Pathologic concept change of intrahepatic cholangiocarcinoma 19th Seminar of IHPBA

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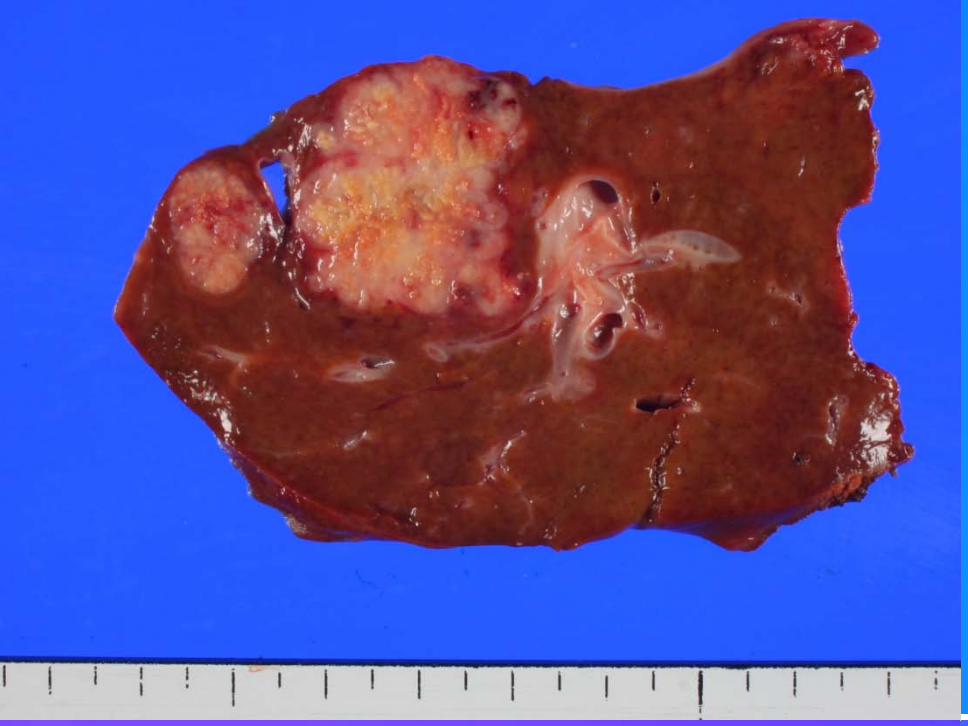
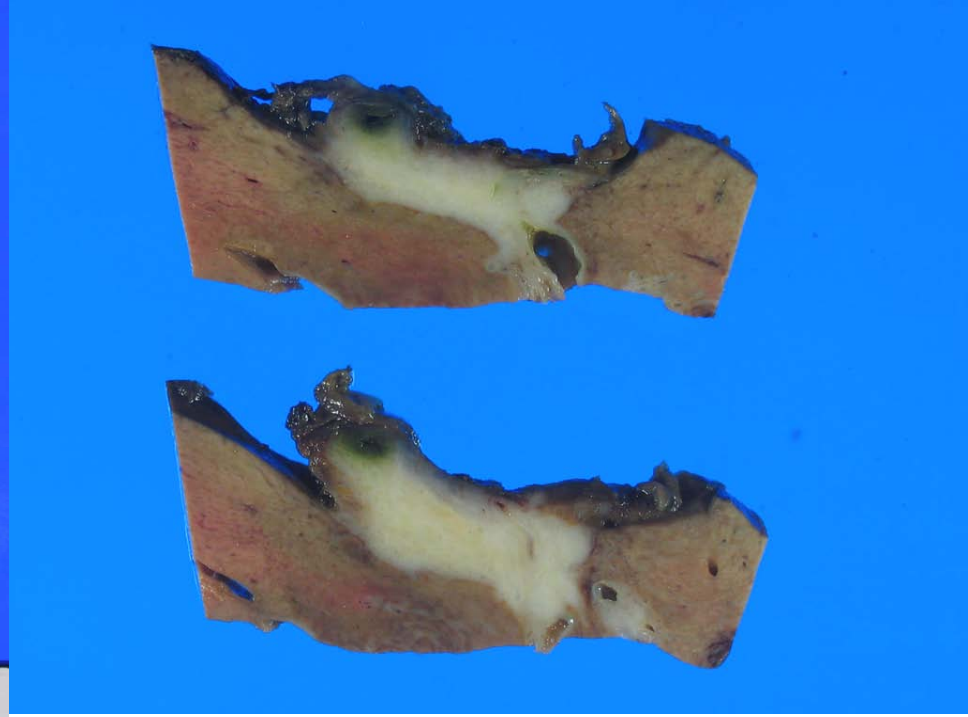
Practical Issues

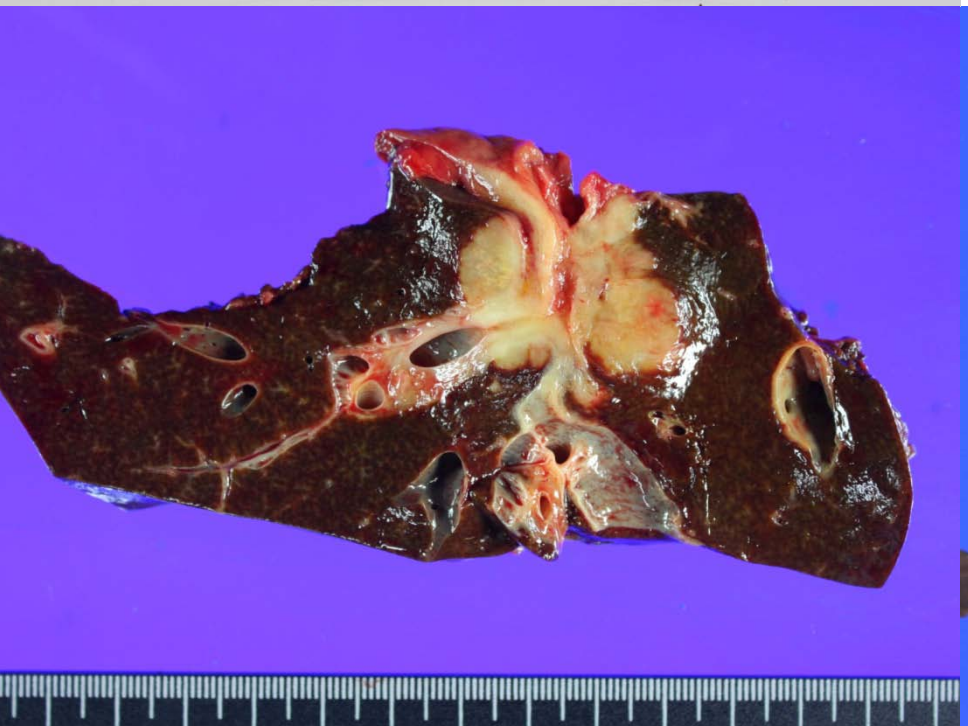
- Histopathologic subtypes of intrahepatic cholangiocarcinoma (mass-forming type)
- Histopathologic spectrum of intrahepatic cholangiocarcinoma
- What is clinical meaning of above finding to surgeon?
- What is most important issue in handling intrahepatic cholangiocarcinoma?

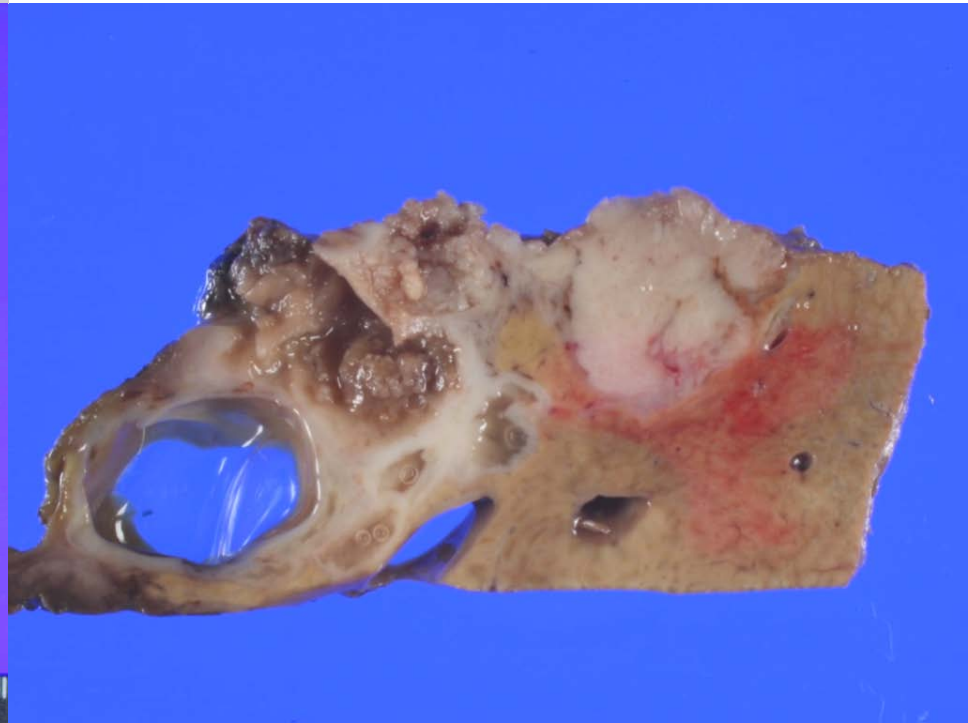
Intrahepatic Cholangiocarcinoma

- 2nd most common liver cancer
- Incidence: East asia >> Western contury
- Risk factors: hepatolothiasis, liver flukes (C. sinensis, Ophisthorchis viverrini), PSC, thorotrast, biliary tract anomaly, hepatitis virus infection
- Morphologic classification: mass-forming, periductal-infiltrative, intraductal type

