

Liver Tumors

Selected Topics

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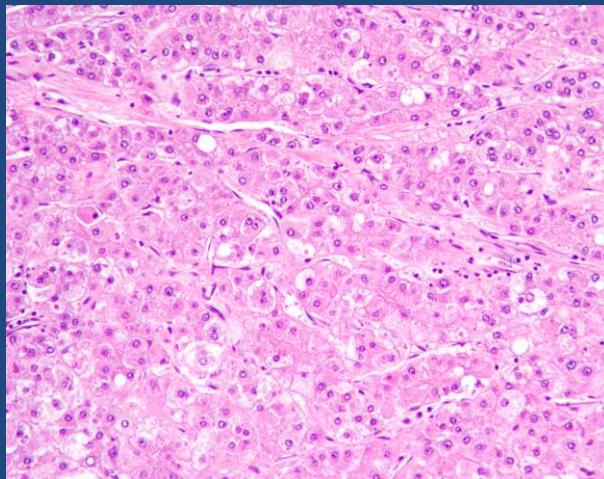


Hepatocellular carcinoma

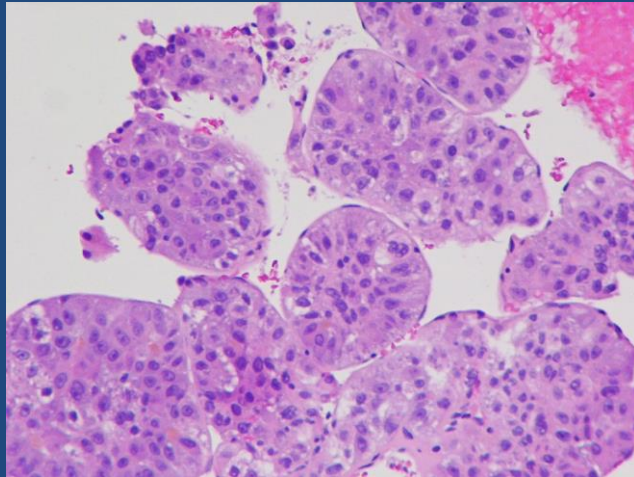
- Most common primary malignant liver tumor (~90%) in Europe and North America
- Tumor recapitulates architecture and cytology of liver
 - large cells
 - abundant eosinophilic cytoplasm
 - prominent central nucleus
 - prominent eosinophilic nucleolus
 - trabecular, sinusoidal pattern
- Tumor expresses markers of hepatocellular differentiation

**Hepatocellular carcinoma recapitulates
architecture and cytology of the liver**

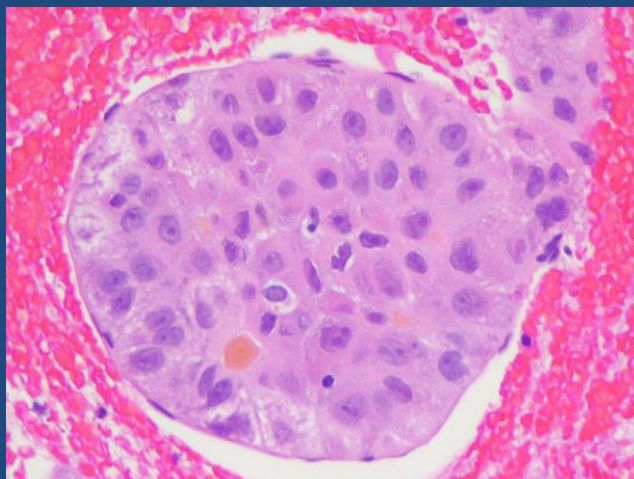
Hepatocellular carcinoma



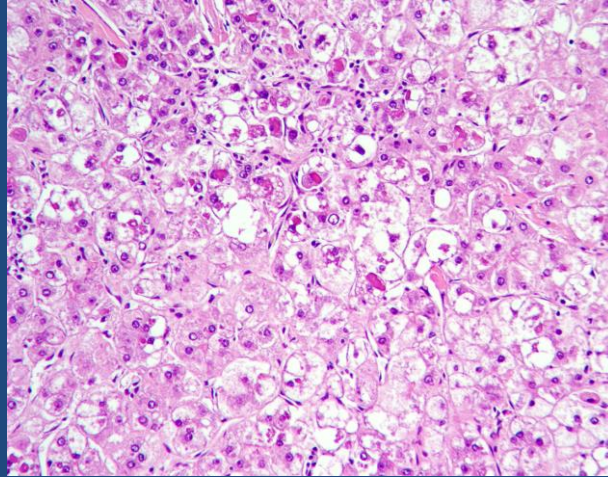
Hepatocellular carcinoma - Cytology



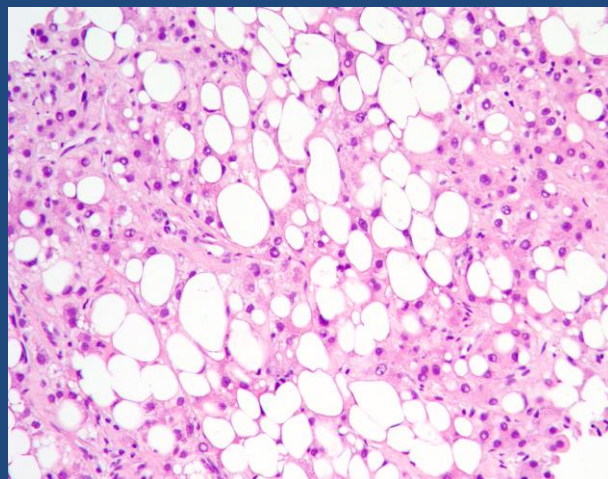
Hepatocellular Carcinoma - Bile



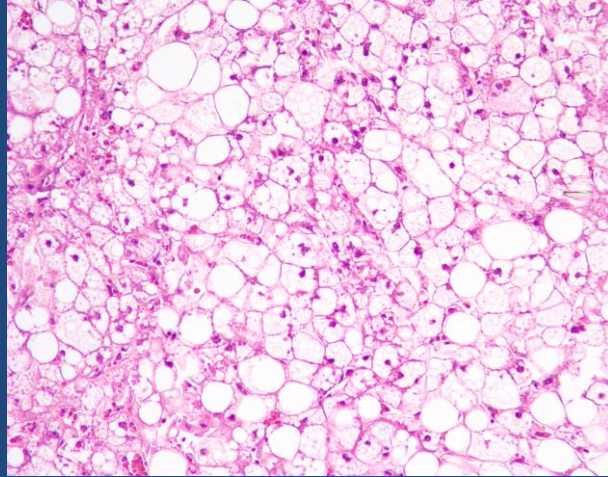
HCC – Mallory hyaline



Hepatocellular carcinoma – Fat/ Steatosis

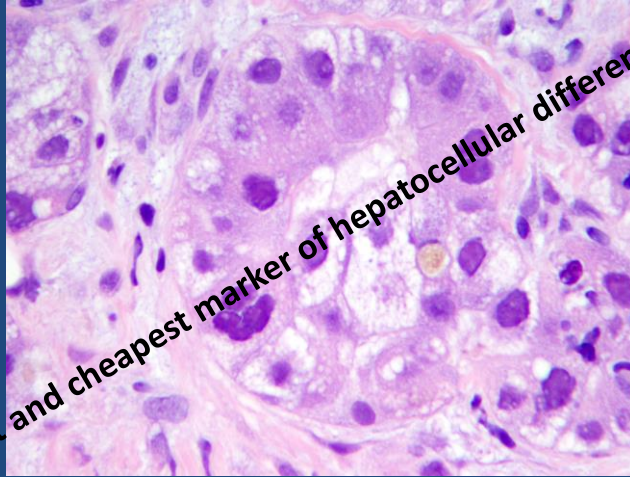


HCC – Ballooned cells/ features of steatohepatitis



HCC expresses markers of hepatocellular differentiation

Only hepatocytes produce bile



Best and cheapest marker of hepatocellular differentiation!

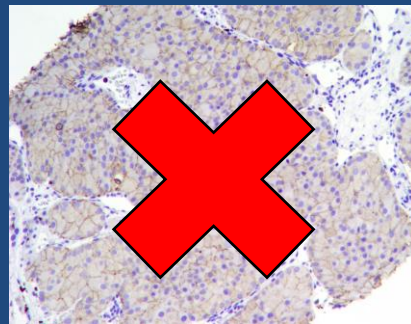
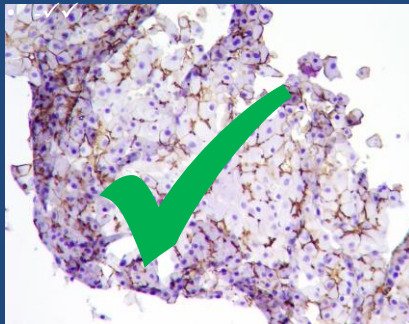
Immunohistochemical markers cytoplasmic +/- nuclear

- Hep Par 1 (also called Hepatocyte Specific Antigen)
 - carbamoyl phosphate synthetase, urea cycle enzyme
- Arginase 1
 - manganese metalloenzyme, catalyzes hydrolysis of arginine to ornithine and urea
- Glypican 3
 - membrane anchored, heparin-sulfate proteoglycan normally expressed in fetal liver and placenta
- Alpha fetoprotein
 - expressed in fetal liver

IHC – canalicular markers

- Polyclonal CEA
 - cross reacts with a glycoprotein on bile canalicular membrane
- Bile salt export pump (BSEP)
 - liver-specific ATP binding transporter involved in export of bile salts from hepatocytes
- Others
 - CD10, villin

IHC – canalicular markers



	Sensitivity	Specificity
HepPar1	PD HCC: 30%	Stomach, lung, esophagus
Arginase 1	PD HCC: 90-95%; all HCC: 85-90% Usually diffuse Works well in cytology material	pancreas, cholangio rarely - breast, prostate
GPC 3	PD HCC: 80-85%, WD HCC: 15% Diffuse -15% (not useful in biopsy)	Negative: non-neoplastic liver Positive: cholangio, placental, germ cell
AFP	All HCC: 30-50% Background staining a problem	Variety of tumors
pCEA	PD HCC:<50%	Membranous and luminal pattern in adeno
BSEP	PD HCC: <50% Diffuse staining: 10%	Only expressed in liver

Nguyen et al. Arch Pathol Lab Med 2015; 139: 1028 -34

Best markers

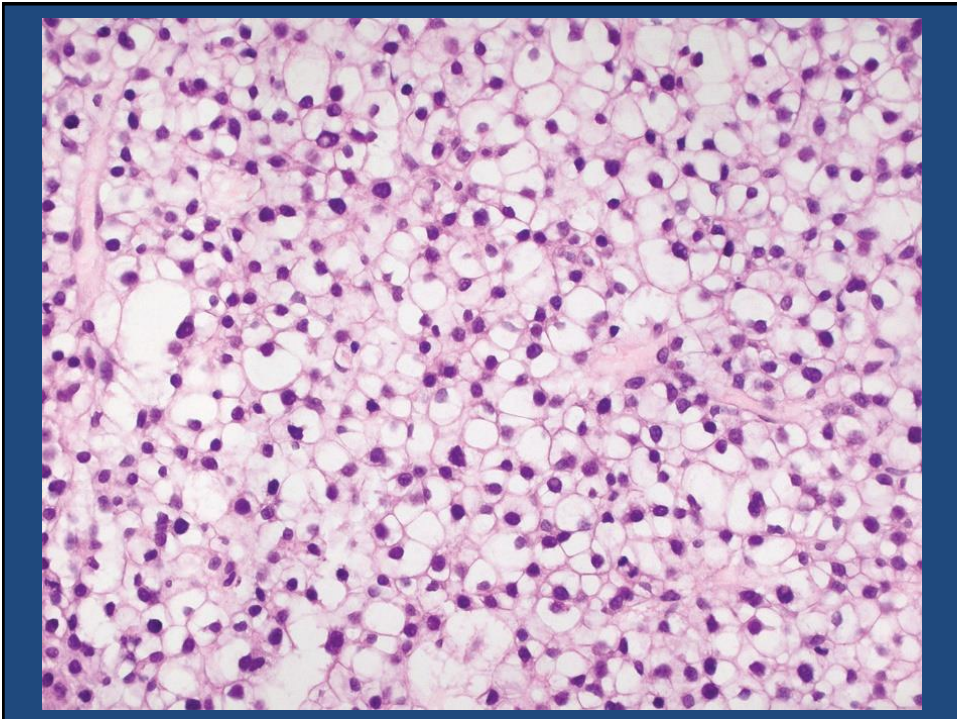
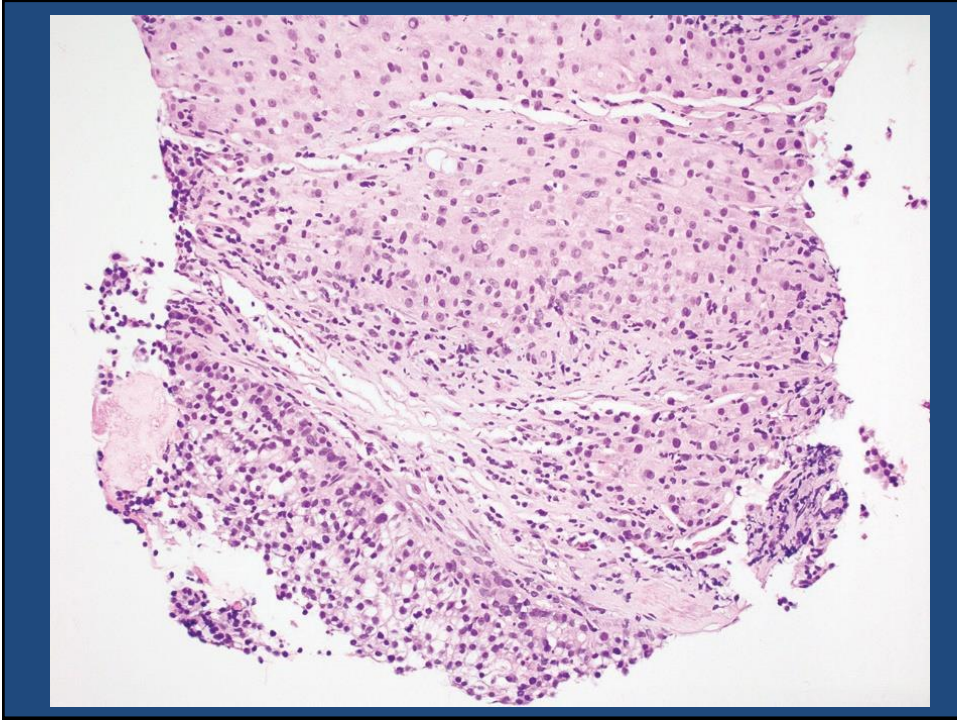
- Best overall: Arginase 1
- Poorly differentiated HCC: Arginase 1 + GPC3
- Well and moderately differentiated HCC: Hep Par1 + Arginase 1
- Personal favorite: pCEA

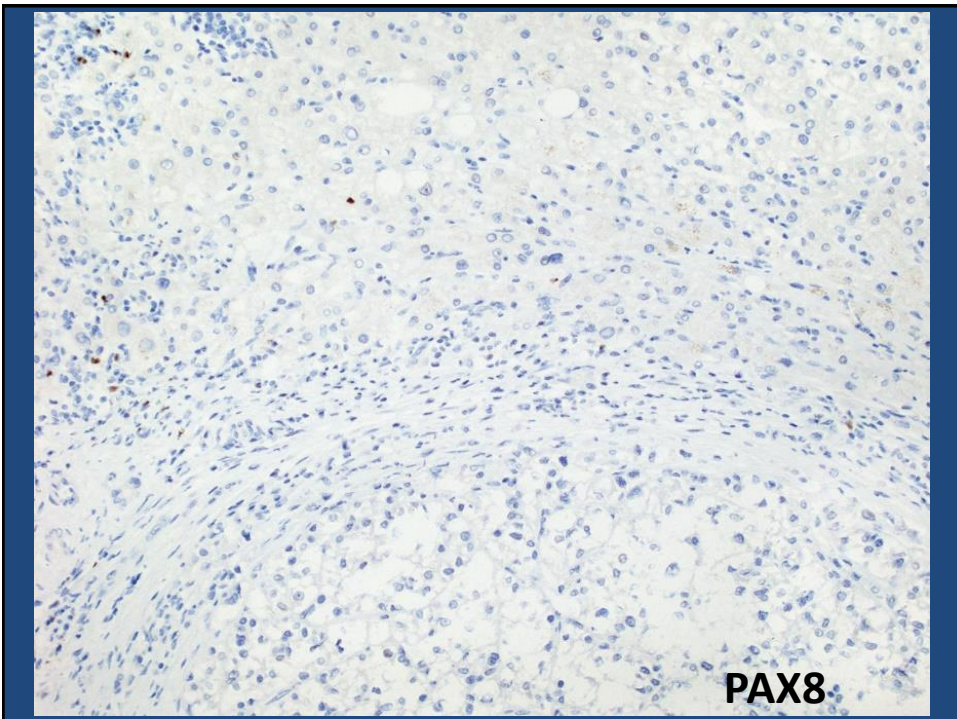
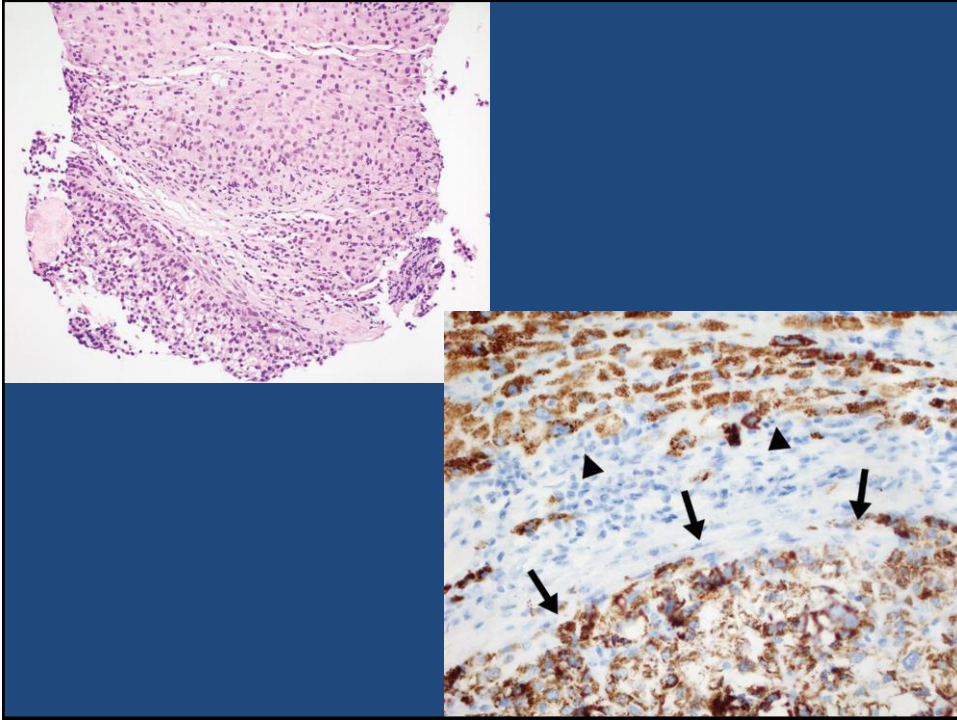
Hepatocellular carcinoma Avatar 2



Case 1

- 71-year-old female with symptomatic cholelithiasis
- Incidental liver lesion discovered during cholecystectomy
- CT - solitary hepatic tumor within an otherwise normal appearing liver

