, HM Sanchinarro University Hospital, Madrid, Spain.
11 European Society for Medical Oncology, Lugano, Switzerland.
12 Department of Medical Oncology, INSERM Unit 981, Institut Gustave Roussy, Villejuif, France.

Abstract

BACKGROUND: NTRK1, NTRK2 and NTRK3 fusions are present in a plethora of malignancies across different histologies. These fusions represent the most frequent mechanism of oncogenic activation of these receptor tyrosine kinases, and biomarkers for the use of TRK small molecule inhibitors. Given the varying frequency of NTRK1/2/3 fusions, crucial to the administration of NTRK inhibitors is the development of optimal approaches for the detection of human cancers harbouring activating NTRK1/2/3 fusion genes.

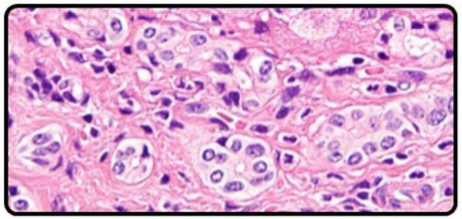
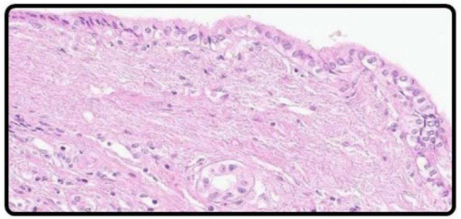
MATERIALS AND METHODS: Experts from several Institutions were recruited by the European Society for Medical Oncology (ESMO) Translational Research and Precision Medicine Working Group (TR and PM WG) to review the available methods for the detection of NTRK gene fusions, their potential applications, and strategies for the implementation of a rational approach for the detection of NTRK1/2/3 fusion genes in human malignancies. A consensus on the most reasonable strategy to adopt when screening for NTRK fusions in oncologic patients was sought, and further reviewed and approved by the ESMO TR and PM WG and the ESMO leadership.

RESULTS: The main techniques employed for NTRK fusion gene detection include immunohistochemistry, fluorescence in situ hybridization (FISH), RT-PCR, and both RNA-based and DNA-based next generation sequencing (NGS). Each technique has advantages and limitations, and the choice of assays for screening and final diagnosis should also take into account the resources and clinical context.

CONCLUSION: In tumours where NTRK fusions are highly recurrent, FISH, RT-PCR or RNA-based sequencing panels can be used as confirmatory techniques, whereas in the scenario of testing an unselected population where NTRK1/2/3 fusions are uncommon, either front-line sequencing (preferentially RNA-sequencing) or screening by immunohistochemistry followed by sequencing of positive cases should be pursued.

Molecular subclassification of intrahepatic cholangiocarcinoma

Inflammation subclass (38%)	Proliferation subclass (62%)
Activation of inflammatory pathways	Activation of oncogenic signalling pathways
Overexpression of cytokines (IL-10/IL-6)	RAS, MAPK
STAT3 activation	C-MET, BRAF, mutations in *KRAS*
Cholangiolar differentiation	Genomic resemblance to poor-prognosis hepatocellular carcinoma
	Aggressive clinical behaviours and poor prognosis
	Hepatic stem cell-like features
	Chromosomal instability
	IDH mutations
	Moderate/poor differentiation and intraneural invasion

Intrahepatic Cholangiocarcinoma		
Classification	**Small Duct Type**	**Large Duct Type**
Gross Type	**Mass-forming**	**Mixed** **Periductal Infiltrating**
Cell of Origin		
	Canal of Hering **Bile ductule**	**Columnar cholangiocytes** **Peribiliary glands**
Main Etiology	**Chronic hepatitis** **HBV / HCV** **Alcoholic / Metabolic**	**Hepatolithiasis** **Liver fluke** **PSC**
Immuno-histochemistry & Mucin stain	**NCAM** **N-cadherin** **CRP**	**S100P** **Mucin**
Frequent Mutations	***BAP1*** ***IDH1/2*** ***FGFR2 fusion***	***KRAS*** ***TP53*** ***SMAD4***
Suggested Molecular Classification*	**Inflammation Class**	**Proliferation Class**
Patient Outcome	**Favorable**	**Poor**

Chung T, *Front Med (Lausanne)* 2022

Combined hepatocellular-cholangiocarcinoma

Table 1. Evolution of the WHO classification of cHCC-CCA.