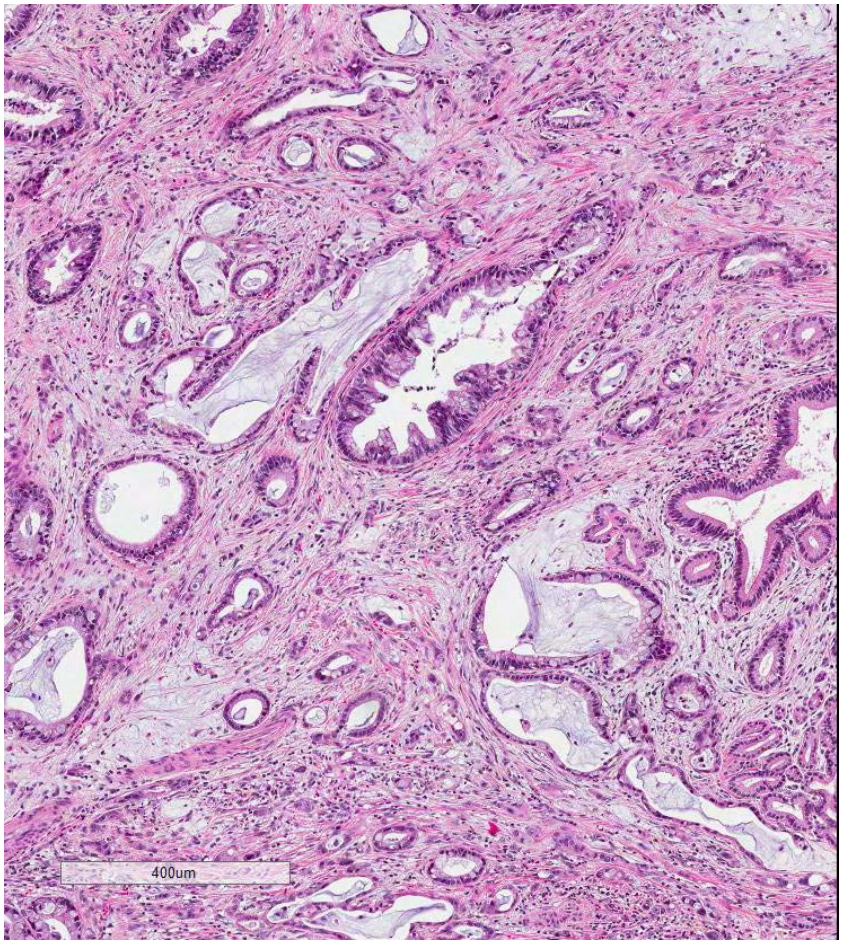


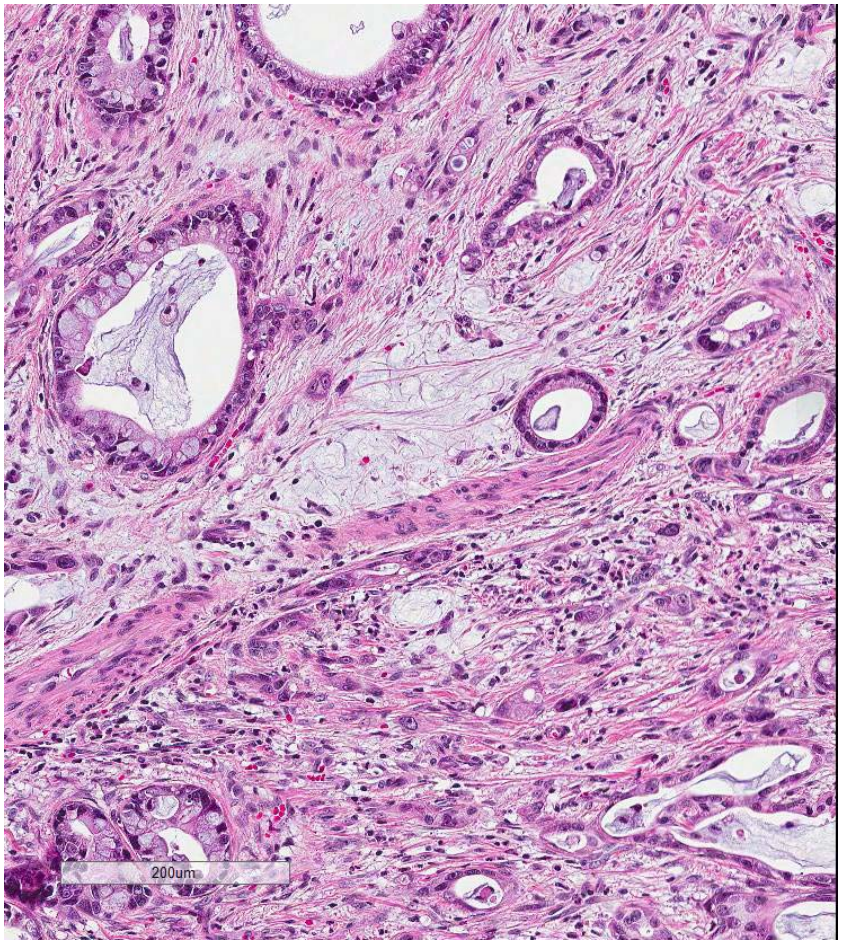






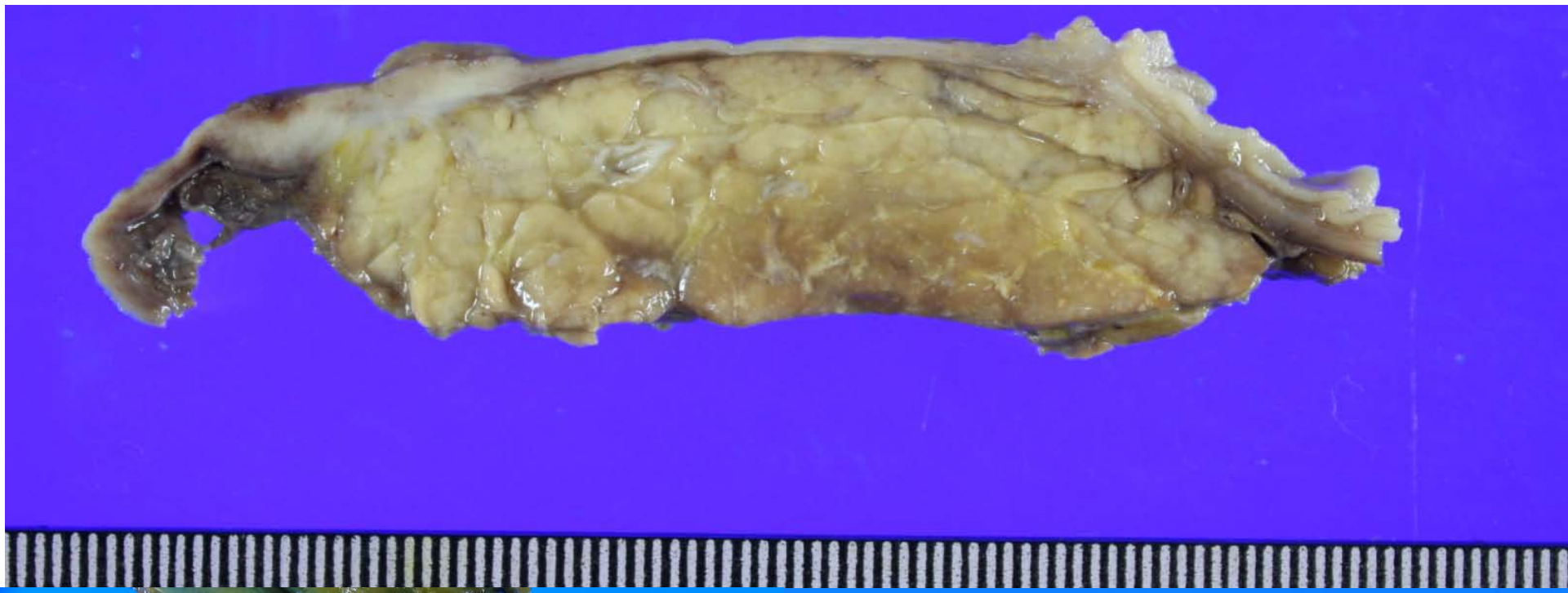
Conventional ductal adenocarcinoma

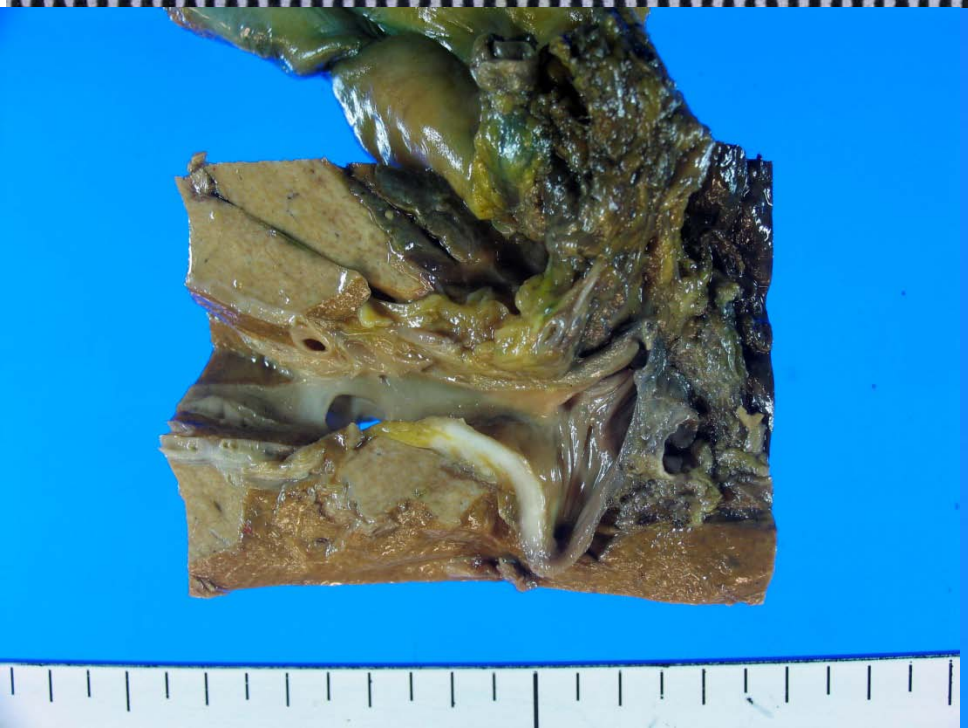


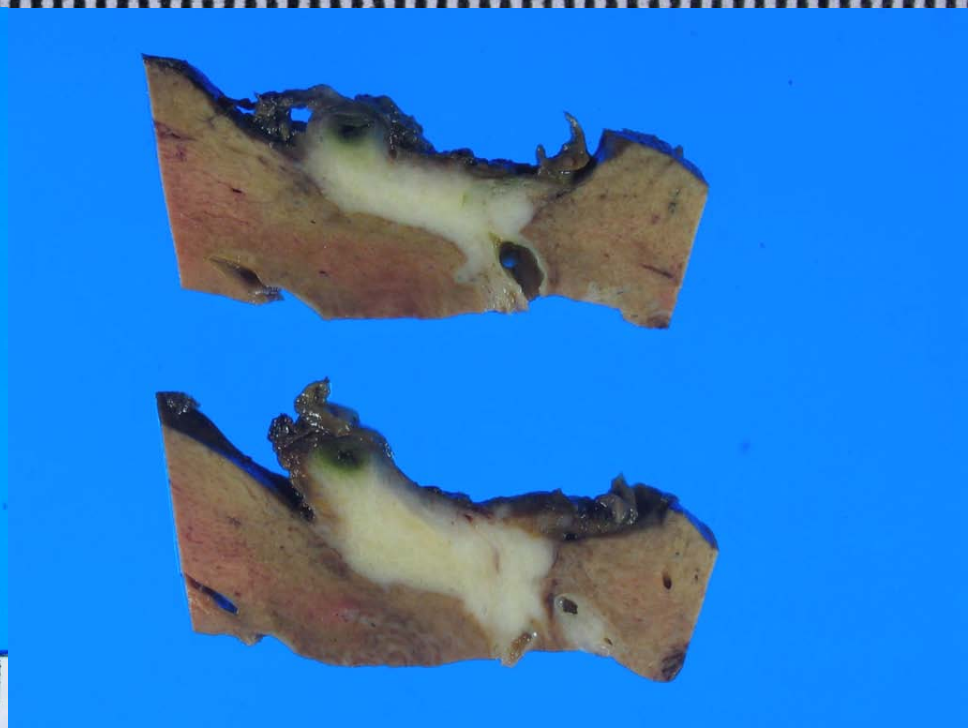


Peri-ductal infiltrative type

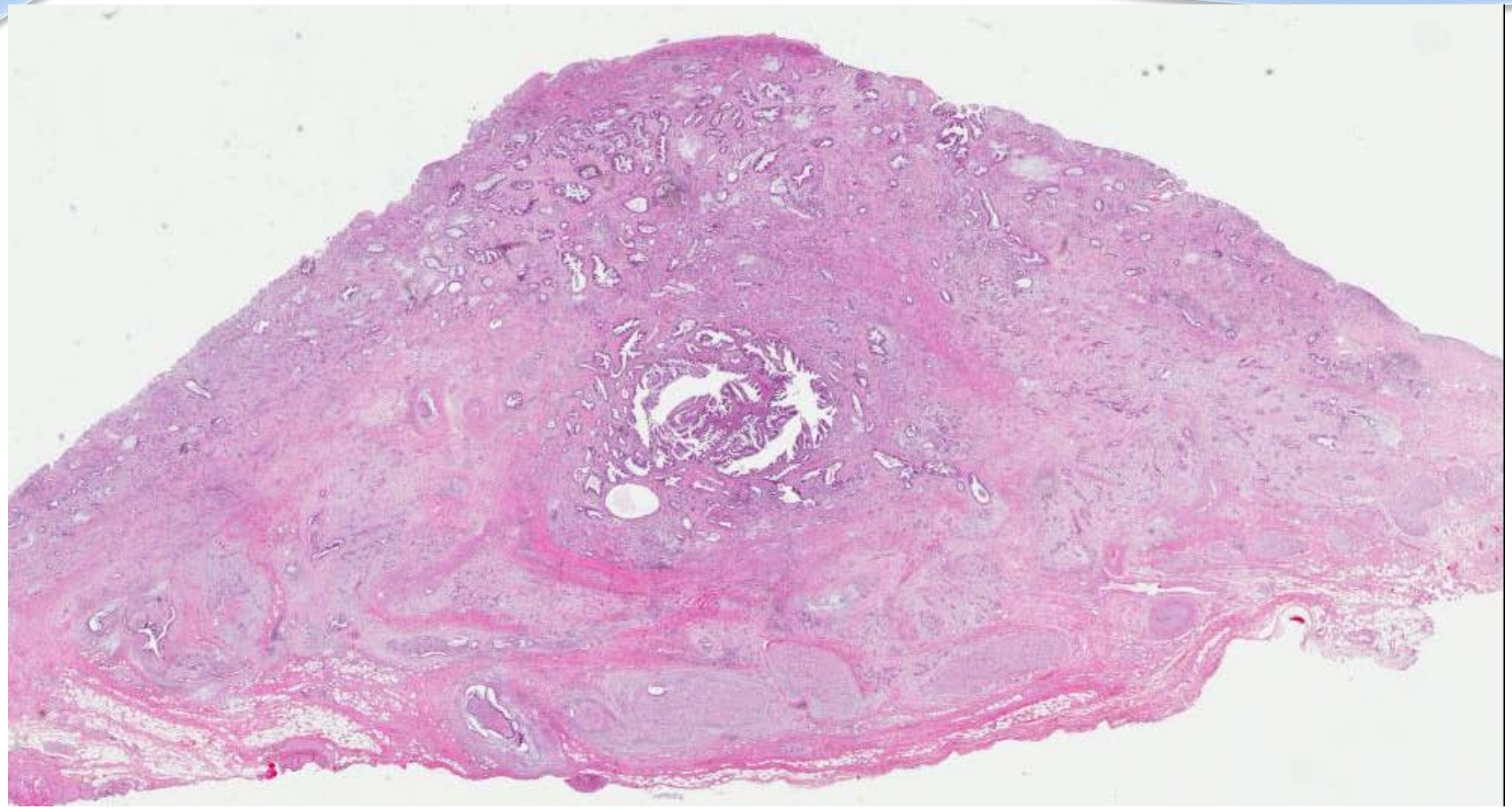
- Site: hilar, extrahepatic bile duct
- Gross: nodular-infiltrative or wall thickening pattern
- Micro: conventional ductal adenocarcinoma with desmoplasia



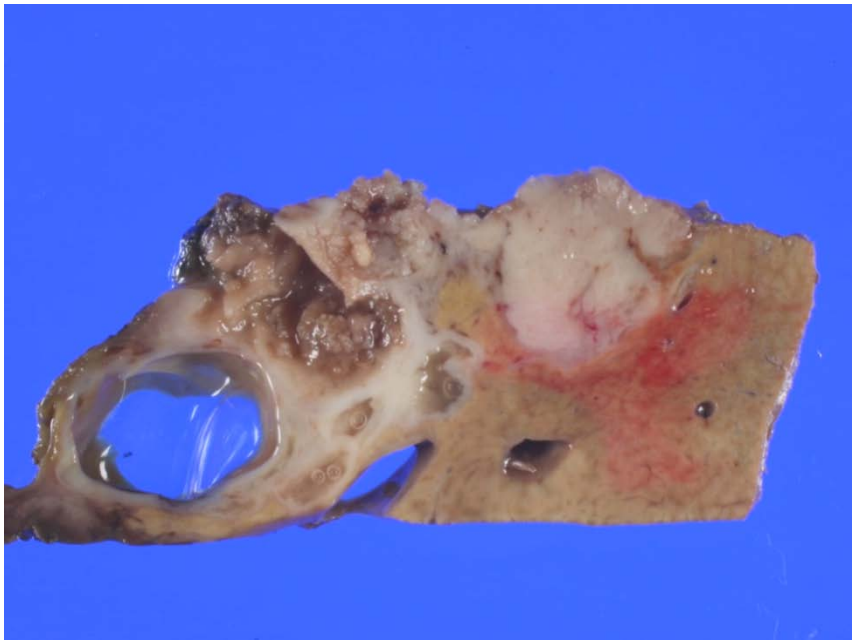




Periductal (nodular) infiltrative

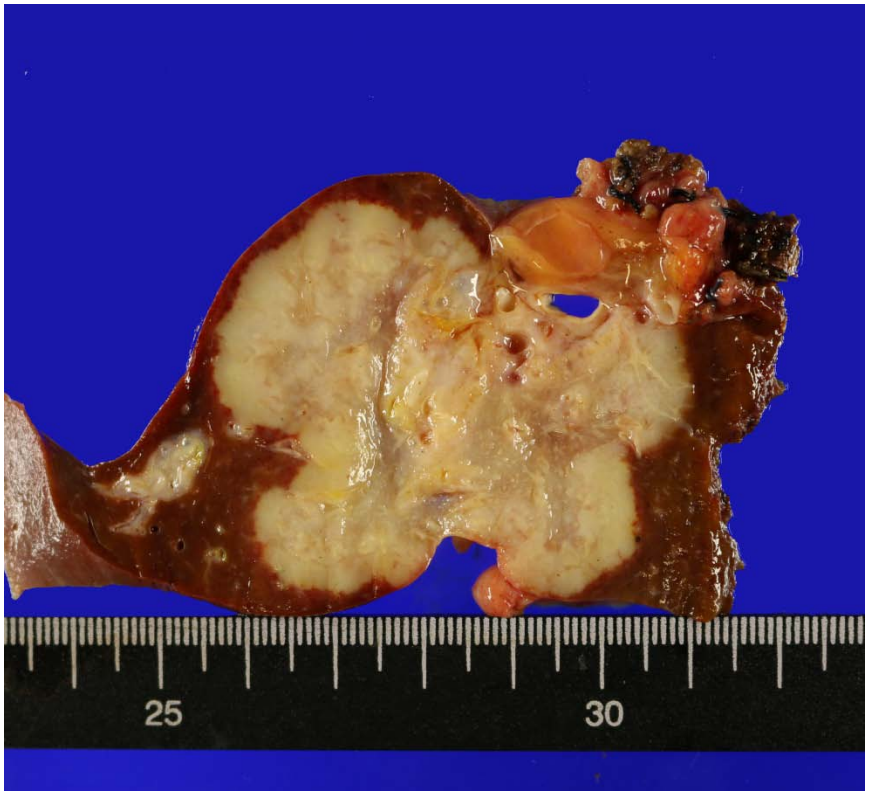


Intraductal type



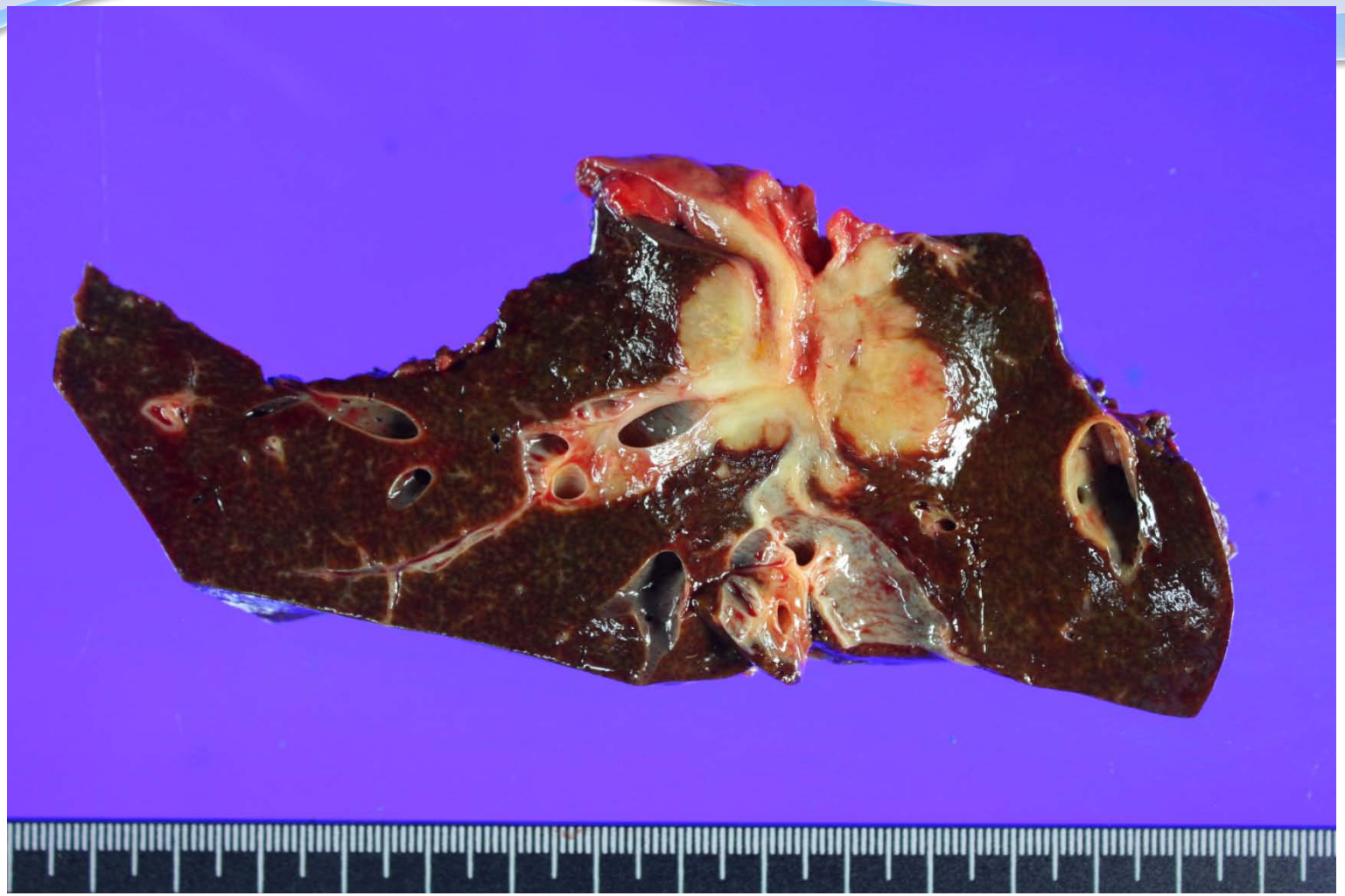
- Intraductal papillary neoplasm of bile duct (IPNB)
- Solitary or multiple (papillomatosis)
- Biliary counterpart of pancreas IPMN
  - less common mucin production
  - more common invasive carcinoma

Mass-forming IHCCa



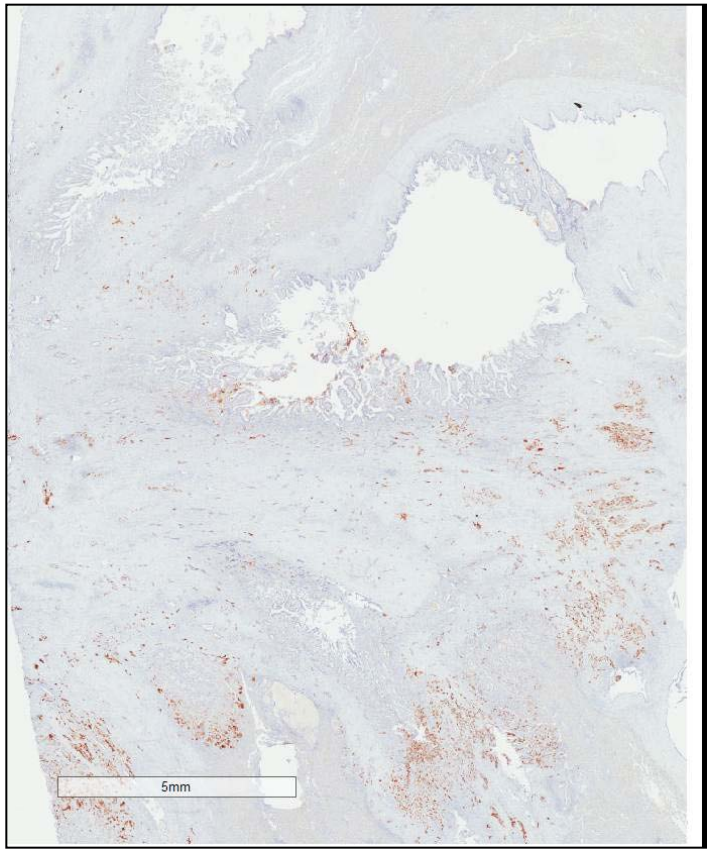
- Most peripheral cholangocarcinoma
- Various histologic spectrum of small to large duct differentiation

