

Neoplasms of the Canine, Feline and Lemur Liver: Classification and Prognosis

**Annual Seminar of the French Society of Veterinary
Pathology**



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North Carolina State University

Primary Hepatic Neoplasia

Hepatocellular

Hepatocellular adenoma

Hepatocellular carcinoma

Mixed hepatocellular and cholangiocellular carcinoma

Biliary

Cholangiocellular adenoma
(Biliary adenoma)

Cholangiocellular carcinoma
(Biliary CA)


Others

Hemangiosarcoma

Carcinoids

Hepatoblastoma

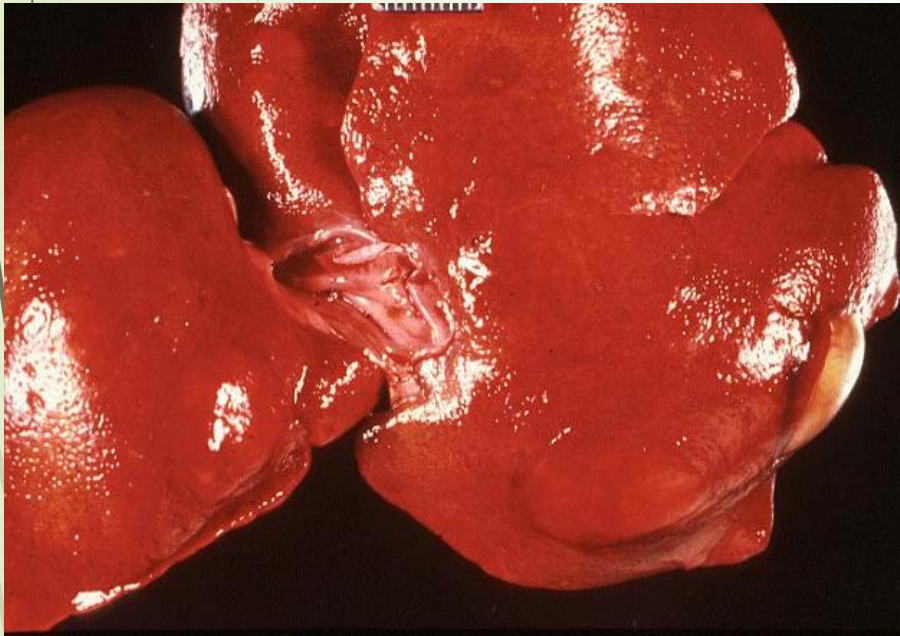
Myelolipoma



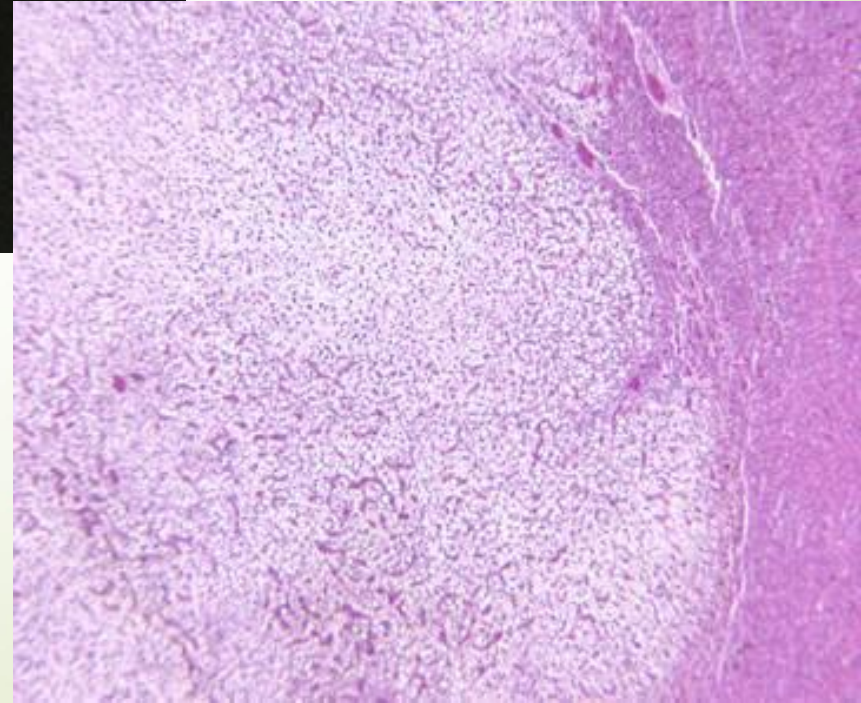
Non-neoplastic Proliferative Lesions

- Nodular hyperplasia
 - Age-related (start at 6 years)
 - Solitary yellow to dark red masses
 - Liver otherwise normal
 - Lobular architecture retained
 - No clinical significance