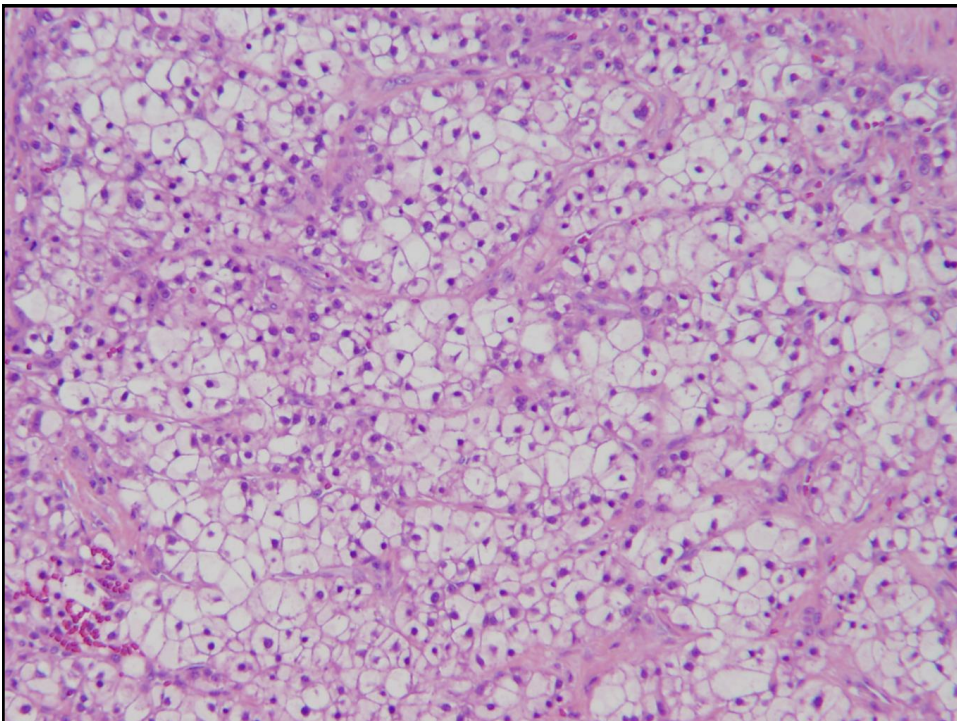
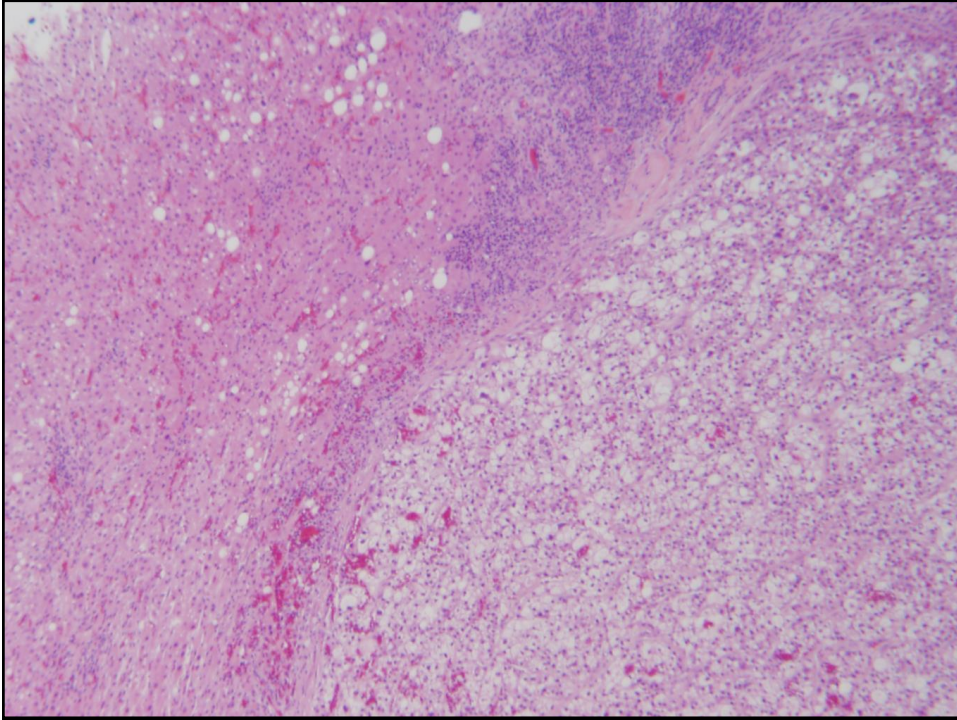


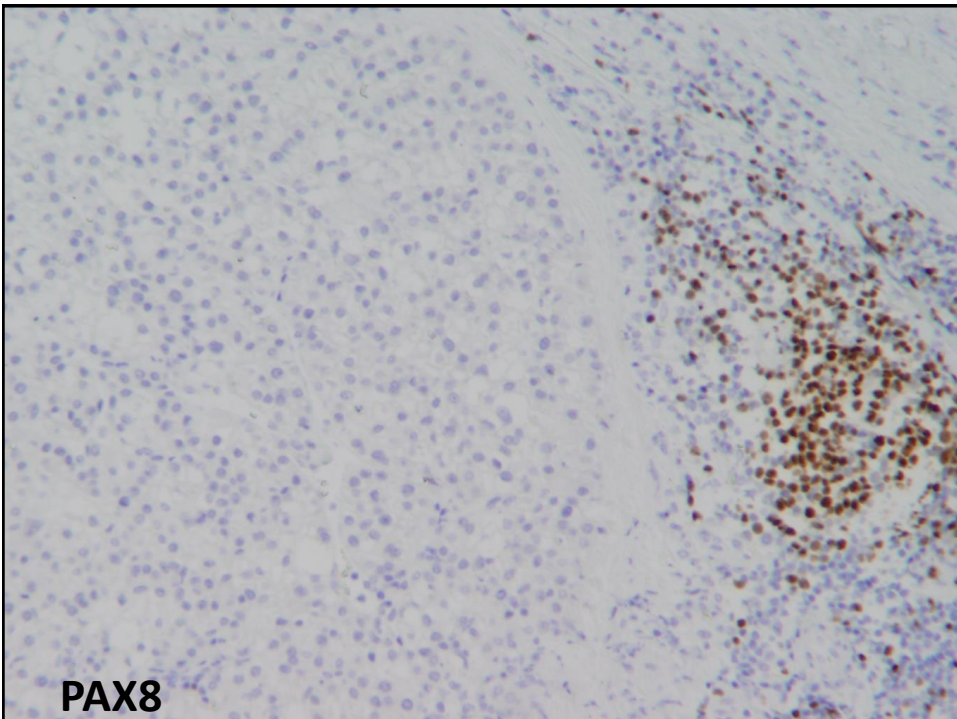
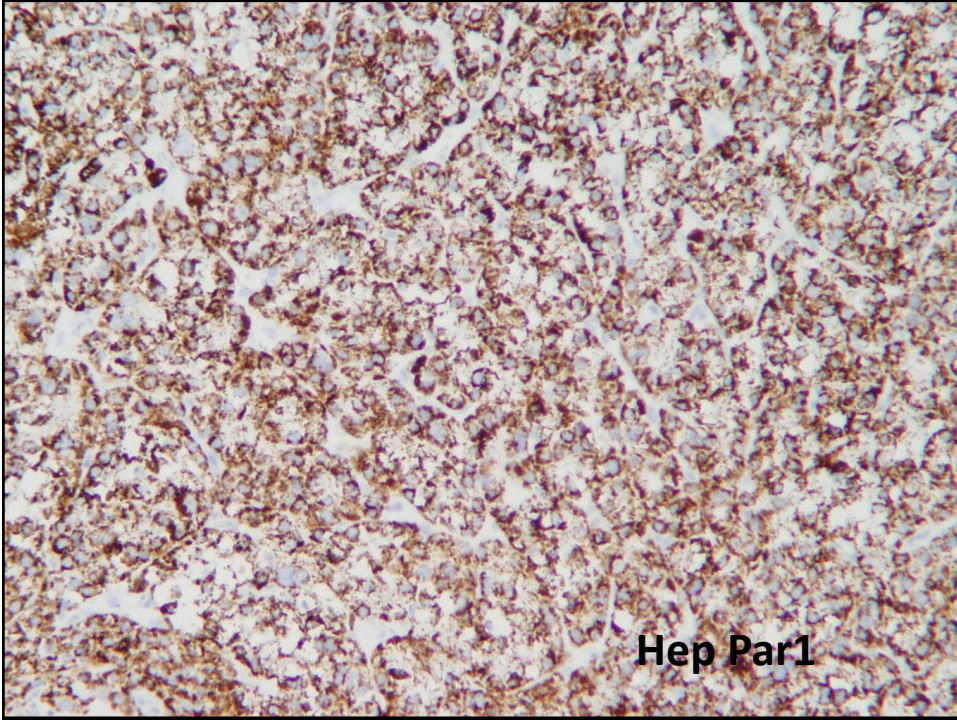


Clear cell hepatocellular carcinoma

Case 2

- 71 year old female with HCC





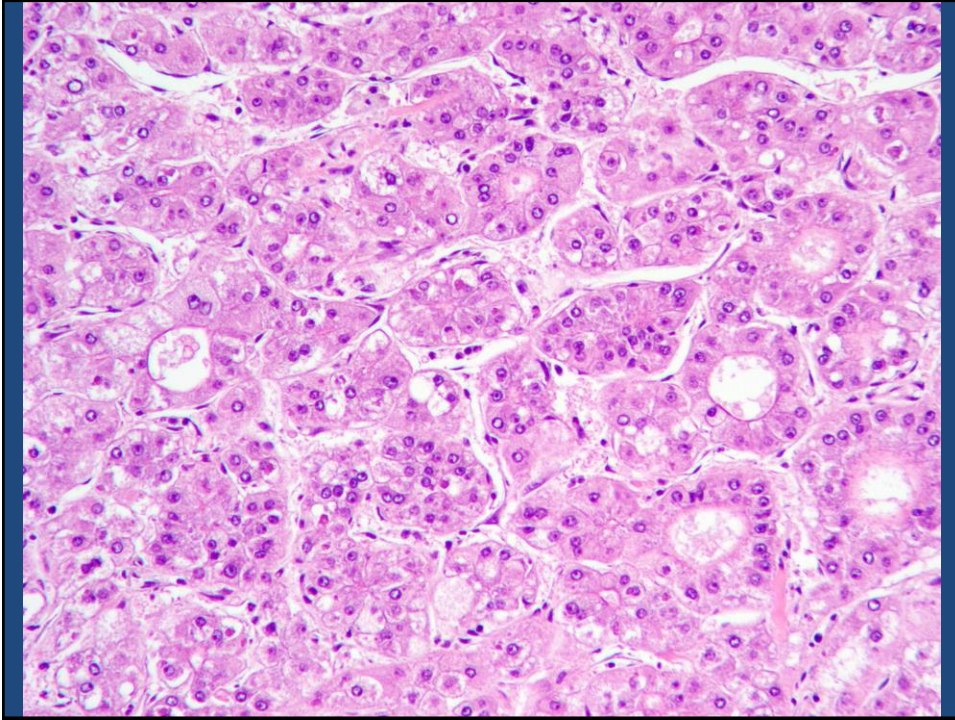
Clear cell hepatocellular carcinoma

mimics renal cell carcinoma

Hepatocellular carcinoma

Avatar 3



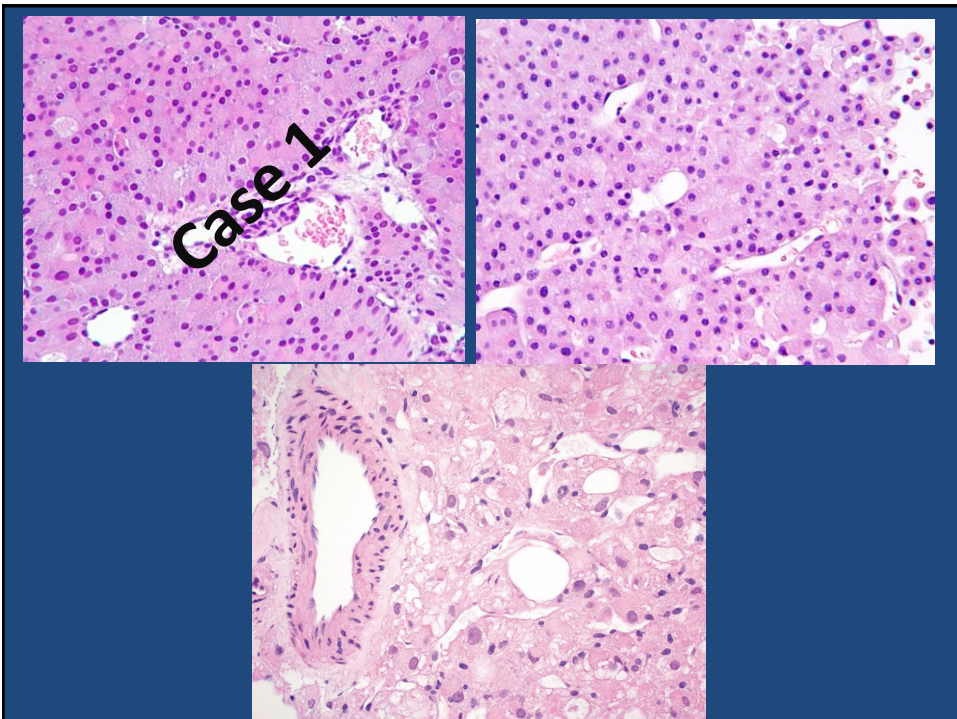


Hepatocellular carcinoma

prominent acinar / pseudoglandular structures
(mimics adenocarcinoma, especially when tissue
is scant, i.e. cytology, frozen section)

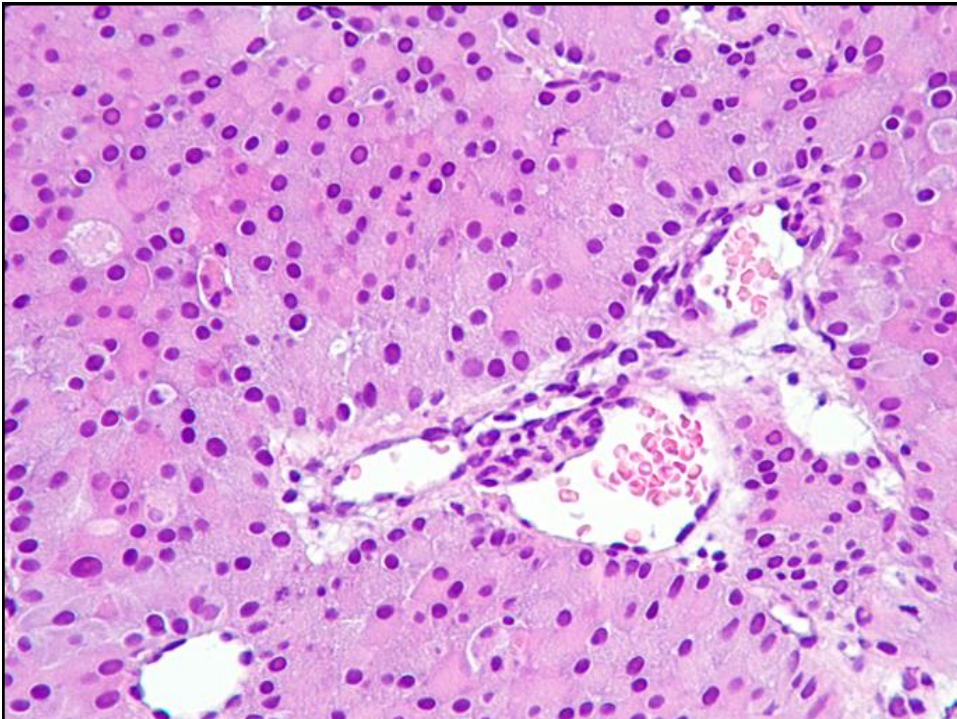
Differential Diagnosis

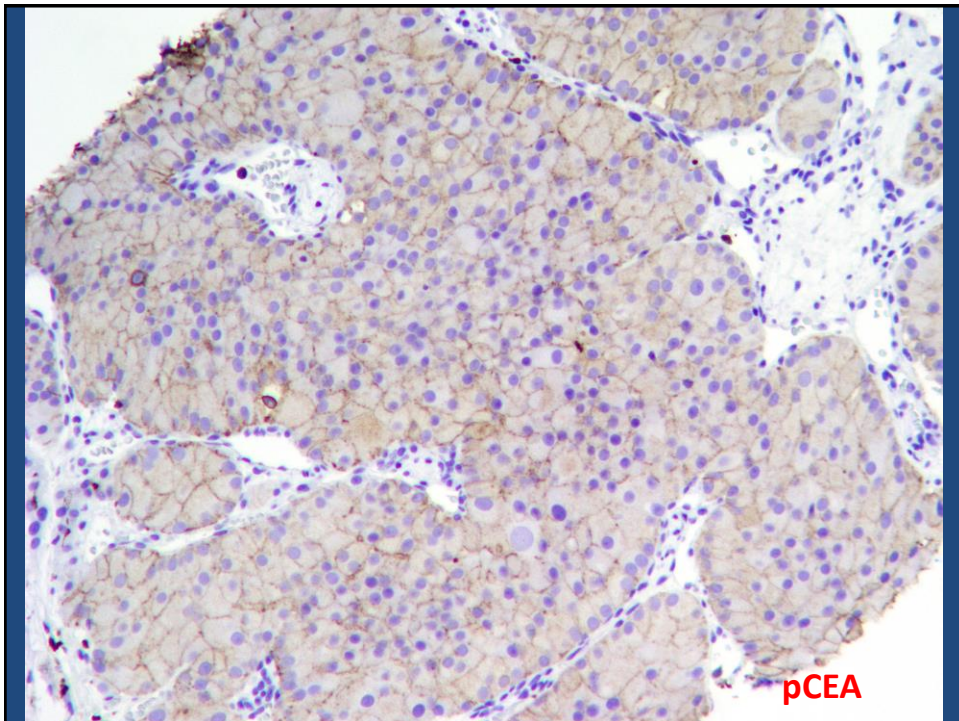
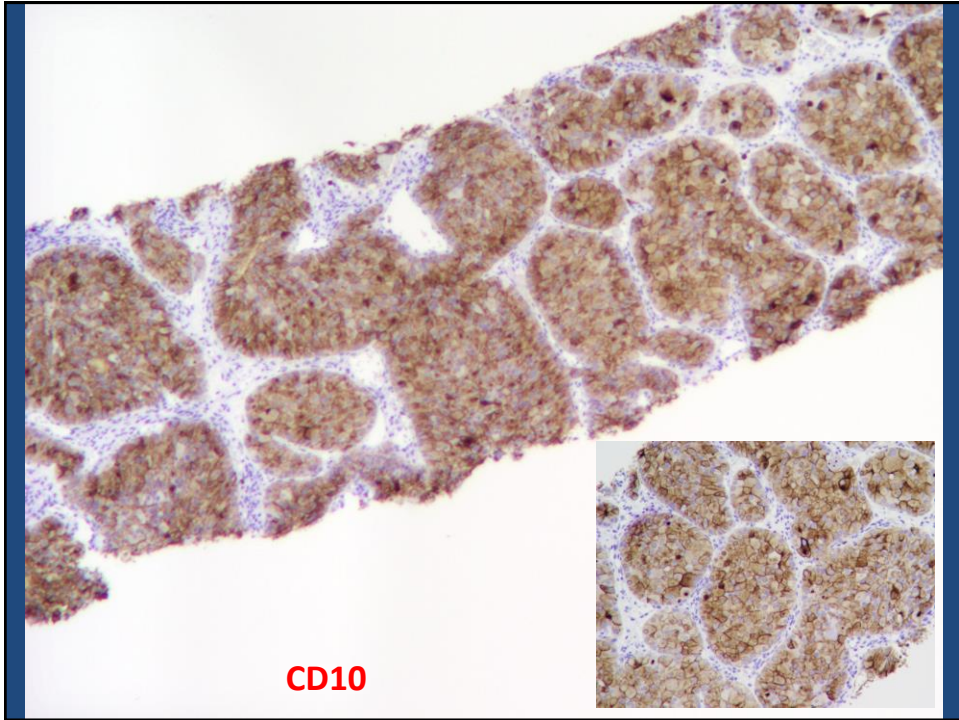
Other tumors with large eosinophilic cells