Mixed MF & PI type

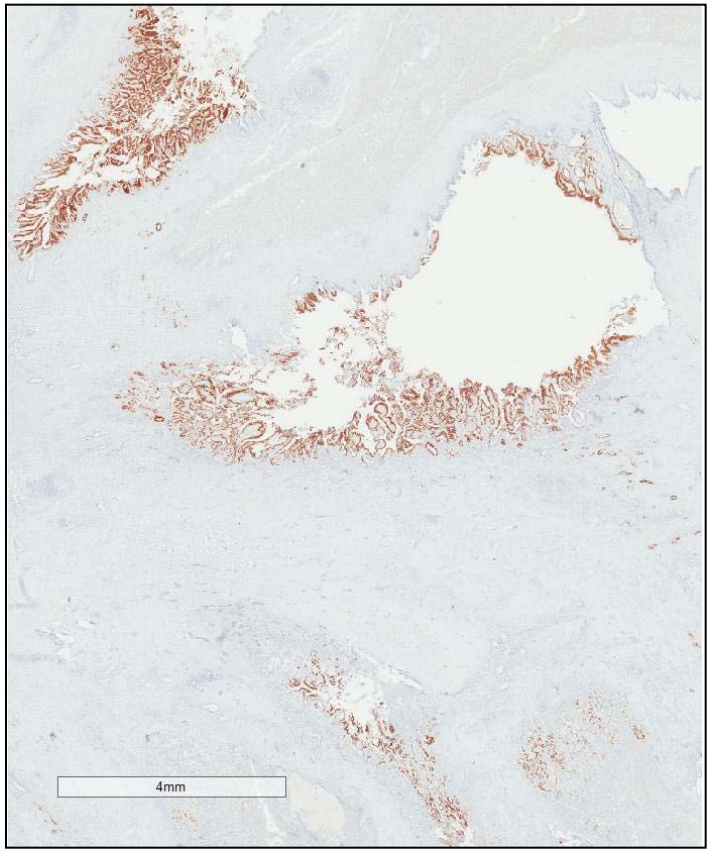


Mixed MF & PI type

MUC1

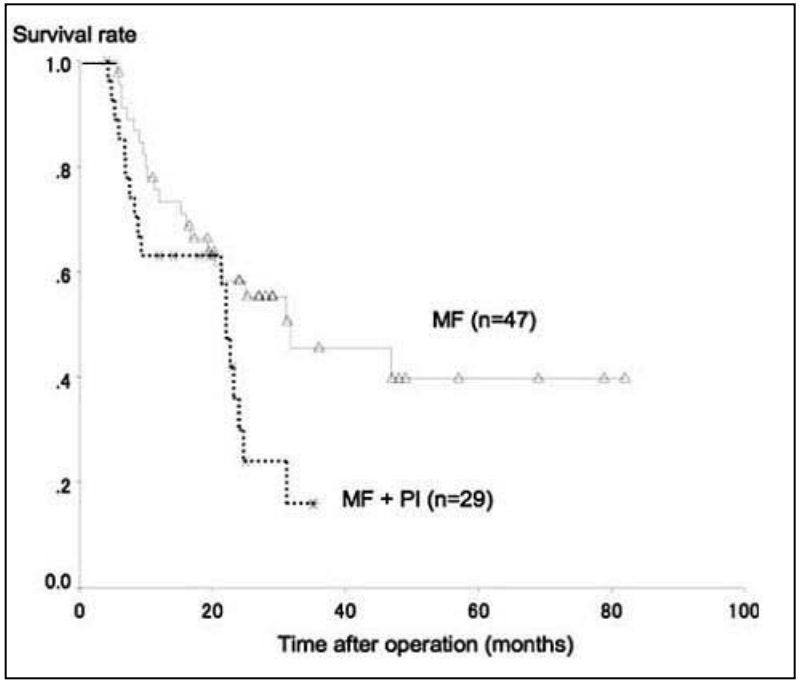


MUC5AC



Survival by tumor gross type

Eastern



World J Surg 2009;33:1247-1254

Western

Table 3 Survival data related with the tumor gross type

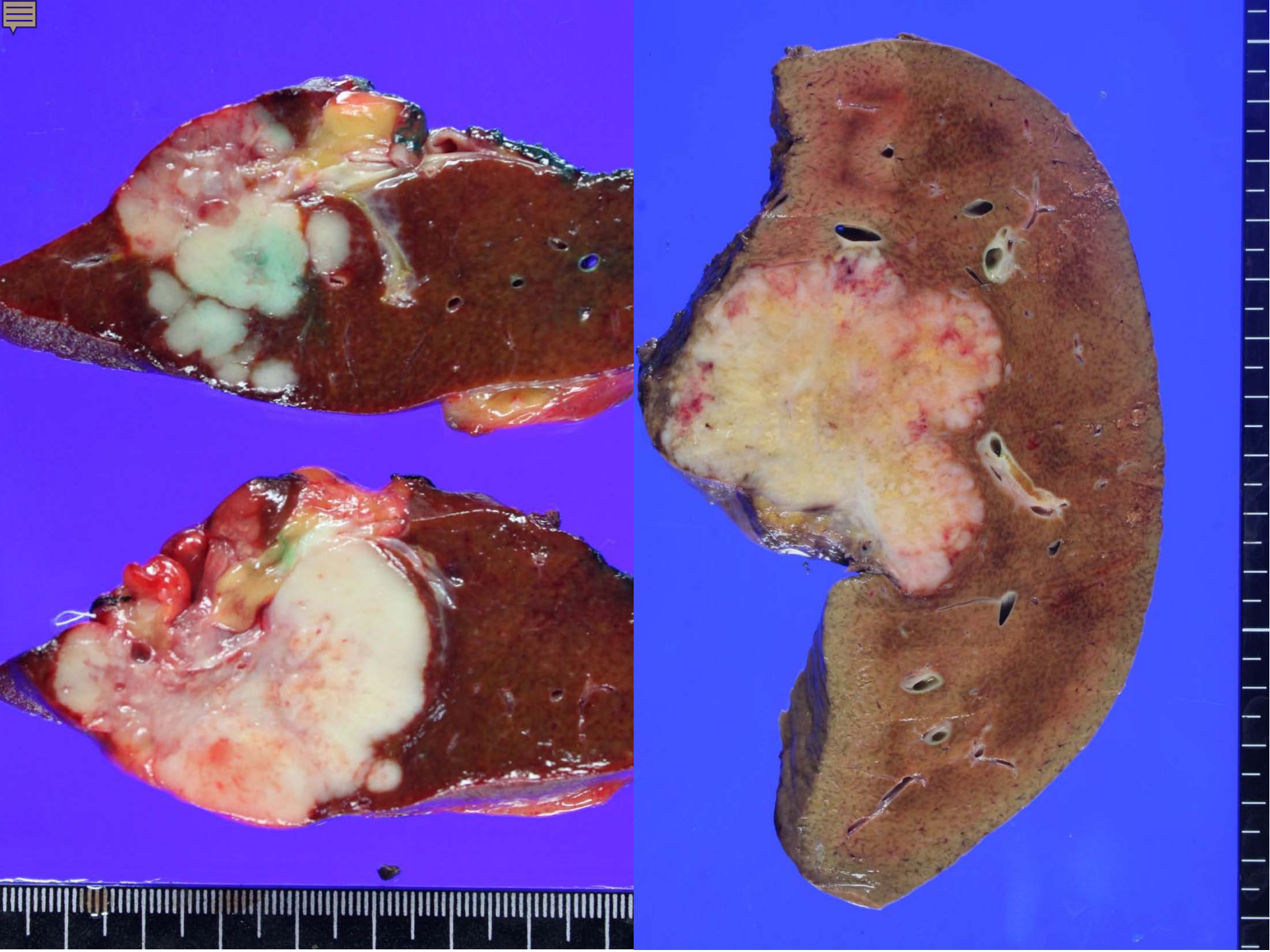
Gross tumor type	No.	Survival		
		Median and (95% IC)	3 Years	5 Years
IG	2	17 (–)	–	–
MF	34	50 (24–76)	61	29
MF + PI	13	19 (3–35)	29	0
PI	3	15 (–)	–	–

MF vs. MF + PI: $p < 0.05$

World J Surg 2009;33:1247-1254

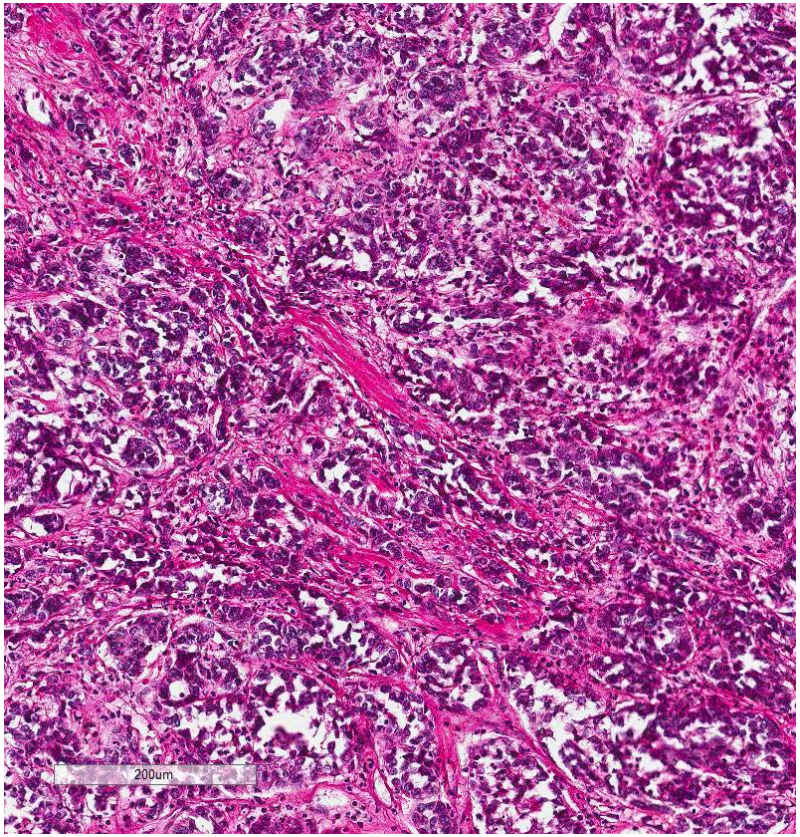
Mass-forming type IHCCa

- Mainly occur in intrahepatic cholangiocarcinoma (peripheral >> perihilar)
- Mass or nodular lesion in hepatic parenchyma
- Non-cirrhotic liver
- Gross: grey to grey-white, firm & solid, well-demarcated tumor with peritumoral pseudocapsule

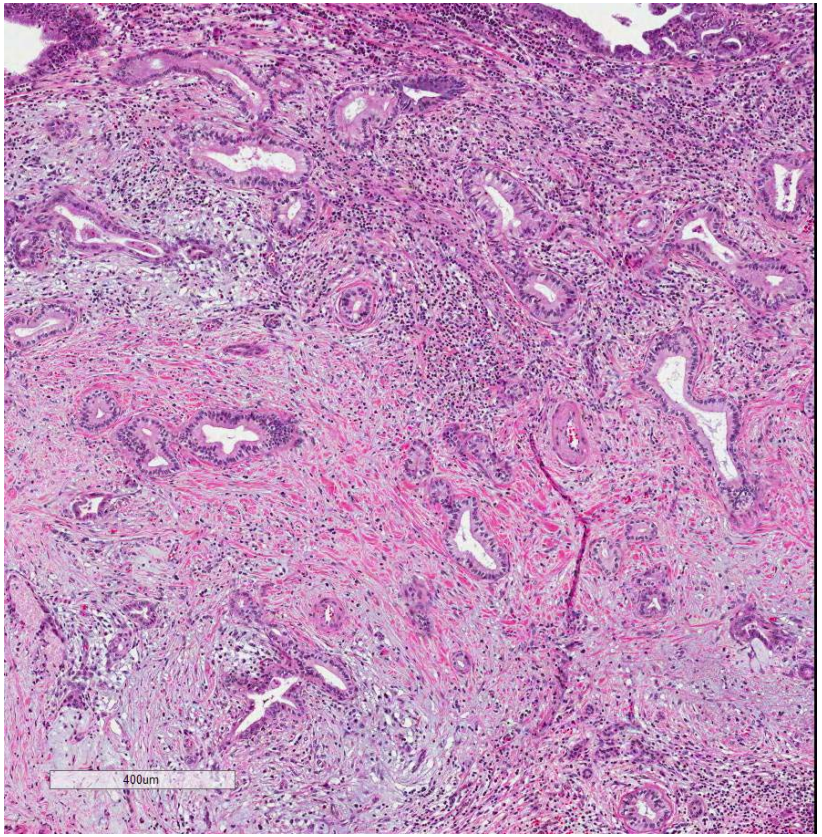


Difference in differentiation ?

Poorly differenitated?

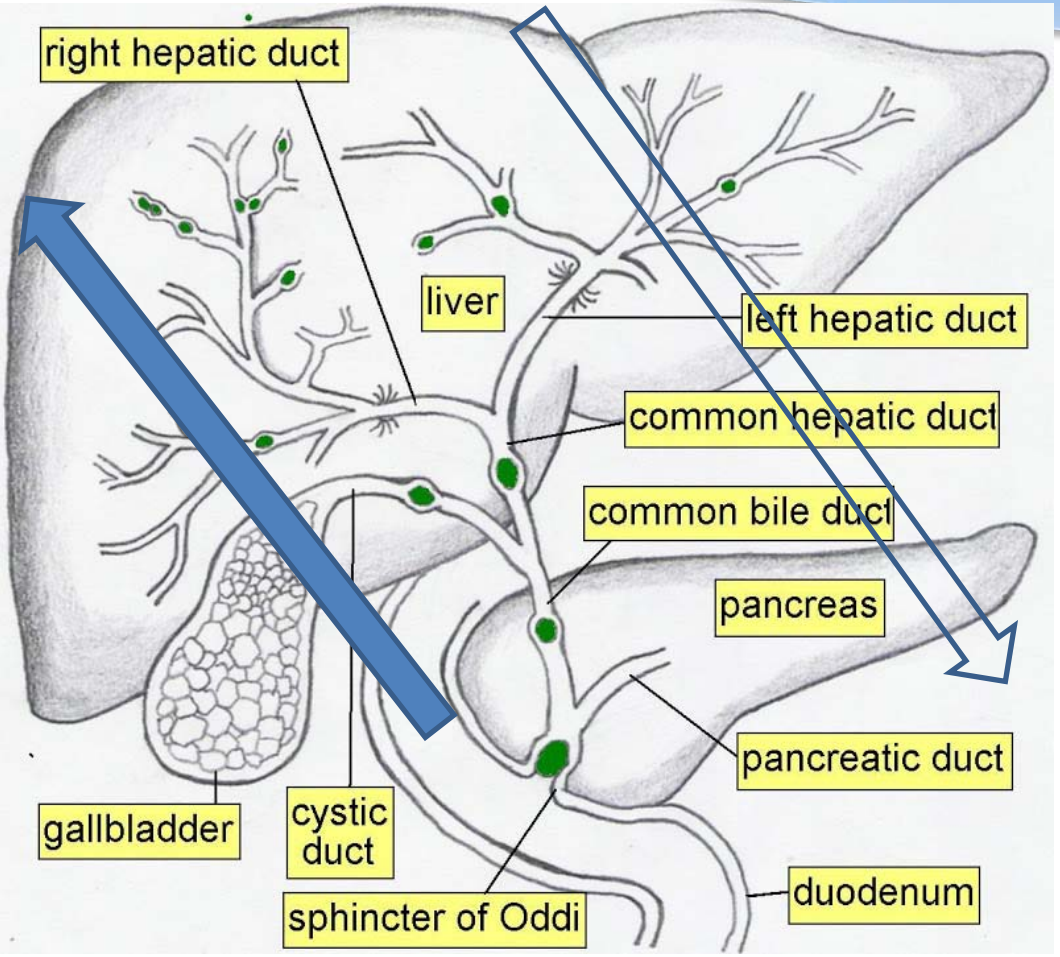


Well differentiated ?



Biliary tract anatomy

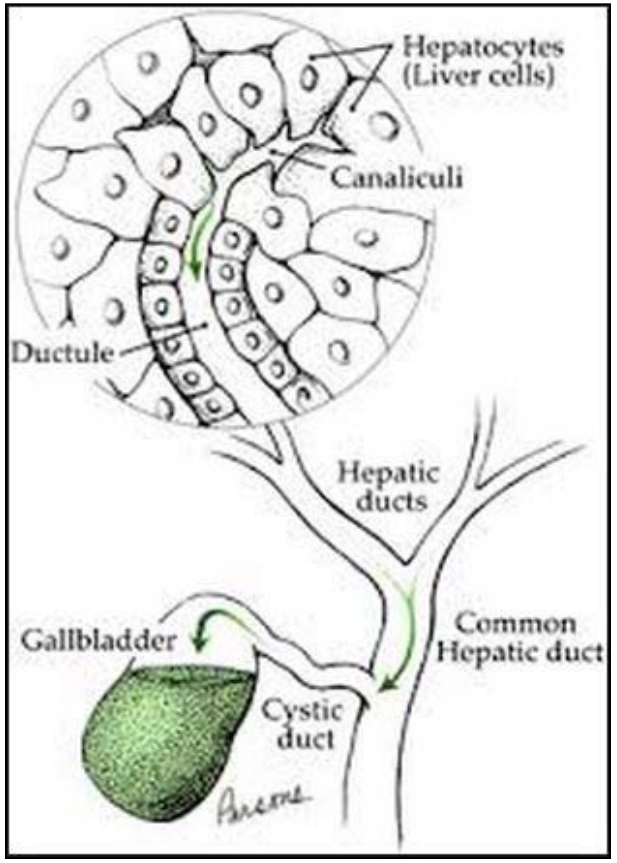
proximal, small bile duct, ductular, cholangiolar



distal, large bile duct

Bile flow and bile duct

- Hepatocyte
- Bile ductule
- Interlobular bile duct
- Septal bile duct
- Segmental bile duct
- Right & left bile duct
- Hilar bile duct
- Extrahepatic bile duct



IHCCa by bile duct cell origin

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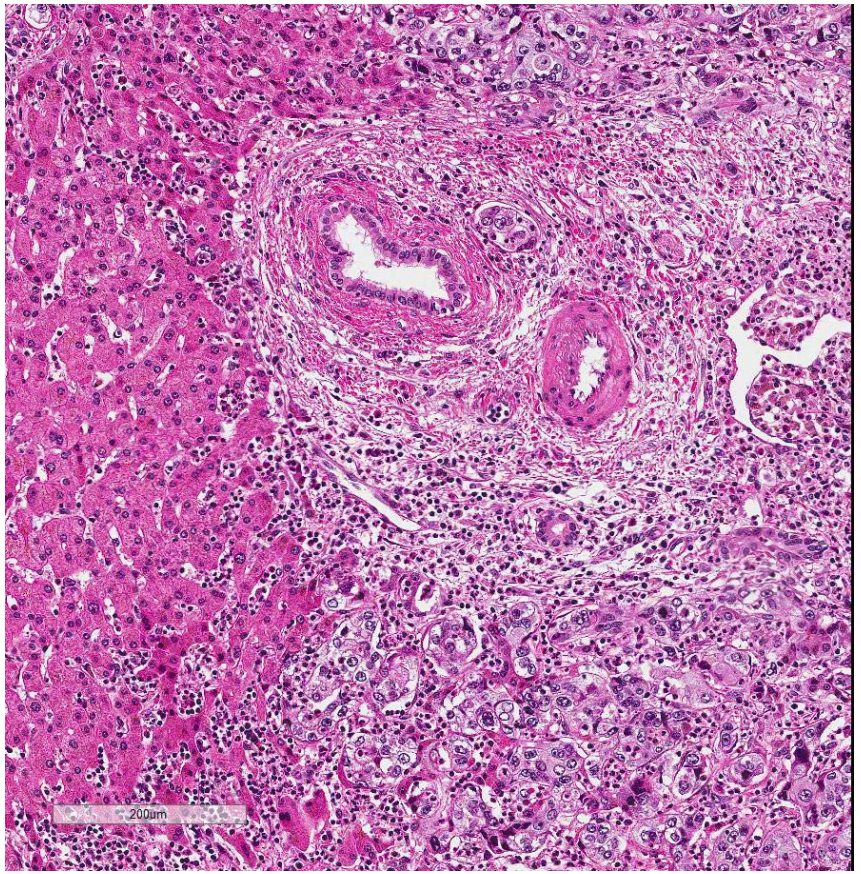
- Hilar bile duct
- Extrahepatic bile duct