Nodular Hyperplasia



Nodular Hyperplasia

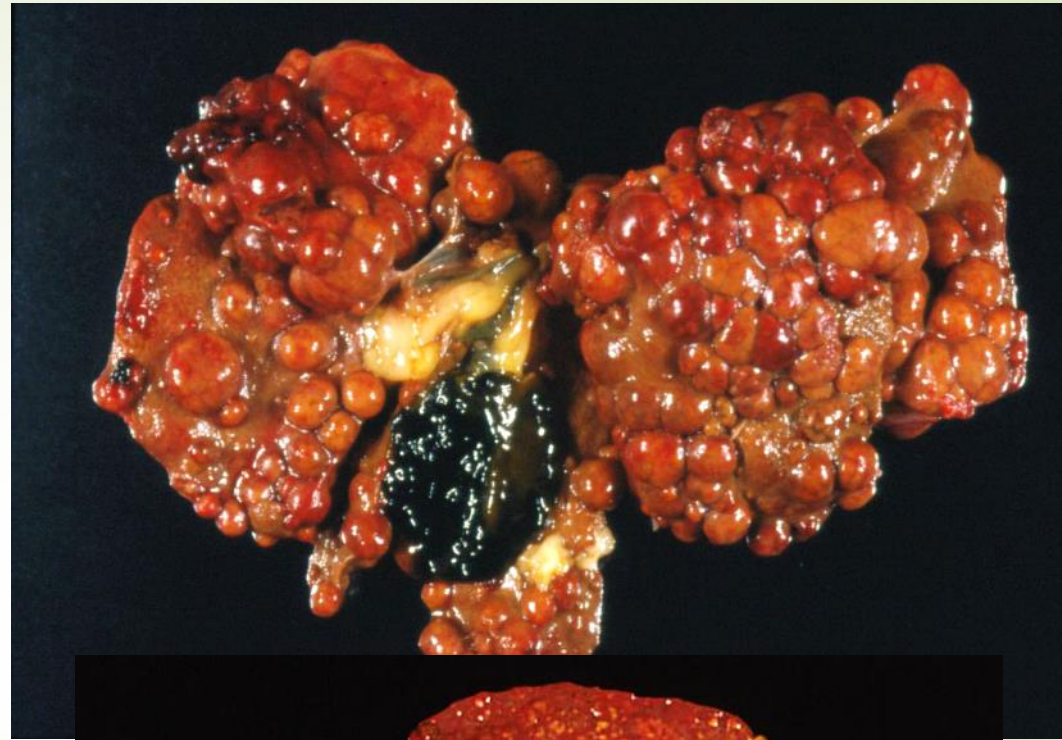


Regenerative Nodules

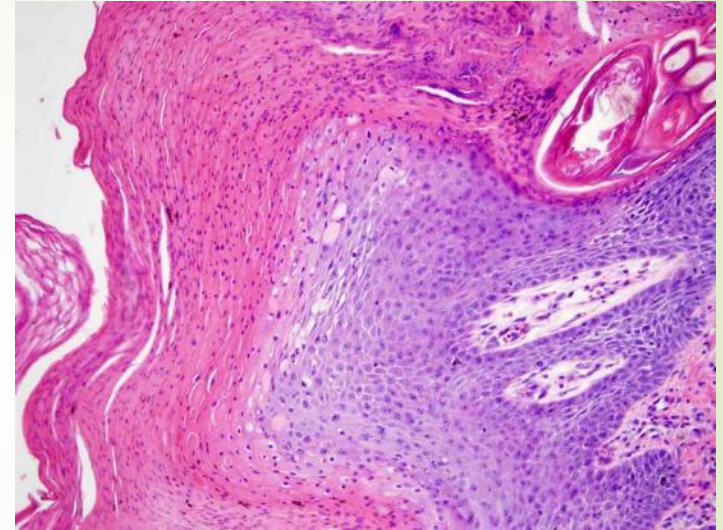
Multiple Nodules

Non-neoplastic:
Regenerative Nodules