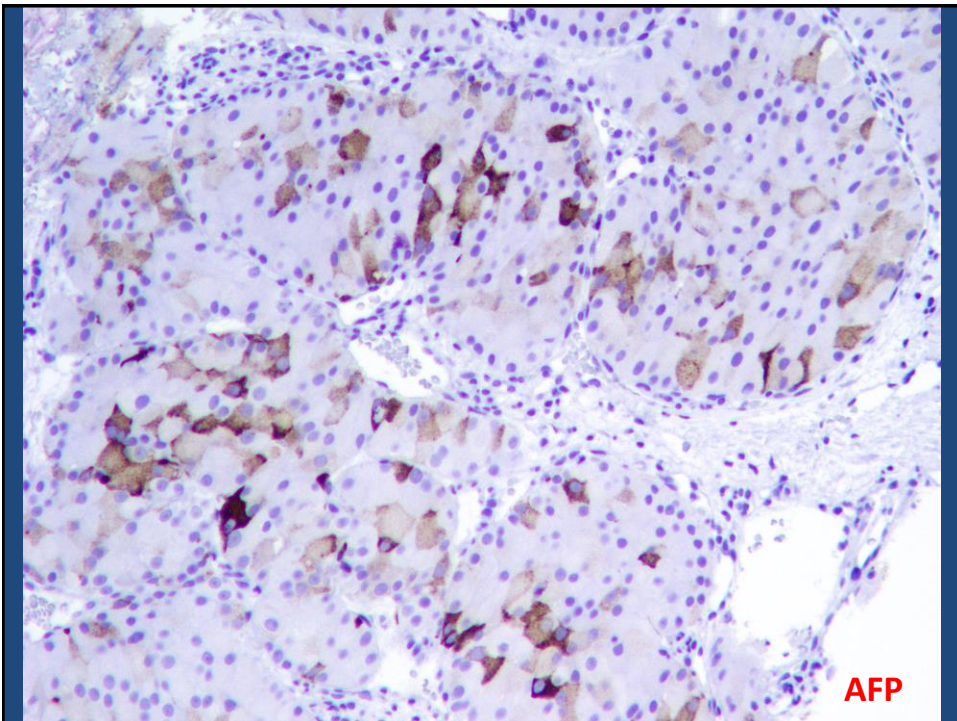
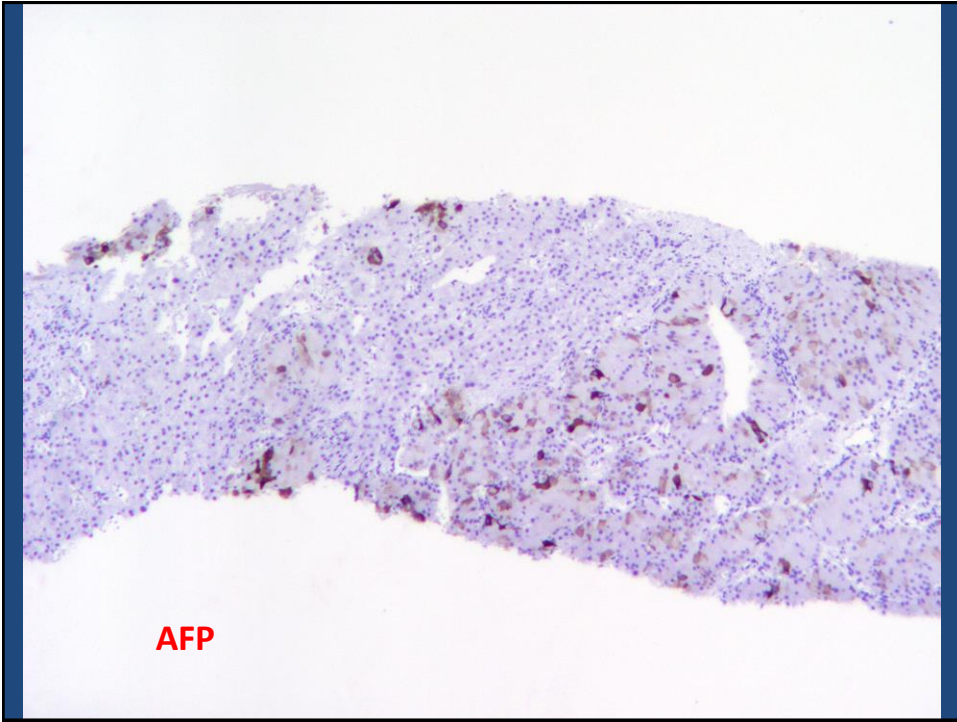


Case 1

- Consult case
- 55 year old male
- PET - multiple liver lesions, largest 8.2 cm
- No cirrhosis, no disease outside liver
- weight loss 15 lbs over 6 months, bad night sweats
- AFP 1994



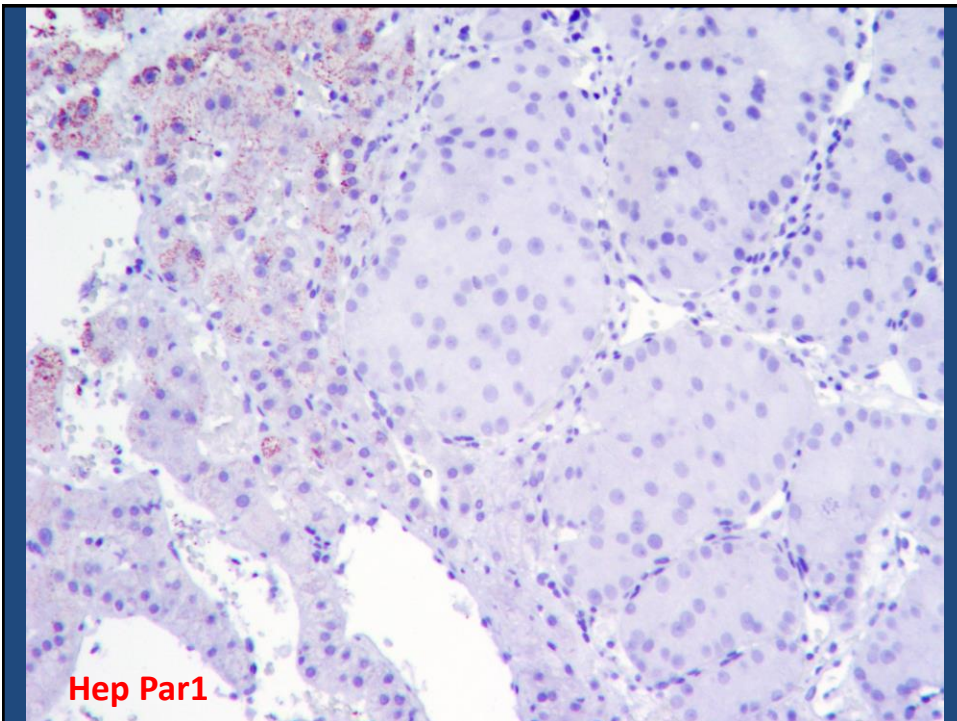
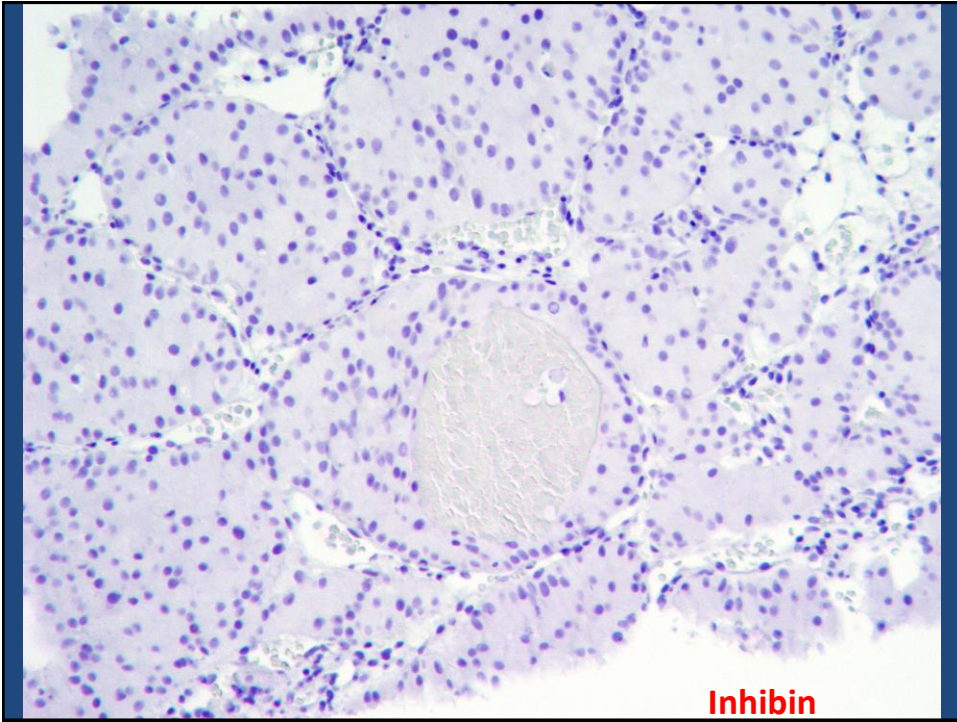


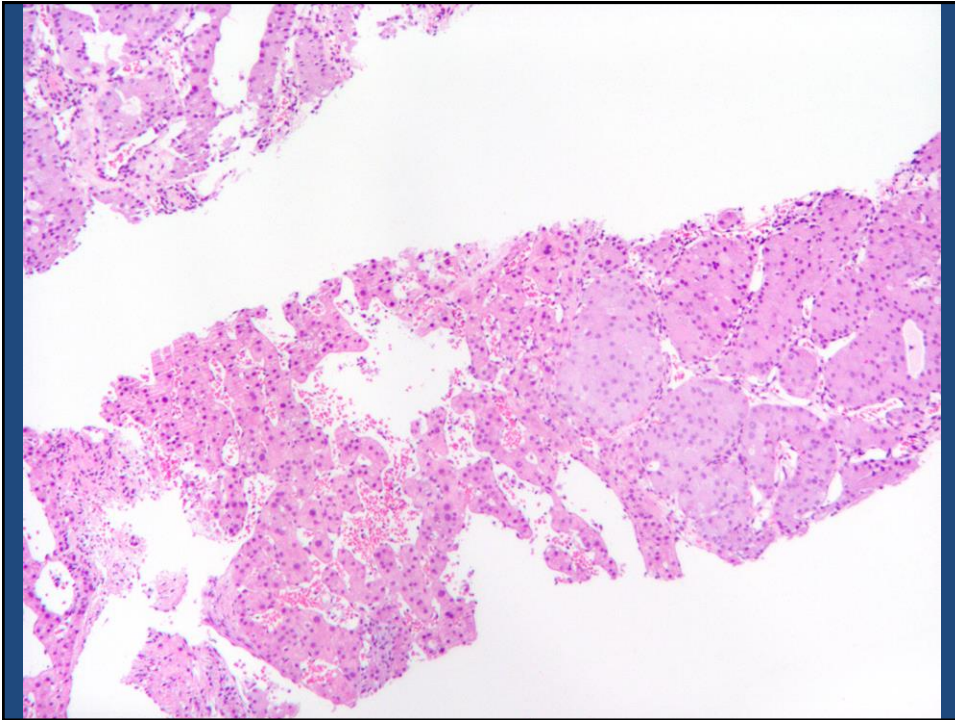


IHC

- Positive:
 - CD10 (cytoplasmic, membranous)
 - AFP (cytoplasmic, patchy)
- Negative:
 - Hep Par1, HMB45, EMA, CEA mono, CEA poly (membranous), CK20, CK7
- *Diagnosis: WD HCC vs metastatic hepatoid adenocarcinoma*



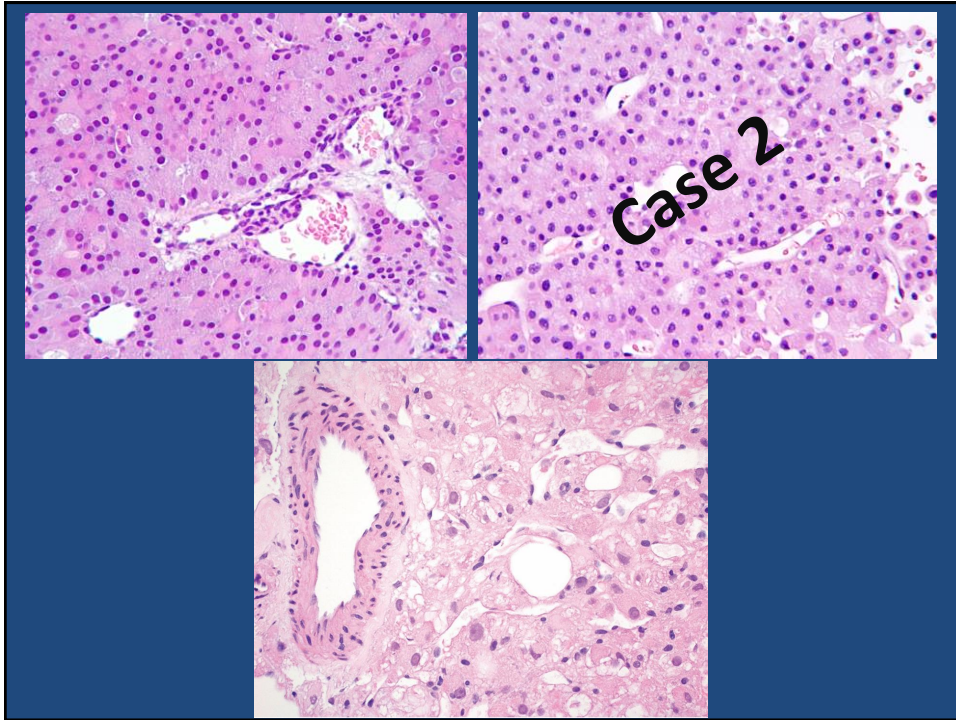




Neuroendocrine tumor

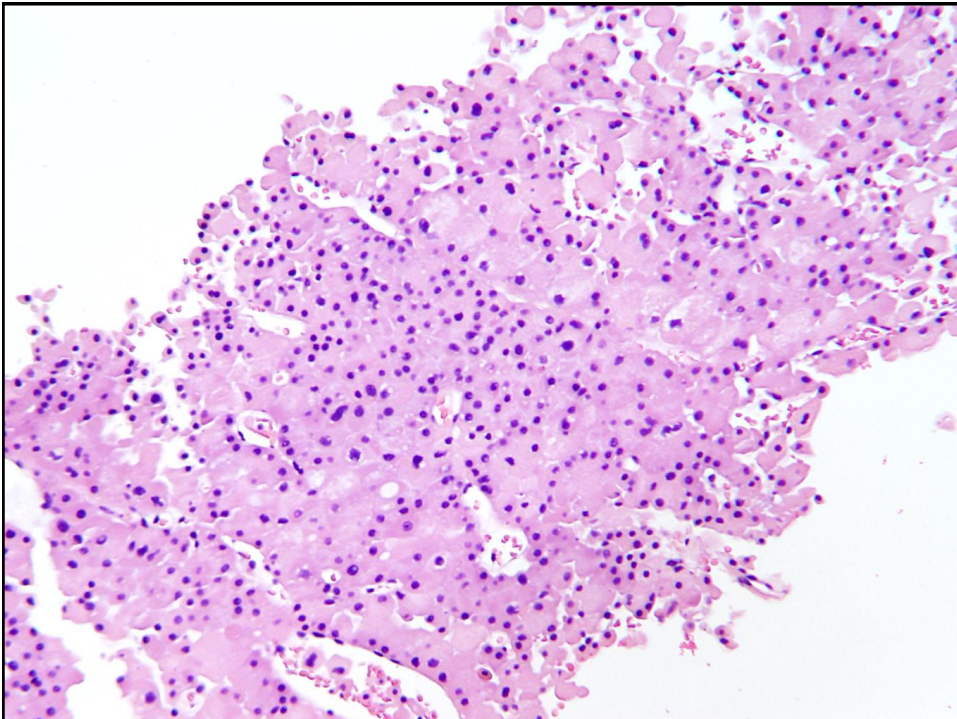
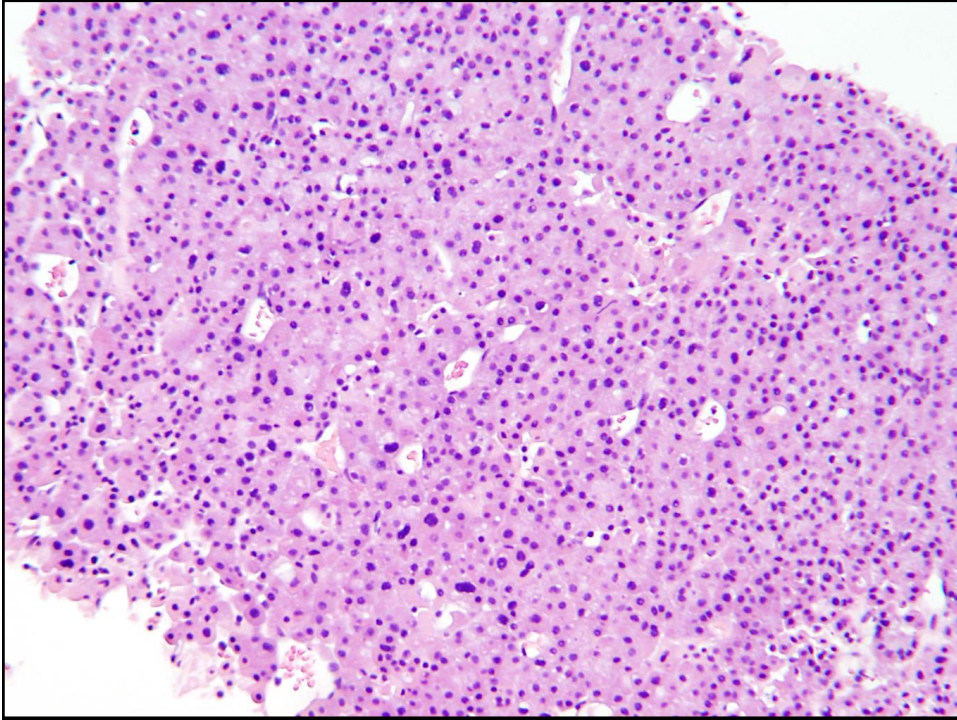
Positive: Chromogranin, synaptophysin