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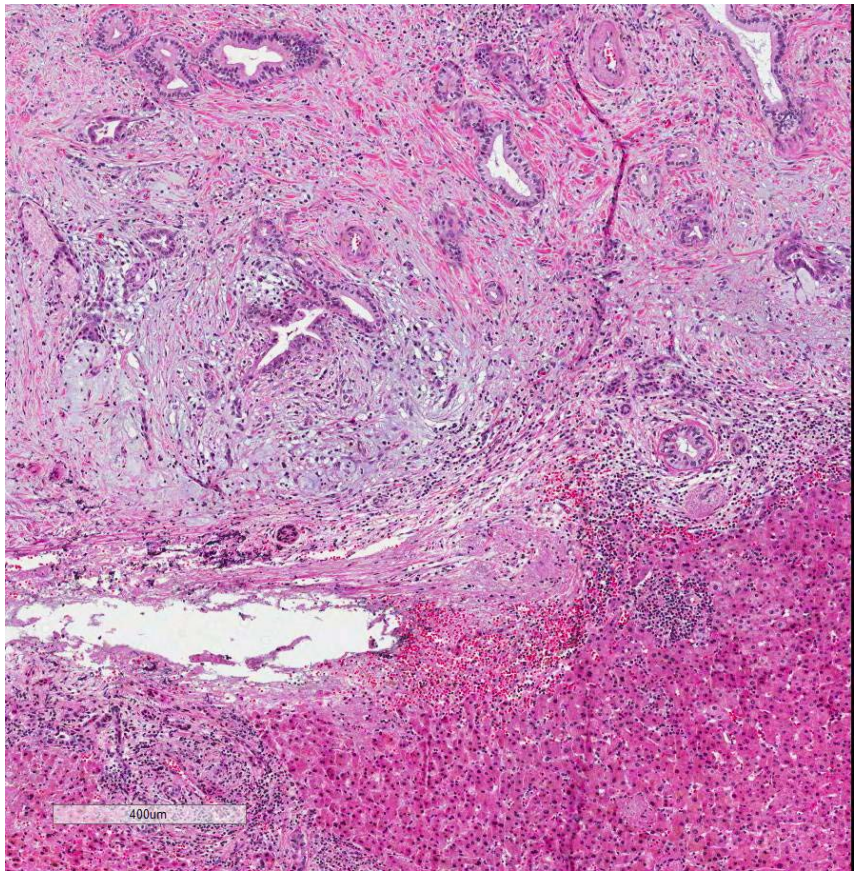

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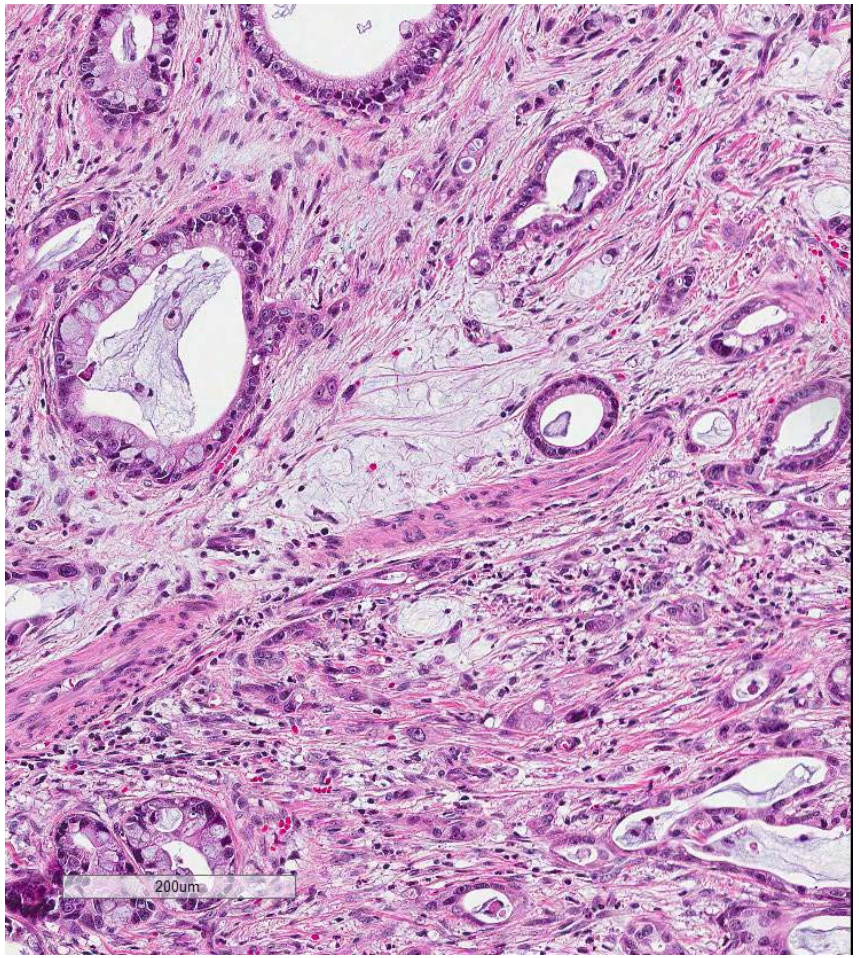
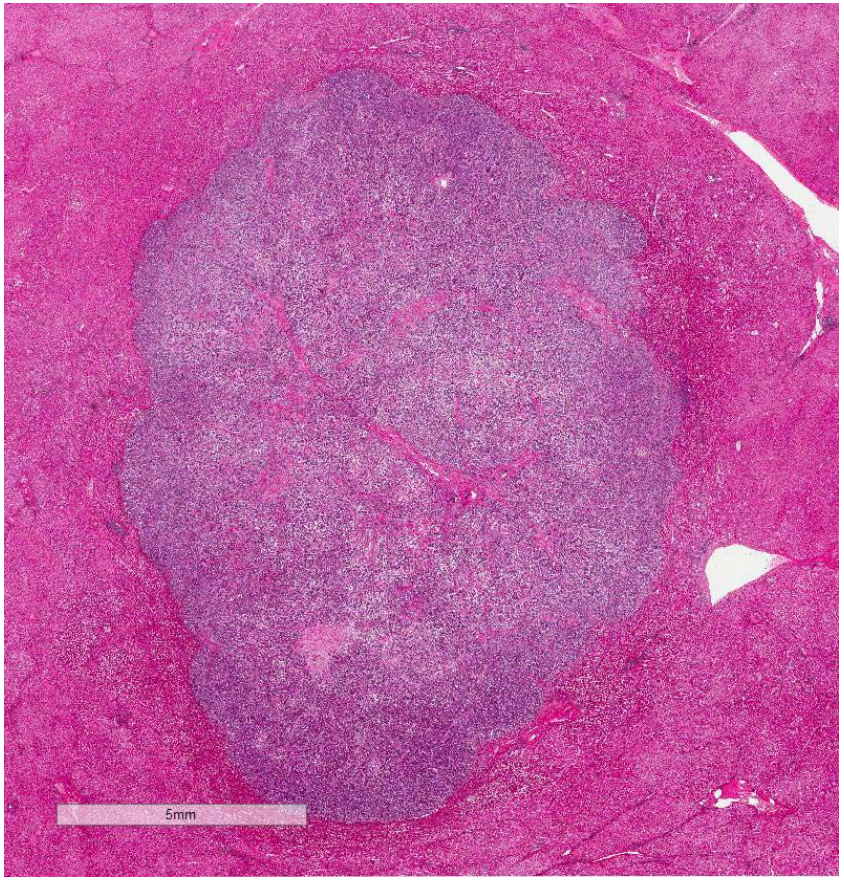
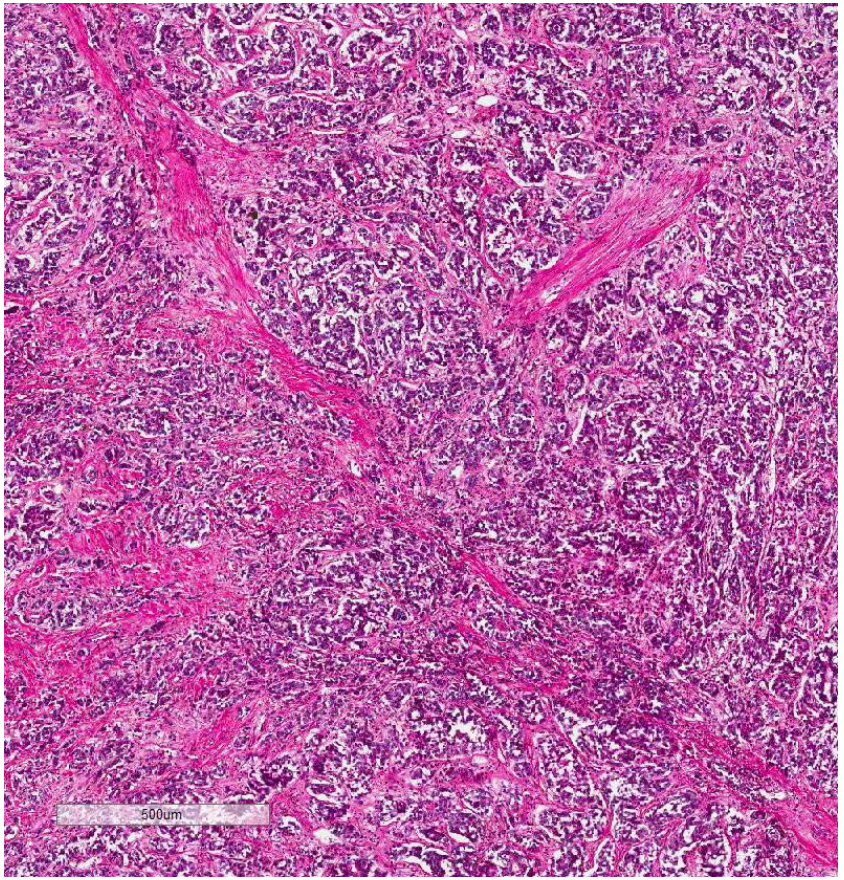


Microscopic findings of IHCCa





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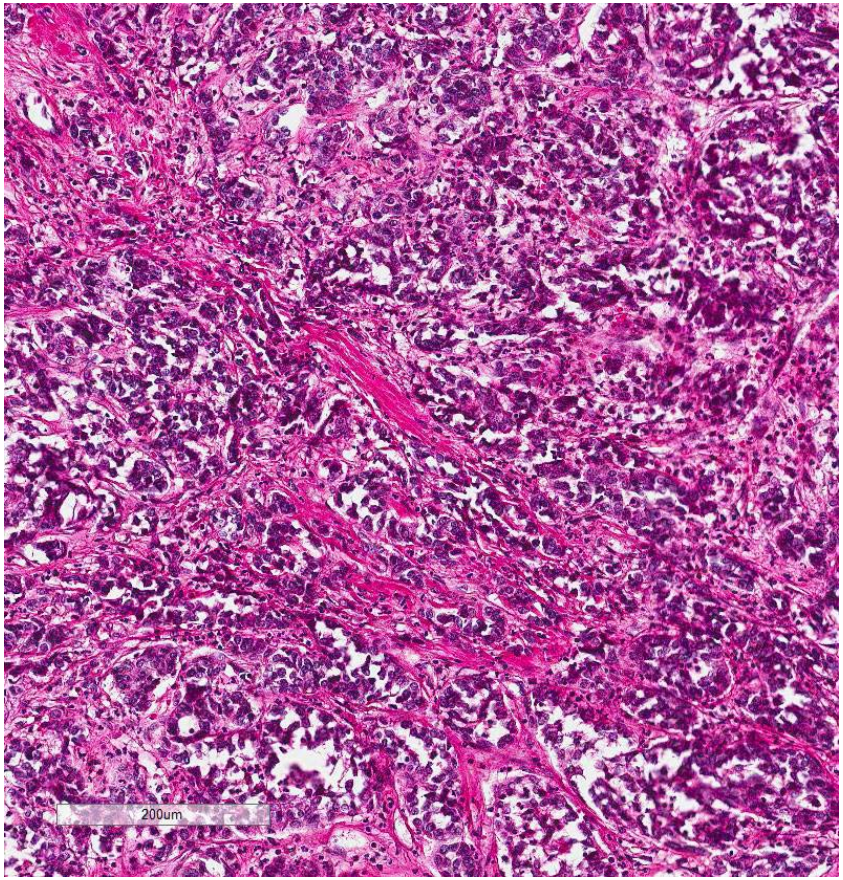
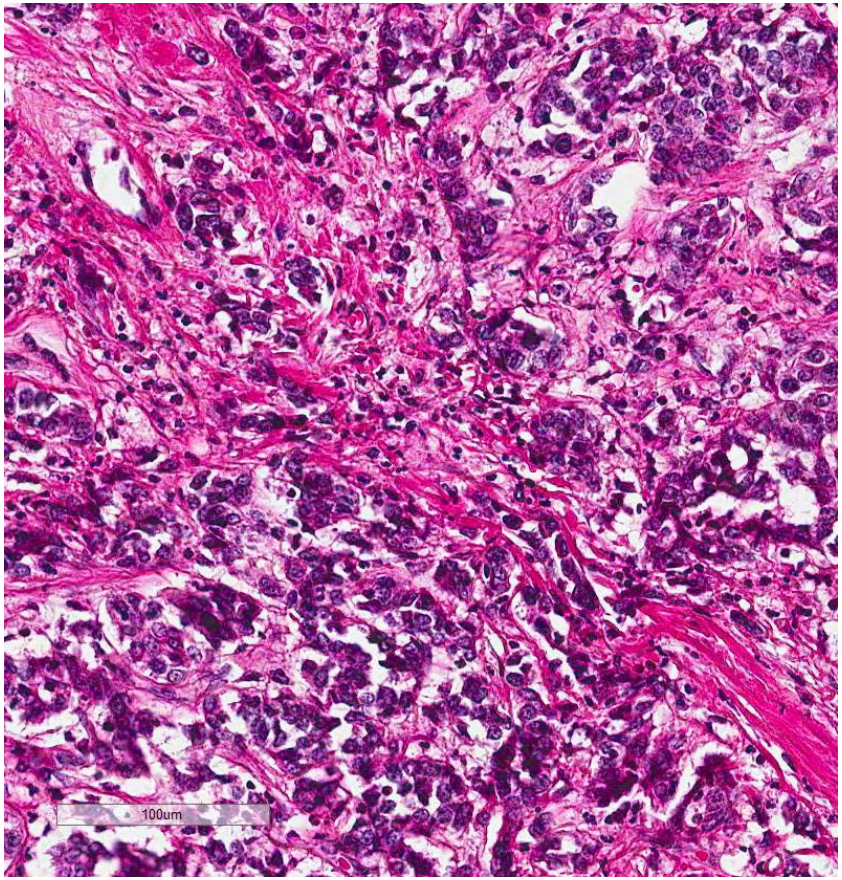
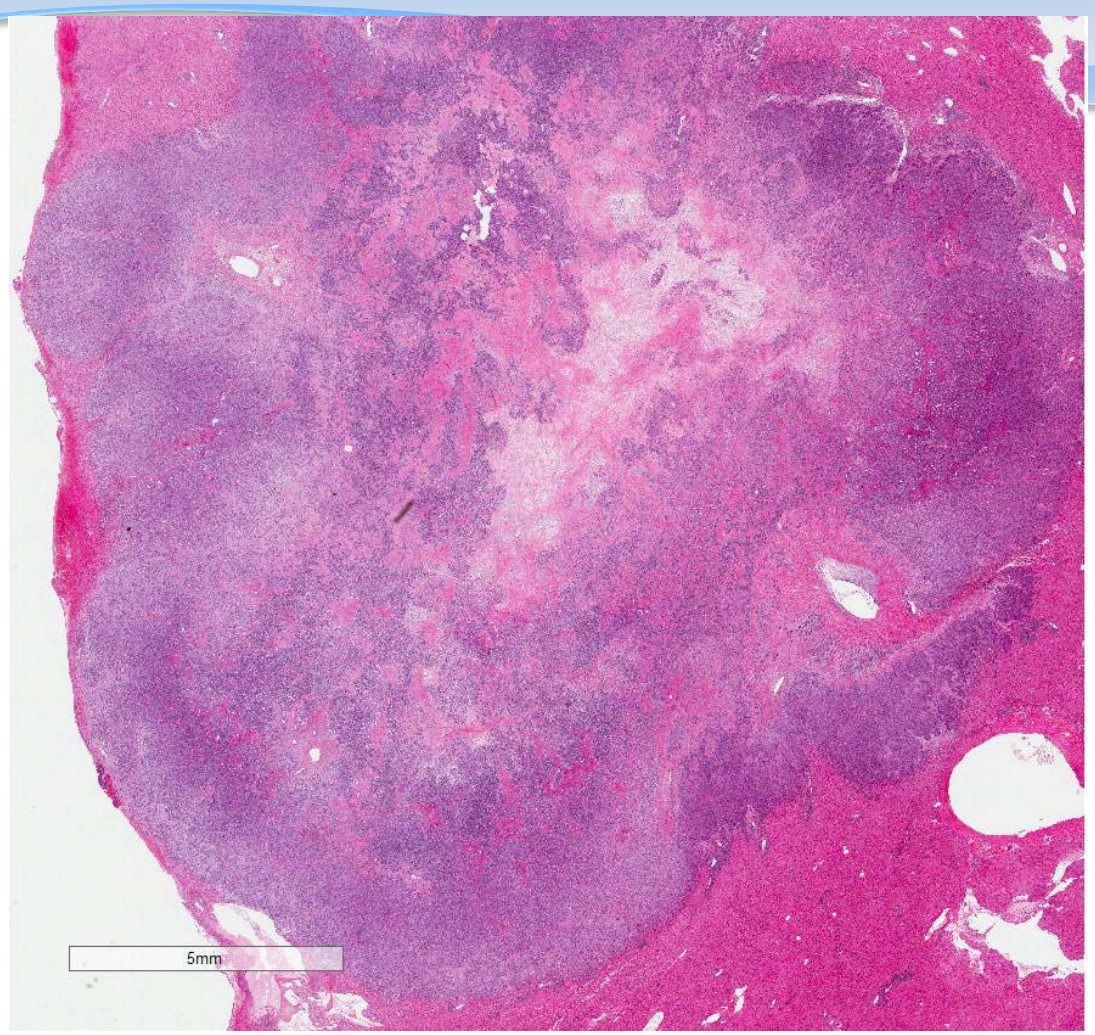
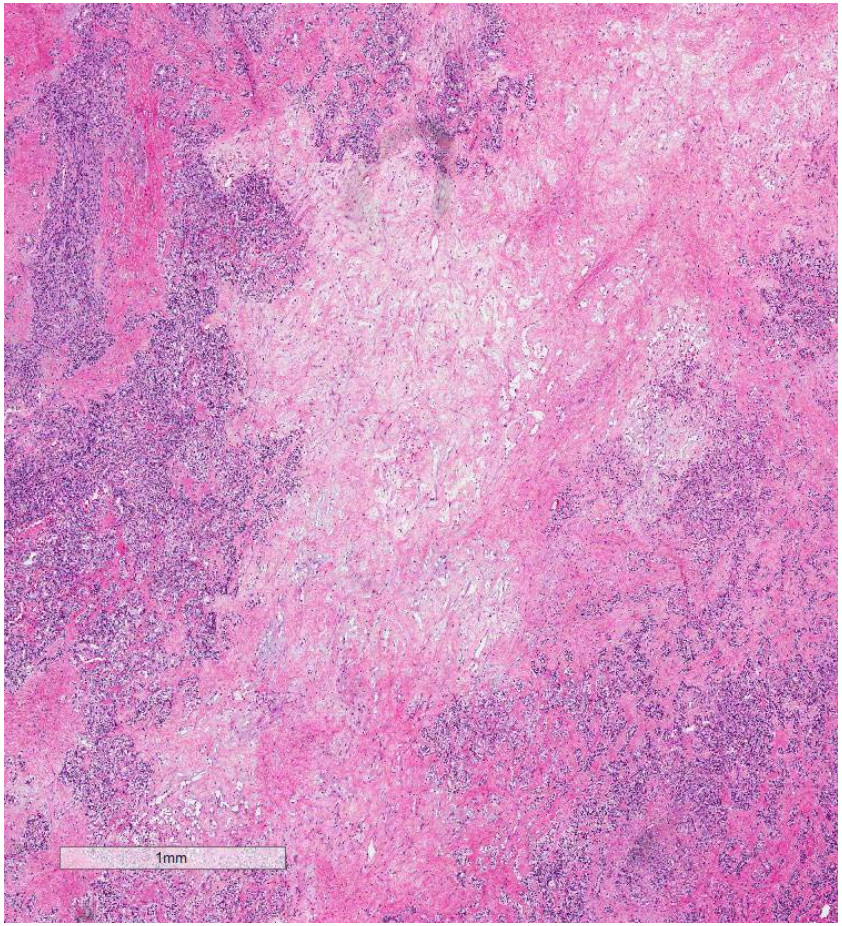


