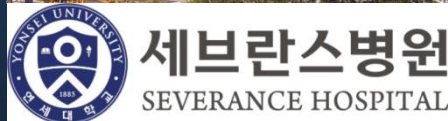


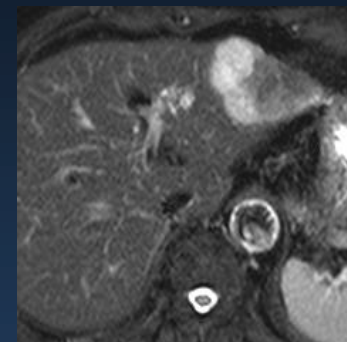
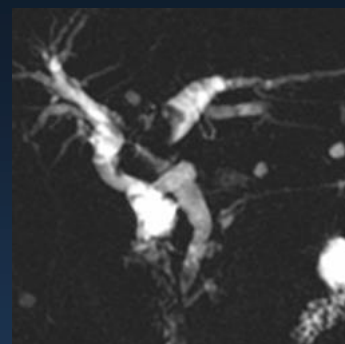
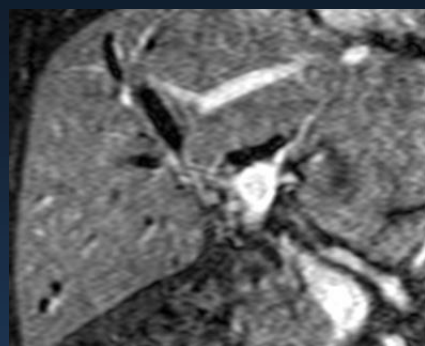
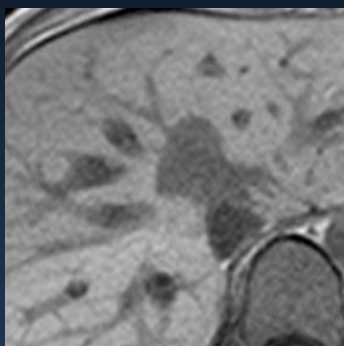
# An update on the imaging-pathologic correlation of cholangiocarcinomas based on new histologic classification



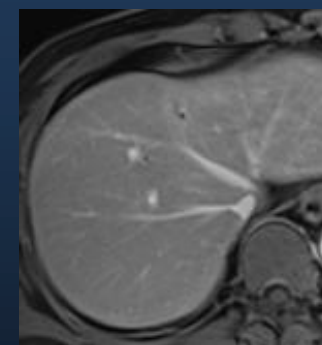
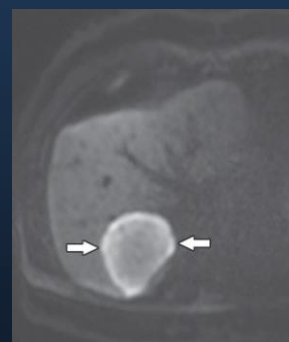
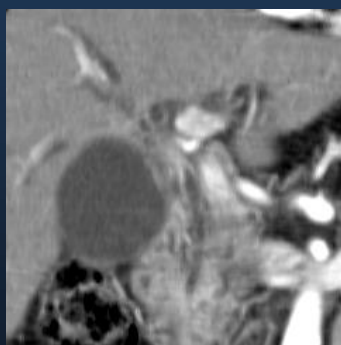
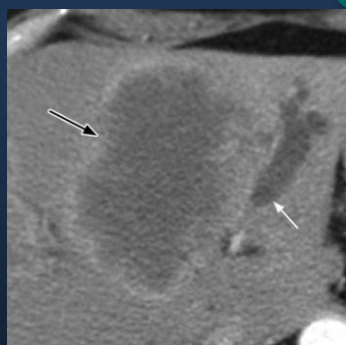
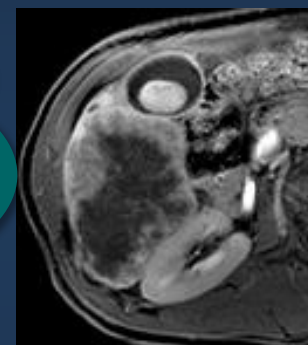
Myeong-Jin Kim, M.D.

*Severance Hospital, Yonsei University, Seoul, Korea*

*kimnex@yuhs.ac*



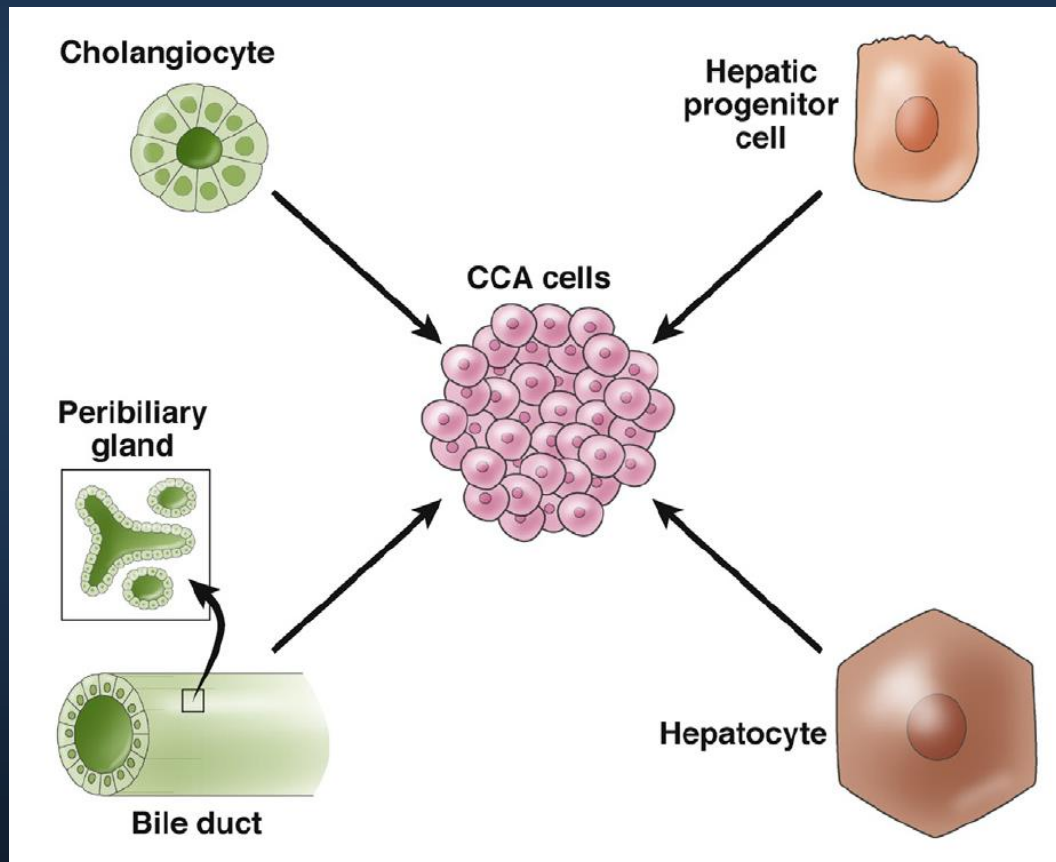
***Cholangiocarcinoma (CCA)  
is characterized by  
Wide Variety of  
Imaging Features ...***



## ... because it develops from various cells of origin

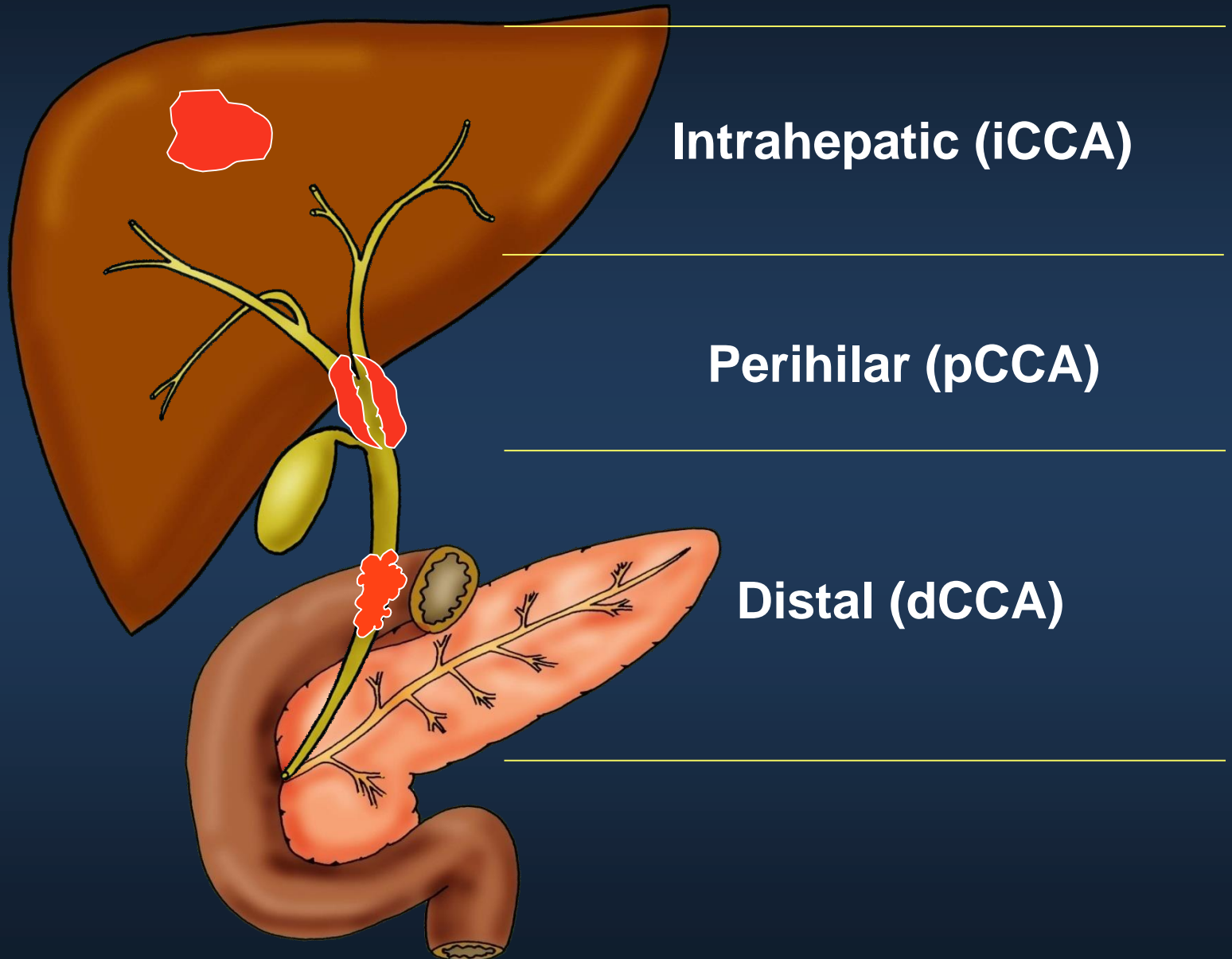
- Cholangiocarcinoma (CCA) is a hepatobiliary malignancies of various cells of origin, showing cholangiocyte differentiation.

• Banales, J.M., et al., *Nat Rev Gastroenterol Hepatol* (2016)



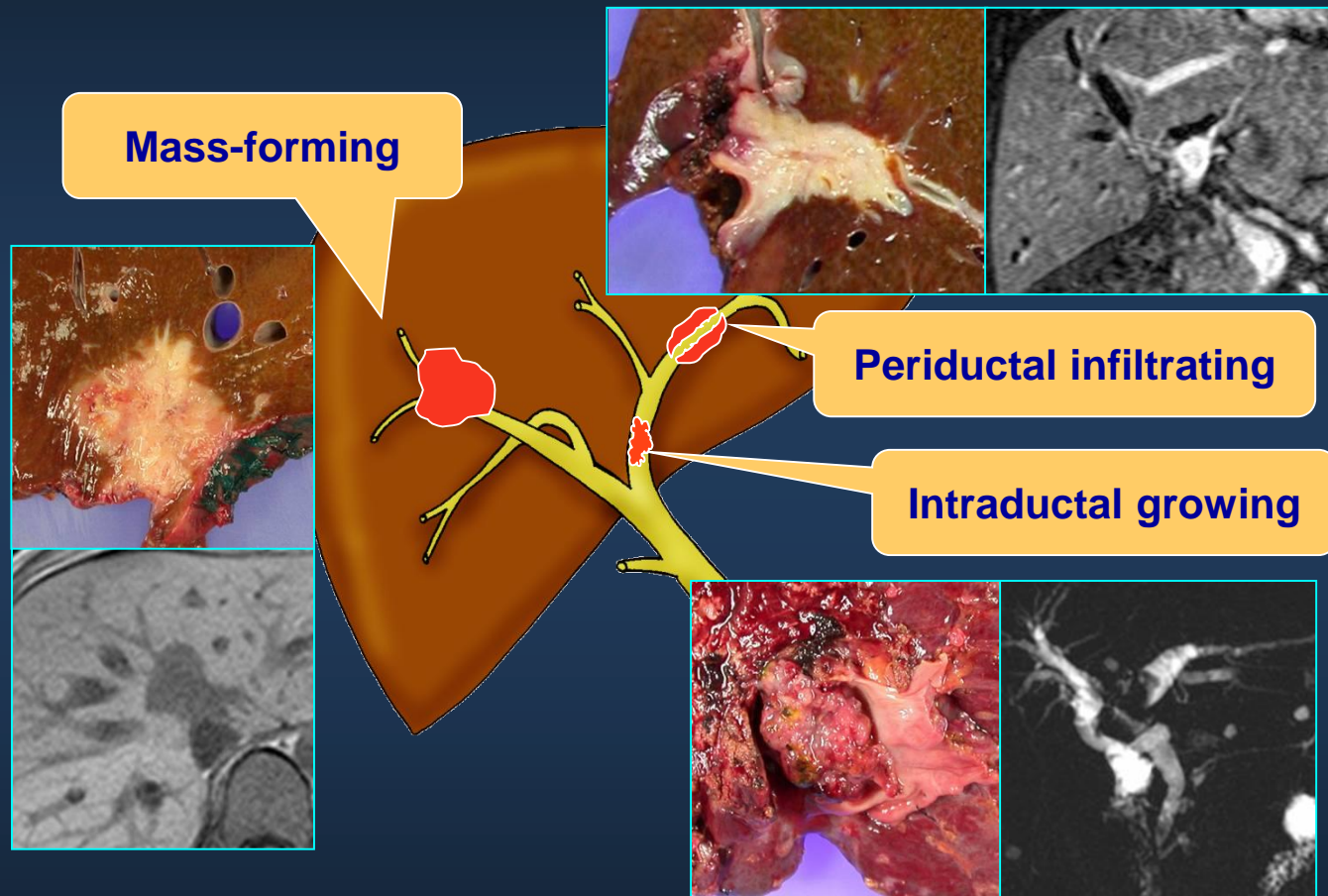
Rizvi, S. and G. J. Gores (2013). *Gastroenterology*