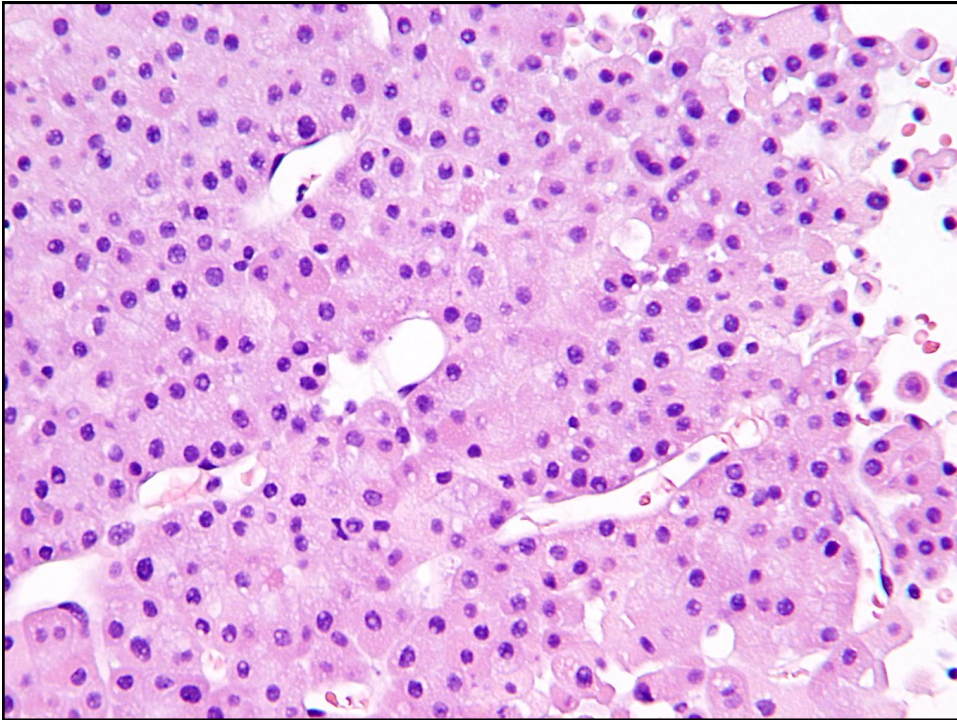
Negative: Inhibin, PAX8



Case 2

- 71 year old female
- Biopsy of liver mass
- History of renal cell carcinoma

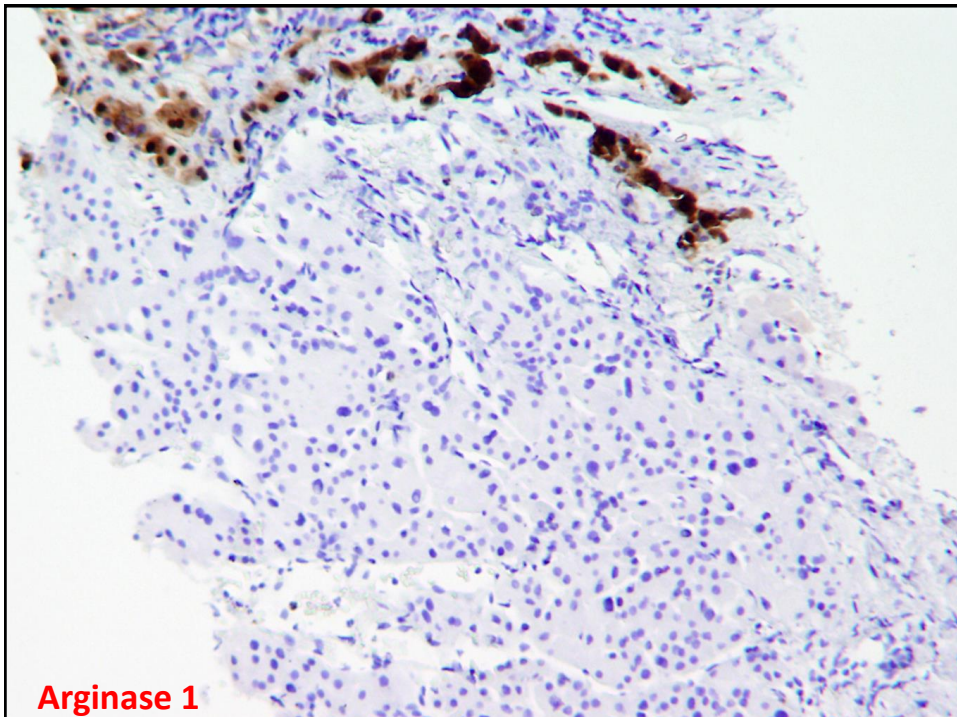


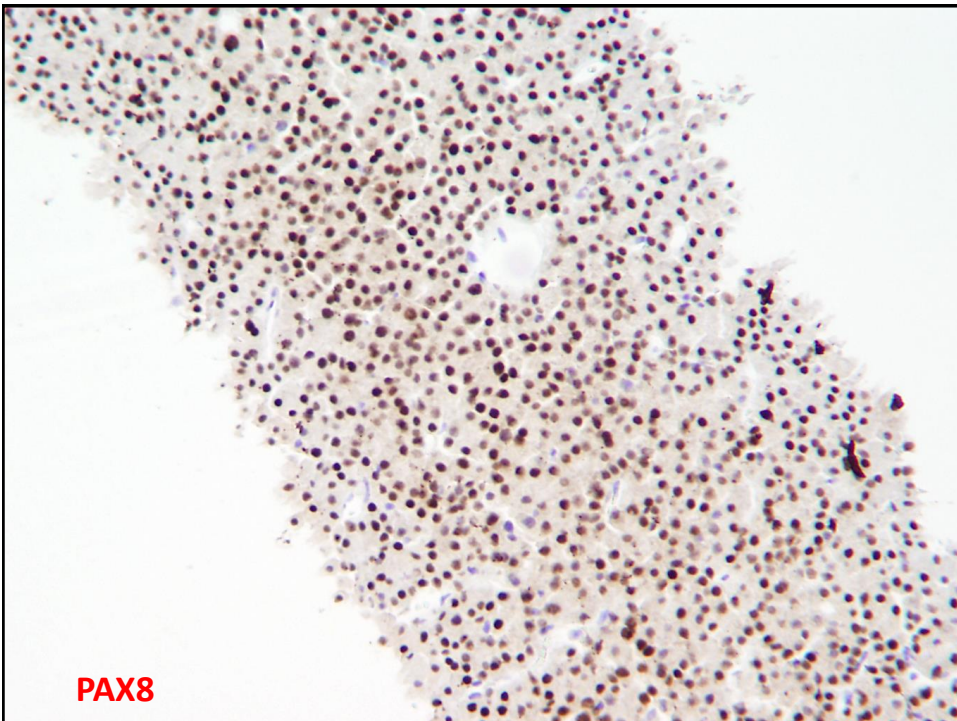
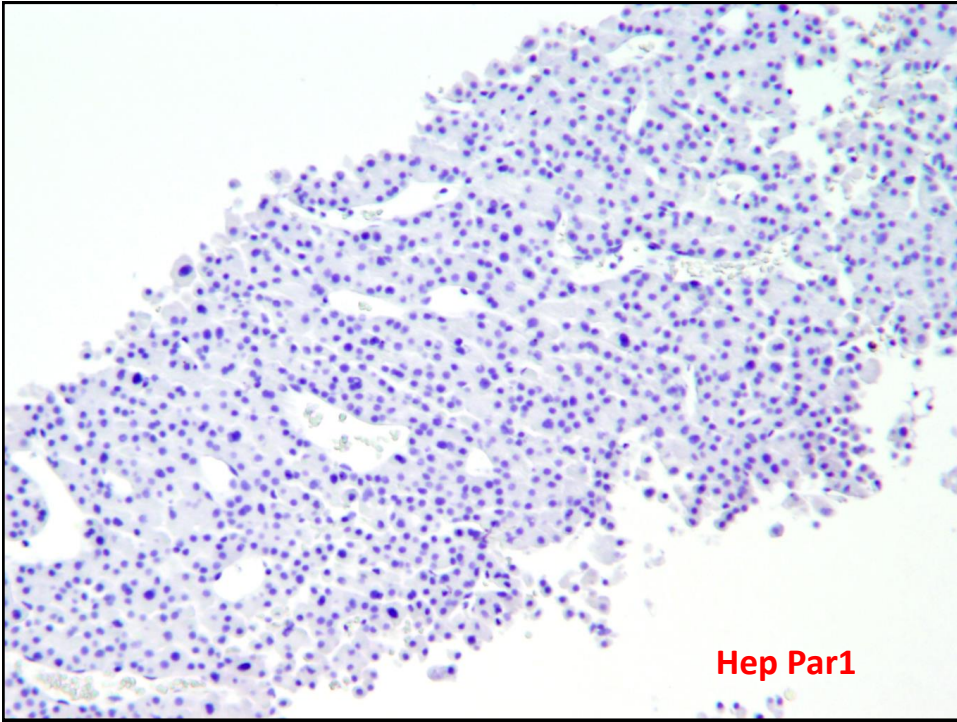


- Positive: CK7, CD10, GATA3, GPC3
- Negative: AFP, CDX2, vimentin, CK20, Hep Par1
- *Diagnosis: Neoplastic lesion, pending consultation*

Consultation report

- Malignant epithelial neoplasm with eosinophilic cytoplasm
- Additional stains done
 - Positive: EMA, GPC3, ckit
 - Negative: pCEA, arginase, ER
- *Diagnosis: Metastatic RCC, chromophobe type*
 - *Remote history of RCC 15 years ago*

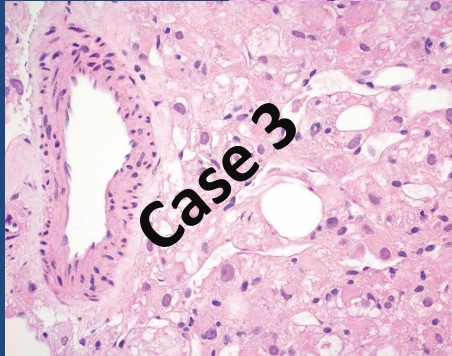
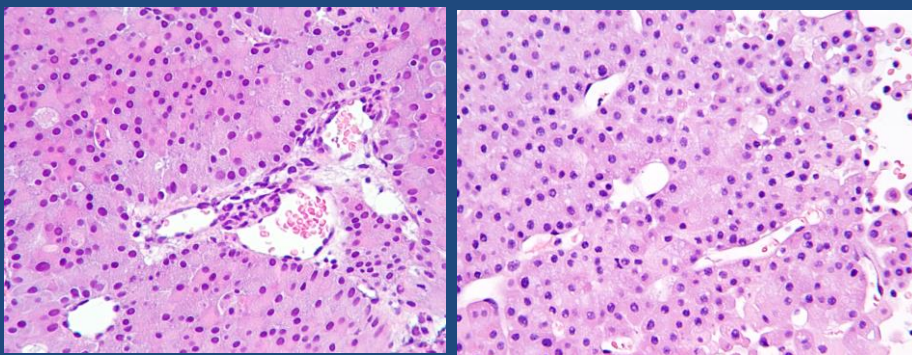




Metastatic renal cell carcinoma, chromophobe type

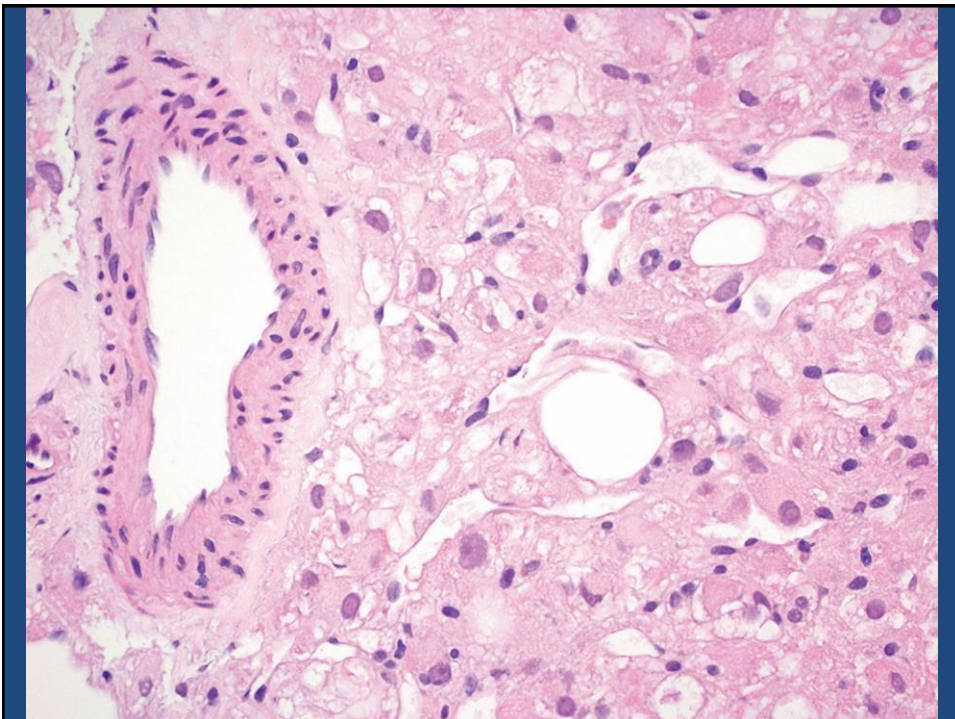
Positive: PAX8

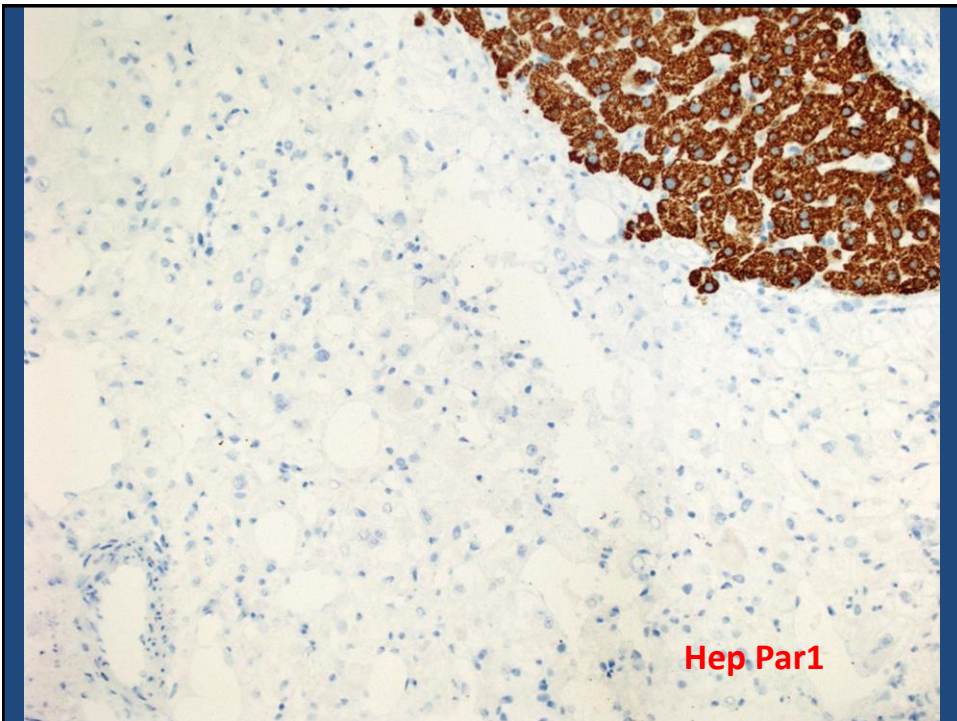
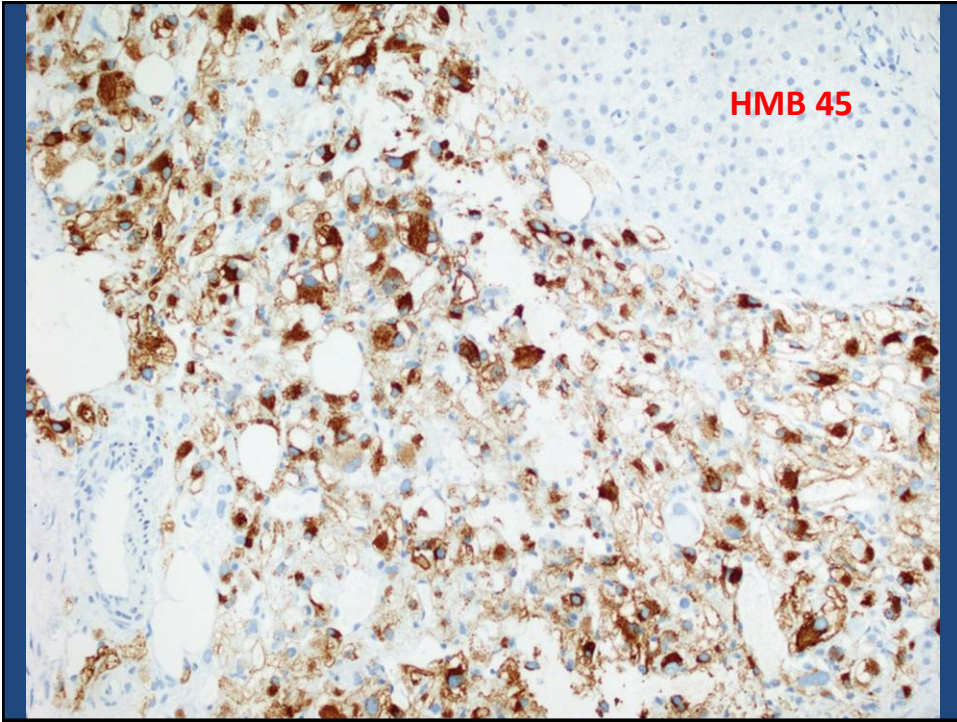
Negative: Hep Par1, Arginase 1



Case 3

- 41 year old female
- Left flank pain, myalgia, fatigue for 1 month
- CT – left lower lung nodules (largest 1.5 cm)
 - Right hepatic mass 8 cm
- Pathology:
 - FNA lung: non diagnostic
 - Liver mass: HCC
- Referred to IU and second biopsy performed





Angiomyolipoma, epithelioid type

Positive: HMB 45

Negative: Hep Par1

Angiomyolipoma

- PEComa
- Less common in liver than in kidney
- Middle aged individuals, usually incidental
- Symptoms: localized (abdominal pain), or generalized (fever, malaise etc)
- Usually single, may be multifocal
- Variegated appearance grossly (hemorrhage, necrosis, yellow)
- Three components:
 - Blood vessels, fat and myoid cells
 - Myoid cells may be spindled (SMA +) or epithelioid (HMB45 +)
 - Epithelioid (pure/ predominant) variant common in liver

Lesion composed of large eosinophilic cells

	Hepatocellular	Not hepatocellular
Benign		
Malignant		

Lesion composed of large eosinophilic cells

	Hepatocellular	Not hepatocellular
Benign	<ul style="list-style-type: none"> Evidence of hepatocellular differentiation Morphologic: Bile, Mallory Denk bodies, steatosis Immunohistochemical: Hep Par1, arginase 1, pCEA, GPC3, BSEP 	
Malignant	<ul style="list-style-type: none"> Evidence of alternative differentiation Adrenal: Inhibin Renal: PAX8 Neuroendocrine: synaptophysin, chromogranin Melanoma: HMB45, S100, SOX10, Melan A Angiomyolipoma: HMB45 	

Features	HCC	AdCa	RCC	ACC	OCT	NET / NEC	AML	MEL
Histological / histochemical								
Trabecular architecture	•		•	•	•	•	•	•
Pseudoglandular structures	•	•			•	•		
Bile production	•							
Tubuloglandular architecture		•				•		
Desmoplastic reaction		•			•	•		
Organoid pattern					•	•		•
Cytoplasmic fat in tumour cells	•		•	•			•	
Mucin		•						
Immunohistochemical								
α-Fetoprotein	•							
HSA / carbamoyl phosphatase synthetase-1	•							
CEA, canalicular staining	•							
CEA, cytoplasmic staining		•						
Glypican-3	•							•
Keratins 8/18	•	•	•		•	•		
Keratins 7/19		•			•	•		
MOC31		•				•		
Epithelial membrane antigen		•	•		•	•		
Vimentin			•	•	•		•	•
PAX2			•					
Inhibin				•				
MelanA				•			•	•
Chromogranin						•		
Synaptophysin				•		•		
Smooth muscle actin							•	
HMB-45 antigen							•	•
TTF-1 nuclear staining		• ^c			•	• ^c		
Thyroglobulin					•			