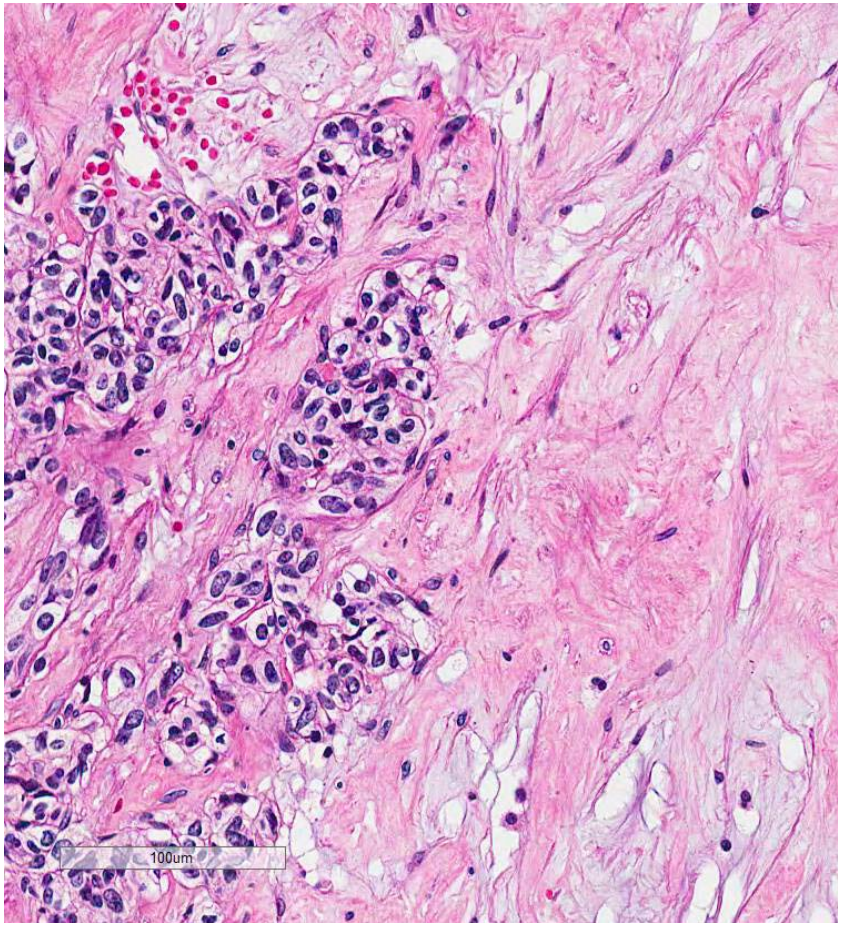


IHCCa with central scar

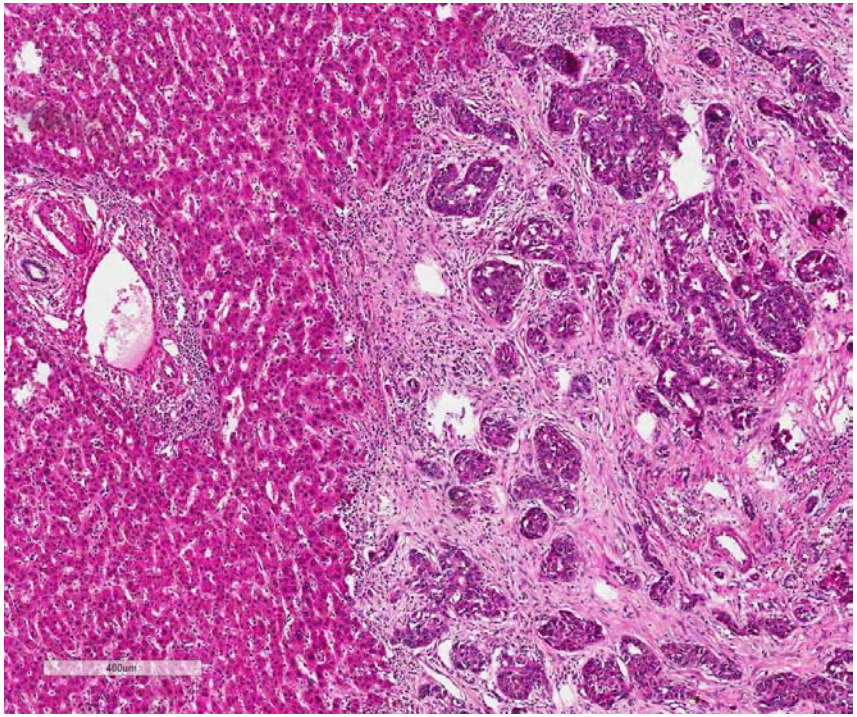


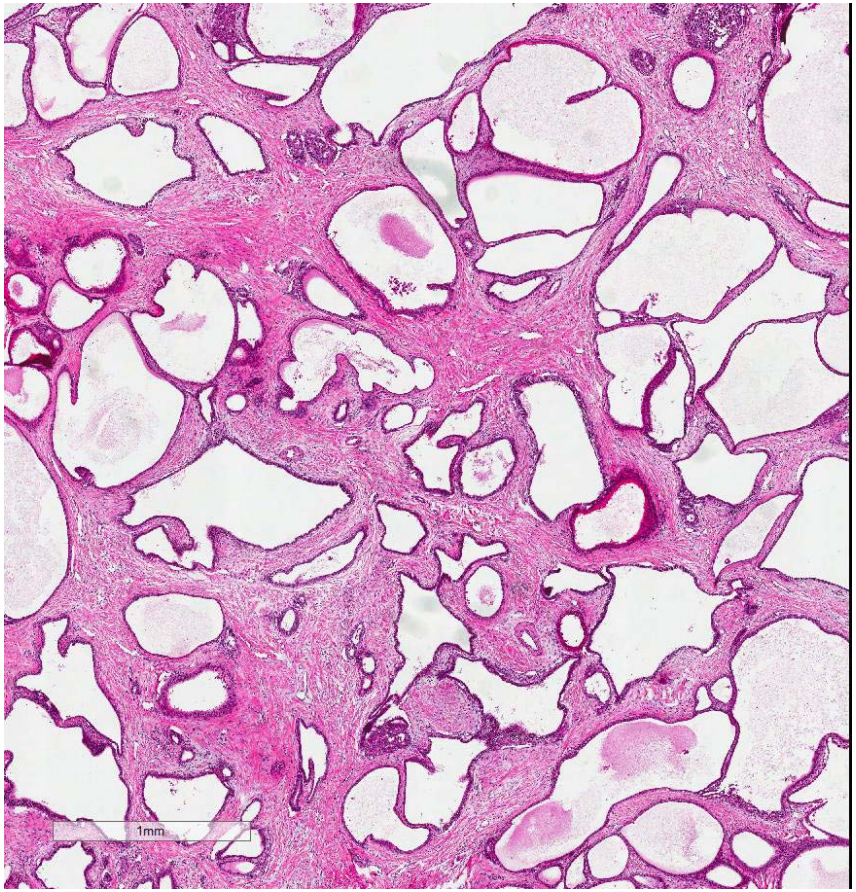
IHCCa with central scar



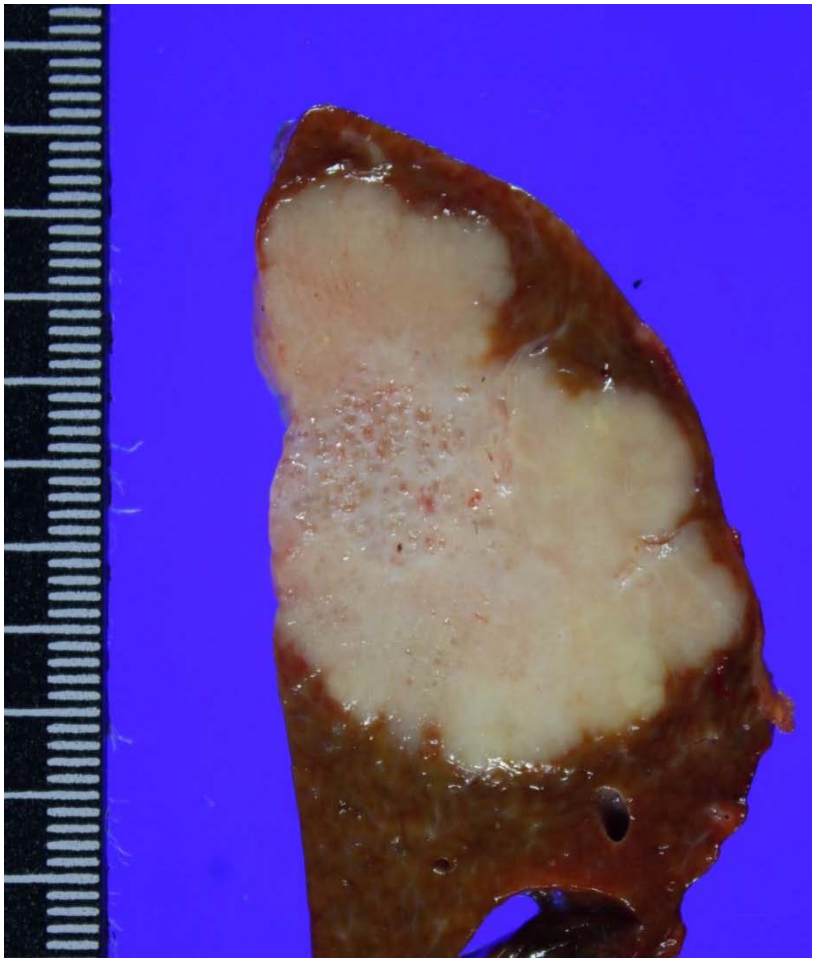


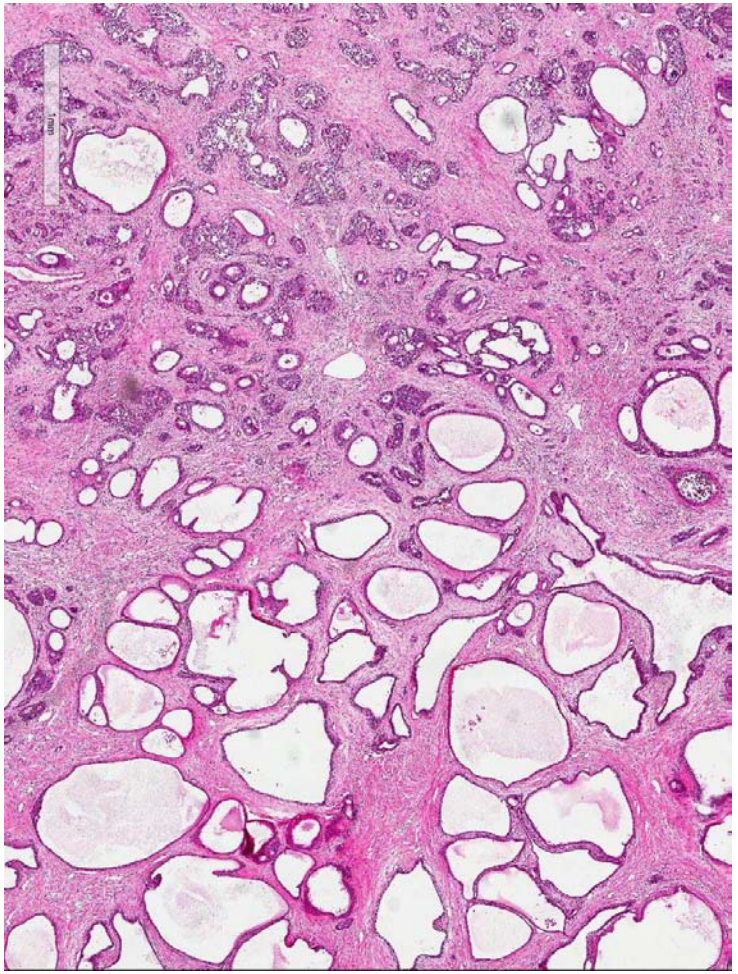
Small vs large bile duct (?)



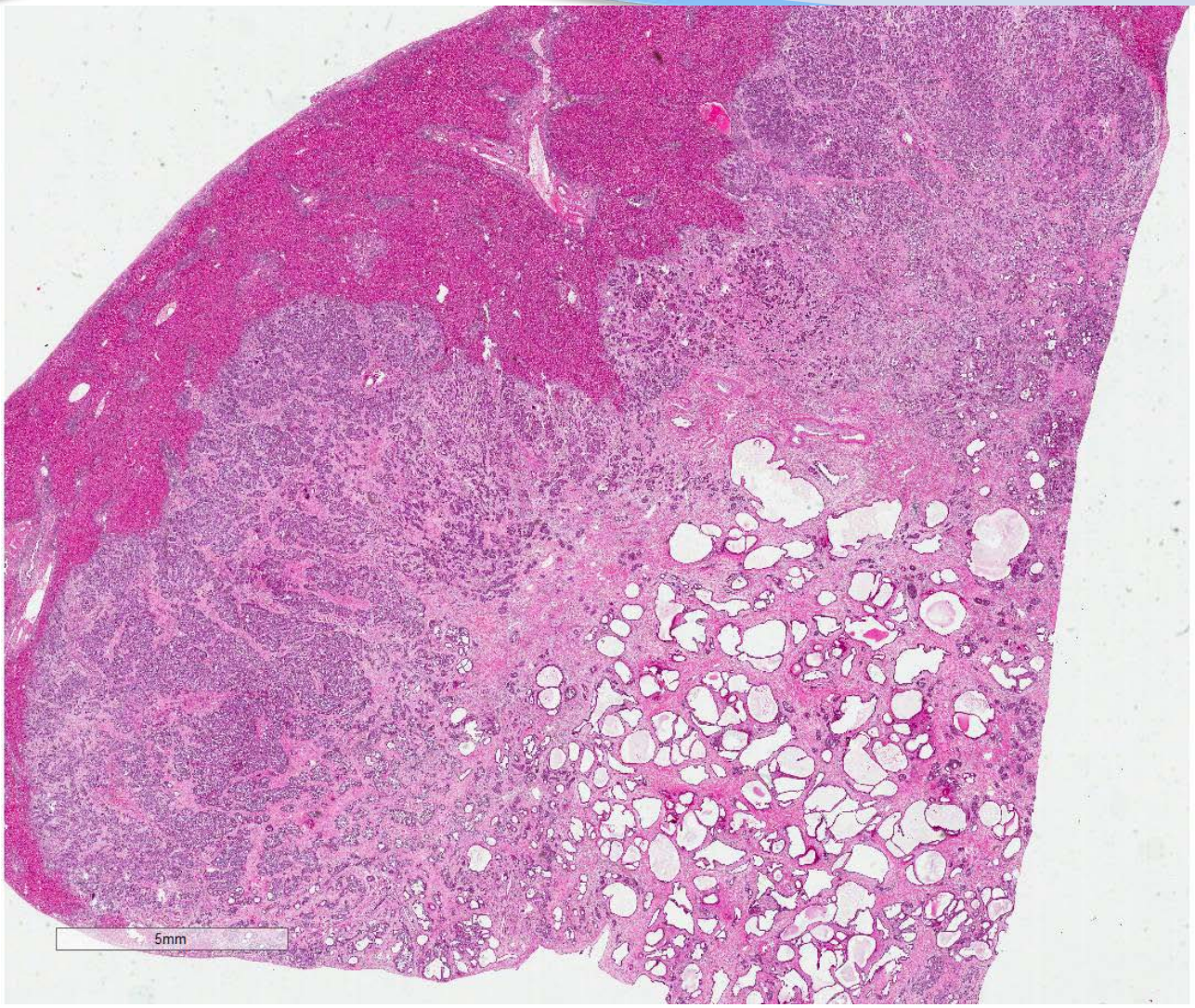


Small & large duct in same case





Spectrum of small to large bile duct



Histologic subtypes of IHCCa

Morphological subclassification of intrahepatic cholangiocarcinoma: etiological, clinicopathological, and molecular features

Jau-Yu Liau[1,2], Jia-Huei Tsai[1,2], Ray-Hwang Yuan[3], Chih-Ning Chang[1,2], Hsin-Jung Lee[1,2] and Yung-Ming Jeng[1,2]

[1]Department of Pathology, National Taiwan University Hospital, Taipei, Taiwan; [2]Graduate Institute of Pathology, College of Medicine, National Taiwan University, Taipei, Taiwan and [3]Department of Surgery, National Taiwan University Hospital, Taipei, Taiwan

On the basis of morphological features, we subclassified 189 intrahepatic cholangiocarcinomas into two subtypes: bile duct and cholangiolar. The cholangiolar type is composed of cuboidal to low columnar tumor cells that contain scanty cytoplasm. The bile duct type is composed of tall columnar tumor cells arranged in a large glandular pattern. In this study, 77 (41%) tumors were classified as the cholangiolar type and 112 (59%) tumors were classified as the bile duct type. The cholangiolar-type intrahepatic cholangiocarcinoma was more frequently associated with viral hepatitis, whereas all but one intrahepatic cholangiocarcinoma associated with intrahepatic lithiasis were classified as the bile duct type. Biliary intraepithelial neoplasm or intraductal papillary neoplasm of the bile duct could be identified in 50 bile duct-type intrahepatic cholangiocarcinomas (45%), but in only 3 cholangiolar-type intrahepatic cholangiocarcinomas (4%). Cholangiolar-type intrahepatic cholangiocarcinomas frequently expressed N-cadherin, whereas bile duct intrahepatic cholangiocarcinomas were more likely to express S100P, Trefoil factor 1, and anterior gradient 2. *KRAS* is mutated in 23 of 98 (23%) bile duct-type intrahepatic cholangiocarcinomas and in only 1 of 76 (1%) cholangiolar-type intrahepatic cholangiocarcinomas. Cholangiolar-type intrahepatic cholangiocarcinomas had a higher frequency of *IDH1* or *2* mutations than did the bile duct-type intrahepatic cholangiocarcinomas. The molecular features of the bile duct-type intrahepatic cholangiocarcinoma were similar to those of hilar cholangiocarcinoma. Patients with the cholangiolar-type intrahepatic cholangiocarcinoma had higher 5-year survival rates than those of patients with the bile duct-type intrahepatic cholangiocarcinoma. Our results indicated that intrahepatic cholangiocarcinoma was a heterogeneous tumor. Subclassification of intrahepatic cholangiocarcinomas based on cholangiocytic differentiation divides them into two groups with different etiologies, clinical manifestations, and molecular pathogeneses.