, and also from different anatomical environment



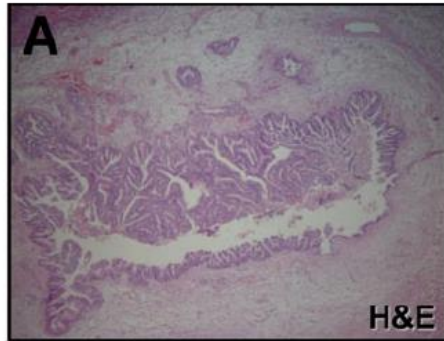


# Varying appearances of iCCA also depend on morphologic types of the tumor

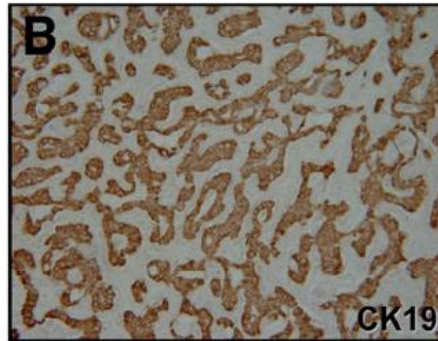


(Chung, Kim et al. 2009 Radiographics)

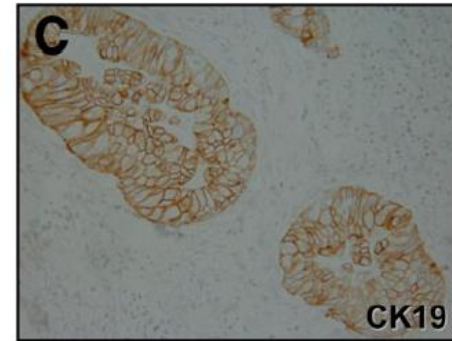
# CCA also shows vast histological diversity



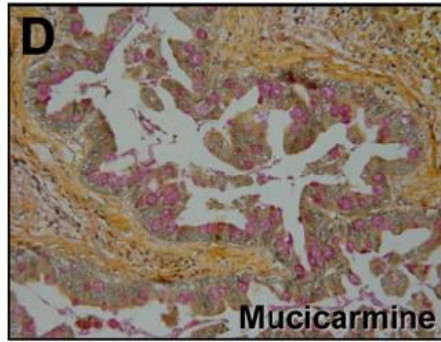
*Large duct papillary*



*WD small duct*

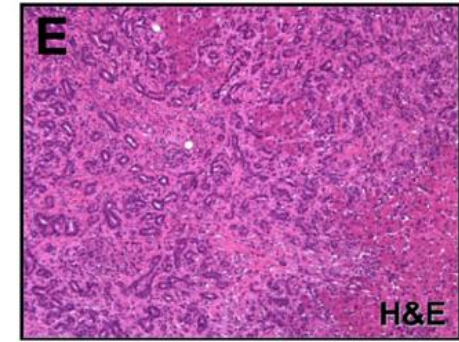


*WD large duct tubular*

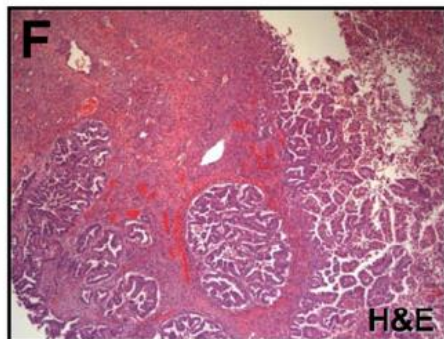


*Large duct 'intestinal type'*

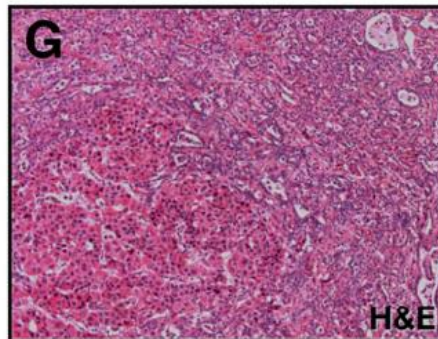
Histological ICC  
Subtypes



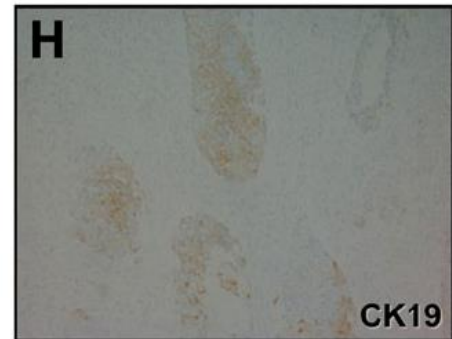
*Cholangiolocellular*



*Biliary cystadenoma*



*HCC-CCA*

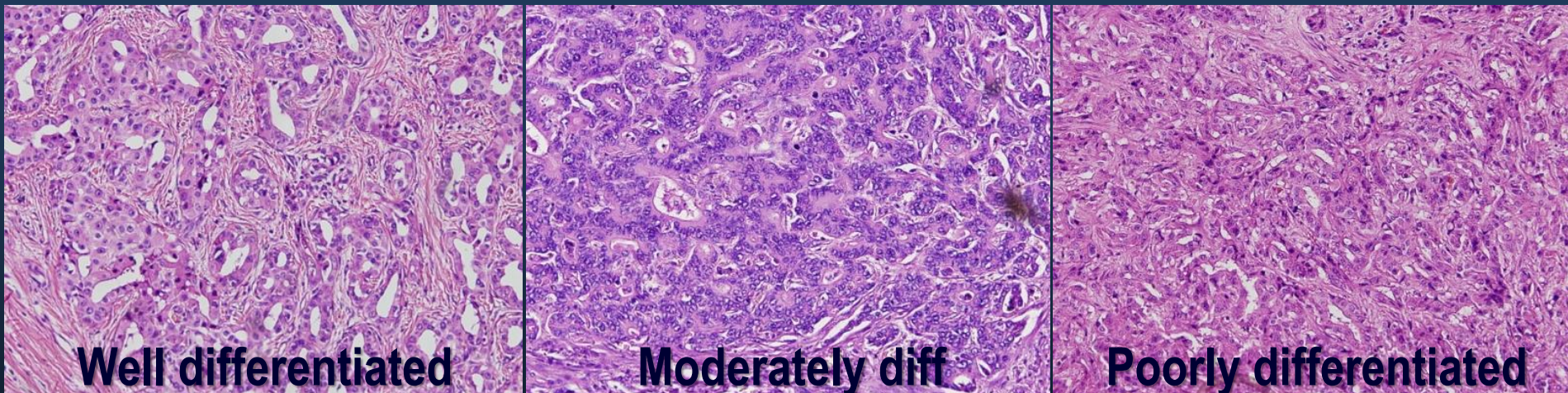


*Poorly differentiated*



# Cholangiocarcinoma: Histology

- Traditionally cholangiocarcinoma has been classified into well-, moderate-, and poorly differentiated adenocarcinoma.
  - Consisting of tubules, acini, solid nests, or trabeculae with
  - Varying amount of fibrous (desmoplastic) stroma
- Immunohistochemical stain for CEA, mucin and cytokeratin have been used for differentiation from other tumors as well as to understand its pathogenesis.



# New Pathologic Classification of iCCA

- According to a new histologic classification, conventional iCCA is classified into small bile duct type and large bile duct type.

**Table 1A**

Classification of intrahepatic cholangiocarcinoma (iCCA).

---

**Conventional type (bile duct type)**

***Small bile duct type***

Well, moderately, poorly differentiated adenocarcinoma

***Large bile duct type***

Well, moderately, poorly differentiated adenocarcinoma

**Bile ductular type** (*Cholangiolocellular ca*)

**Intraductal type**

Papillary type

Tubular type

Superficial spreading type

**Rare variants**

Squamous/adenosquamous cell type

Mucinous/signet ring cell

Clear cell type

Undifferentiated type

Lymphoepithelial type

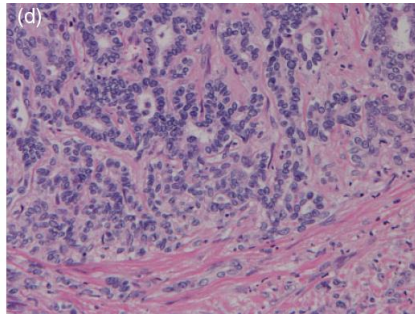
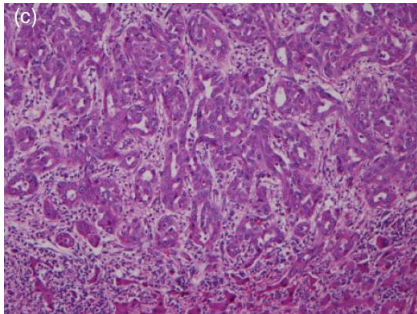
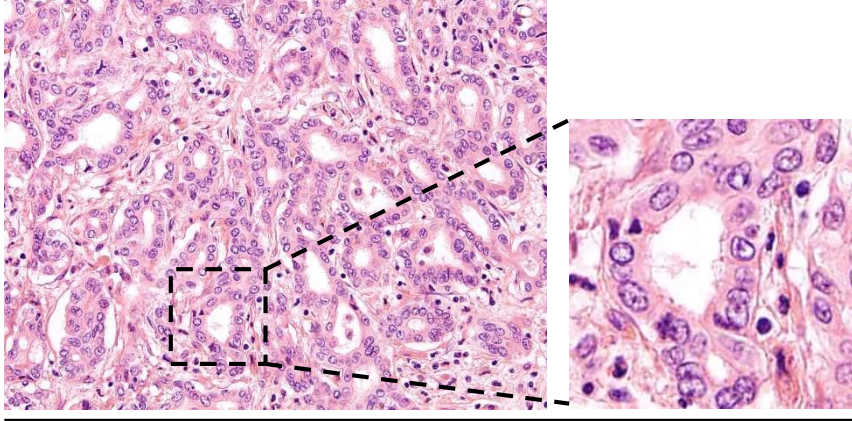
Other

---

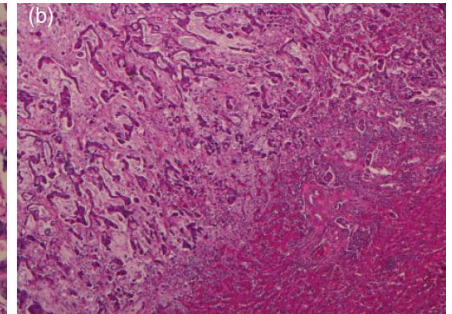
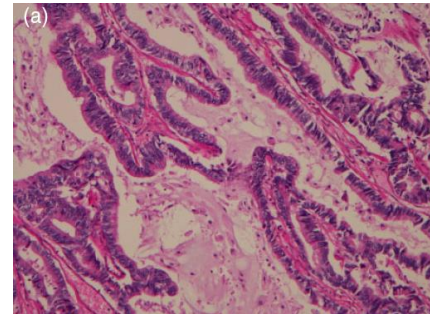
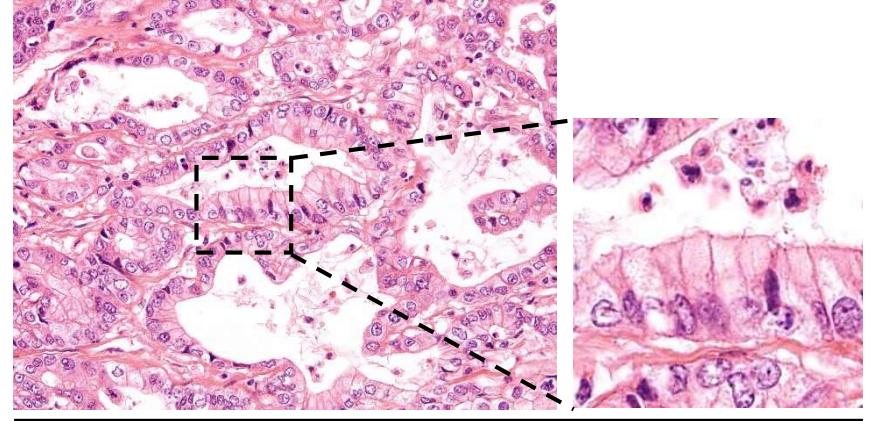


# Histologic classification of iCCA

## Small bile duct type

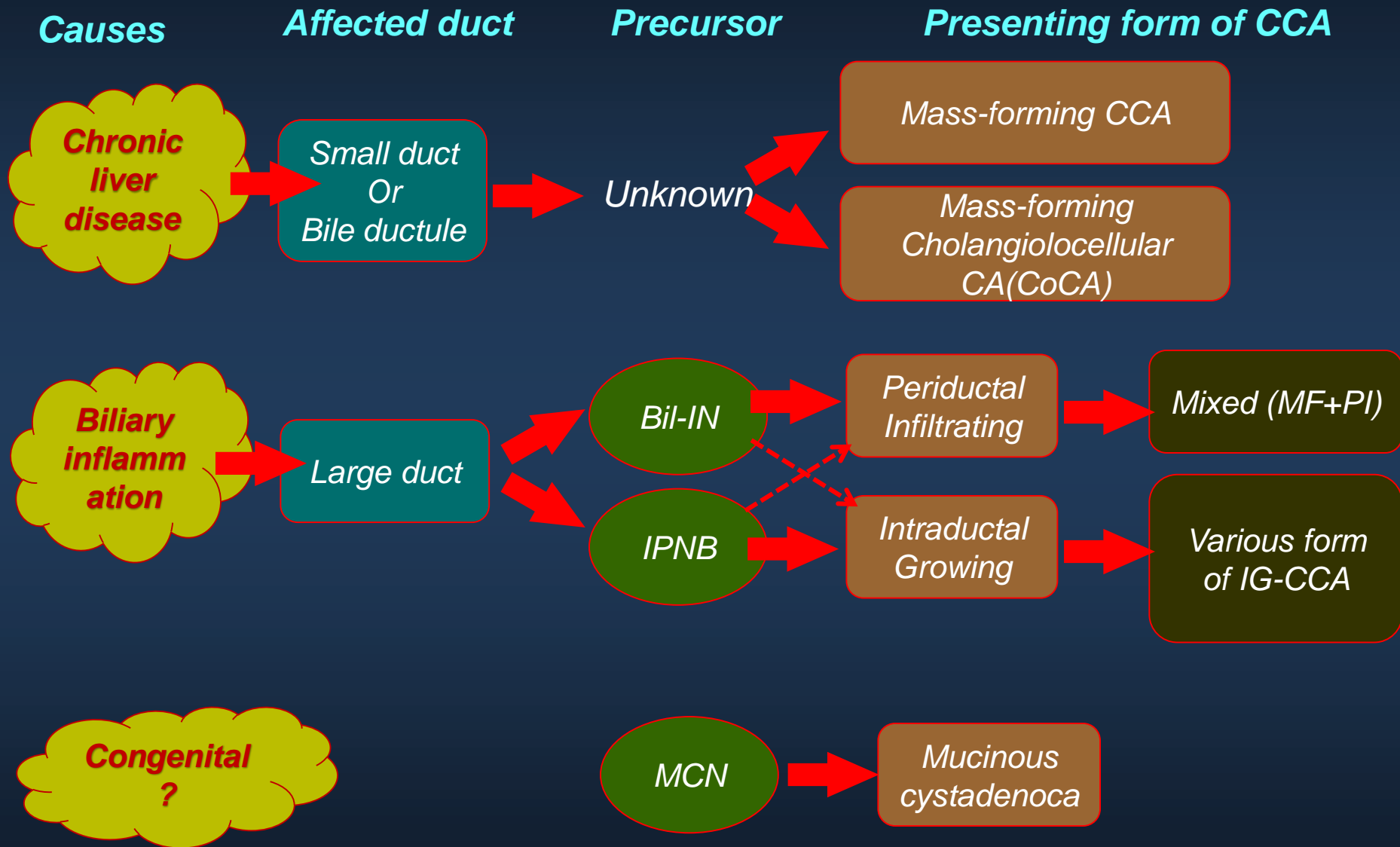


## Large bile duct type



- Small bile duct type CCA is composed of cuboidal or low columnar cells with scant cytoplasm and enlarged nuclei, and show tubular or ductular pattern of growth. Contrarily, large bile duct type is composed of tall columnar cells with eosinophilic cytoplasm, and characterized by low cellularity and abundant mucin and fibrous stroma.
  - Aishima, S & Y Oda J Hepatobiliary Pancreat Sci (2015), JY Liao, et al, Mod Pathol (2014).