Saxena et al. Diagnostic algorithms for tumors of the liver. In WHO Classification of Tumors of Digestive Diseases 4th ed. 2010, p 255

Lesion composed of large eosinophilic cells

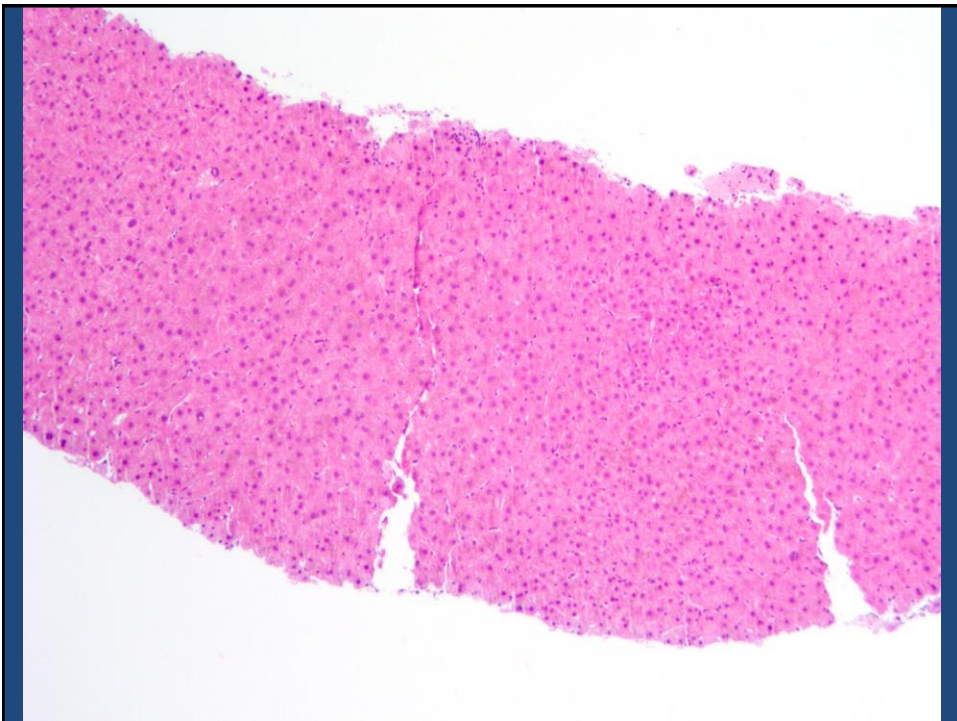
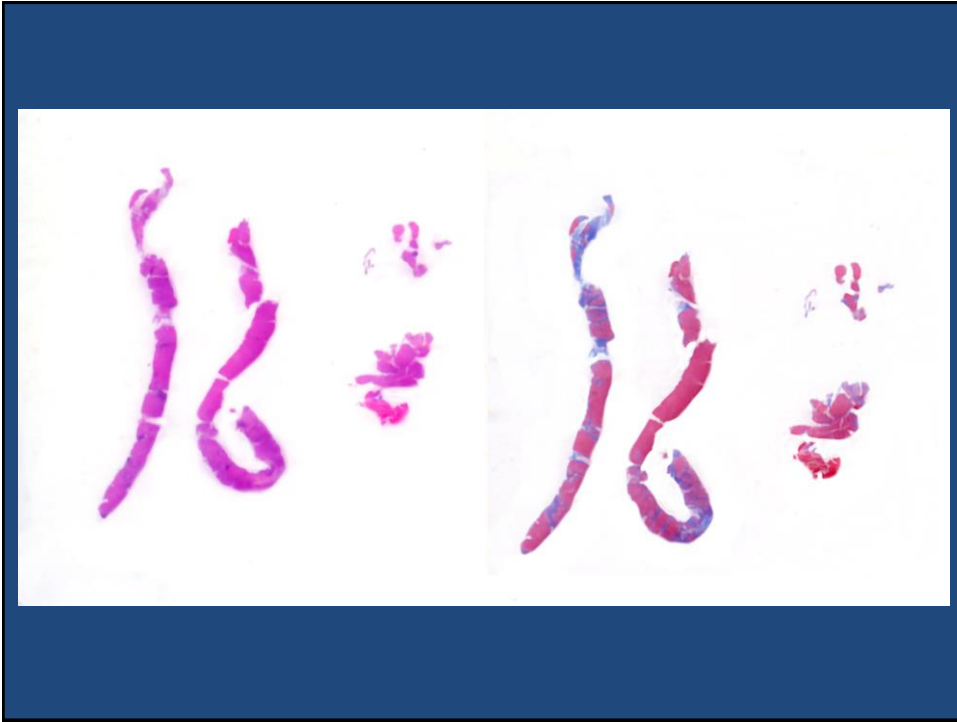
	Hepatocellular	Not hepatocellular
Benign		Features of malignancy • Characteristic histologic features •
Malignant		

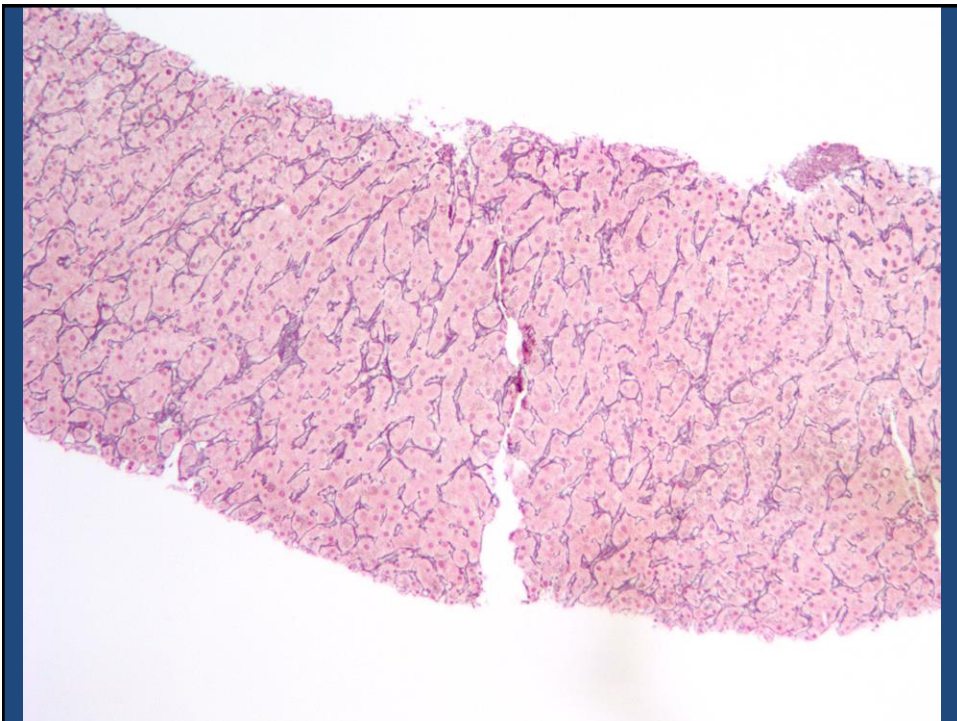
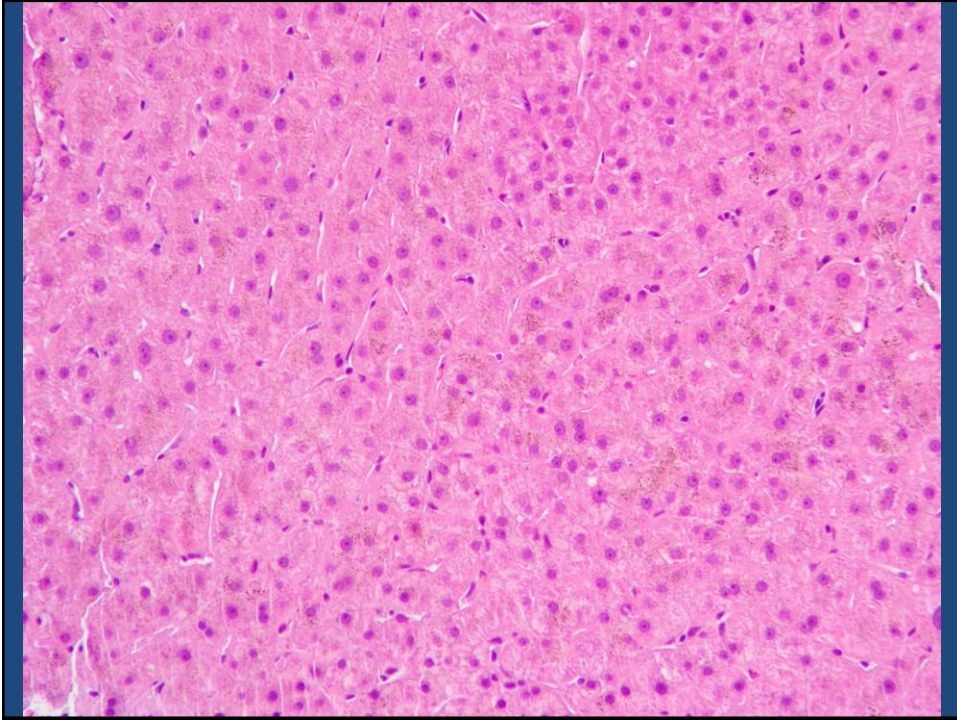
Lesion composed of large eosinophilic cells

	Hepatocellular	Not hepatocellular
Benign		
Malignant	<ul style="list-style-type: none"> • Reticulin stain • CD34 stain 	<ul style="list-style-type: none"> • Features of malignancy • Characteristic histologic features

Case 1

- 50 year old male
- Chronic hepatitis B
- Cirrhosis
- Liver mass



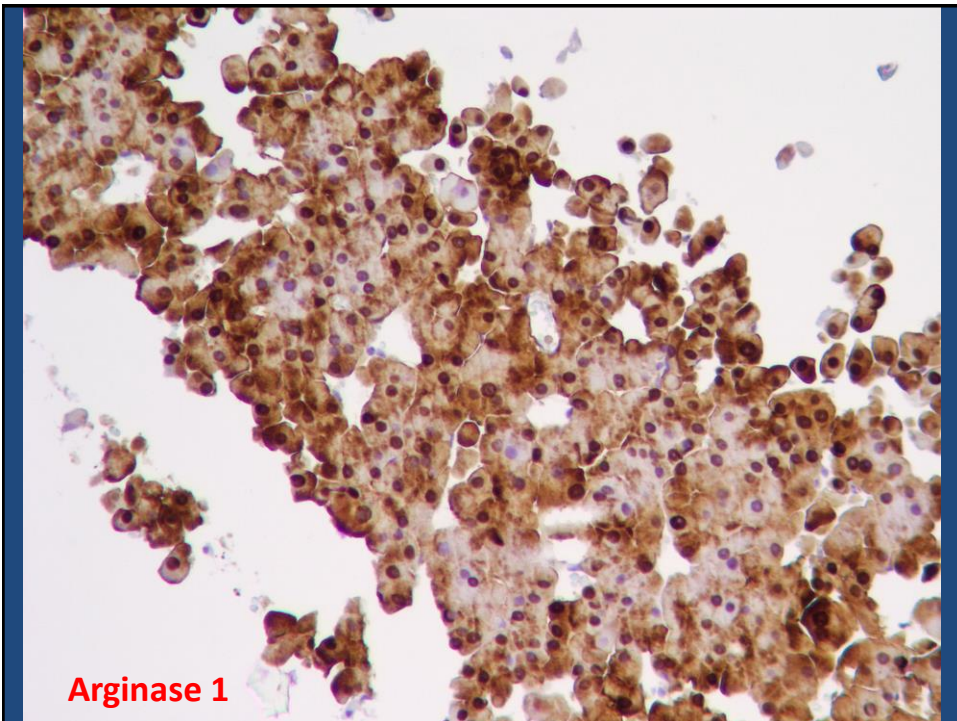
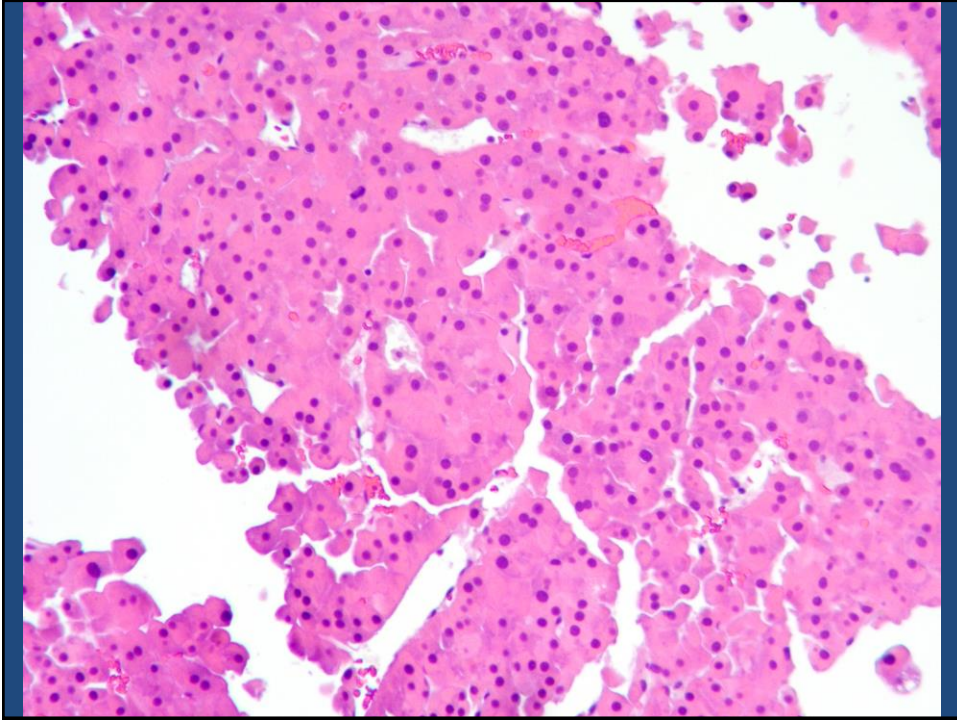


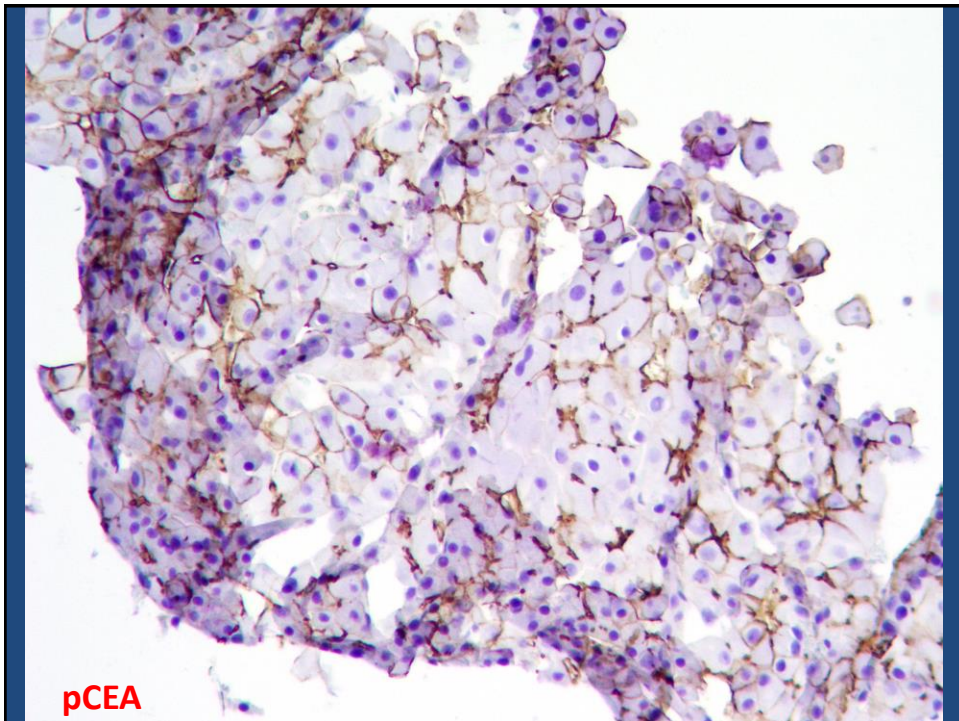
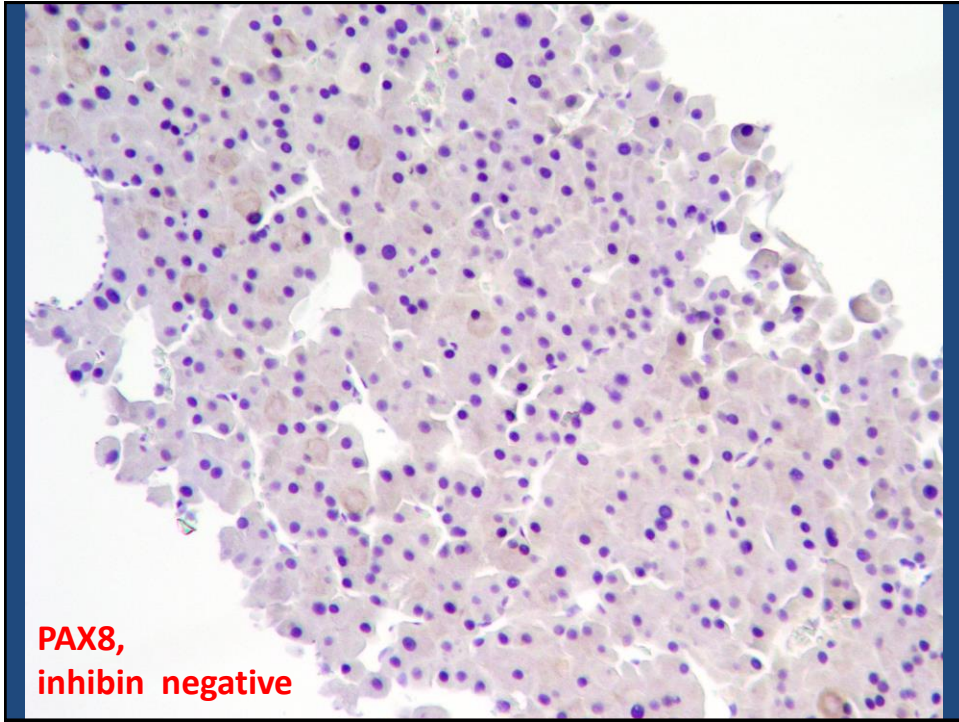
Benign regenerative nodule