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Keywords: cholangiolar; intrahepatic cholangiocarcinoma; isocitrate dehydrogenase; N-cadherin

Intrahepatic cholangiocarcinoma is the second most common primary liver cancer after hepatocellular carcinoma. The incidence of intrahepatic cholangiocarcinoma varies widely worldwide and is more prevalent in East Asia than in Western countries,[1] mainly because of infestation by the liver flukes *Clonorchis sinensis* and *Opisthorchis viverrini*.[2,3]

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Other known etiological factors for intrahepatic cholangiocarcinoma include hepatolithiasis, primary sclerosing cholangitis, exposure to the radiopaque medium thorium dioxide (Thorotrast), biliary tract anatomical anomalies, and hepatitis B and C infections.[4–9] However, most patients diagnosed with cholangiocarcinoma do not have a recognized risk factor. The molecular mechanisms for carcinogenesis and tumor progression of intrahepatic cholangiocarcinoma are still poorly characterized. Despite intensive research, managing this cancer remains challenging, because most patients are at an advanced stage at the time of diagnosis, and no effective therapy for unresectable tumors exists.[10]

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Histological Diversity in Cholangiocellular Carcinoma Reflects the Different Cholangiocyte Phenotypes

Mina Komuta,[1] Olivier Govaere,[1] Vincent Vandecaveye,[2] Jun Akiba,[3] Werner Van Steenbergen,[4] Chris Verslype,[4] Wim Laleman,[4] Jacques Pirenne,[5] Raymond Aerts,[6] Hirohisa Yano,[3] Frederik Nevens,[4] Baki Topal,[6] and Tania Roskams[1]

Cholangiocellular carcinoma (CC) originates from topographically heterogeneous cholangiocytes. The cylindrical mucin-producing cholangiocytes are located in large bile ducts and the cuboidal non–mucin-producing cholangiocytes are located in ductules containing bipotential hepatic progenitor cells (HPCs). We investigated the clinicopathological and molecular features of 85 resected CCs (14 hilar CCs [so-called Klatskin tumor], 71 intrahepatic CCs [ICCs] including 20 cholangiolocellular carcinomas [CLCs], which are thought to originate from HPCs]) and compared these with the different cholangiocyte phenotypes, including HPCs. Immunohistochemistry was performed with biliary/HPC and hepatocytic markers. Gene expression profiling was performed in different tumors and compared with nonneoplastic different cholangiocyte phenotypes obtained by laser microdissection. Invasion and cell proliferation assay were assessed using different types of CC cell lines: KMC-1, KMCH-1, and KMCH-2. Among 51 ICCs, 31 (60.8%) contained only mucin-producing CC features (muc-ICCs), whereas 39.2% displayed histological diversity: focal hepatocytic differentiation and ductular areas (mixed-ICCs). Clinicopathologically, muc-ICCs and hilar CCs showed a predominantly (peri-)hilar location, smaller tumor size, and more lymphatic and perineural invasion compared with mixed-ICCs and CLCs (predominantly peripheral location, larger tumor size, and less lymphatic and perineural invasion). Immunoreactivity was similar in muc-ICCs and hilar CCs and in mixed-ICCs and CLCs. *S100P* and *MUC1* were significantly up-regulated in hilar CCs and muc-ICCs compared with mixed-ICCs and CLCs, whereas *NCAM1* and *ALB* tended to be up-regulated in mixed-ICCs and CLCs compared with other tumors. KMC-1 showed significantly higher invasiveness than KMCH-1 and KMCH-2. *Conclusion*: Muc-ICCs had a clinicopathological, immunohistochemical, and molecular profile similar to that of hilar CCs (from mucin-producing cholangiocytes), whereas mixed-ICCs had a profile similar to that of CLCs (thought to be of HPC origin), possibly reflecting their respective cells of origin. (HEPATOLOGY 2012;55:1876-1888)

Cholangiocellular carcinoma (CC) is a primary liver tumor originating from cholangiocytes (epithelial cells that line the bile duct). Cholangiocytes are topographically heterogeneous within the different levels of the biliary tree.[1] The biliary tree is divided anatomically into extra- and intrahepatic bile duct (BD). Hilar BD and right and left hepatic BD are considered extrahepatic BD, and they are lined by cylindrical mucin-producing cholangiocytes. Inside the liver, a large intrahepatic BD (such as segmental, area, and septal BD) has a lining of similar mucin-producing cylindrical cells, whereas a small intrahepatic BD (such as interlobular BD and ductules) is lined with mucin-negative cuboidal cholangiocytes. In addition, ductules contain hepatic progenitor cells (HPCs),[2] which can differentiate into both hepatocytes

Abbreviations: ANXA3, annexin A3; BD, bile duct; CC, cholangiocellular carcinoma; CLC, cholangiolocellular carcinoma; DR, ductular reaction; EMA, epithelial membrane antigen; EpCAM, epithelial cell adhesion molecule; HCC, hepatocellular carcinoma; hep-dif, hepatocytic differentiation; HPC, hepatic progenitor cell, ICC, intrahepatic CC; mixed-ICC, ICC with mixed features; MRI, magnetic resonance imaging; muc-ICC, mucin-producing ICC; NCAM, neural cell adhesion molecule; pCEA, polyclonal carcinoembryonic antigen; PSC, primary sclerosing cholangitis; RT-PCR, reverse-transcription polymerase chain reaction; TACSTD2, tumor-associated calcium signal transducer 2; WHO, World Health Organization.

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Subtype of IHCCa

Proposal of Progression Model for Intrahepatic Cholangiocarcinoma: Clinicopathologic Differences Between Hilar Type and Peripheral Type

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Abstract: It is important to clarify the histologic progression of intrahepatic cholangiocarcinoma (ICC) in consideration of its origin from the intrahepatic large or small biliary ducts. On the basis of the gross and histologic assessment, we classified 87 cases of ICC smaller than 5 cm in diameter into hilar type (H-ICC, n = 38) or peripheral type (P-ICC, n = 49) to compare their clinical and histologic features. Biliary dysplasia was observed in 65.8% (25/38) of H-ICC cases, whereas hepatitis virus infection and liver cirrhosis were associated with 46.7% (21/45) and 28.6% (14/49) of P-ICC, respectively. The frequency of perineural invasion, lymph node metastasis, and extrahepatic recurrence of H-ICC was significantly higher than that of P-ICC ($P < 0.0001$, 0.0106, and 0.0279, respectively). H-ICC cases showed frequent vascular invasion and intrahepatic metastasis even with small tumor size, compared with P-ICC cases. H-ICC showed large duct involvement within the tumor, and in the cases of large tumor size, intraductal spread was detected in the tumor periphery. P-ICC of small size contained preserved architecture of the portal tracts. The survival of patients with H-ICC was worse than that of patients with P-ICC ($P = 0.0121$). The independent and best prognostic factor by multivariate analysis was intrahepatic metastasis for H-ICC and lymph node metastasis for P-ICC. Our results suggest that ICCs derived from a different level of biliary ducts were related to different premalignant conditions and different tumor progression. Some ICCs arising from the large biliary duct are likely to exhibit an aggressive course even in cases of small tumor size. The recognition of the above events induces the proper therapy.

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Key Words: cholangiocarcinoma, hilar, peripheral, prognosis

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Intrahepatic cholangiocarcinoma (ICC) is a relatively rare liver cancer; however, the incidence and mortality rates of ICC are increasing worldwide.[26,36] A complete surgical resection is the only effective therapy, but the outcome of patients with ICC remains unsatisfactory because of the late clinical presentation and tumor detection.[4,11] The concept of multistep carcinogenesis and progression of hepatocellular carcinoma (HCC) has been proposed with the development of imaging modalities and histopathologic analysis of early HCC and preneoplastic lesions.[7,14,15,18,24] In contrast, the progression of ICC is not fully understood, because small-sized ICC are rarely diagnosed and the study of these tumors has been limited.[38]

Some established risk factors for ICC have been identified, including parasitic infection,[35] hepatolithiasis, primary sclerosing cholangitis,[17] and congenital anomalies.[8] Additional risk factors such as cirrhosis and infection with hepatitis B virus (HBV) and hepatitis C virus (HCV) are now becoming recognized in the pathogenesis of the mass-forming type of ICC.[9,13,33] It is essential to determine in detail the characteristics of tumors caused by these backgrounds.

ICCs arise from the epithelial cells of the biliary tree, from either intrahepatic large bile ducts or smaller bile ducts, such as septal and interlobular ducts. Because the clinical features and extent of the surgery depend on the site of the tumor, it is important to clarify the pathologic and biologic behavior of ICC on the basis of the different anatomic sites where it can occur.[23] Okuda et al[25] separated ICCs into the hilar type, which are tumors involved in the hilum, and the peripheral type, which are tumors occupying the hepatic periphery, and proposed that the hilar type resembled extrahepatic bile duct carcinoma and that the peripheral type was between ICC and HCC. Although the differences of etiology,[3] imaging,[21] surgical outcome,[20,27] and pathologic features[22,39] in hilar type and peripheral type ICCs have

Intrahepatic Cholangiocarcinoma: New Insights in Pathology

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ABSTRACT

Cholangiocarcinomas are malignant tumors that derive from cholangiocytes of small intrahepatic bile ducts or bile ductules (intrahepatic cholangiocarcinoma; ICC), or of large hilar or extrahepatic bile ducts (extrahepatic cholangiocarcinoma; ECC). ICC and ECC differ in morphology, pathogenesis, risk factors, treatment, and prognosis. This review focuses on ICC, which is rising in incidence with the emergence of hepatitis C virus (HCV) infection as a risk factor. The authors examined 73 ICC, which were resected at The Mount Sinai Medical Center in New York City, and reviewed the literature. The tumors were categorized into classical and nonclassical ICCs based on histopathology. Classical ICCs (54.8%) were characterized by a tubular, glandular, or nested pattern of growth, were significantly associated with tumor size of more than 5 cm and the absence of underlying liver disease and/or advanced fibrosis. Nonclassical ICCs (45.2%) consisted of tumors with trabecular architecture, tumors that exhibited features of extrahepatic carcinomas, and carcinomas considered to be derived from hepatic progenitor cells, i.e., combined hepatocellular/cholangiocarcinomas and cholangiolocellular carcinomas (ductular type of ICC). They were smaller and often arose in chronic liver disease, mostly HCV infection, and/or with significant fibrosis. The role of immunohistochemistry in the diagnosis of ICC and the importance of the new American Joint Committee on Cancer Staging System for ICC are also discussed.

KEYWORDS: Intrahepatic cholangiocarcinoma, cholangiolocarcinoma, histopathology, immunohistochemistry, HCV infection, hepatic progenitor cells

Cholangiocarcinomas are adenocarcinomas that arise from the malignant transformation of bile duct epithelium anywhere along the biliary tree from small bile ducts and bile ductules (intrahepatic cholangiocarcinomas; ICCs), to large bile ducts at the hilum of the liver or outside the liver (extrahepatic cholangiocarcinomas; ECCs).[1–3] Nomenclature of bile duct tumors is still a matter of debate. It has been proposed that the term "cholangiocarcinoma" be reserved for intrahepatic peripheral lesions and tumors arising from large bile ducts both at the hilum and along the extrahepatic biliary tree, be designated "bile duct carcinomas."[4] Indeed, hilar

Gross & histologic features for classification of IHCCa

	Hilar type	Peripheral type
Gross feature (level of involved ducts)	Second branches or segmental branches	Smaller than segmental branches
Histologic features	Papillary or large tubular component composed of tall columnar cells	Small glands, closely packed small ducts, or cordlike structure composed of cuboidal cells

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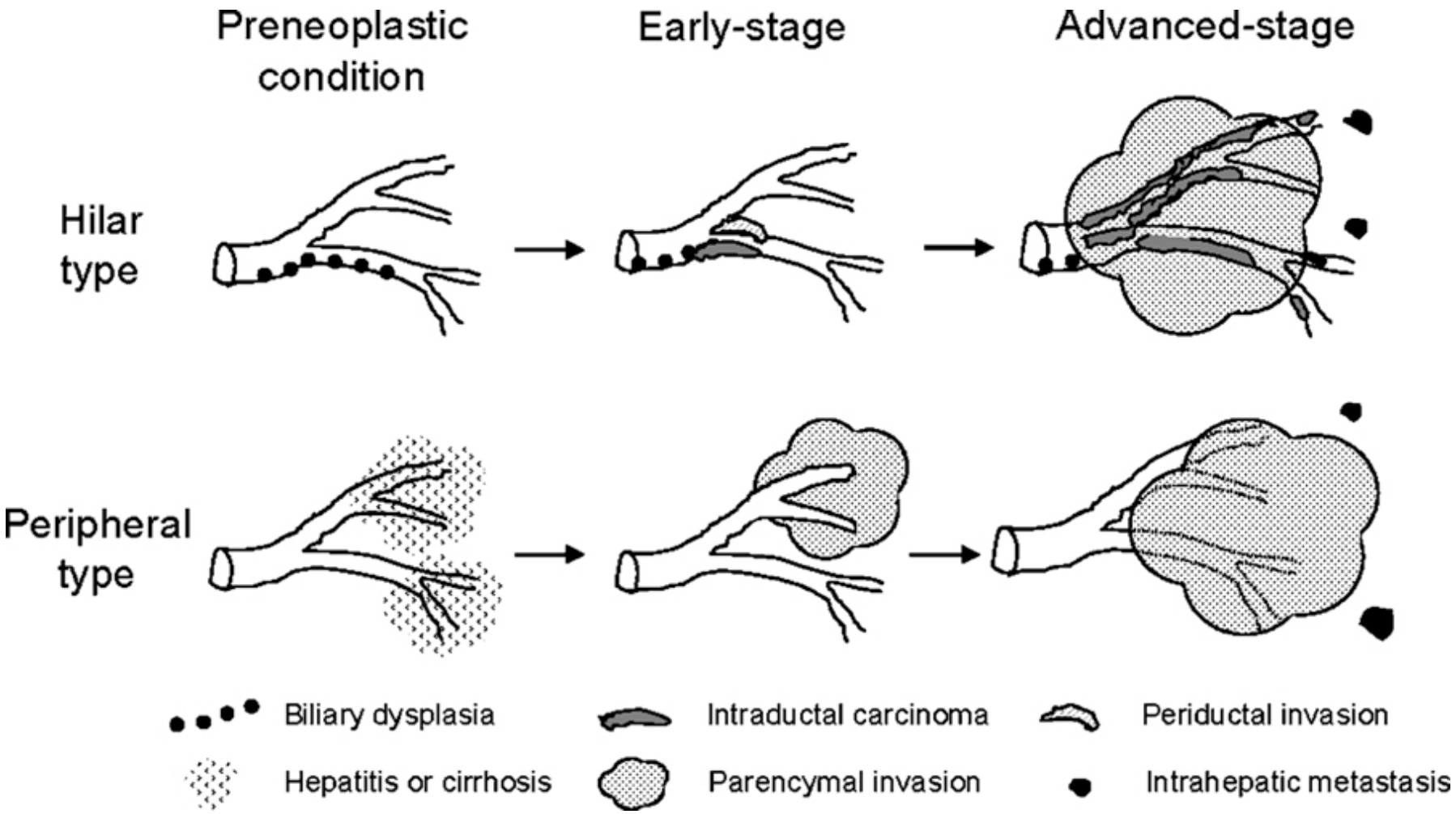
Proposal progression model of cholangiocarcinoma



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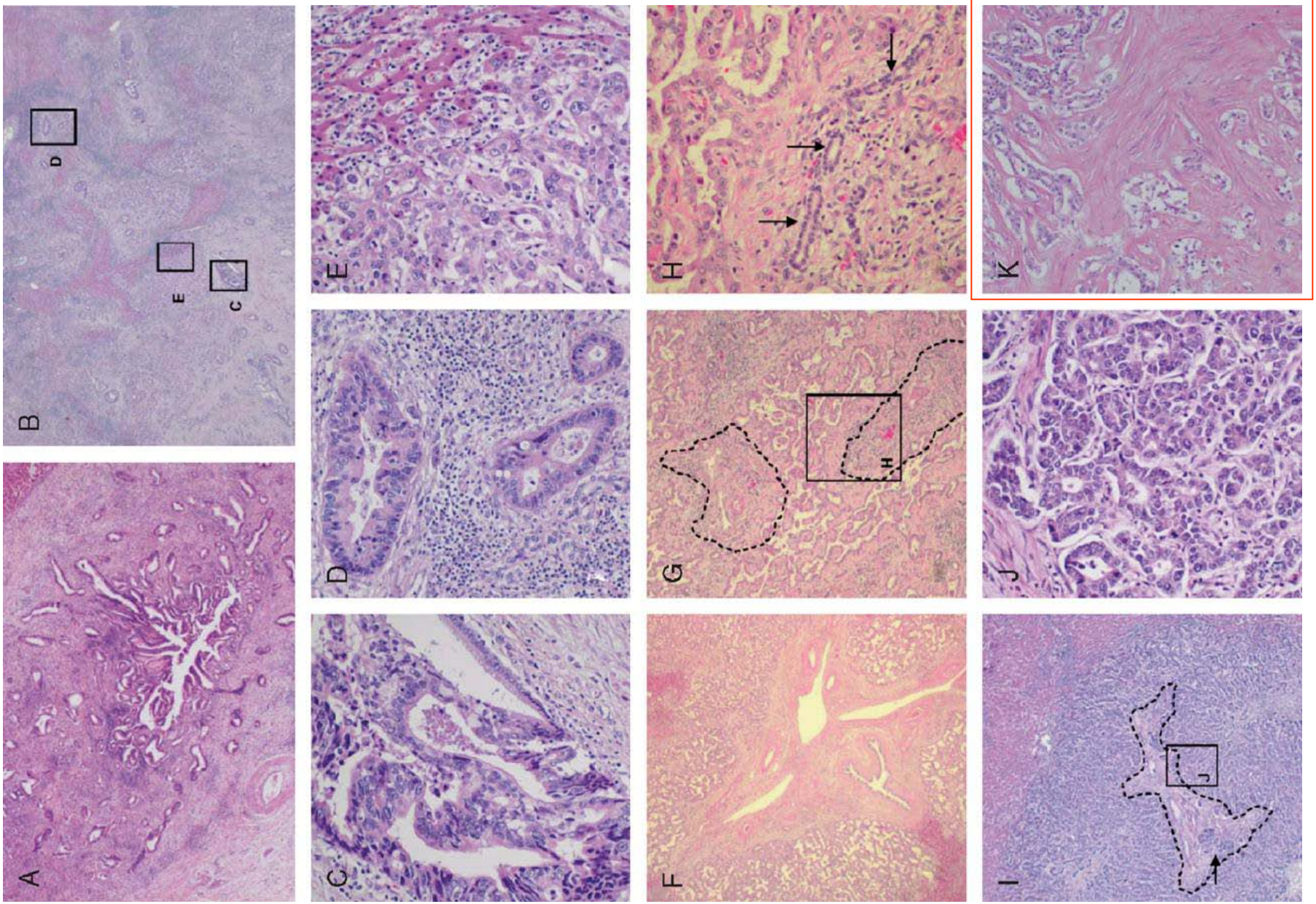
Mass-forming type