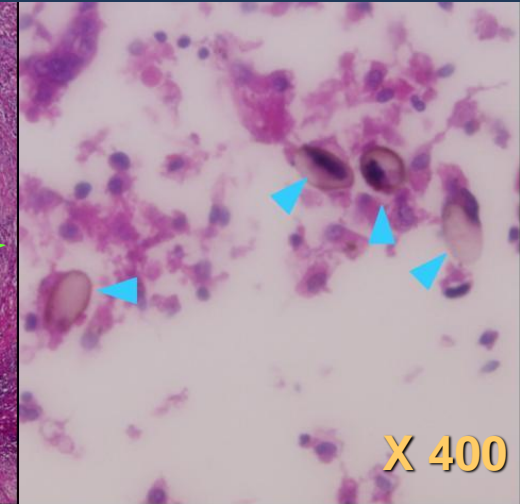
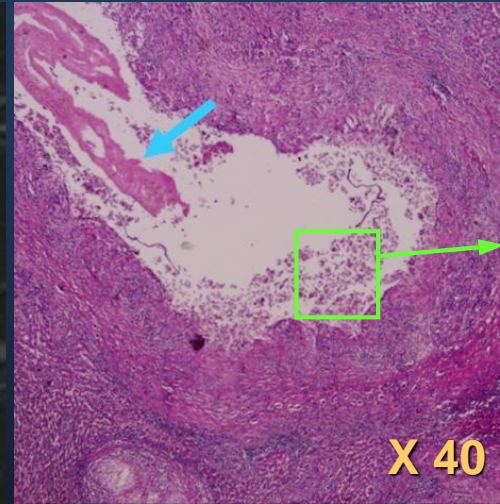
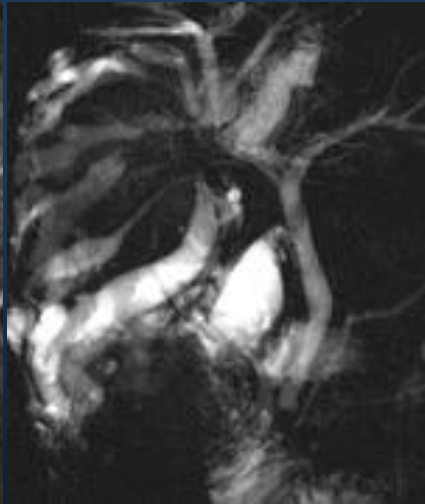
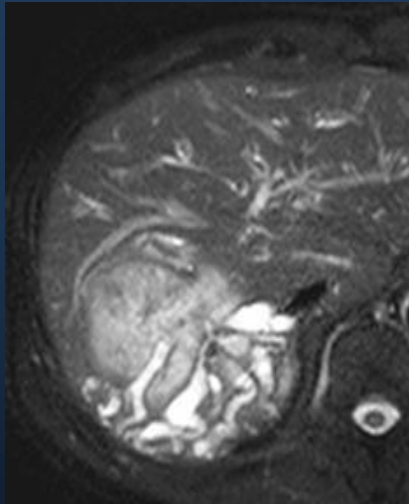
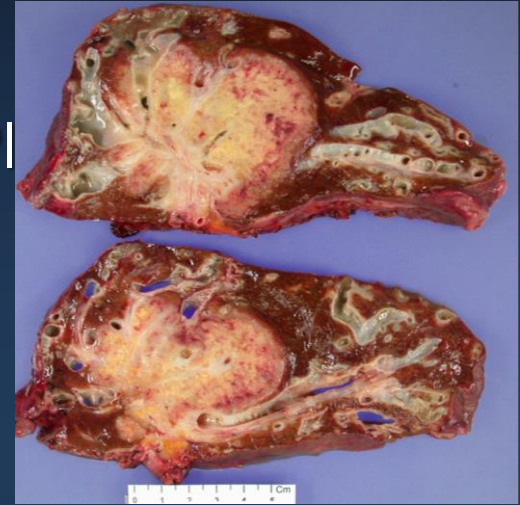
# Carcinogenesis and Evolution of CCA



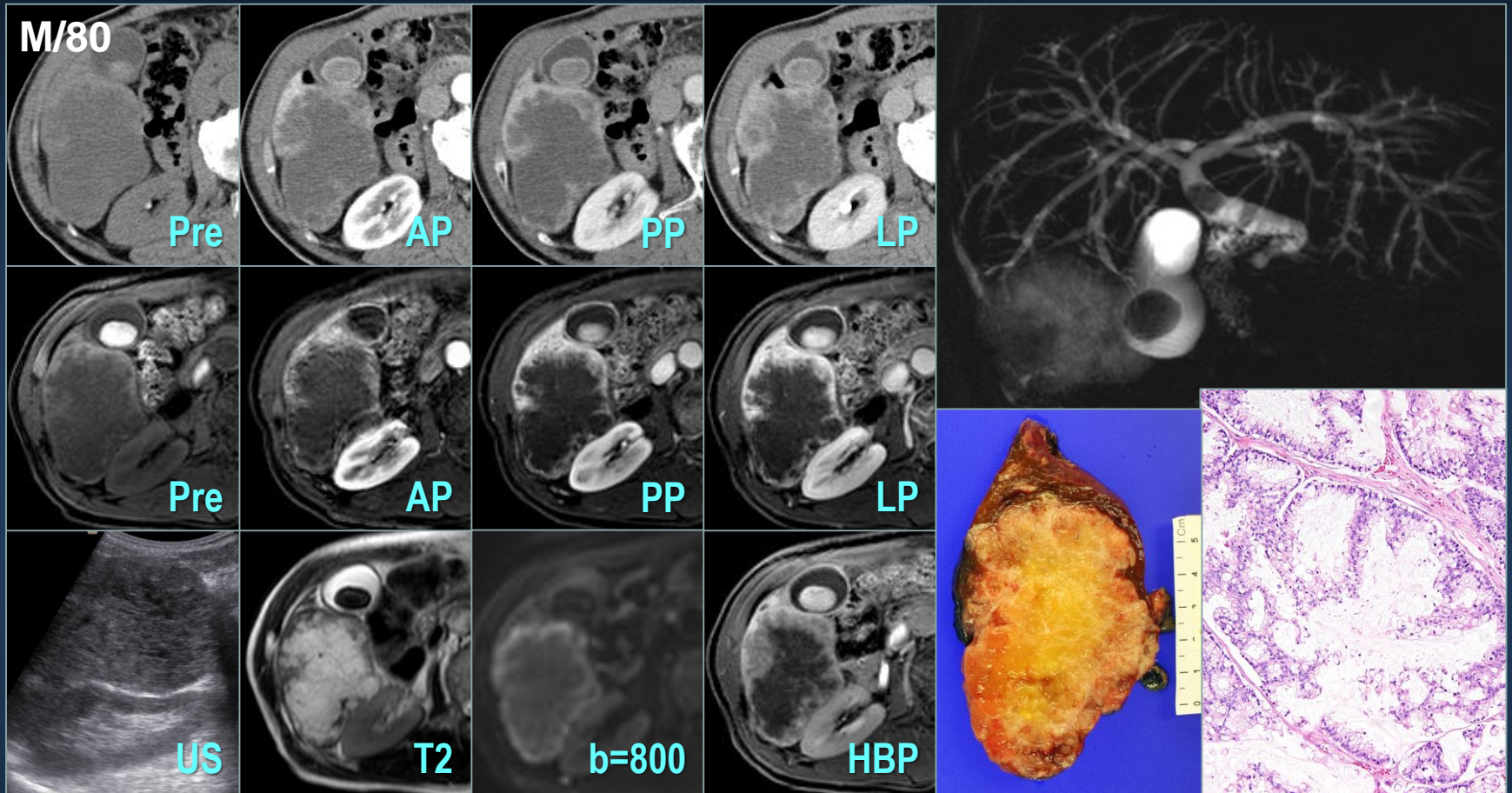


# Large duct type CCA a/w Clonorchiasis

- Large duct CCA frequently a/w findings of underlying biliary diseases
- In this example of CCA a/w clonorchiasis, mixed MF-PI tumor accompanies ...
  - Ductal dilatation in the peritumoral/remote liver, Larva/eggs in the ductal lumen, Marked periductal fibrosis & inflammation



# Large duct type iCCA (mucinous)

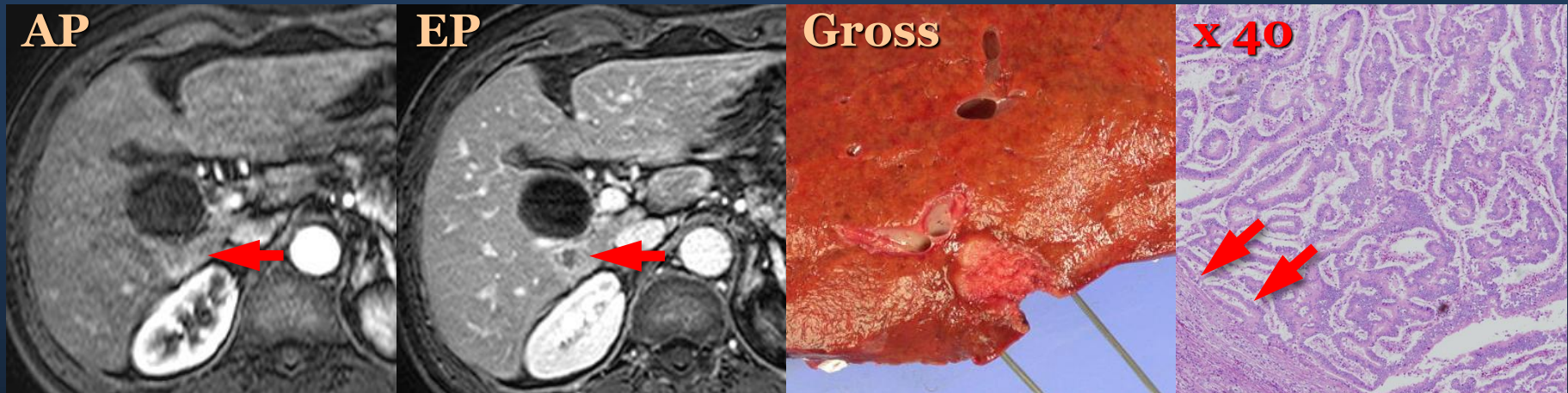


A 80-yr-old man with large-duct CCA with high amount of mucin pool. The tumor shows homogeneous hyperintensity on T2WI, peripheral rim-enhancement with gradual filling-in, and rim-like diffusion restriction on DWI. MRCP image shows diffuse duct dilation with gallstone and choledocholithiasis.



# Small duct type CCA a/w Chronic Liver Disease

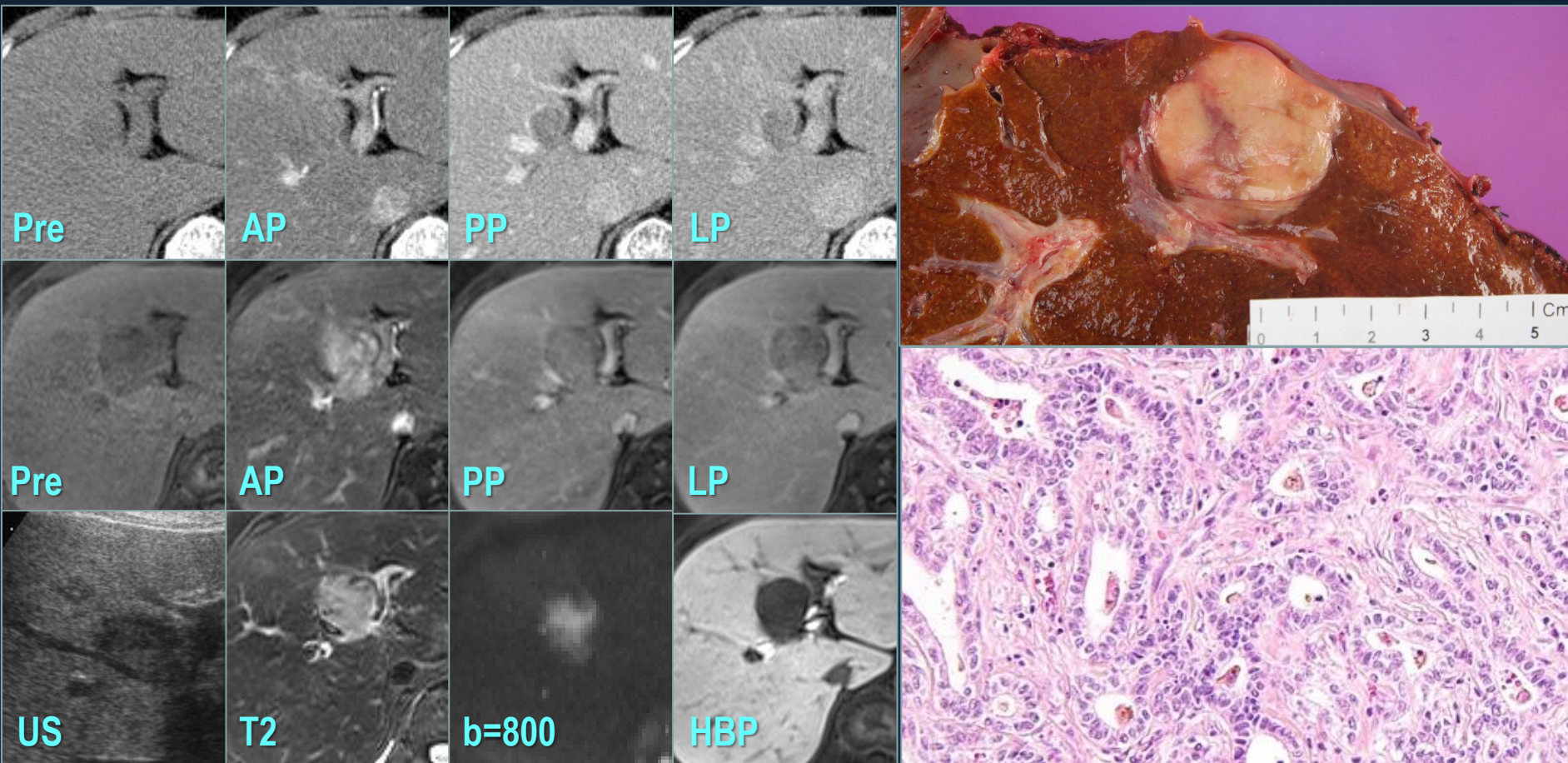
- Small duct CCA tends to be found as a small lesion, possibly because patients are in a surveillance program.
- APHE & 'washout' appearance on dynamic imaging
  - Make difficulty to distinguish from HCC
- May be surrounded by a fibrotic pseudocapsule
  - Unusual in CCA arising from a non-cirrhotic liver



Small duct type CCA in a 68-yr-old man. The tumor shows arterial enhancement and washout pattern on dynamic imaging. Gross specimen and microscopic slide shows fibrotic capsulation around the tumor, which is uncommon in usual CCA.