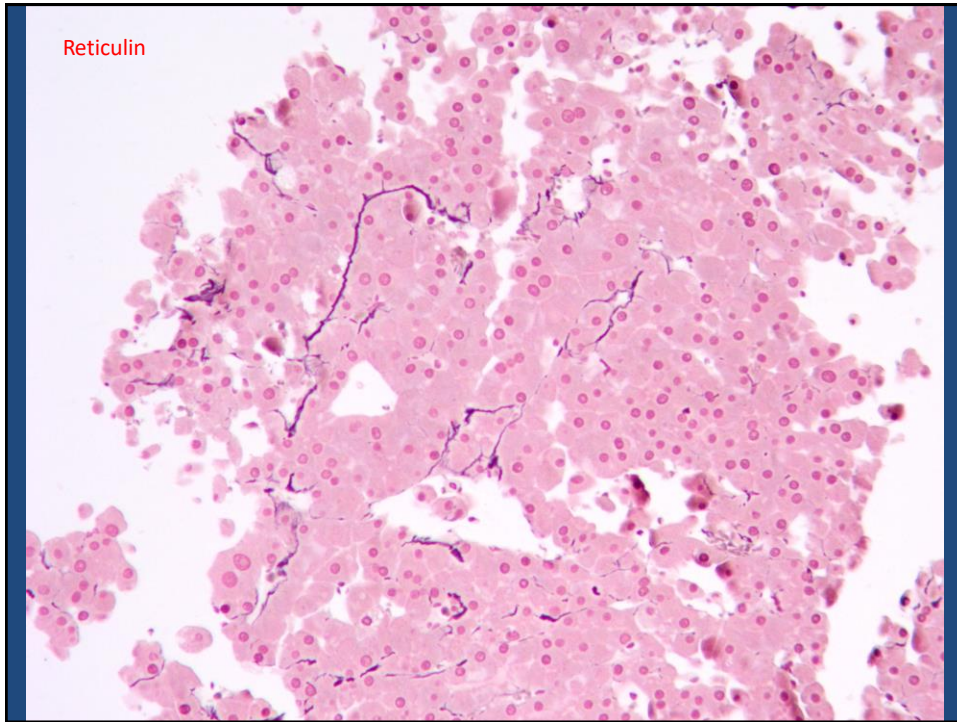
Reticulin: 1 to 2 cell thick plates

Case 2

- 75 year old male
- 18 cm mass in non-cirrhotic liver
- AFP 45
- Weight loss, fatigue, elevated LFTs for 2 months
- No h/o hepatitis
- Quit alcohol 10 years ago
- Quite smoking 10 years ago (never smoked heavily anyway)







Hepatocellular carcinoma

Positive: Arginase 1, pCEA

Negative: Inhibin, PAX8

Reticulin: Thickened plates

Intraductal bile duct lesions

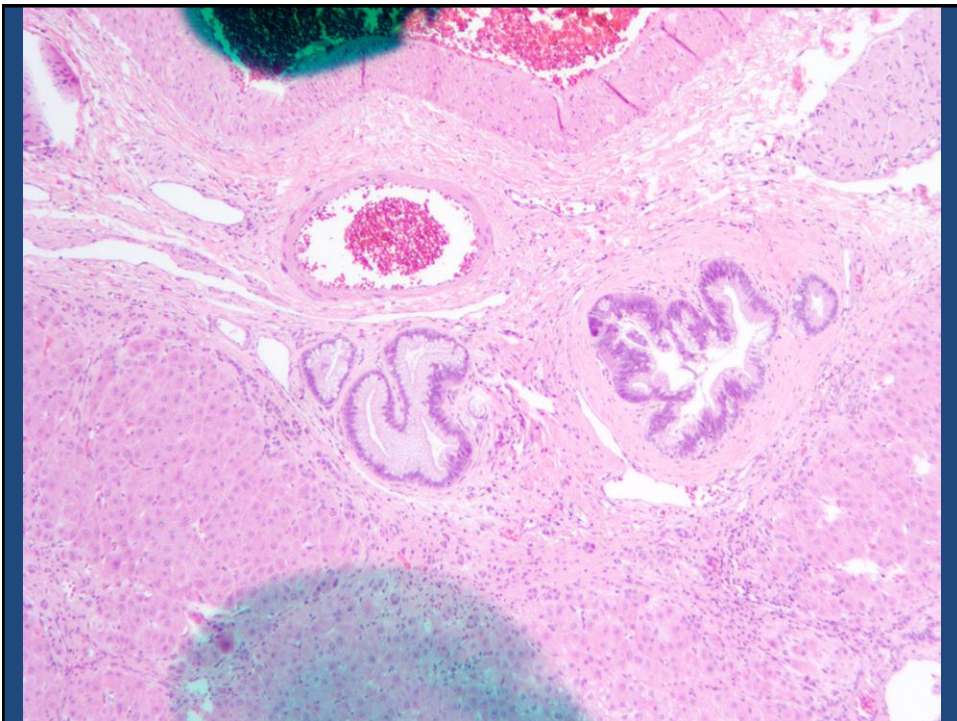
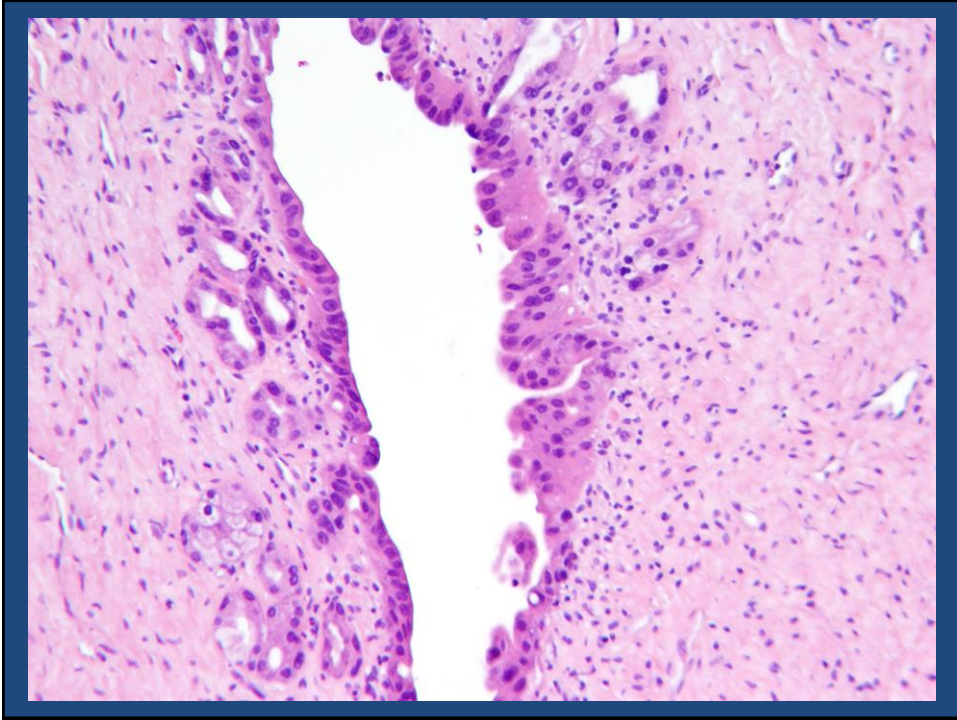
Non-invasive lesions

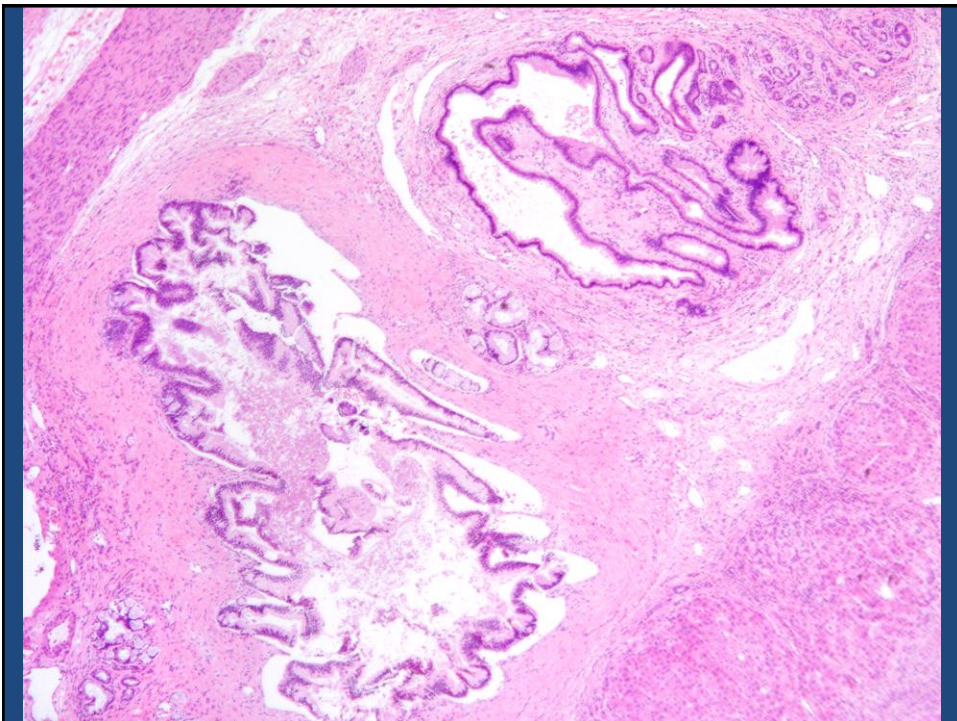
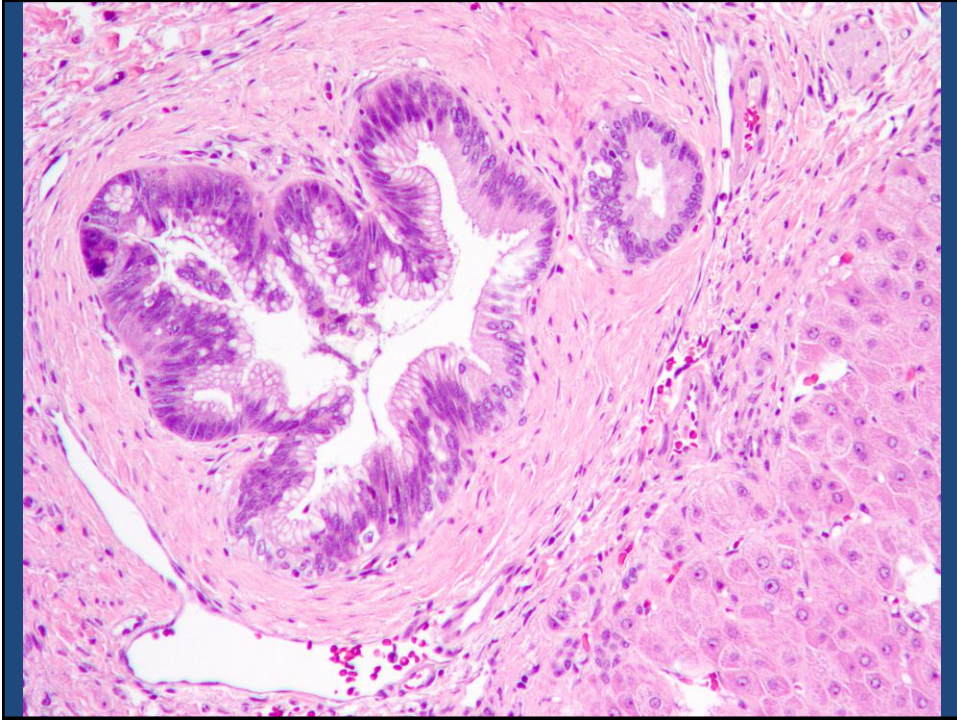
Pancreas	Liver – WHO 2010 terminology	Liver – former terminology
PanIN – Pancreatic intraepithelial neoplasia	Biliary intraepithelial neoplasia (BillIN)	Biliary dysplasia
IPMN – Intraductal papillary mucinous neoplasm	Intraductal papillary neoplasm of bile duct	Biliary papilloma(tosis)
MCN – Mucinous cystic neoplasm	Hepatic mucinous cystic neoplasm	Biliary cystadenoma

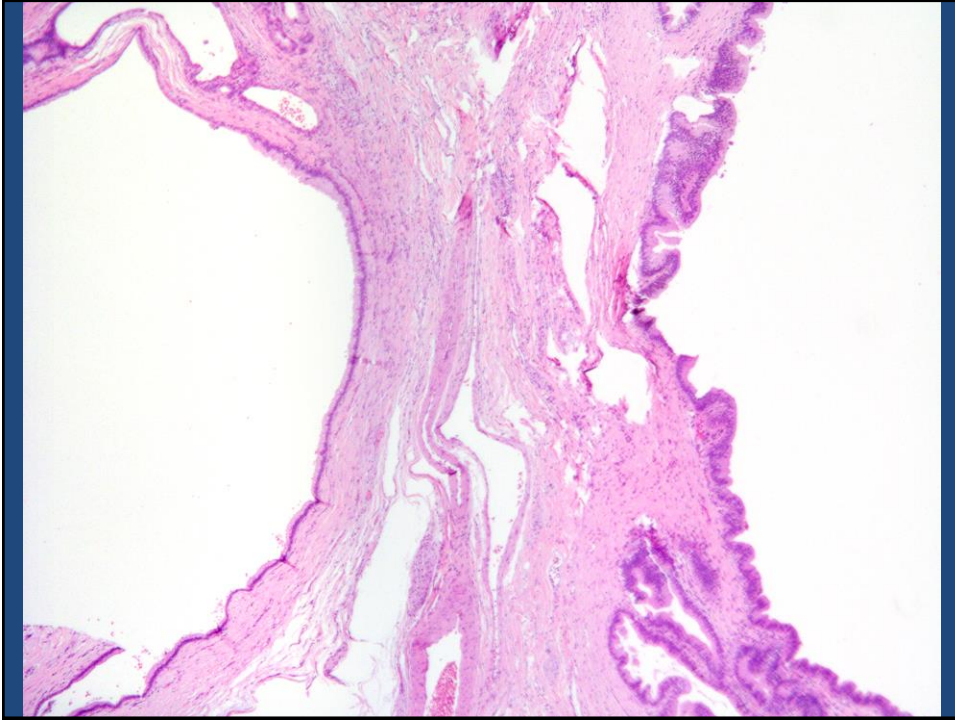
Invasive lesions

Pancreas	Liver – WHO 2010 terminology	Liver – former terminology
PanIN – Pancreatic intraepithelial neoplasia	Biliary intraepithelial neoplasia (BillIN)	Biliary dysplasia
IPMN – Intraductal papillary mucinous neoplasm	Intraductal papillary neoplasm of bile duct <i>with invasion</i>	Intraductal (papillary) cholangiocarcinoma, Biliary cystadenocarcinoma
MCN – Mucinous cystic neoplasm	Hepatic mucinous cystic neoplasm <i>with invasion</i>	Biliary cystadenocarcinoma

Biliary intraepithelial neoplasia (BillIN)







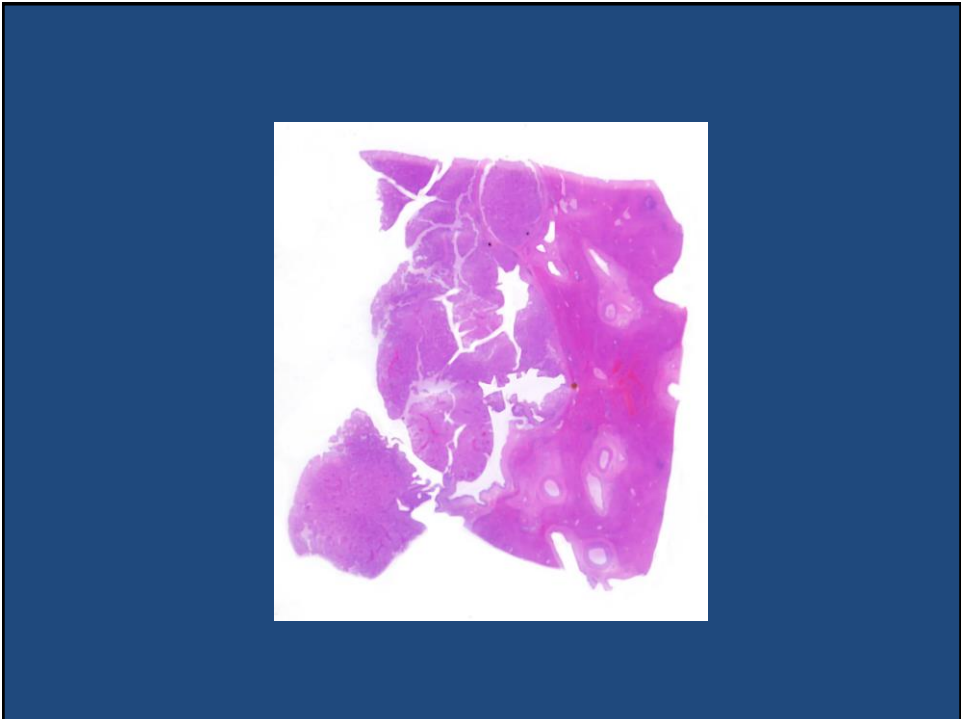
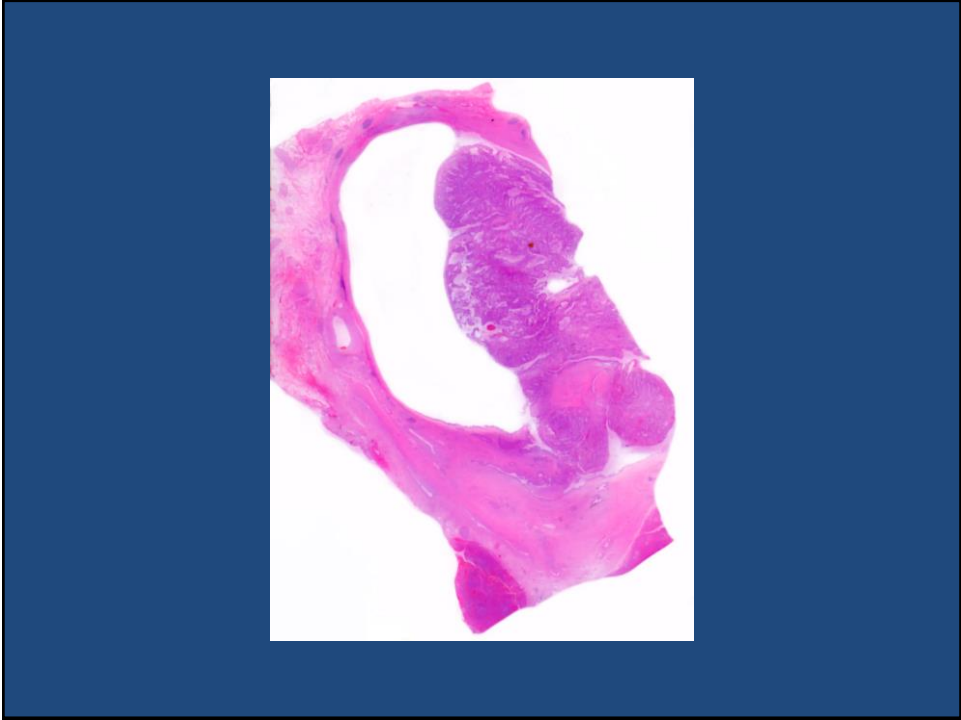
Biliary Intraepithelial Neoplasia (BilIN)