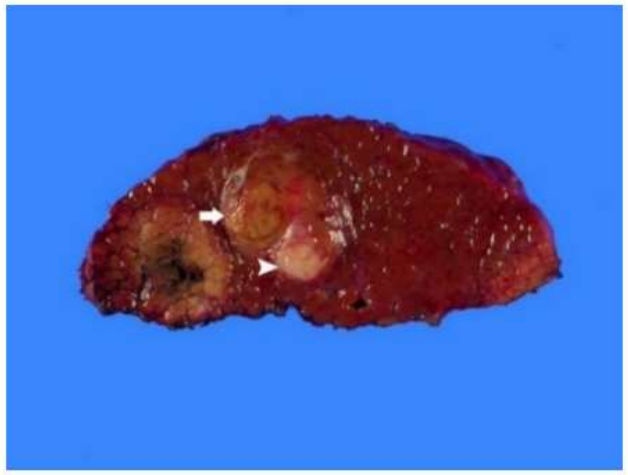
	2000 WHO Classification (3rd Edition)	2010 WHO Classification (4th Edition)	2019 WHO Classification (5th Edition)
Tumor category	Malignant epithelial tumors	Malignancies of mixed or uncertain origin	Malignant biliary tumors
Tumor entities or subtypes	cHCC-CCA	cHCC-CCA, classical type	cHCC-CCA [b]
		cHCC-CCA with stem cell features [a], typical subtype	
		cHCC-CCA with stem cell features, intermediate-cell type	Intermediate cell carcinoma [c]
		cHCC-CCA with stem cell features, cholangiolocellular type	Cholangiolocarcinoma [d]

Choi JH, *Biomedicines* 2022

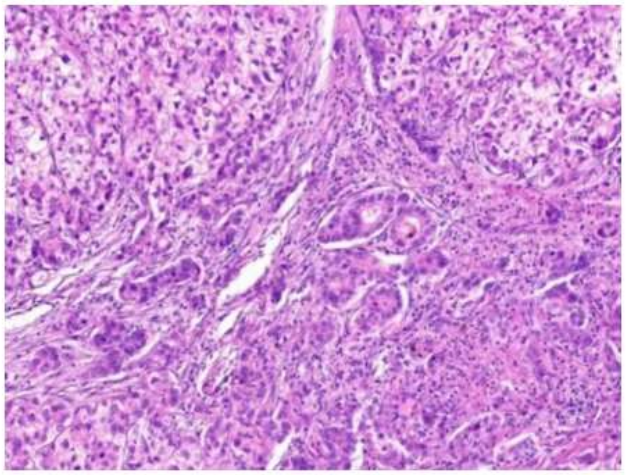
Combined hepatocellular-cholangiocarcinoma

- Unequivocal presence of both hepatocytic and cholangiocytic differentiation
- 2-5% of primary liver carcinomas
- Synonyms: miced HCC-CCA, mixed hepatobiliary carcinoma, hepatocholangiocarcinoma, biphenotypic primary liver cancer

Combined hepatocellular-cholangiocarcinoma

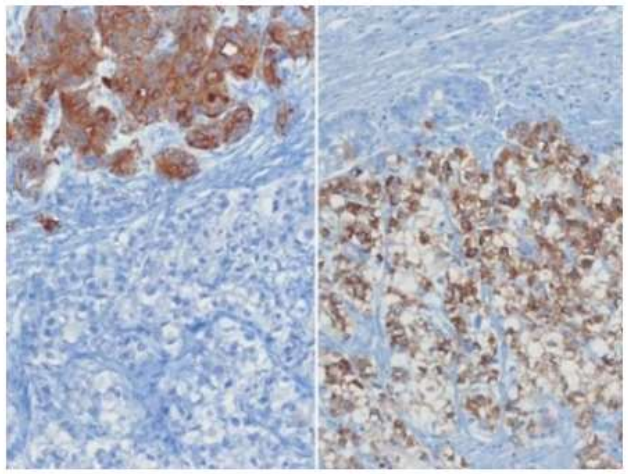


(A)



(B)

CK19



(C)