# MF-iCCA: Small duct type

F/71



A small duct type CCA in a 71-yr-old woman.

The tumor shows arterial enhancement and washout pattern on dynamic imaging, and composed of cuboidal or low columnar cells with scant cytoplasm/enlarged nuclei, with tubular/ductular pattern.



# Histologic type of iCCA & Clinical Outcome: CT

- A recent study evaluated the relationship between histologic type and clinical outcome.
- According to this study, small duct type tumors tend to show rim or hypervascular pattern, while large duct type tumors tend to show hypovascular pattern and poor disease-free survival, and more commonly associated with lymphatic, perineural, and biliary invasion.

	Hypovascular (n=13)	Rim-enhancement (n=18)	Hypervascular (n=16)	p-value
ICC type				<0.001
Perihilar type	8	2	0	
Peripheral type	5	16	16	



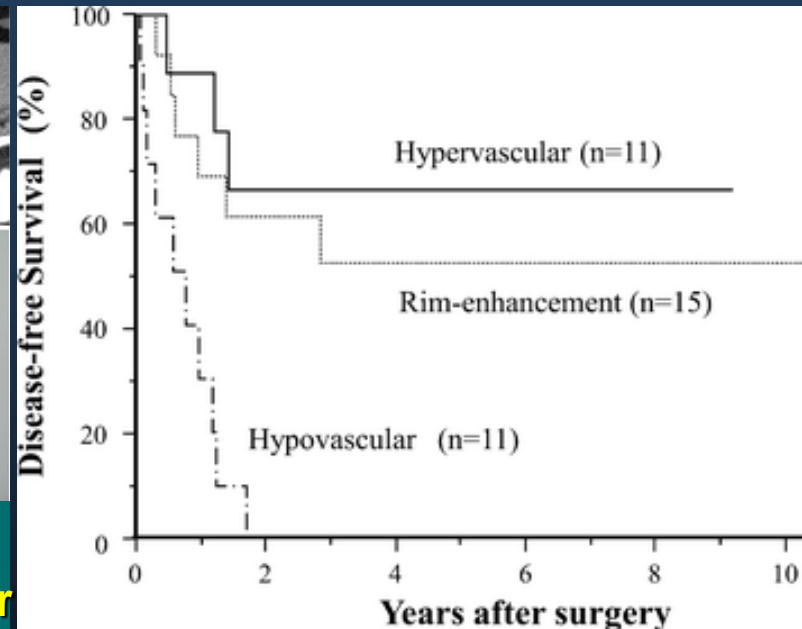
**Perihilar  
Hypovascular**



**Peripheral  
Rim-enhancing**

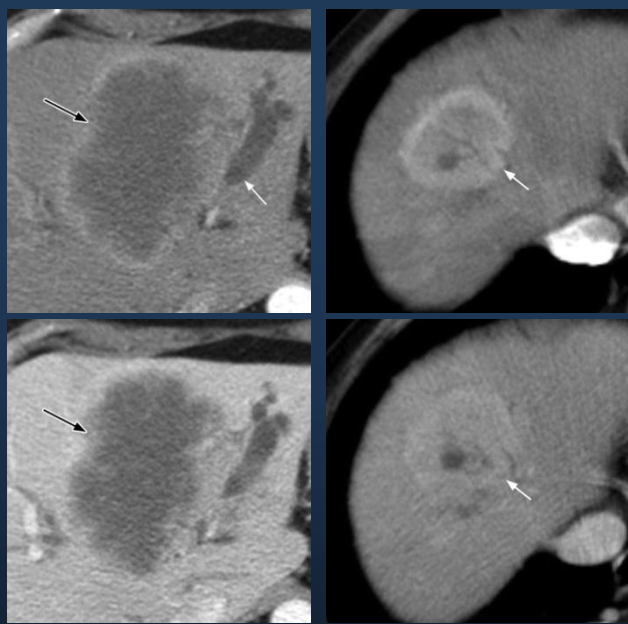


**Peripheral  
Hypervascular**

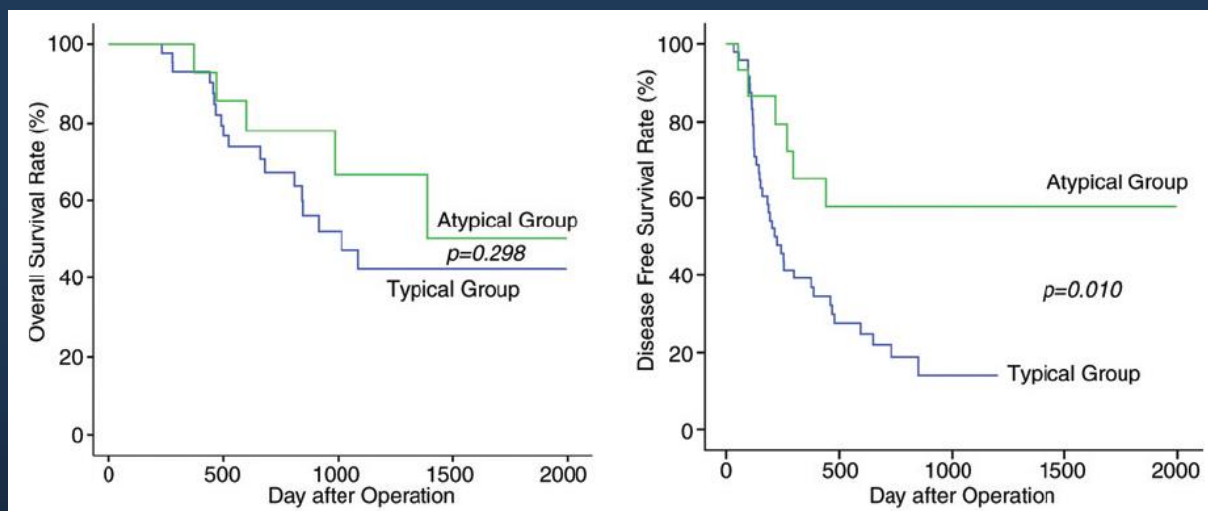


# Hypervascular iCCA: Better prognosis

- The results may be comparable with previous studies showing that hypervascular tumors, which are associated with CLD, absence of central stroma and necrosis, and presence of cholangiolocellular component, tended to show longer disease-free survival.



Typical (71%)    Atypical (29%)

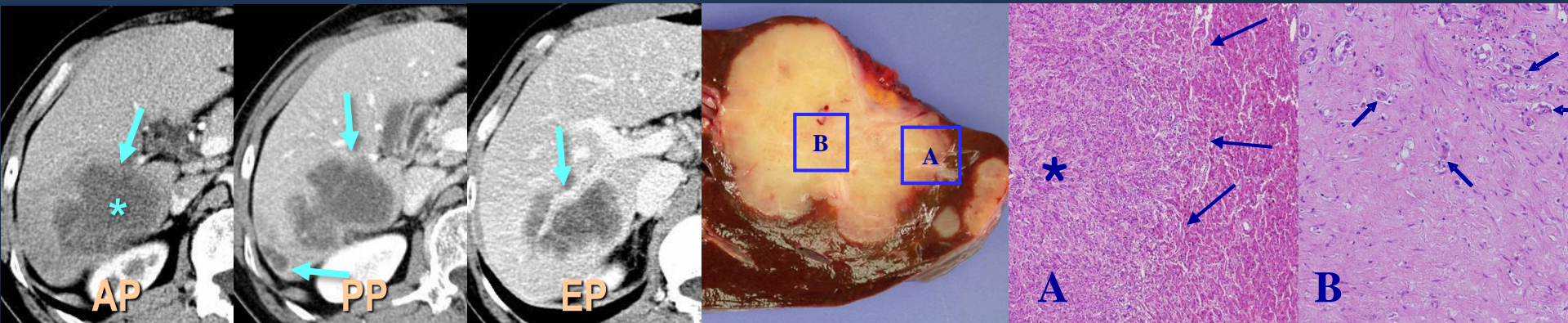


Kim, S.A., et al. (2011) *Radiology*  
Ariizumi, S., et al. (2011) *J Surg Oncol*  
Nanashima, A., et al. (2013) *Abdom Imaging*  
Yamamoto, Y., et al. (2016) *Ann Surg Oncol*  
Turkoglu, M. A., et al. (2016) *Surgery*



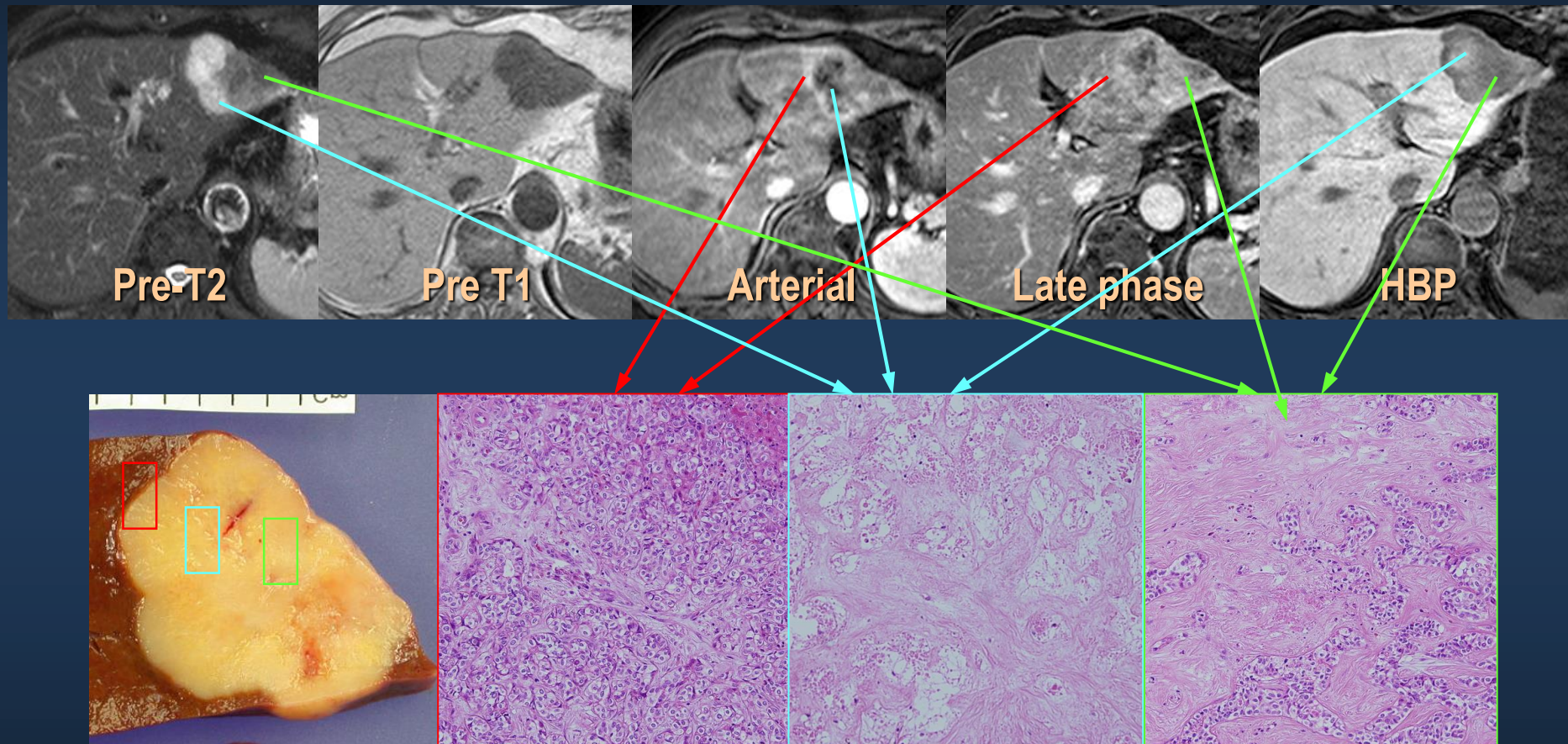
# Classical appearance of Mass-forming iCCA

- Homogeneous texture, irregular lobulated margin, absence of capsule
  - Periphery: viable tumor cells
  - Center: variable degree of fibrosis and coagulative necrosis
- Early peripheral & delayed centripetal enhancement
  - Capsular retraction, satellite nodules
  - Vascular encasement s/ gross thrombosis
  - Dilation of bile ducts, frequent nodal metastasis



(Chung, Kim et al. 2009 Radiographics)

# MF-iCCA: Radiopathologic correlation with MRI



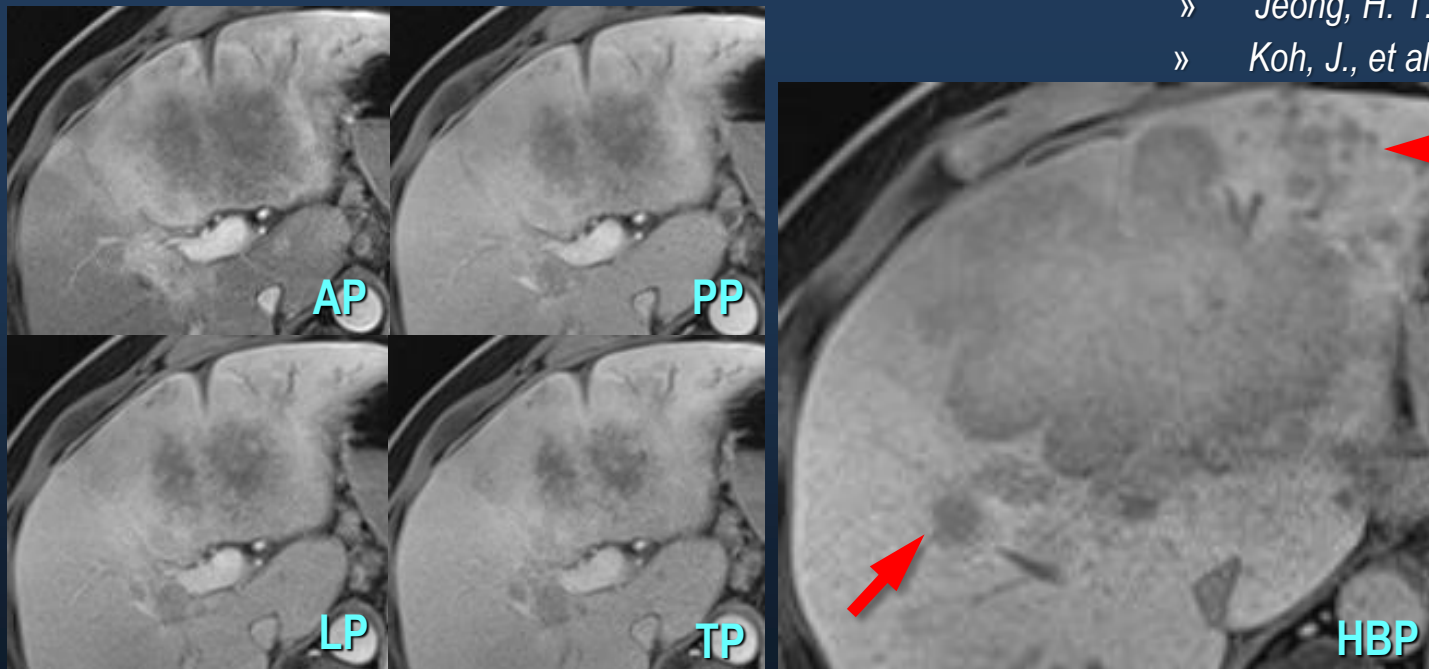
The peripheral area (red) with abundant tumor cells shows irregular, ragged, rim-like enhancement with washout on delayed phase. The inner area (blue) with abundant extracellular matrix shows T2 hyperintensity and prominent delayed enhancement. And the central area (green) with dense fibrosis shows T2 hypointensity and transient enhancement.