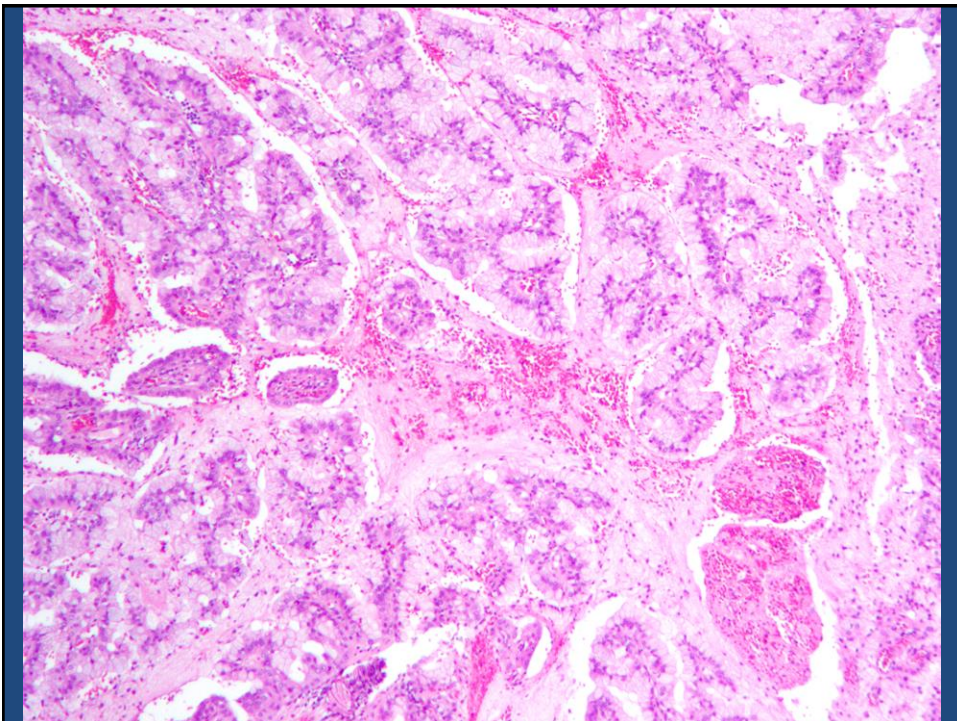
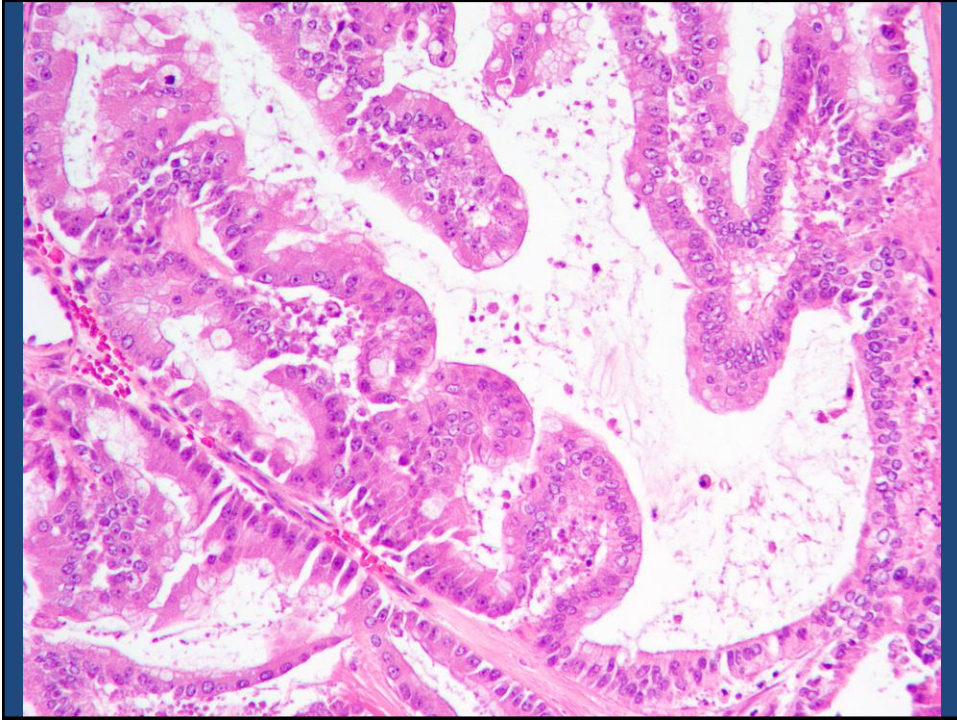
- Flat, premalignant intraepithelial lesion
- Field change, multiple foci
- Precursor lesion of cholangiocarcinoma
- Risk factors: hepatolithiasis, PSC, chronic liver fluke infection

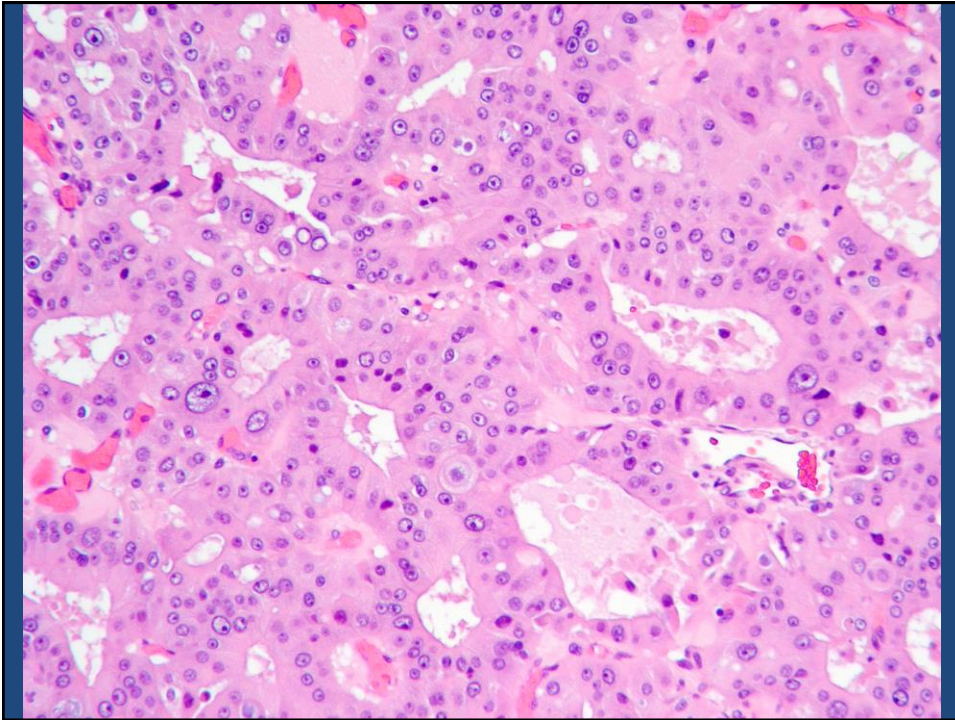
Microscopy

- Atypical intraepithelial proliferation
 - Multilayering of nuclei
 - Flat or micropapillary projections into duct lumen
- Graded as low, intermediate or high grade (BillIN 1,2,3)
- Foci of invasion may be seen

Intraductal papillary neoplasm of bile duct





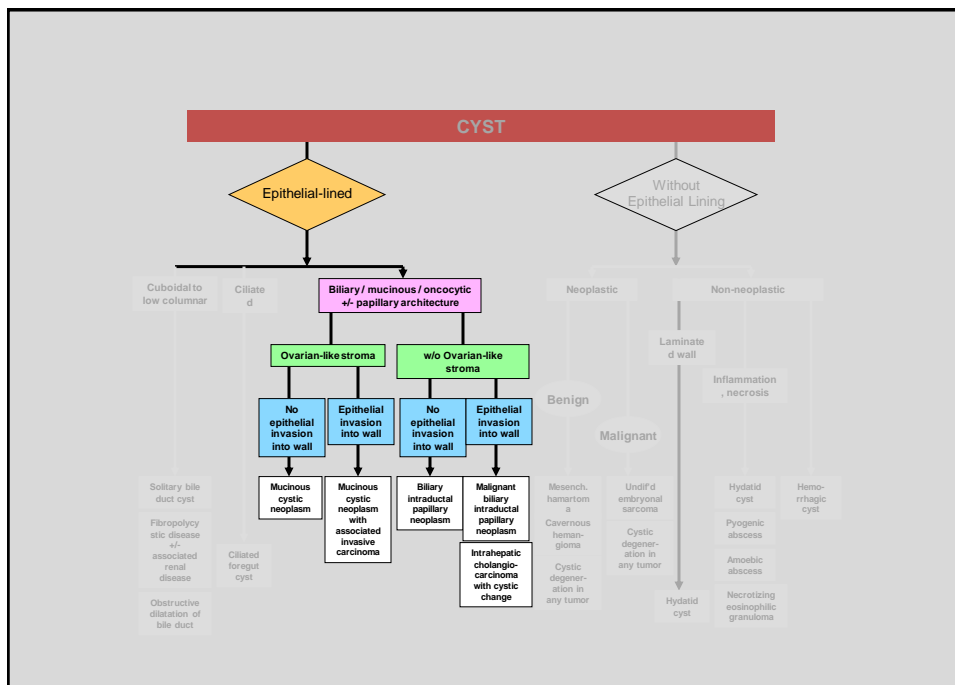


Intraductal Papillary Neoplasm of Bile Duct

- Grossly visible lesion
- Fusiform or cystically dilated bile ducts, or unilocular or multilocular cysts
- Single lesion, or multiple with skip areas
- Soft, friable intraductal papillary, villous, or polypoid lesion(s)
- Communicate with biliary system; may be difficult to demonstrate
- Mucin hypersecretion in 1/3 of cases

Intraductal Papillary Neoplasm of Bile Duct

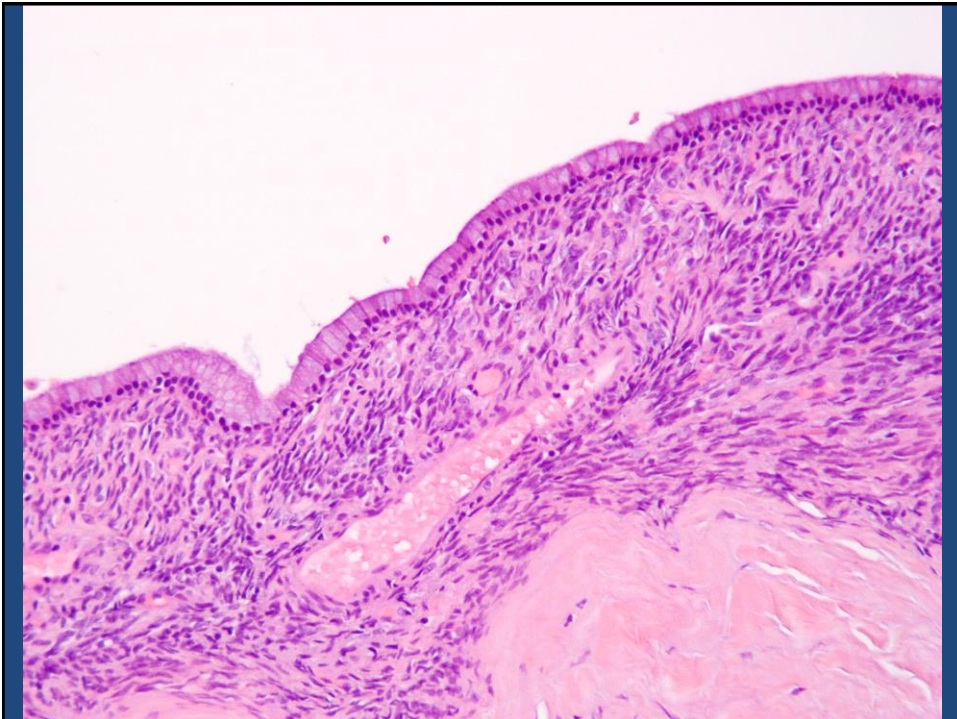
- Lining epithelium: pancreatobiliary, gastric, intestinal, oncocytic
- Dysplasia graded as low, intermediate, high
- Preinvasive neoplasm, may progress to invasive carcinoma
 - Usually tubular adenocarcinoma, less frequently mucinous (colloid) adenocarcinoma
 - WHO 2010 term: Intraductal papillary biliary neoplasia *with invasion or with invasive carcinoma*
 - has been variously called intraductal papillary cholangiocarcinoma, biliary papillomatosis, biliary papilloma, mucin-secreting biliary tumor, intraductal papillary mucinous tumor

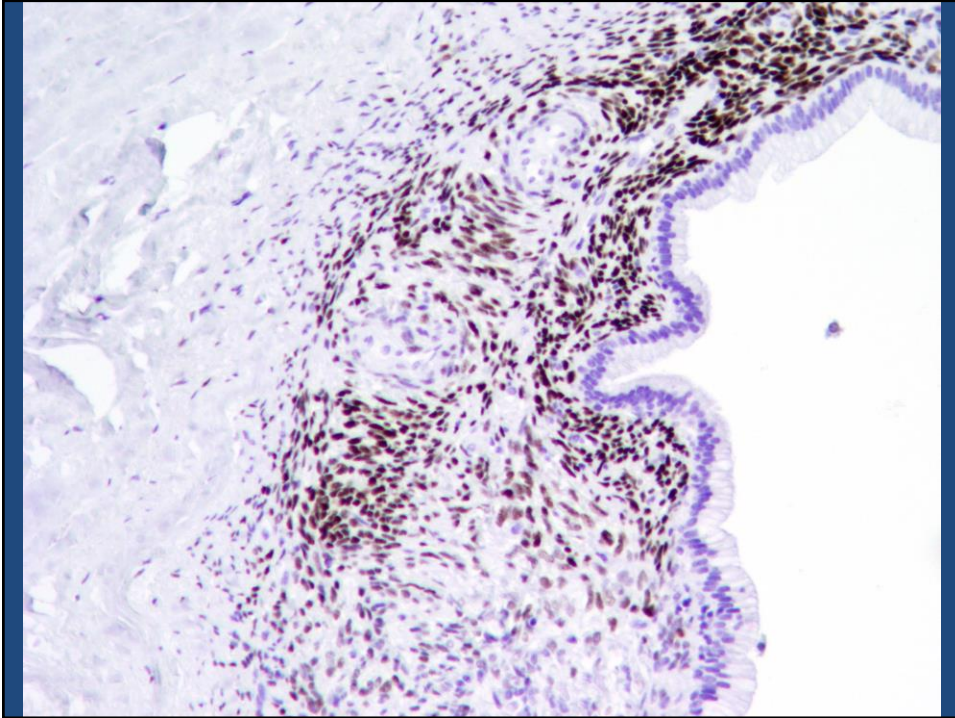


Courtesy ND Theise, MD, NYU

Adapted from Saxena et al. Diagnostic Algorithms for Tumors of the Liver. In: WHO Classification of Tumors of Digestive Diseases 4th ed. 2010, p 259

Hepatic mucinous cystic neoplasm





Hepatic Mucinous Cystic Neoplasm

- Occurs exclusively in women
- Grossly visible cyst
 - Unilocular or multilocular
 - No communication to biliary system
- Epithelium: single layer or stratified
- Ovarian stroma
 - Positive for ER, PR and inhibin
- Benign
 - Rare reports in literature of malignant lesions
 - MCN *with invasion* or *with invasive carcinoma*
 - Formerly, biliary cystadenocarcinoma

Hybrids

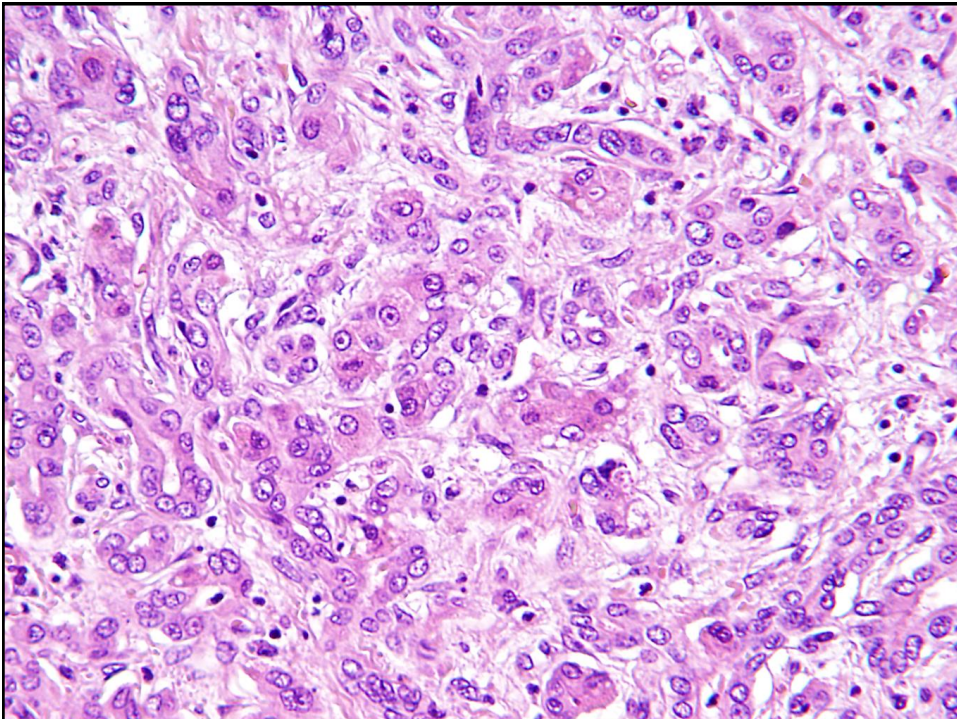
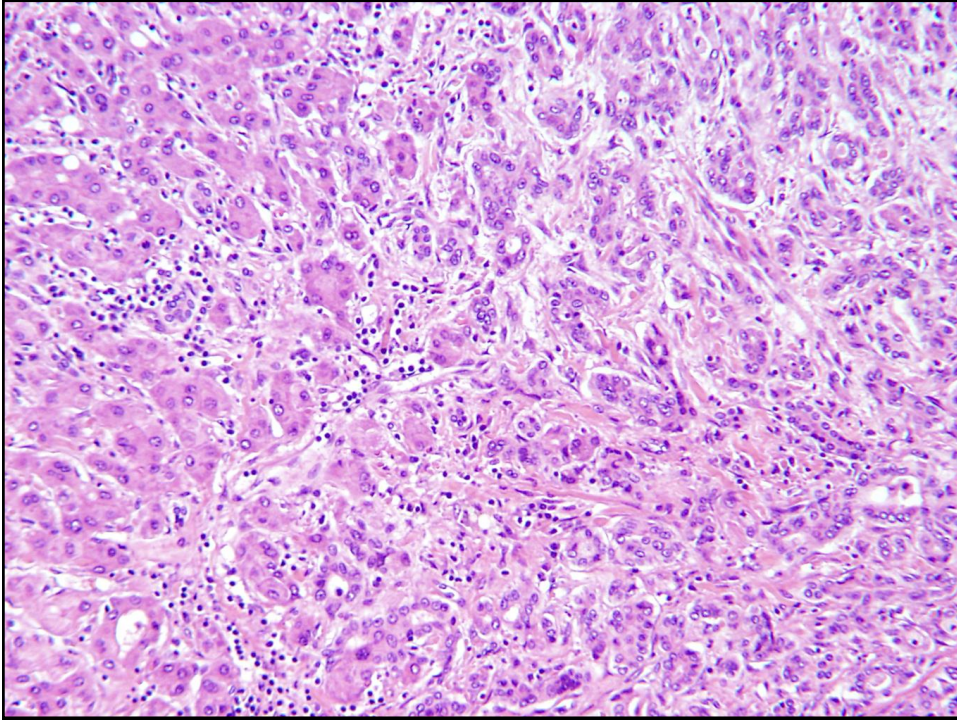