Periductal infiltrative type

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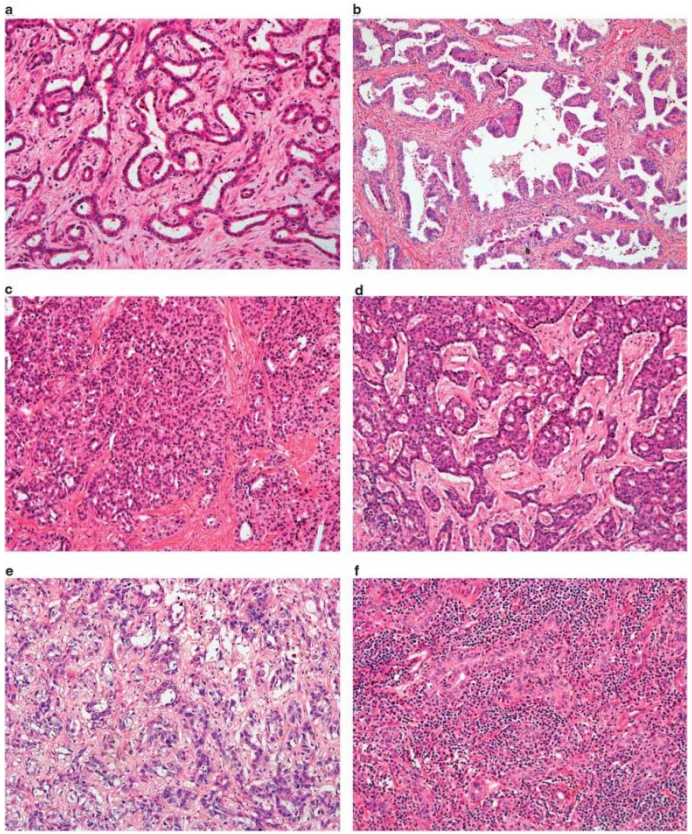
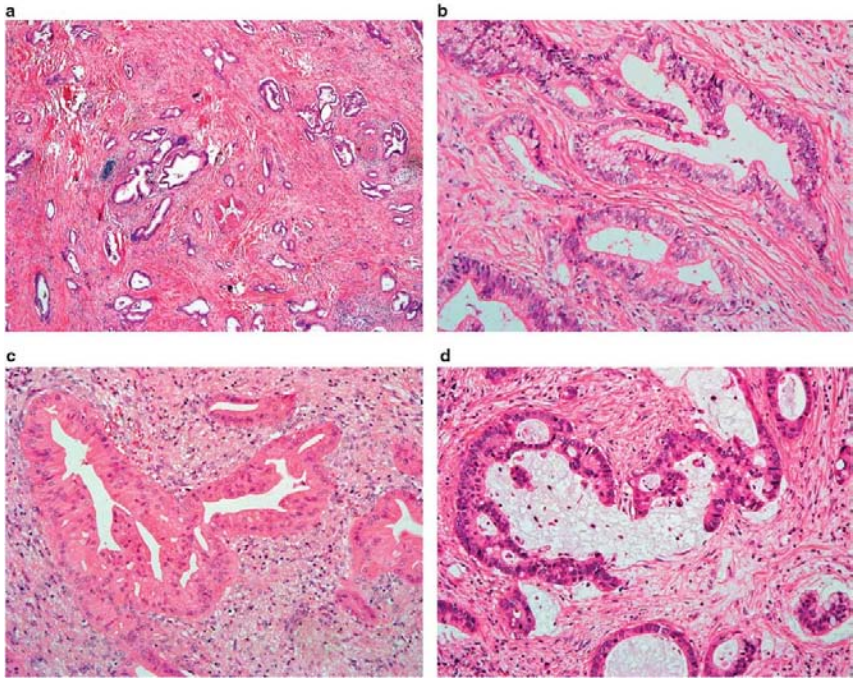
Histologic type of IHCCa

Cholangiolar type

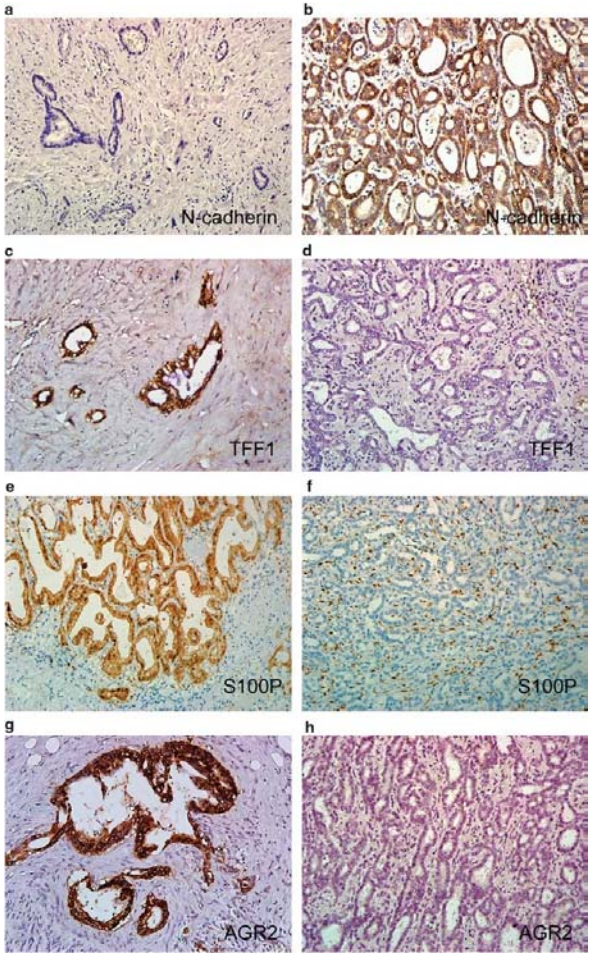


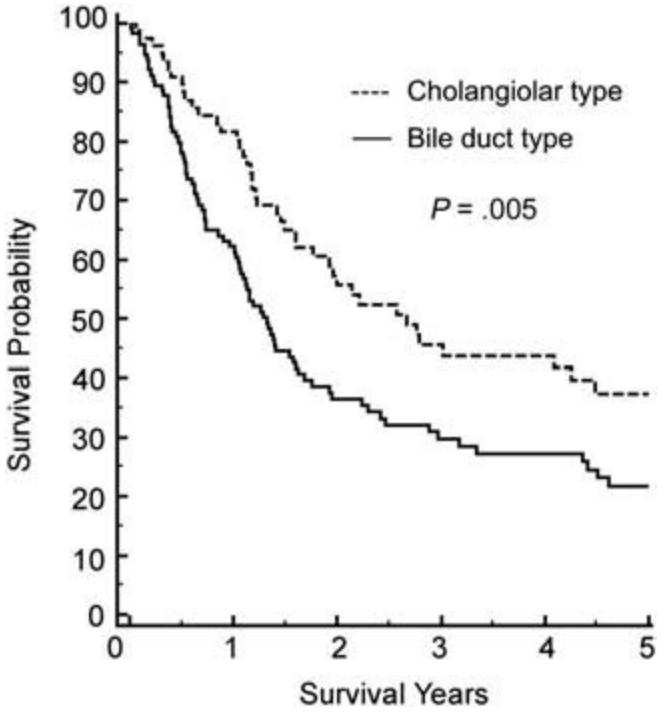
Bile duct type



Mod Pathol 2014;27:1163-1173

Survival by IHCCa subtype





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Clinicopathologic findings

Variables	*Histological subtype*		*Odds ratio*	*P-value*
	Bile duct, n = 112	*Cholangiolar, N = 77*		
Age (mean ± s.d.)	61.7 ± 10.4	60.7 ± 12.6		0.5973
Sex				
Male	56	37	1.08	0.7924
Female	56	40	0.58 < OR < 2.01	
Jaundice				
Negative	95	73	0.35	0.0600
Positive	15	4	0.09 < OR < 1.18	
Viral hepatitis				
Negative	42	25	2.08	0.0318
Positive	34	42	1.01 < OR < 4.30	
Intrahepatic lithiasis				
Present	24	1	21.0	0.00005
Absent	87	76	2.91 < OR < 426	
Size (cm) (mean ± s.d.)	6.9 ± 3.4	5.9 ± 2.7		0.2113
Gross morphology				
Intraductal/periductal	35	0		10^{-7}
Mass forming	77	77		
Precursor lesion				
Present	50	3	19.9	$<10^{-7}$
Absent	62	74	5.59 < OR < 84.2	
Lymph node metastasis				
Positive	24	7	2.70	0.0244
Negative	88	70	1.03 < OR < 7.34	

Mod Pathol 2014;27:1163-1173

Molecular and immunoprofile difference by subtype

Variables	*Histological subtype*		*Odds ratio*	*P-value*
	Bile duct, n = 112	*Cholangiolar, N = 77*		
S100P expression				
Negative	23	54	0.11	$<10^{-7}$
Positive	86	23	0.05 < OR < 0.23	
N-cadherin expression				
Negative	73	18	6.14	$<10^{-7}$
Positive	39	59	3.04 < OR < 12.5	
AGR2 expression				
Negative	44	61	0.16	10^{-7}
Positive	66	15	0.08 < OR < 0.34	
TFF1 expression				
Negative	25	39	0.28	0.00007
Positive	84	37	0.14 < OR < 0.56	
KRAS *mutation*				
Negative	75	75	0.04	0.00003
Positive	23	1	0.00 < OR < 0.32	
IDH1/2 *mutation*				
Negative	90	63	3.71	0.0121
Positive	5	13	1.15 < OR < 12.6	

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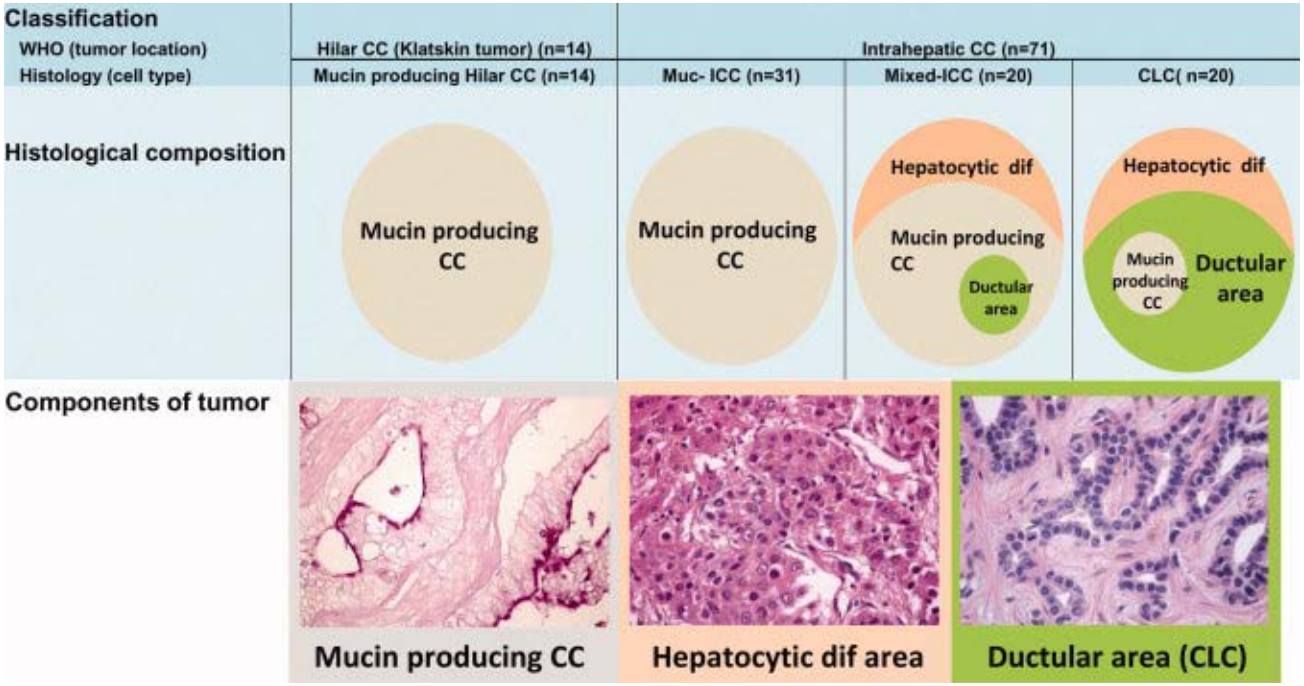
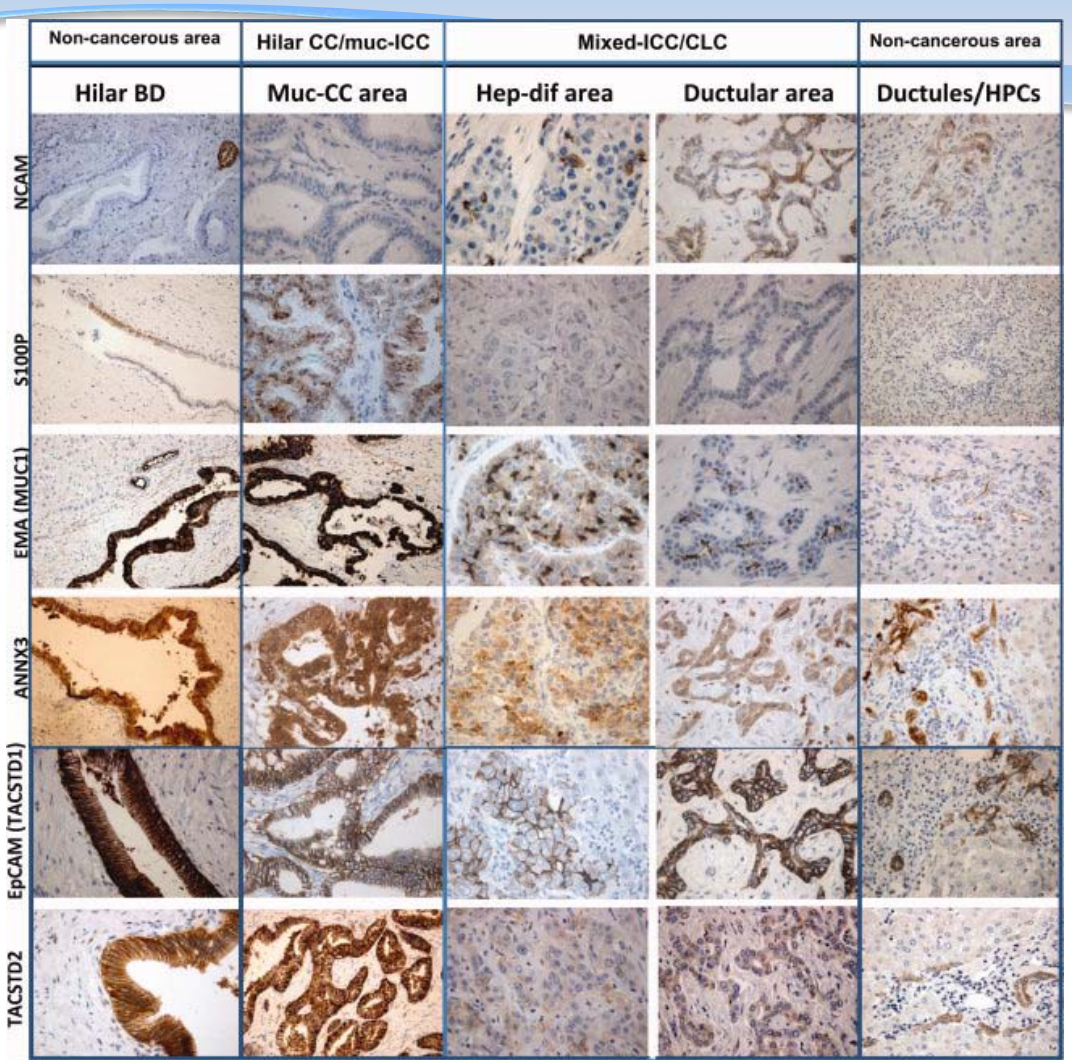
Bile duct cell spectrum of IHCCa



Hepatology 2012;55:1876-1888

Immunoprofile of IHCCa



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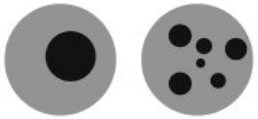
MRI finding by IHCCa subtype

A

T2-weighted imaging	Homogeneous intensity	Heterogeneous Intensity
		
Tumor Type		
Muc-ICC (n=14)	14 (100 %)	0 (0 %)
Mixed-ICC (n=10)	3 (30 %)	7 (70 %)
CLC (n=14)	2 (14 %)	12 (86 %)

B

Tumor type: n (%)	Dynamic series		
	Arterial phase	Portal phase	Venous phase
Muc-ICC: 14 (100 %) Mixed-ICC: 0 (0 %) CLC: 3 (21 %)	 Peripheral enhancement	 Concentric filling	 Concentric filling
Muc-ICC: 0 (0 %) Mixed-ICC: 5 (50 %) CLC: 5 (36 %)	 Peripheral or diffuse enhancement	 Peripheral wash-out and central enhancement	 Peripheral wash-out and central enhancement
Muc-ICC: 0 (0 %) Mixed-ICC: 2 (20 %) CLC: 1 (7 %)	 Diffuse enhancement	 Diffuse enhancement	 Diffuse enhancement
Muc-ICC: 0 (0 %) Mixed-ICC: 3 (30 %) CLC: 5 (36 %)	 Nodular enhancement	 Nodular pattern of wash-out	 Nodular pattern of wash-out