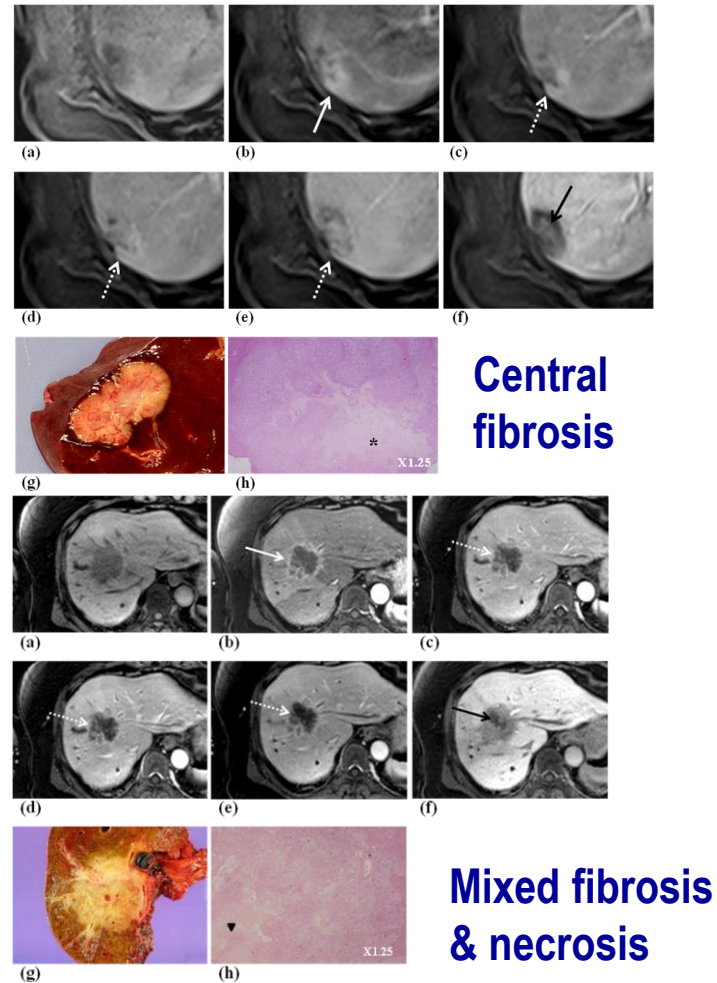
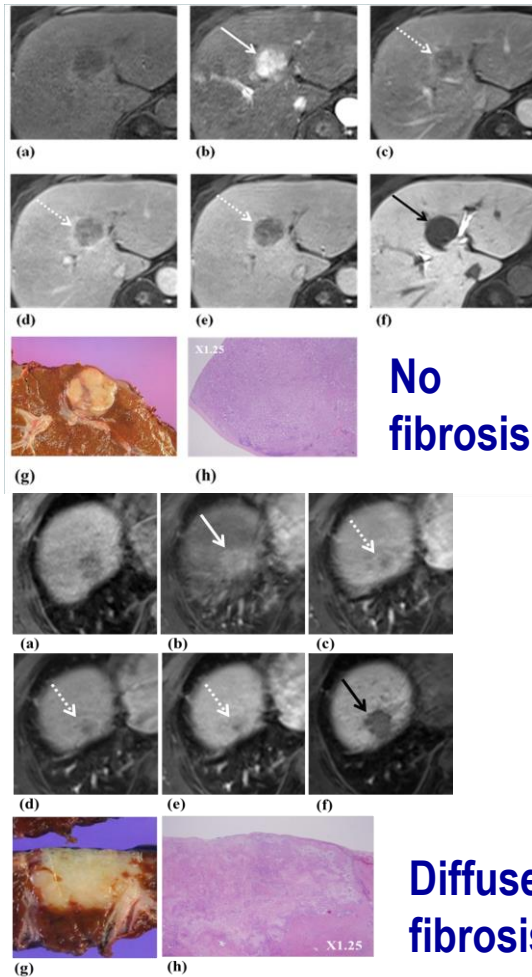
# Hepatobiliary phase images of HSA-MRI

- Increase lesion conspicuity and margin sharpness
- Improve detection of additional daughter nodules
- Degree of intratumoral enhancement on HBP may be correlated with
  - Amount/distribution of internal fibrosis & necrosis
  - Cellular differentiation, nodal status, prognosis

» Kang, Y., et al. (2012) *Radiology*  
» Jeong, H. T., et al. (2013). *AJR*  
» Koh, J., et al. (2016) *Eur Radiol*



# iCCA on EOB-MRI: Histologic correlation



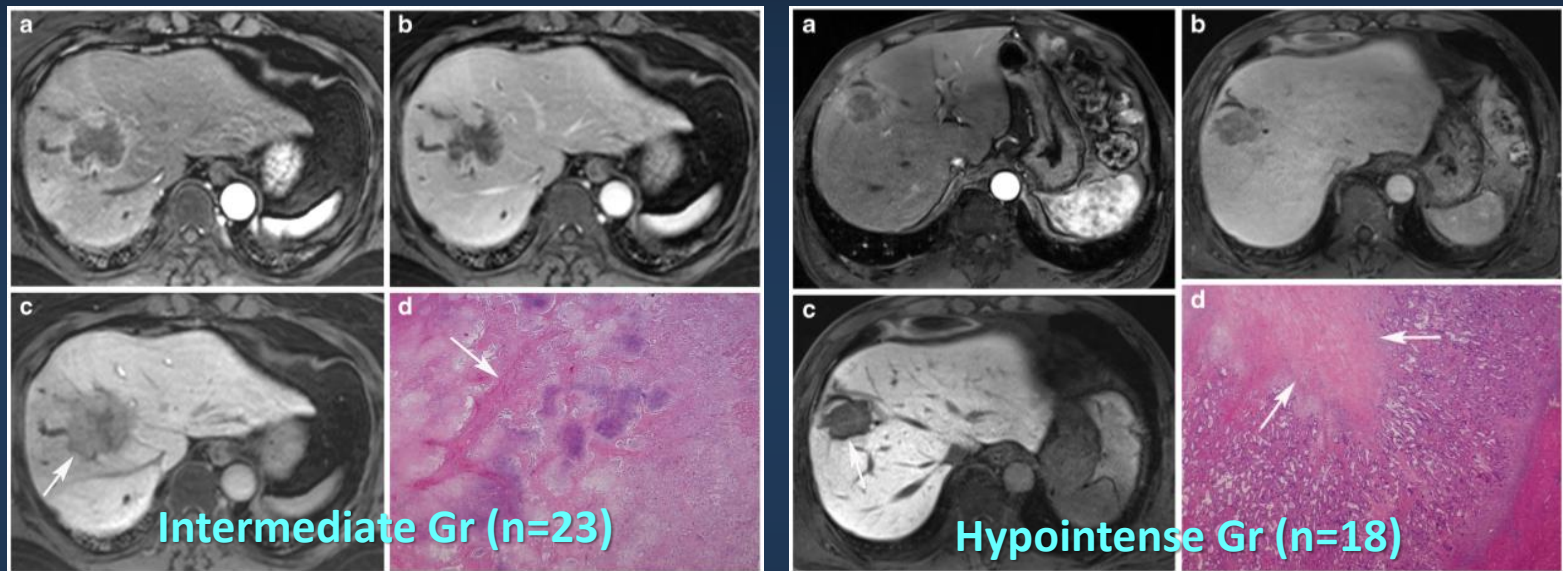
**CCA with no fibrosis showed dark intensity on HBP, while a tumor with central fibrosis showed target-like central enhancement, a tumor with diffuse fibrosis showed diffuse central enhancement, and a tumor with mixed fibrosis and necrosis showed heterogeneous enhancement.**

**- Jeong, HT, & Kim, MJ et al. (2013) AJR**



# Degree of enhancement on HBP was a/w Outcome

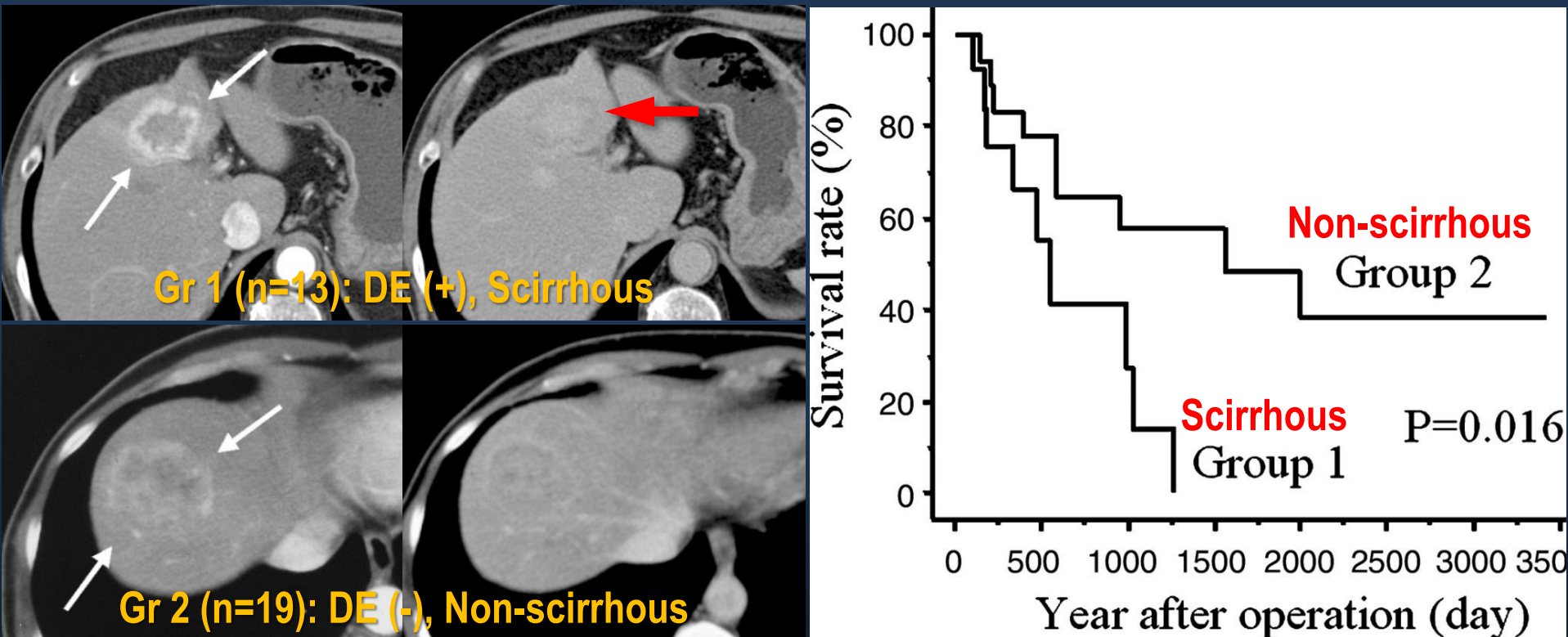
- Higher enhancement on HBP was associated with abundant fibrous stroma and shorter survival and time-to-recurrence.



Factors		Hazard ratio	95 % Confidence Interval	P value
Hepatobiliary phase image	Hypointense group	1		0.012
	Intermediate group	5.0–88	1.629–20.352	
Microvessel invasion	No	1		0.062
	Yes	6.947	0.910–53.058	

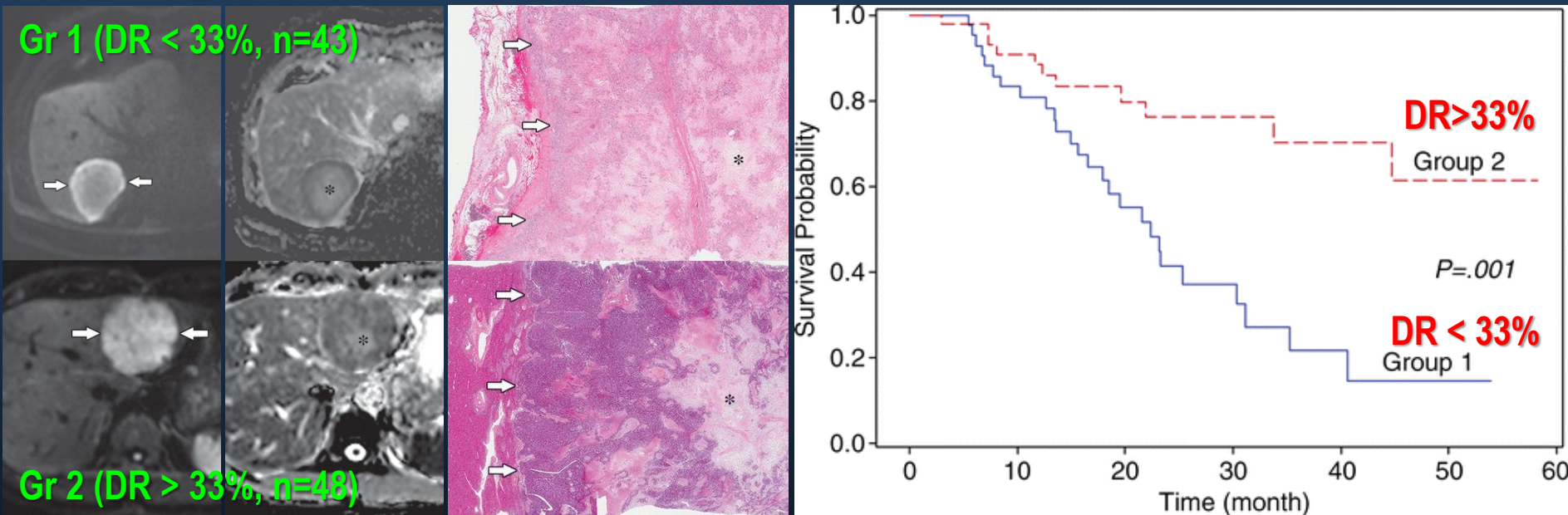
# Prominent Delayed Enhancement: Poor prognosis

- An earlier study also showed that prominent delayed enhancement was seen in scirrhous iCCA, showing abundant fibrous stroma and frequent perineural invasion, and poor survival.



# Smaller Diffusion Restriction: Worse prognosis

- DWI also showed similar pattern of relationship between imaging features implying central fibrosis and tumor aggressiveness.
- In below study, tumors showing diffusion restriction  $< 1/3$  of tumor in periphery demonstrated abundant stromal desmoplasia in the center, advanced TNM stage, frequent lymphatic invasion, were related with poor survival rate.