HepPar-1

Choi JH, *Biomedicines* 2022

Combined hepatocellular-cholangiocarcinoma: pathogenesis

- Three possible pathogenetic processes:
  - HCC and CCA may arise independently and separately
  - cHHC-CCA may originate from stem/progenitor cells that diffentiate into both hepatocytic and cholangiocytic lines
  - HCC may arise first and transform into CCA at varying degrees

Theise ND, *Histopathology* 2003
Li L, *Am J Pathol* 2018
Choi JH, *Biomedicines* 2022

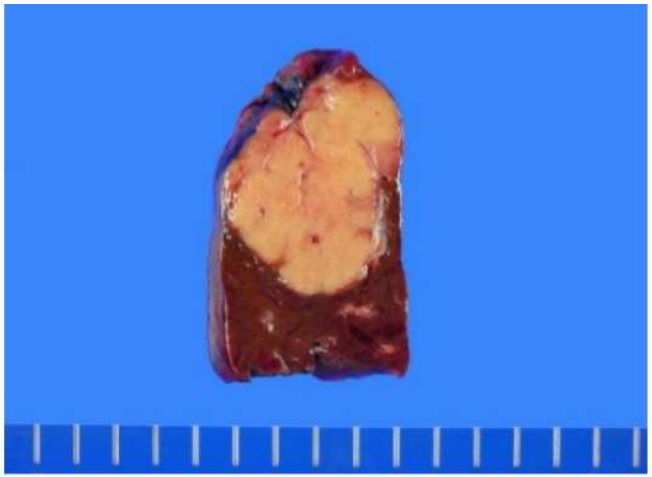
Combined hepatocellular-cholangiocarcinoma: histopathology

- Two components are either close to each other or extensively intermingled
- No consensus regarding a cutoff for each component
- Transitional are between the two components often exhibits mixed features with intermediate morphology
- Distant metastasis can show both components, or one single component

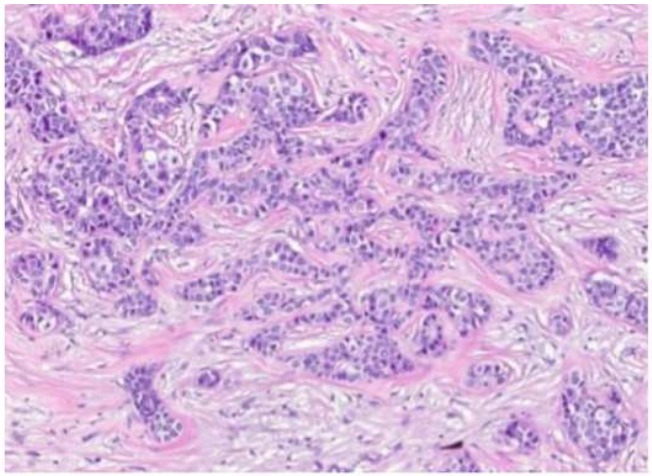
Intermediate cell carcinoma

- 2010, WHO classification: ‘cHCC-CCA with stem cell features, intermediate-cell subtype’
- 2018, Brunt *et al*. :’intermediate cell carcinoma’
- 2019, WHO classification: ‘intermediate cell carcinoma’

Intermediate cell carcinoma

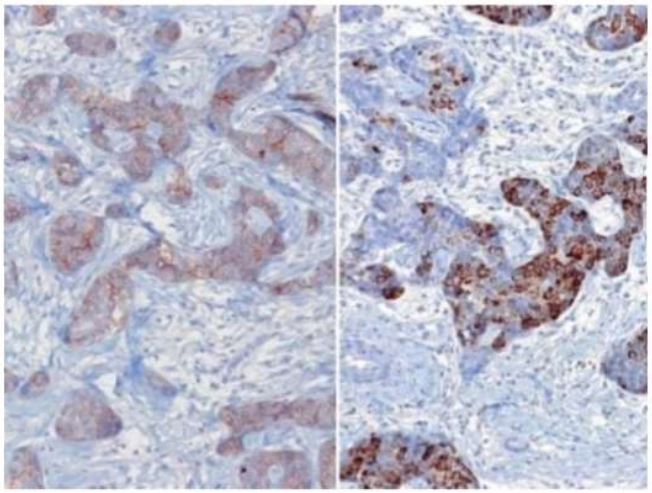


(A)



(B)

CK19



HepPar-1

(C)

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