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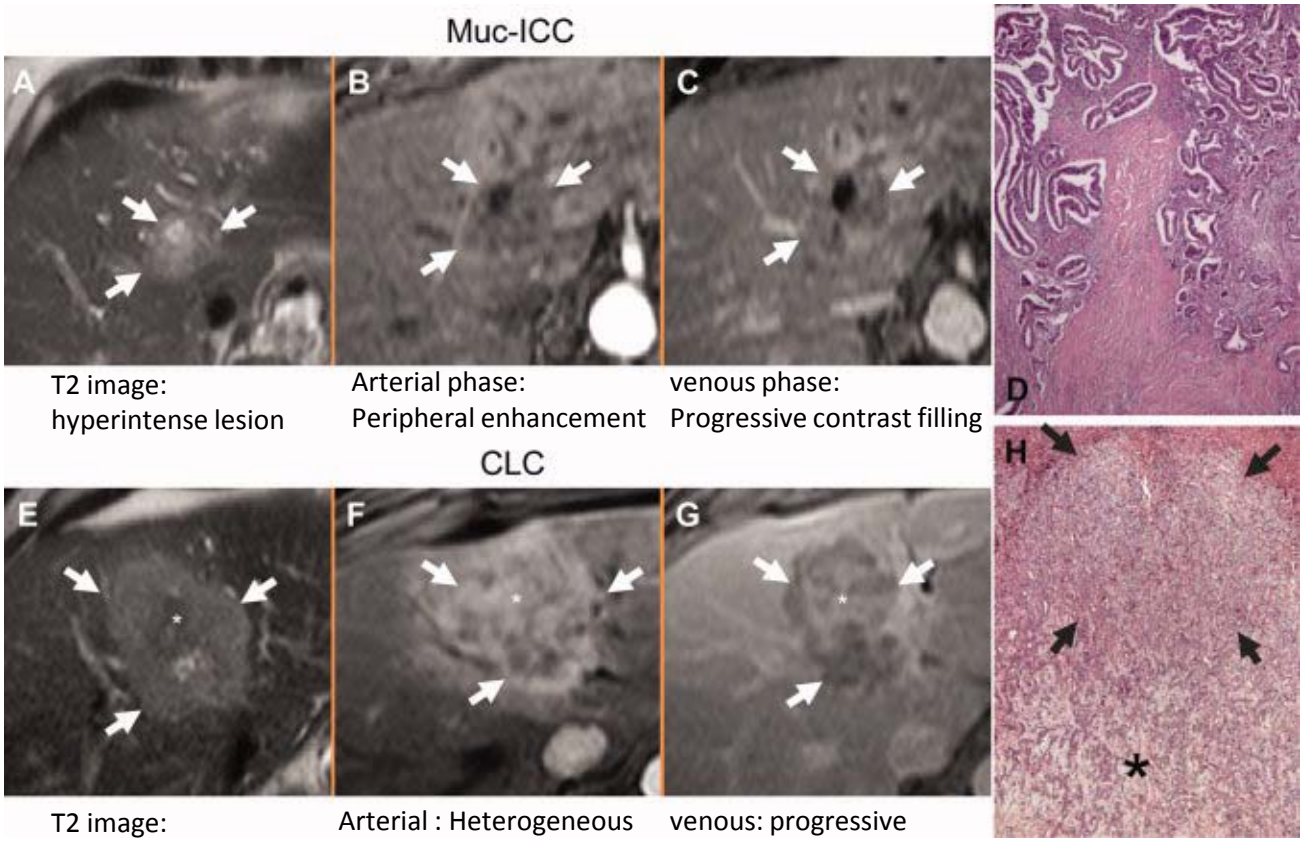
Radiologic-Patholgic correlation of MRI finding by IHCCa subtype



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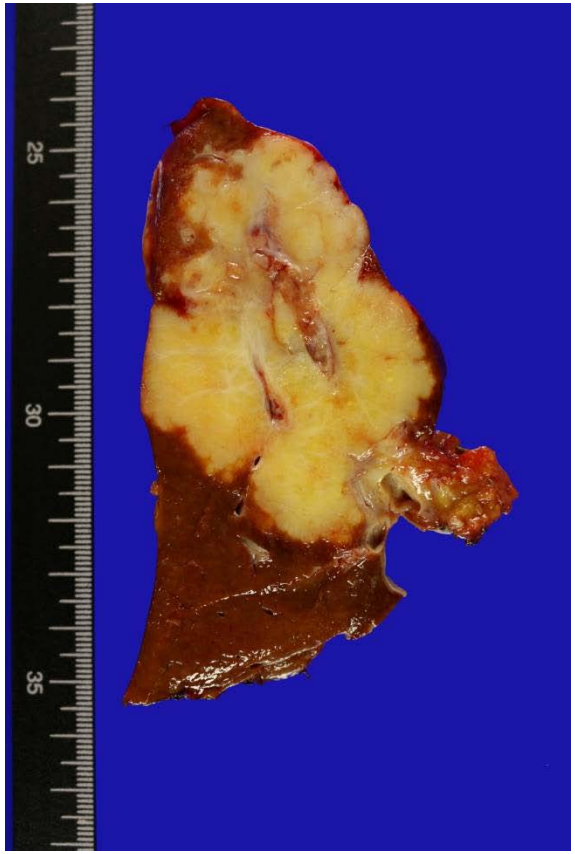
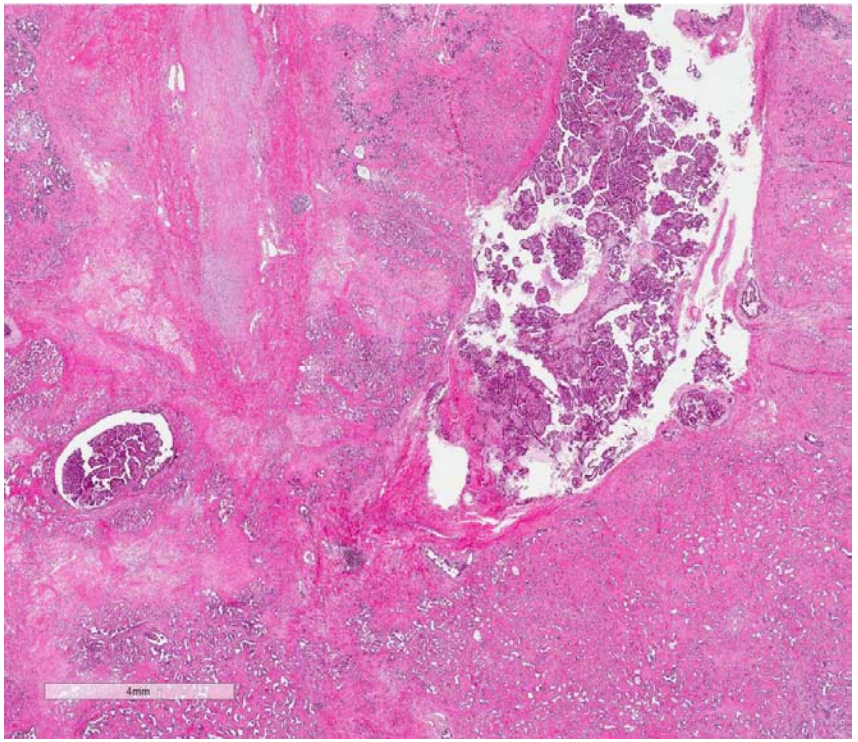
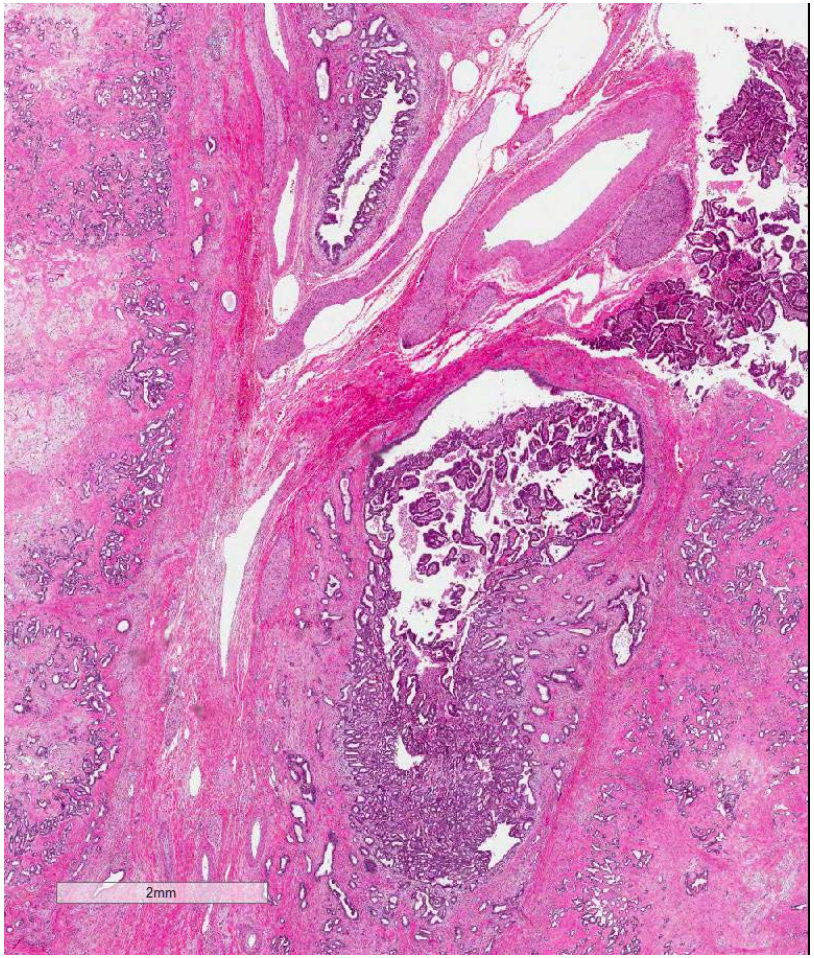
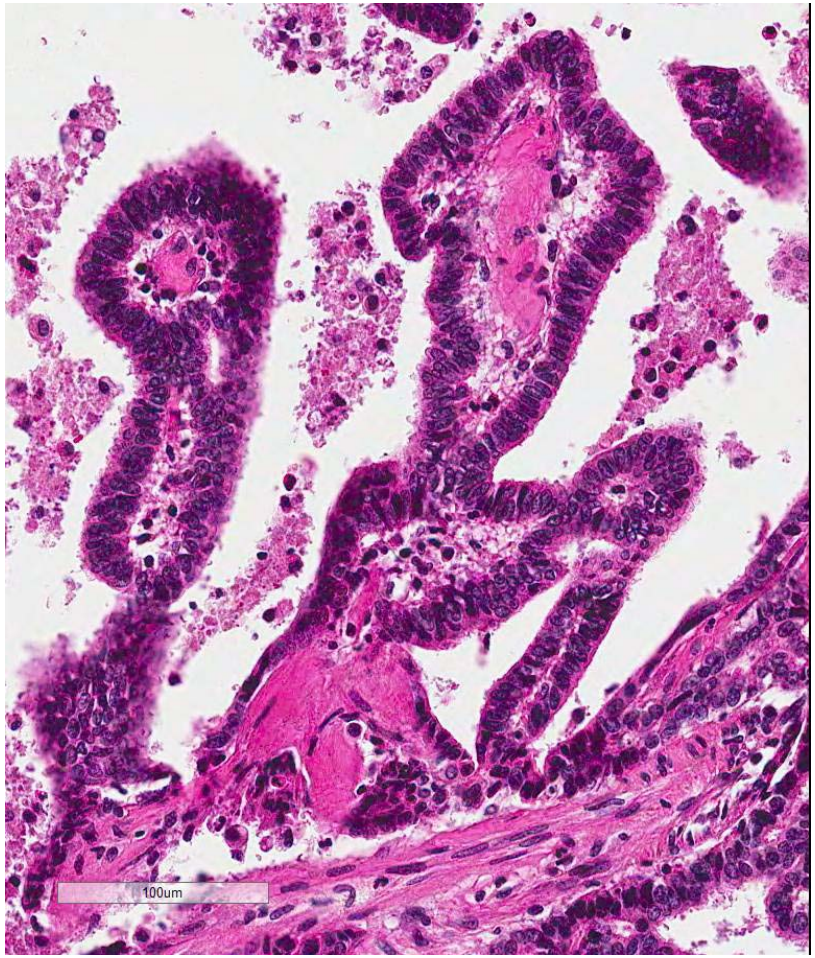
Mass-forming IHCCa with intraductal neoplasia



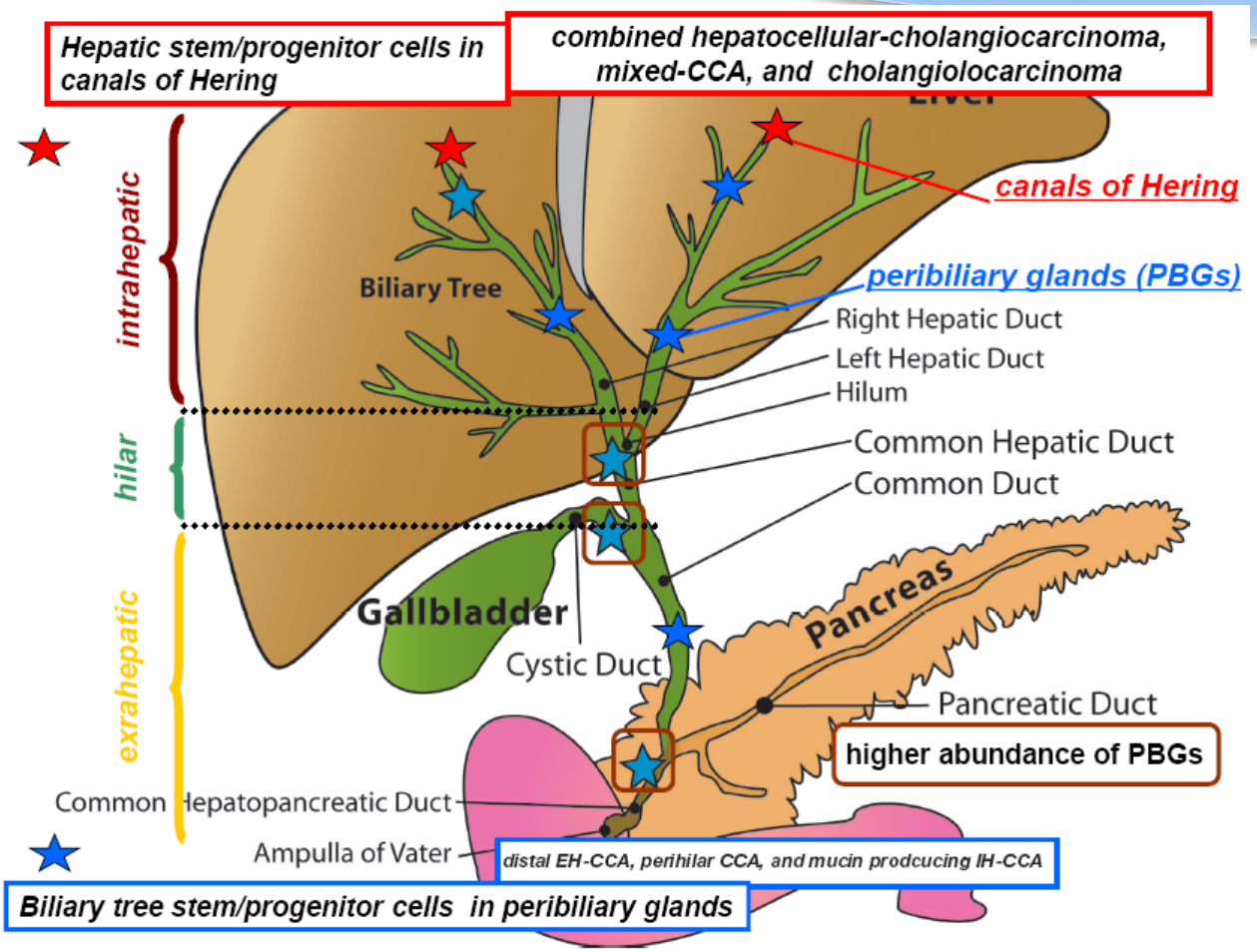


Mass-forming IHCCa with intraductal neoplasia





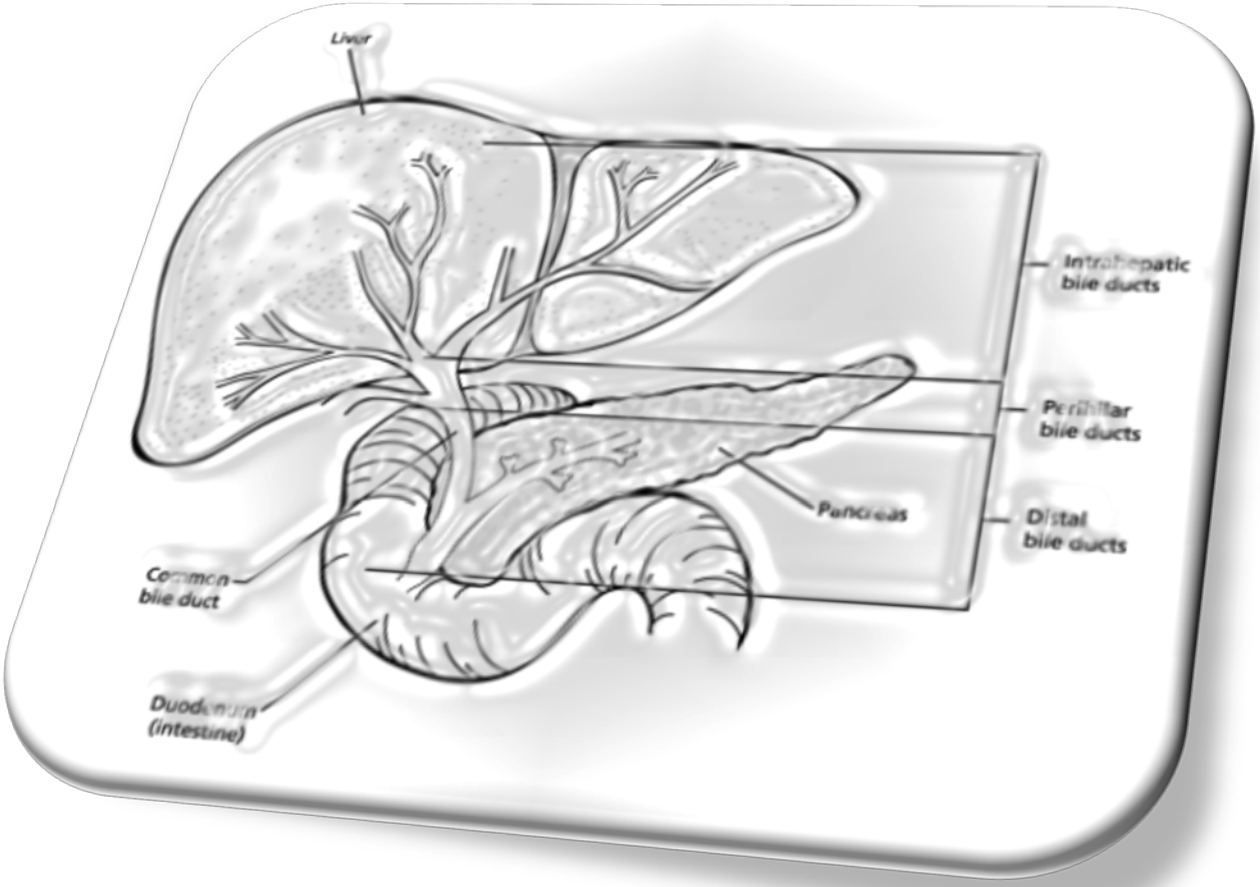
Biliary tree



Summary

- Intrahepatic cholangiocarcinoma
  - Proximal small duct type: classical (peripheral), bile ductular, cholangiolar, cuboidal ductal cell
  - Distal large duct type: non-classical (intermediate), bile duct, mucinous ductal cell
- IHCCa show spectrum change of histopathologic findings and may overlap
- Bile duct margin may be positive in distal large duct type IHCCa
- Good candidate for banking & tissue based study

Thanks for your attention!



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