# Gross and Histologic types of CCA

Small duct



Mass-forming

Large duct



Periductal  
Infiltrating



MF + PI



Intraductal  
Growing

Early BD  
Ca

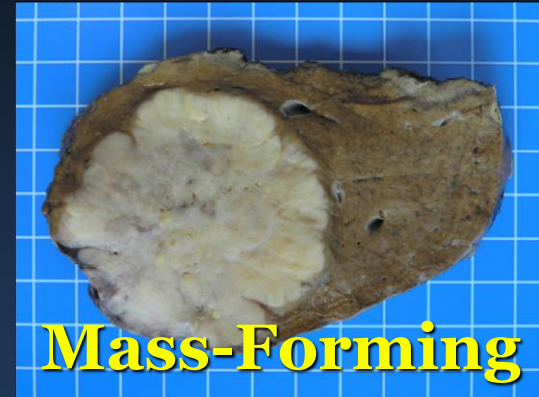


IG + MF(PI)

IPNB



Invasive  
IPNB



**Mass-Forming**



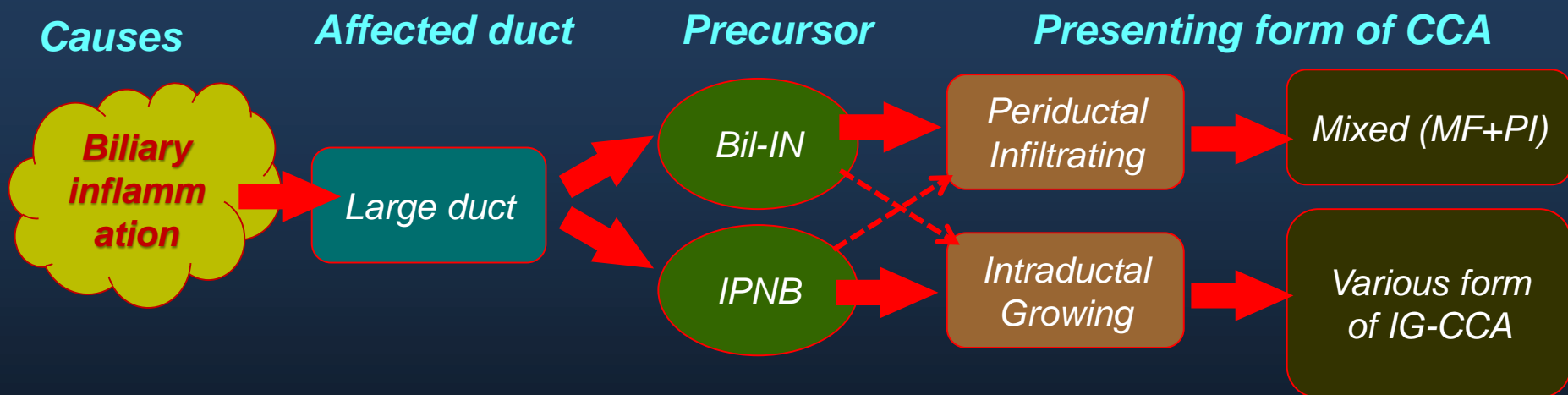
**Periductal  
infiltrating**



**MF+PI**

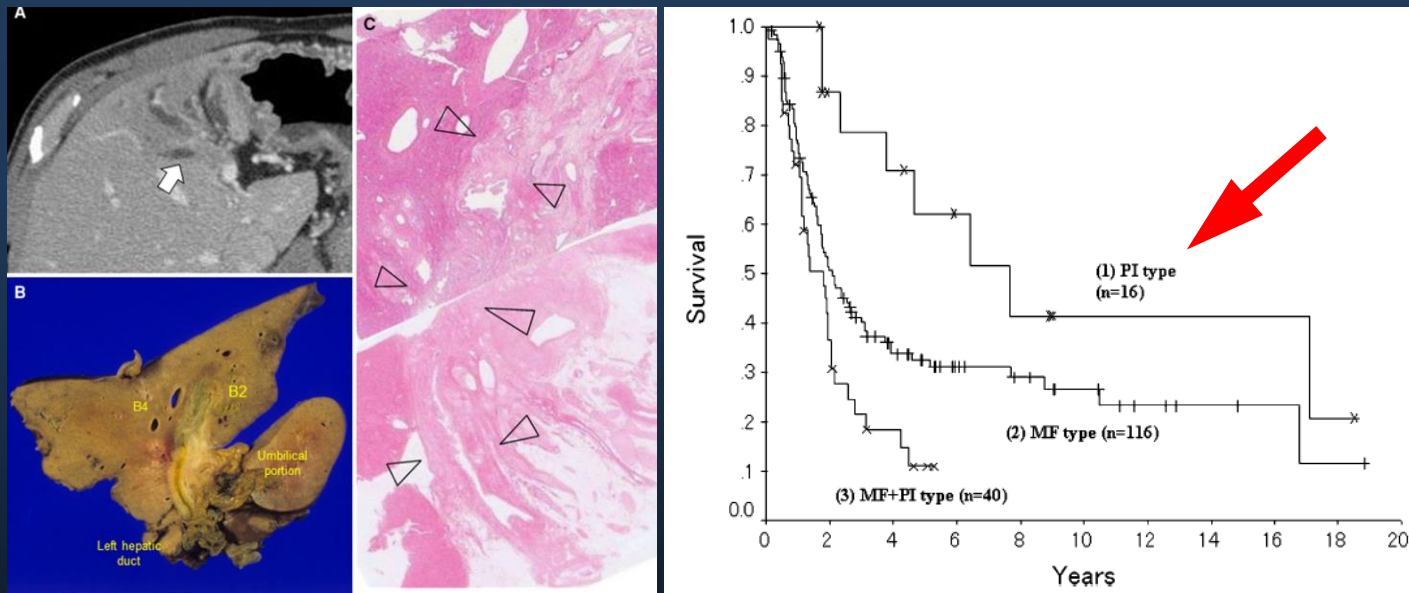
# Gross and Histologic types of CCA

- Pure form of periductal infiltrating CCA is relatively uncommon and may be considered a large duct tumor, presented at an intermediate stage on its way of progression to MF+PI.
- Mixed form of periductal and intraductal growing CCA is also common.



# PI-iCCA: Intermediate stage of MF+PI

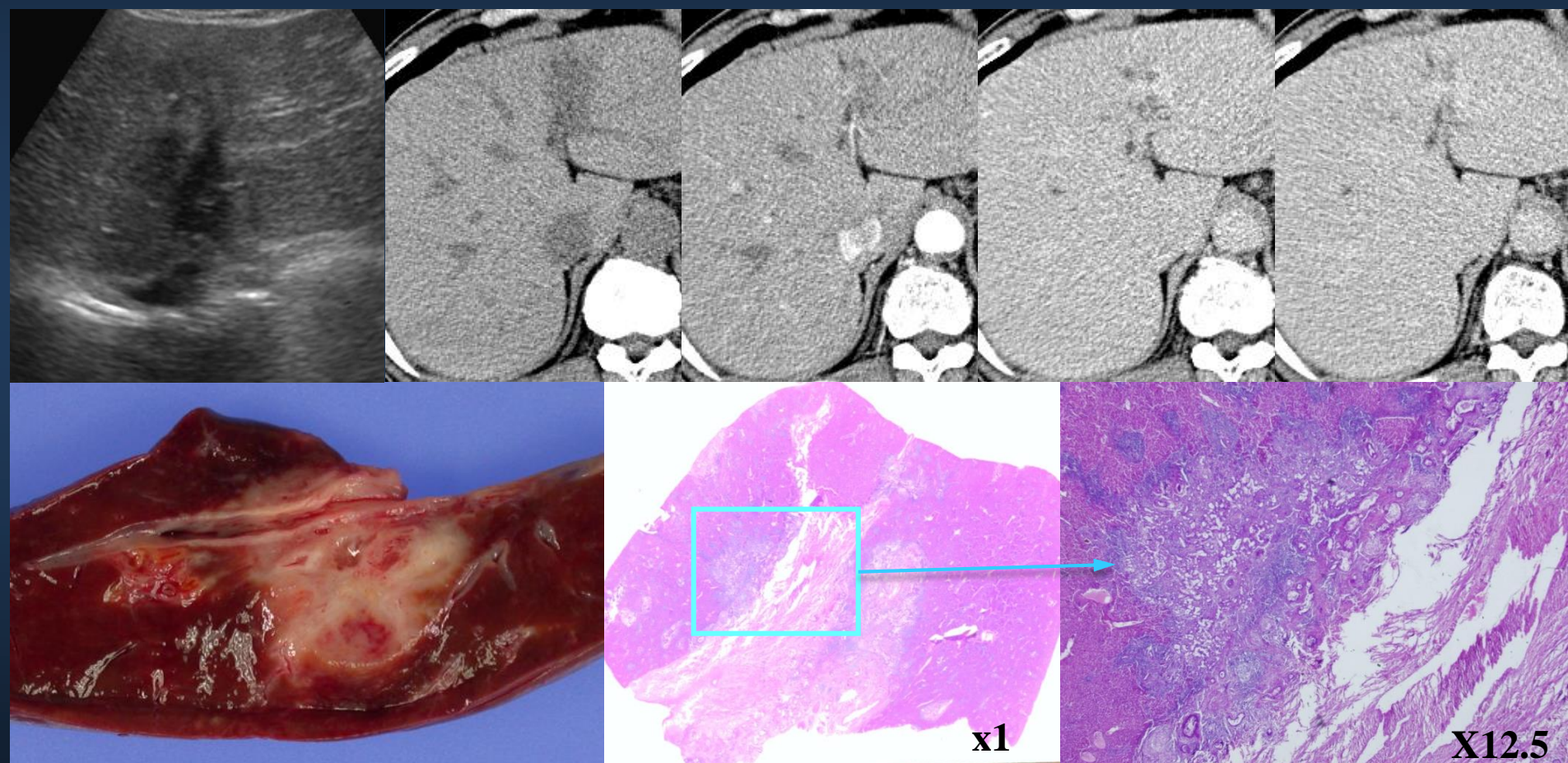
- The reasons why PI-iCCA is considered intermediate stage on the progression to MF+PI is that it is rare (8% , Uno et al. 2012) and present as a smaller tumor than MF type, and has better survival than more progressed form of CCA (MF or MF+PI), with lower incidence of intrahepatic and nodal metastases.





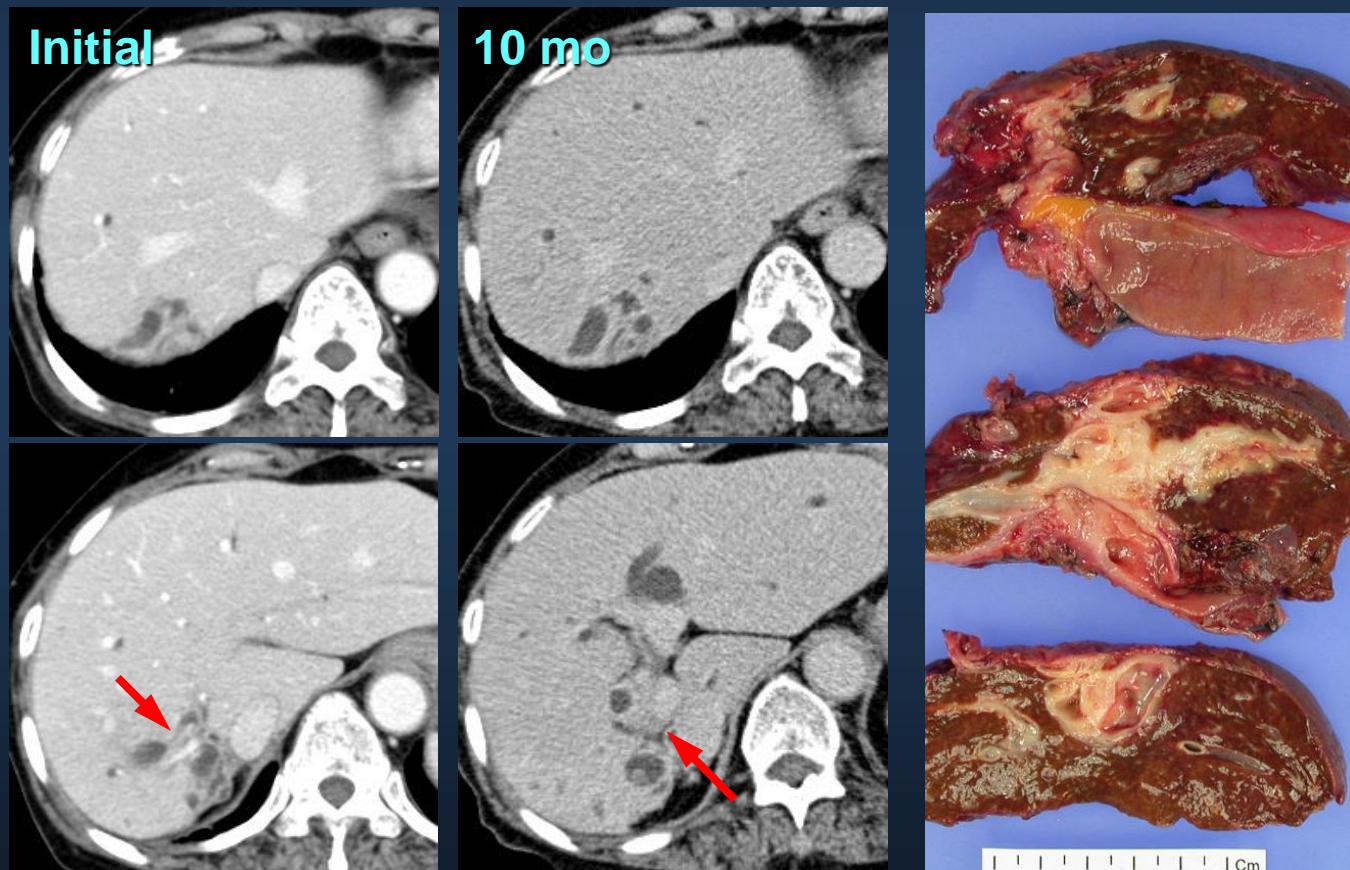
# Mixed PI+MF iCCA

- The mass seems a periductal lesion on CT, but shows mixed form of PI+MF tumor on surgical specimen.