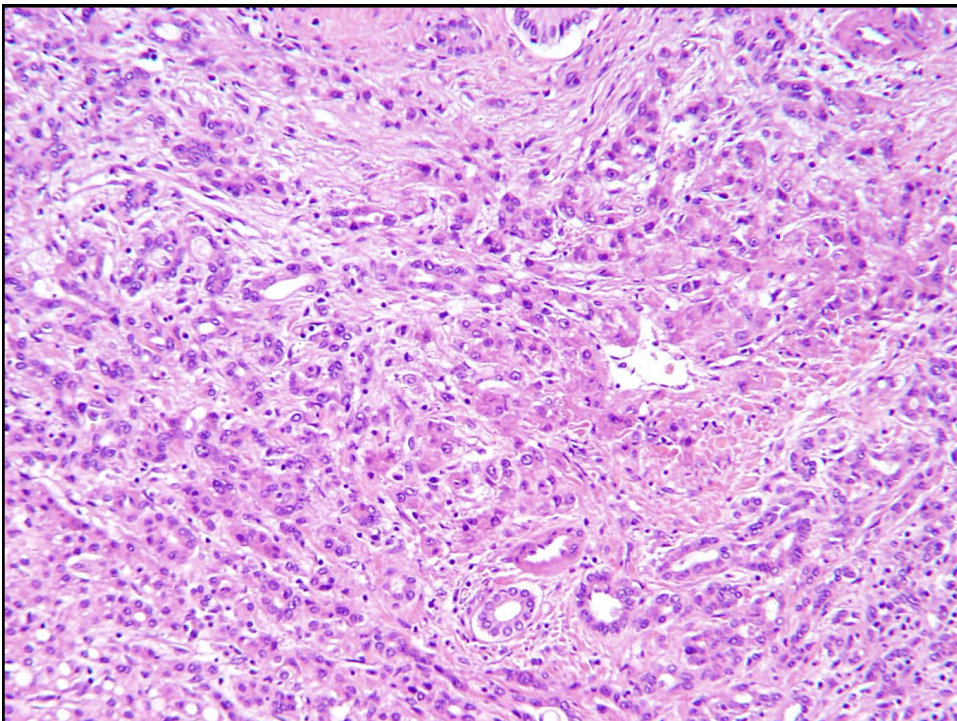
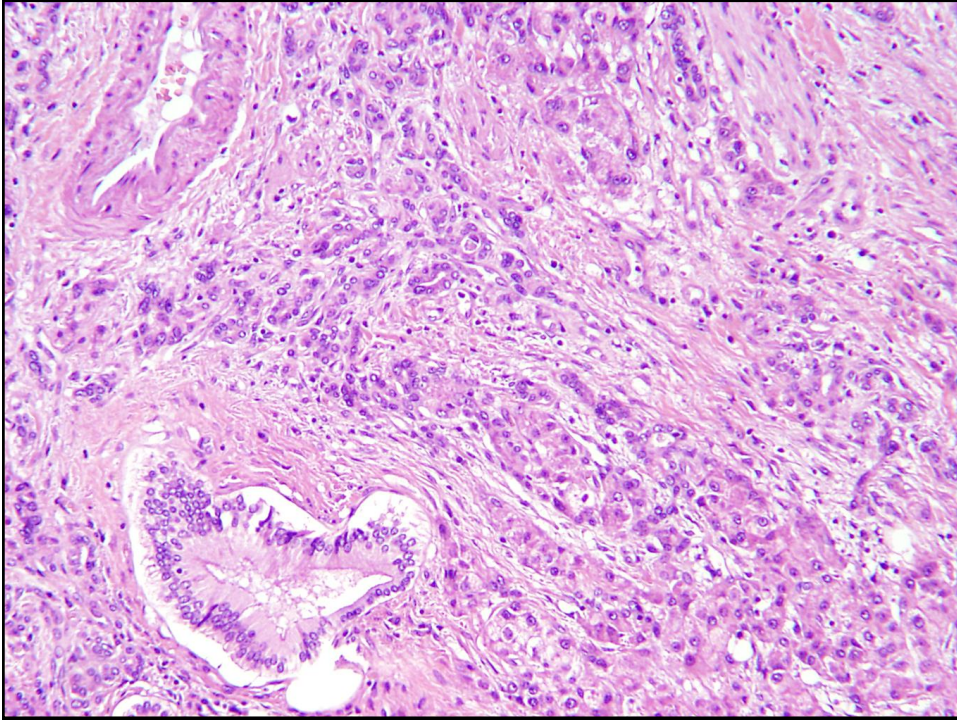
- Tumors that **do not** subscribe to a dichotomous paradigm of differentiation, i.e. hepatocellular **OR** cholangiocytic
- Demonstrate
 - biphenotypic differentiation, or
 - stem/progenitor cell like features, or
 - other variant patterns of differentiation
- ? Trans-differentiation of malignant cells
- ? Origin from stem/progenitor cells with divergent differentiation along variable pathways

- Appropriate nomenclature, diagnostic criteria, prognostic significance and optimal therapeutic approach not completely defined due to lack of large series
 - Not always identified correctly
 - Lack of uniform terminology

Case 1

- 57 year old female
 - cirrhosis and chronic hepatitis C, genotype 1a
- Surveillance : Liver mass
- Dual phase CT with contrast: 3 hypervascular lesions, largest 1.8 cm nodule
- AFP 29.2ng/mL (normal 25 ng/mL)
- Transplanted
- 11 years follow-up, no recurrence of malignancy

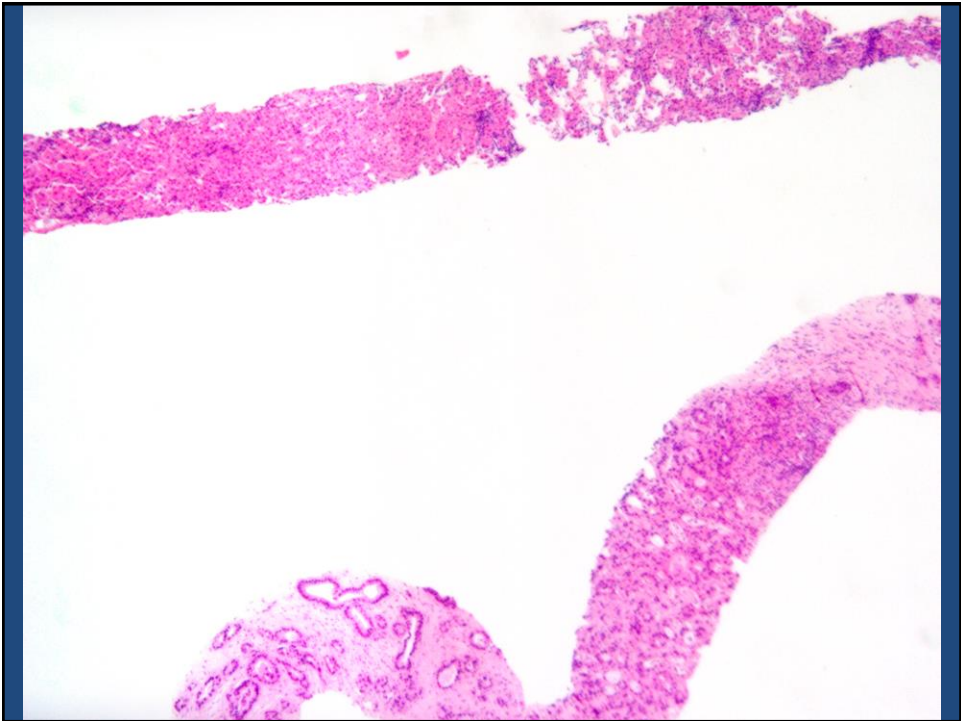
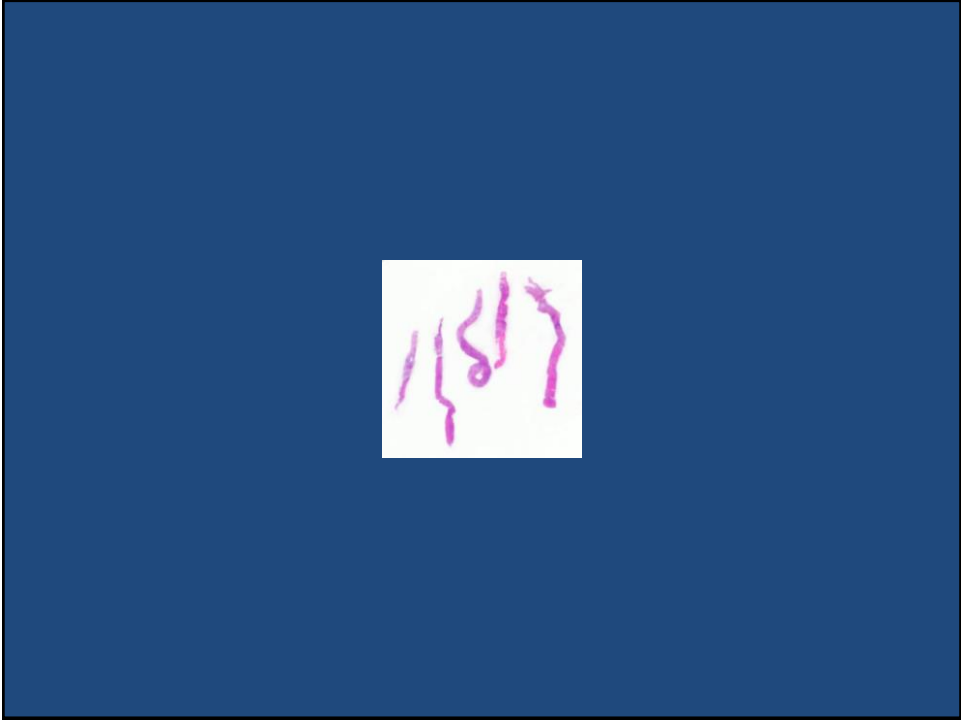


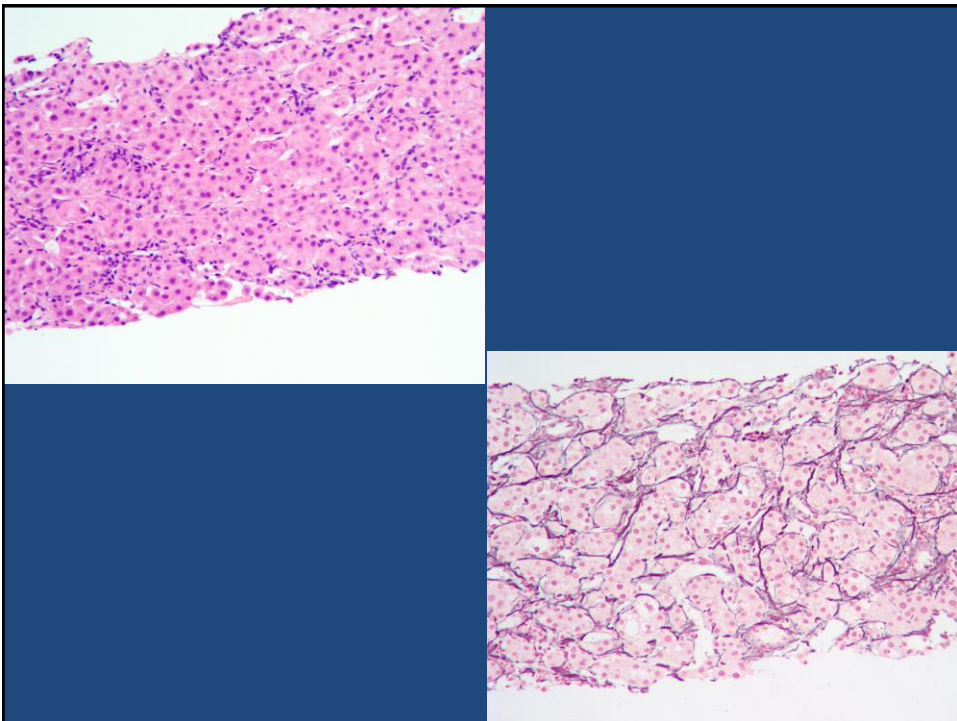
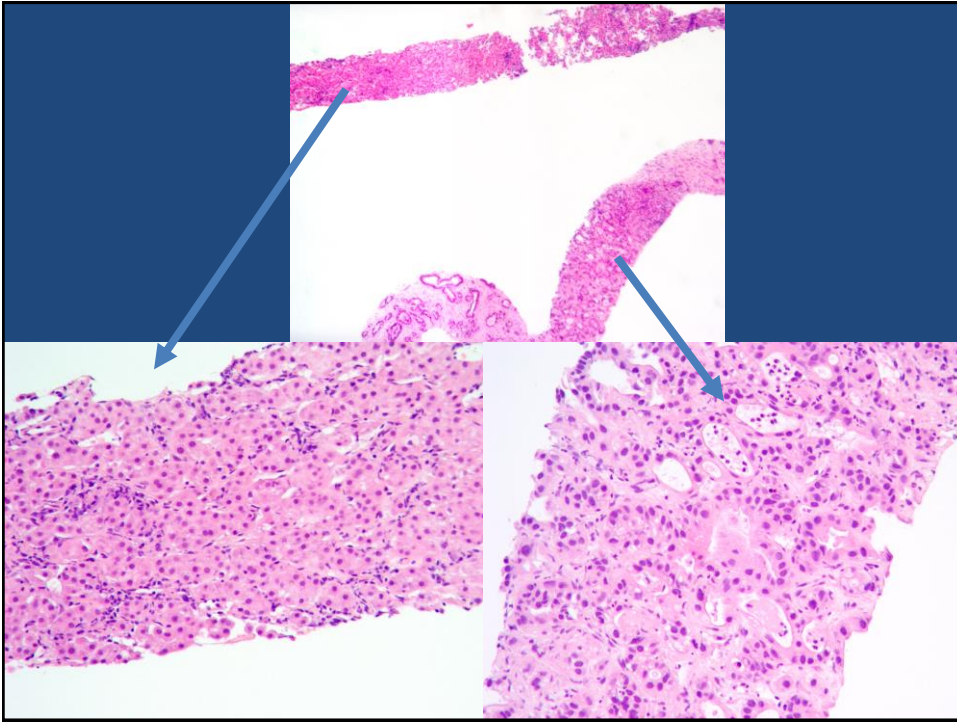


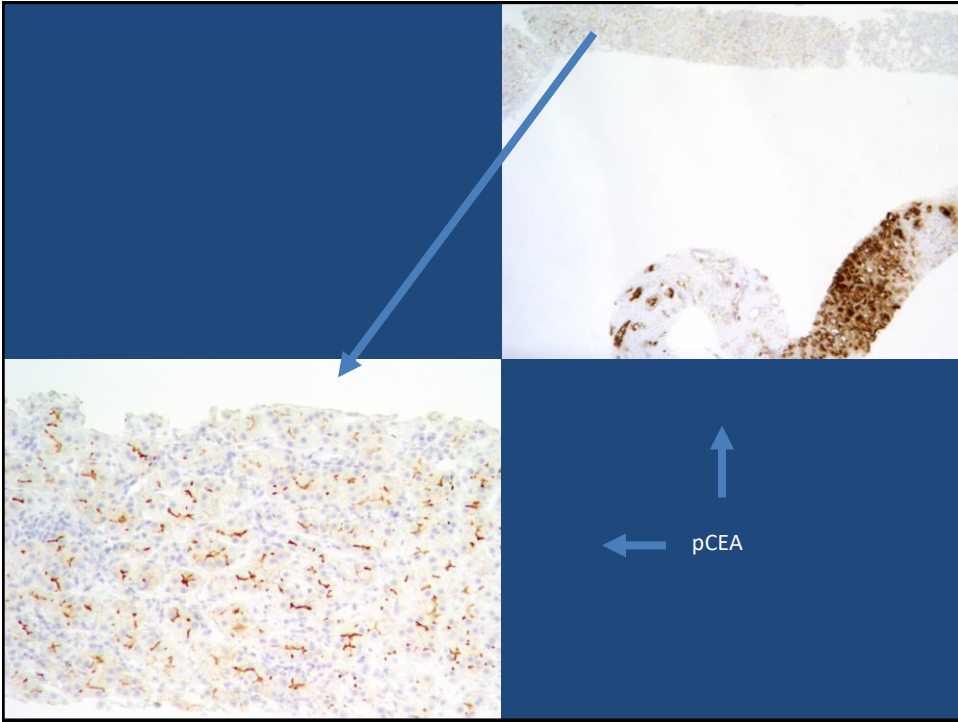
Combined hepatocellular- cholangiocarcinoma (cHCC-CCA)

Case 2

- 74 year old female
- History of liver cirrhosis, right lobe lesion, r/o HCC







Combined hepatocellular-
cholangiocarcinoma
(cHCC-CCA)

Tumor of many names

- Combined HCC-CC
- Mixed HCC-CC
- HCC with dual (hepatocellular/biliary) phenotype
- Primary hepatic carcinoma of intermediate (hepatocyte/ cholangiocyte) phenotype
- Mixed hepatobiliary carcinoma
- Hepato-cholangiocarcinoma
- Biphenotypic primary liver carcinoma

Clinical Features

- Slightly more common in men, 50–70 years of age
- Clinical features similar to other primary liver carcinomas
- Occur in background of chronic liver disease
- Particularly frequent after neo-adjuvant therapy

Clinical Features

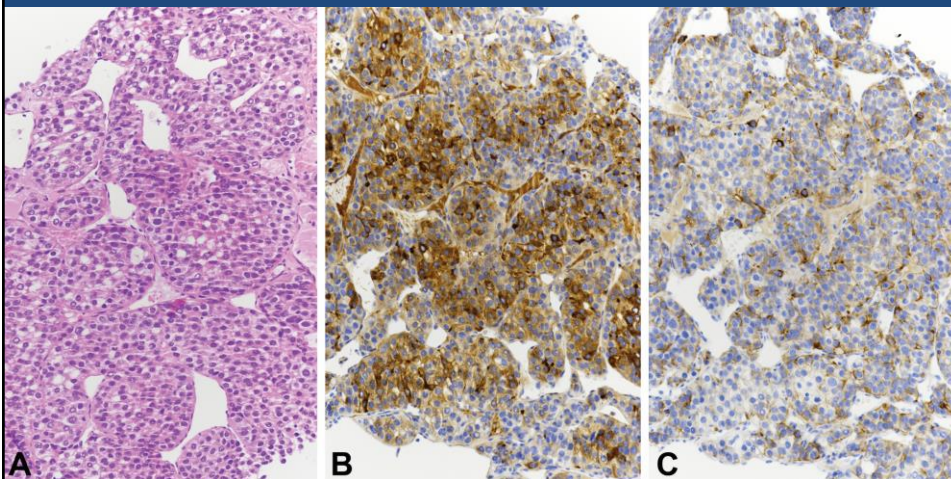
- Variable elevation of serum markers (AFP, CA19-9, CEA)
- Imaging: features of HCC or CC
 - most commonly mimics CC or metastases
- Propensity to invade portal vein as well as regional lymph nodes
- Prognosis intermediate between HCC and CC

Diagnosis

- Suspect combined hepatocellular-cholangiocarcinoma *when*
 - simultaneous elevation of AFP and CA19-9
 - discordance between serum tumor markers and radiologic findings
- Treatment: complete surgical resection + regional lymph node dissection
 - Frozen section recommended for all atypical HCC so that patient may benefit from LN dissection if tumor is combined cHCC-CC

Case 3

- 23 year old woman, pain right lower thorax
- Imaging: multiple hypervascular nodules in liver
 - Largest 7.5 cm, wash-out in portal phase.
- Serum AFP markedly elevated 42,720 IU/l
- Hepatitis B surface antigen +ve, most probably vertical transmission



AFP

CK19

Courtesy: Valerie Paradis, Beaujon Hospital Inserm, Clichy, France

Hepatocellular carcinoma with K19 positivity

HCC with K19 expression

- One third of HCCs express biliary markers, K7 & K19
- K19 expression in >5% of cells
 - higher incidence of vascular invasion
 - higher rate of recurrence after transplantation, TACE, resection
- HCCs that express CC-like and embryonic stem cell gene signatures show shorter recurrence free and overall survival*
 - Enriched genes included K19 and EpCAM

* Woo HG et al. *Cancer Res* 2010;70:3034–3041

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