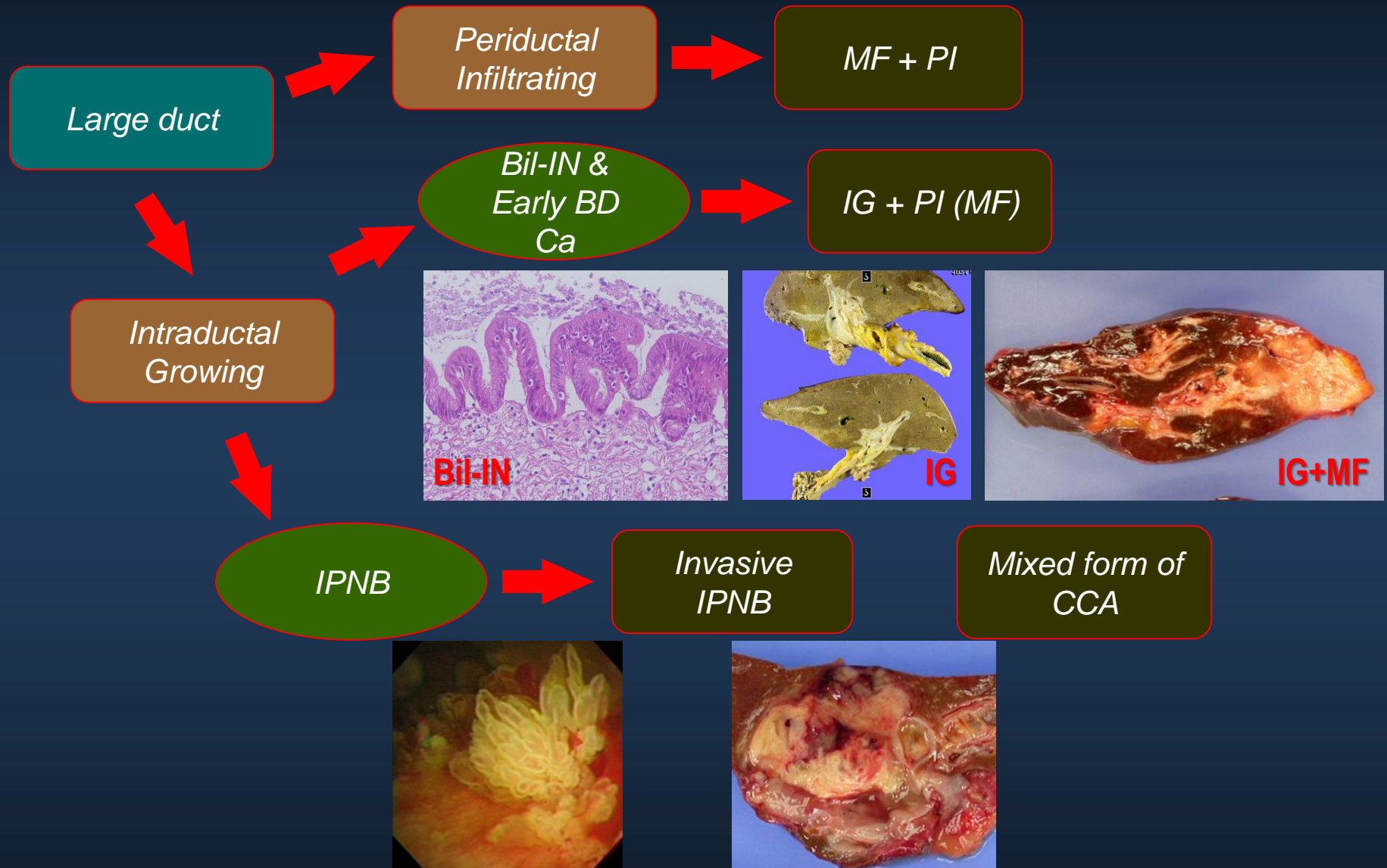
# DDx from benign stricture is difficult for PI-CCA

- PI-CCA is commonly associated with intrahepatic stone disease and may be difficult to differentiate from benign stricture.





# Evolution of Intraductal Growing CCA





# Intraductal growing CCA

## Histologic types

- IPNB/Invasive IPNB/Papillary carcinoma
- Early stage BD ca (Bil-IN/conventional ca)



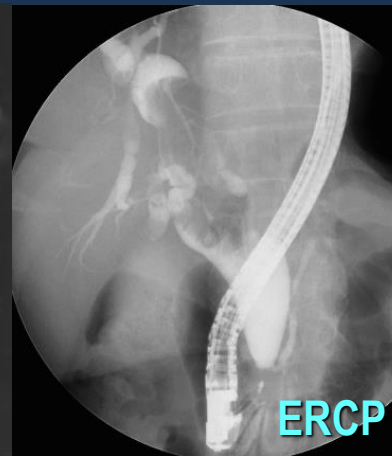
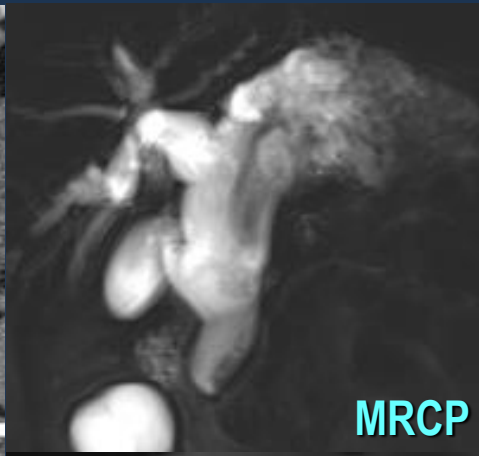
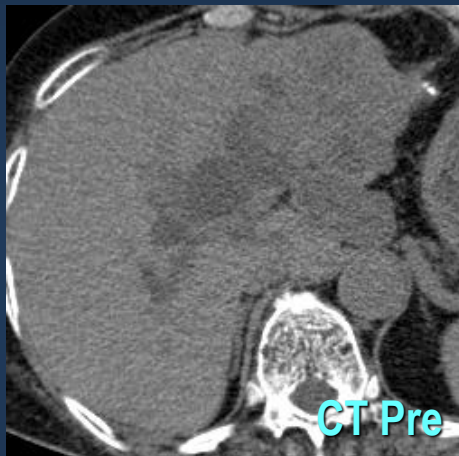
## Imaging patterns

1. Diffuse duct dilation with frond-like lesions
2. Diffuse duct dilation without visible mass
3. Localized duct dilation or cystic mass
4. Intraductal cast-like lesions
5. Focal narrowing or single polypoid

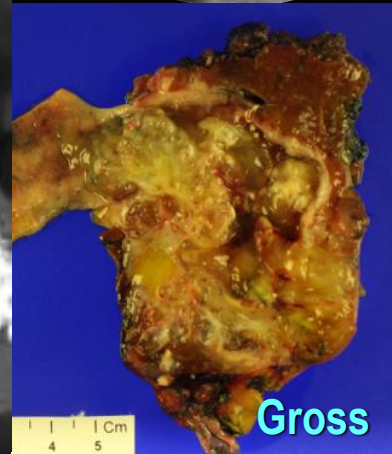
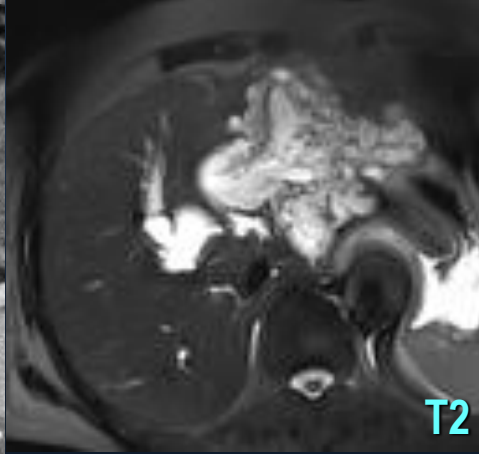
- #1-4 are common forms of tumors arising from IPNB; #5 is more common in intraductal growing of non-IPNB origin

# 1) Diffuse ductectasia with frond-like lesions

- Most typical form
- Duct dilation due to copious mucin production
- Macroscopic papillary lesions, representing carcinoma

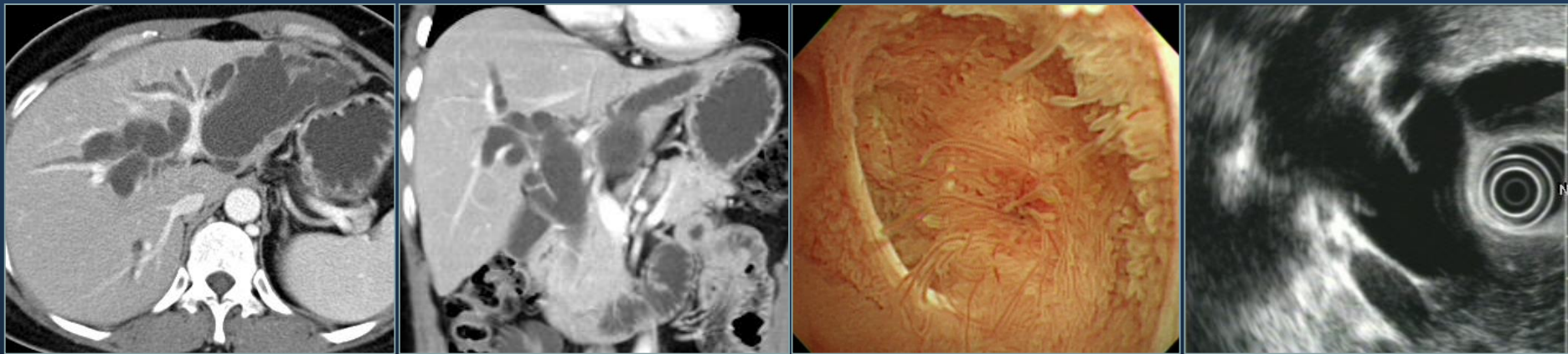


65-yr-old woman with invasive mucinous carcinoma with IPNB. Diffuse ductectasia with intraductal intraductal mass formation is seen on CT. MRCP image shows severe duct dilation due to mu



## 2) Diffuse duct dilation without visible mass

- In this pattern, marked duct dilation is seen due to copious mucin production, but intraductal mass is not visible, because either the tumor is microscopic or not large enough to identify on imaging.
- Radiological clues for correct diagnosis include ..
  - Asymmetrical IHD dilation without obstructive lesion
  - Thread sign



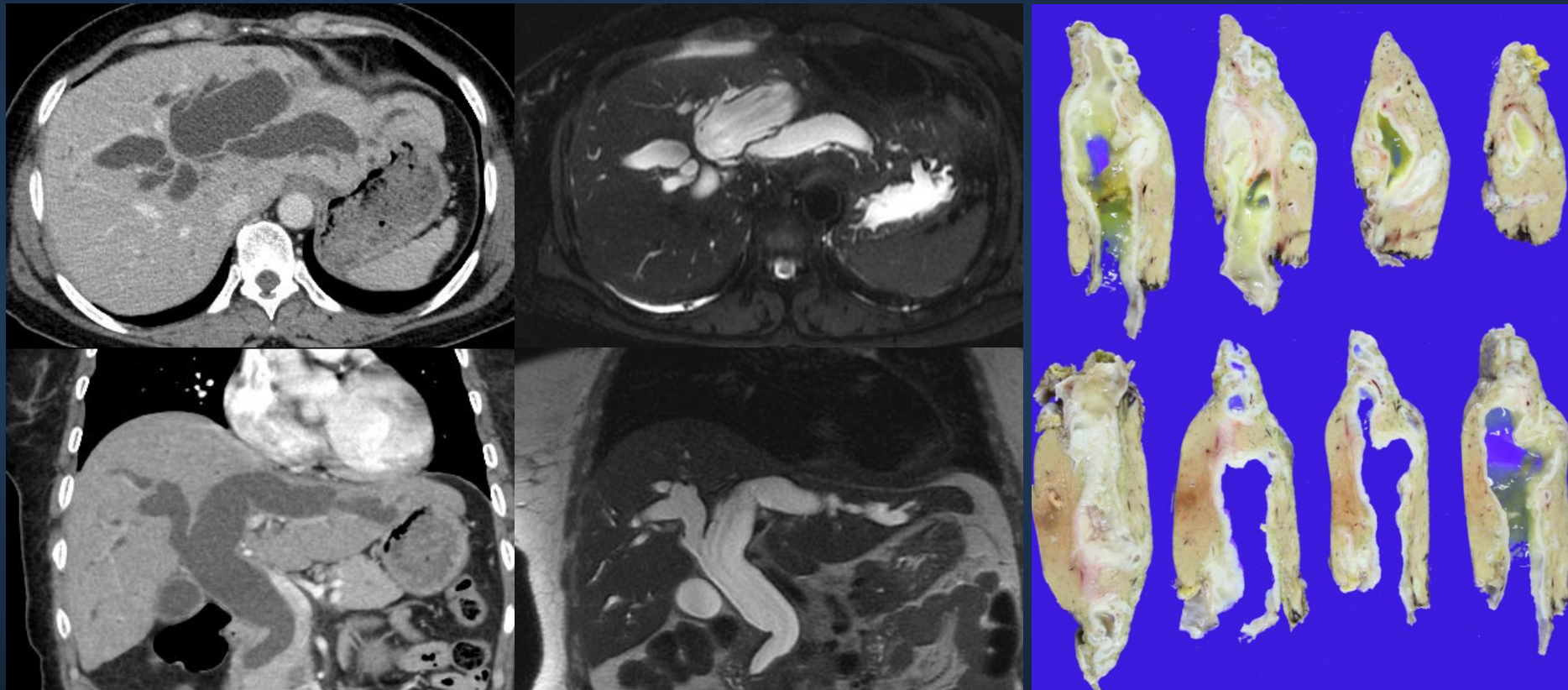
48-yr-old woman with IPNB and adenocarcinoma in situ.

Intraductal mass is not visible, but severe and asymmetrical dilation may suggest correct diagnosis of IPNB. Choledochoscopy show intraductal papillary lesions. EUS shows intramural irregularity corresponding the papillary lesions.



# Thread Sign: A useful sign for Dx of IPNB

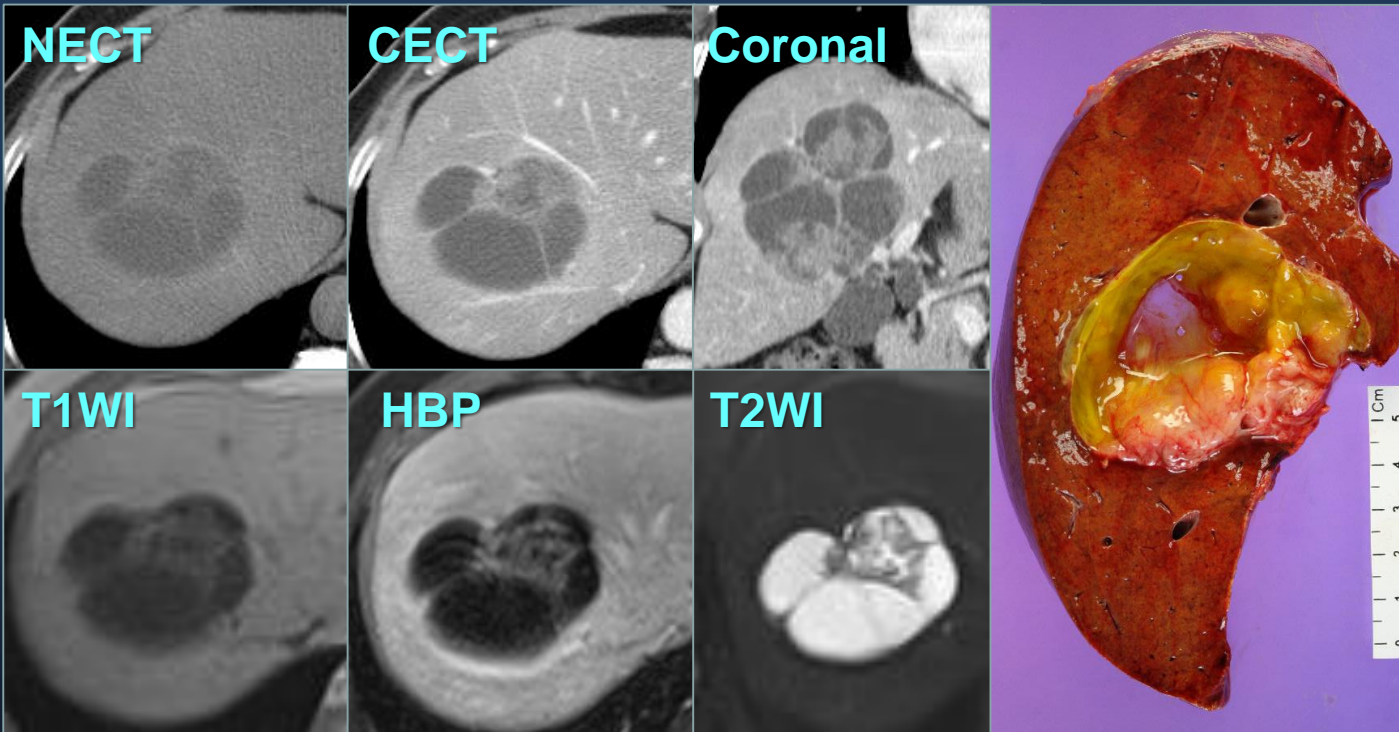
- Thread sign: intraductal linear or curvilinear hypointense striations
  - represents highly viscous mucus bundle with cellular components
    - ◆ Hong, GS et al., *Eur Radiol* (2016)



62-yr-old woman with invasive carcinoma associated with IPNB.  
Intraductal mass is not visible, but severe and asymmetrical dilation with thread sign suggest correct diagnosis of IPNB.

### 3) Localized duct dilation or cystic mass

- IPNB may present as a mucin-containing, cystic mass when ductal communication is narrowed or obstructed.
- Should be differentiated from mucinous cystic neoplasm or complicated cyst.



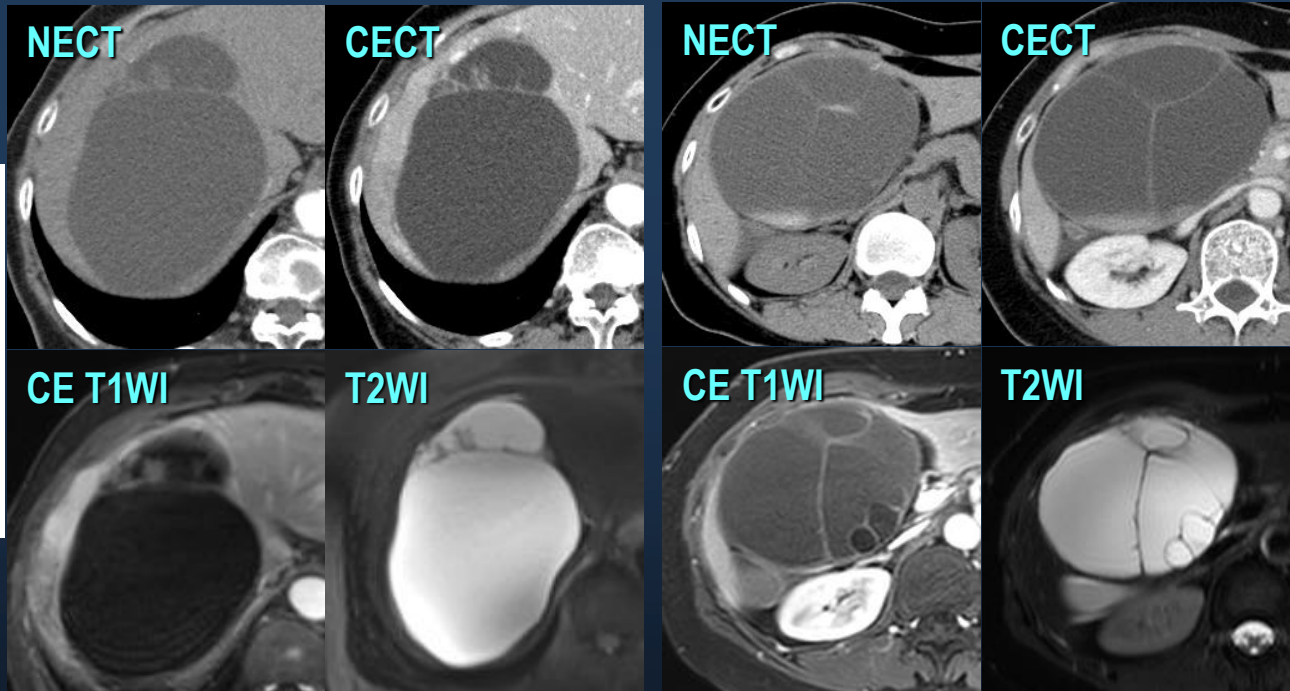
69-yo woman cystic form of intraductal papillary carcinoma. A multiseptated cystic mass is seen without obvious ductal communication.

# Differential diagnosis of Cystic IPNB vs MCN

Differential features	IPNB	MCN
Mural nodules	100%	4~35%
Distal bile duct dilatation	57~73%	0~6%
Multicystic (grape-like)	80%	8%
Multilocular (internal septa or cyst-in-cyst)	10%	81%

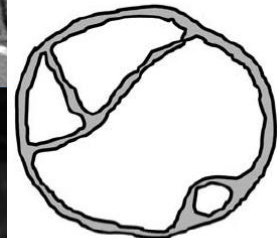
## IPNB

Multicystic  
(Grape-like appearance)



## MCN

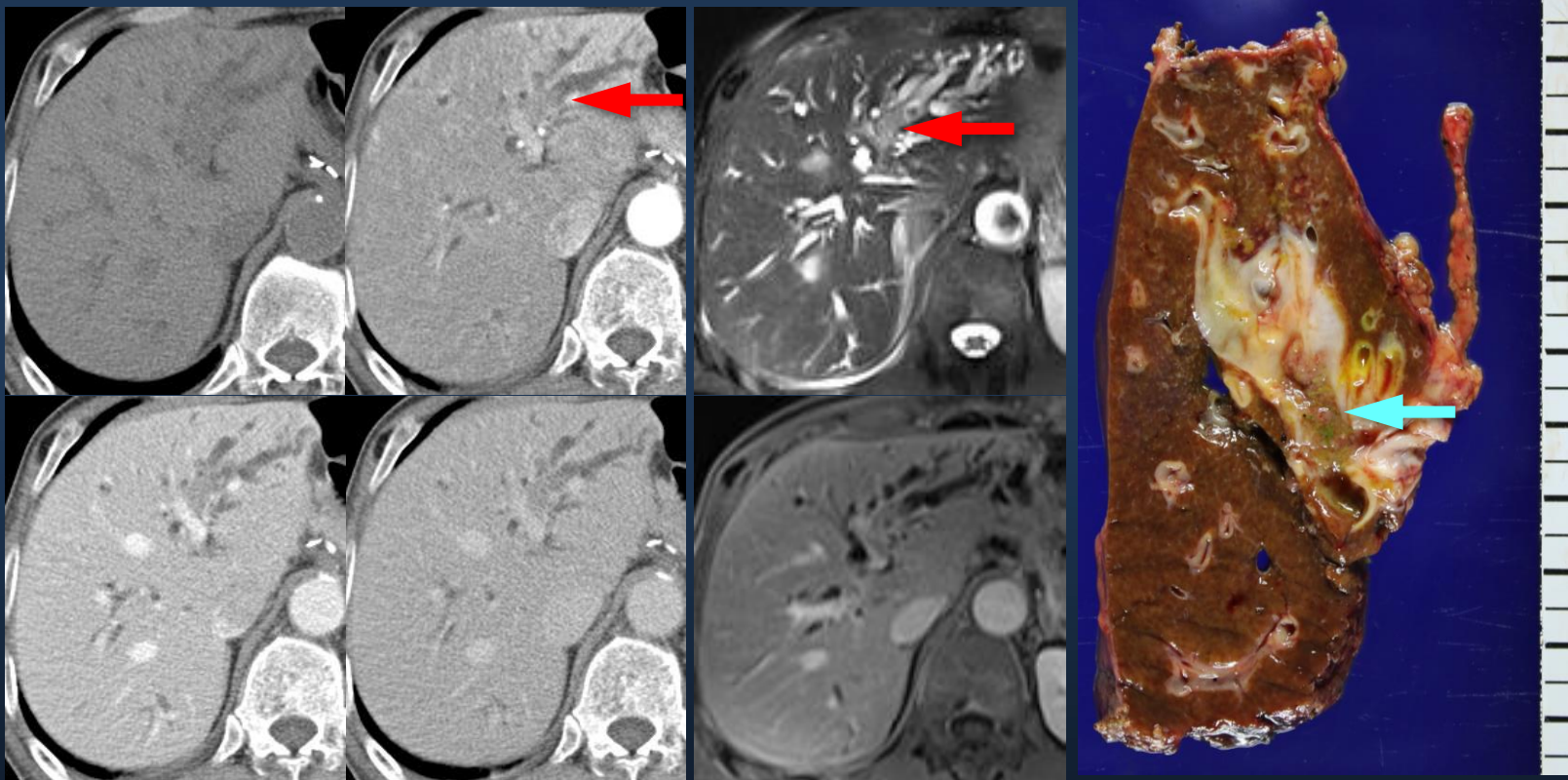
Multilocular  
(With septation or cyst-in-cyst appearance)





## 4) Intraductal cast-like pattern

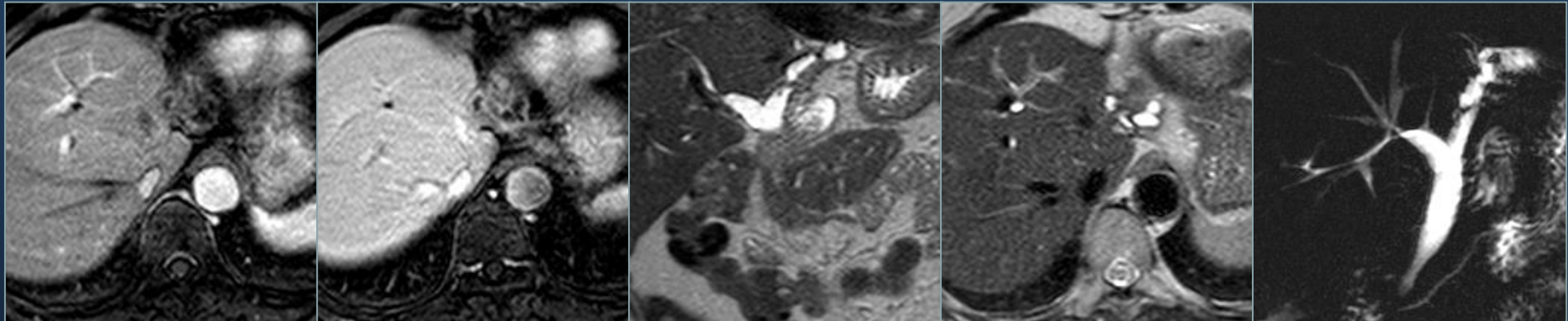
- Manifests minimal duct dilation with irregular filling defects, showing enhancement (+)
- May represent relatively earlier lesion or intraductal tubular/tubulopapillary carcinoma s/ mucin production



**IPNB with severe dysplasia, noninvasive**

## 5A) Focal narrowing in small duct

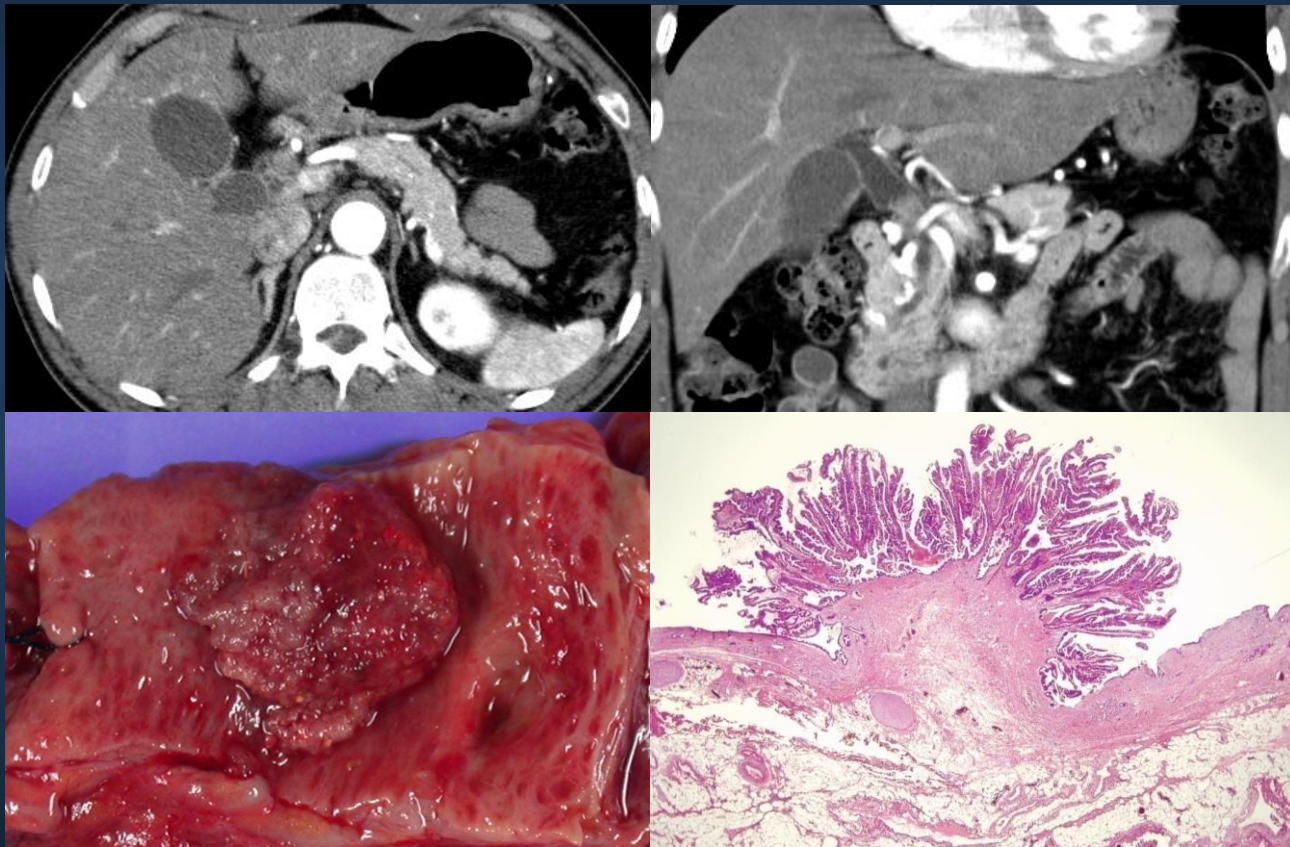
- Relatively uncommon form of IPNB with micropapillary lesion
- More commonly seen in early stage of intraductal tubular carcinoma or inflammatory stricture



A 59-yr-old woman with IPNB and adenocarcinoma in situ. Findings of recurrent pyogenic cholangitis are seen with parenchymal atrophy of Lt liver and focal stricture of intrahepatic bile duct. Surgery confirmed the diagnosis.

## 5B) Single polypoid mass in large duct

- A single polypoid mass pattern may be seen in a large duct (hilar or extrahepatic)



A 56-yr-old man with intraductal papillary tumor confined in the bile duct. A single polypoid mass is seen in the hilar bile duct. Surgical specimen shows a papillary mass protruding into the lumen.



# Summary

- Small-duct type CCAs associated with chronic liver diseases progress to a mass-forming type without known form of precursor form, and usually are not accompanied by biliary dilation.
- Large-duct type CCAs associated with chronic biliary diseases arises as BiL-IN or IPNB, then progressed to periductal or intraductal tumor, and eventually to mixed forms of CCA, frequently accompanying peritumoral duct dilation.
- IG-CCA may represent either IPNB or early stage BD ca, and present as various imaging pattern before further progress to various gross types of CCA.

*Thank you for your attention!*



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