Nodular Hyperplasia

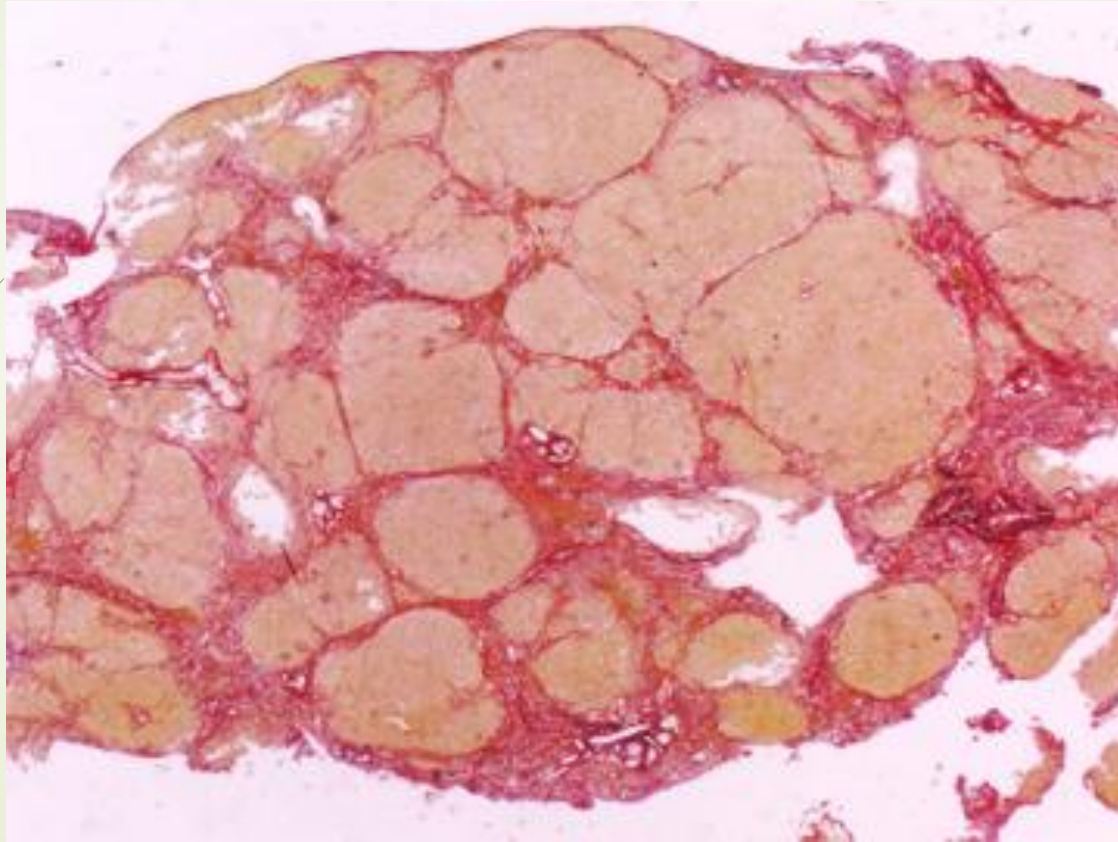
Metastasis
Biliary CA
Hepatocellular CA
Carcinoids



Hepatocutaneous Disease



Regenerative nodule



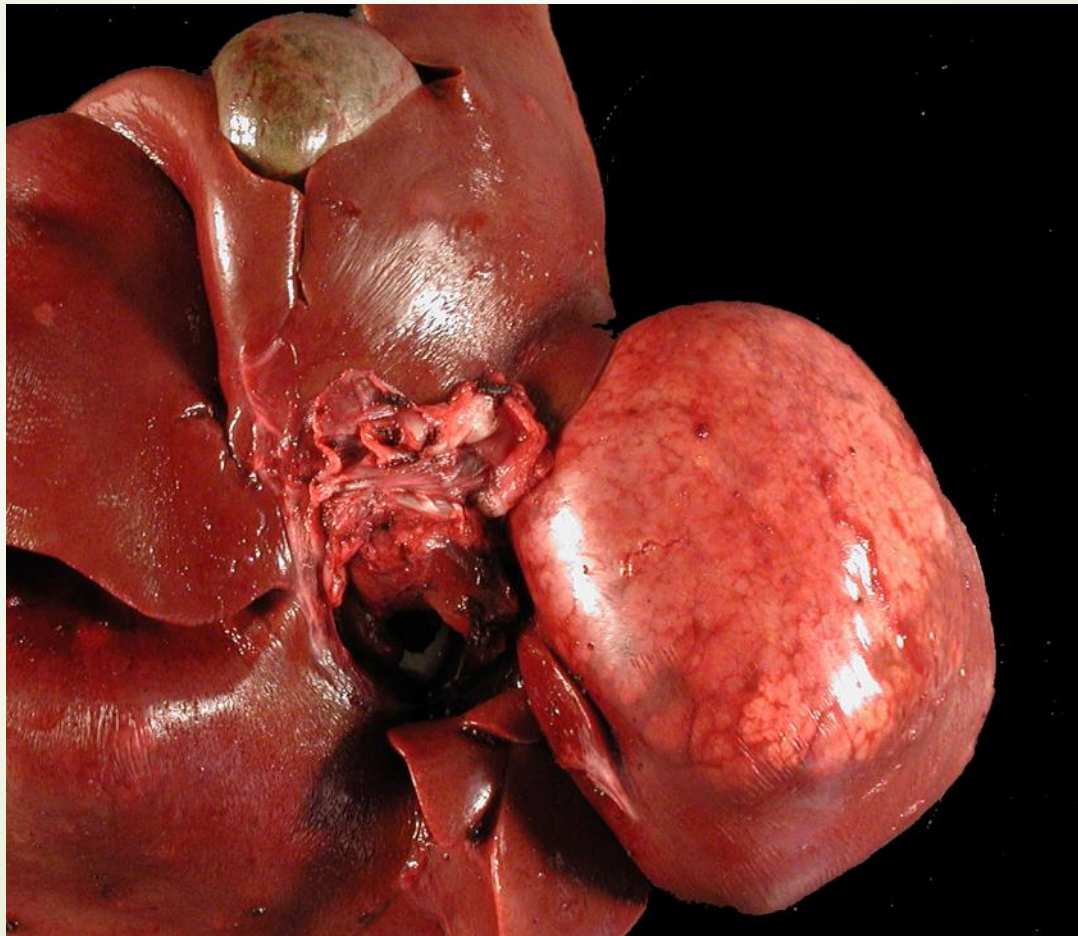
Sirius red



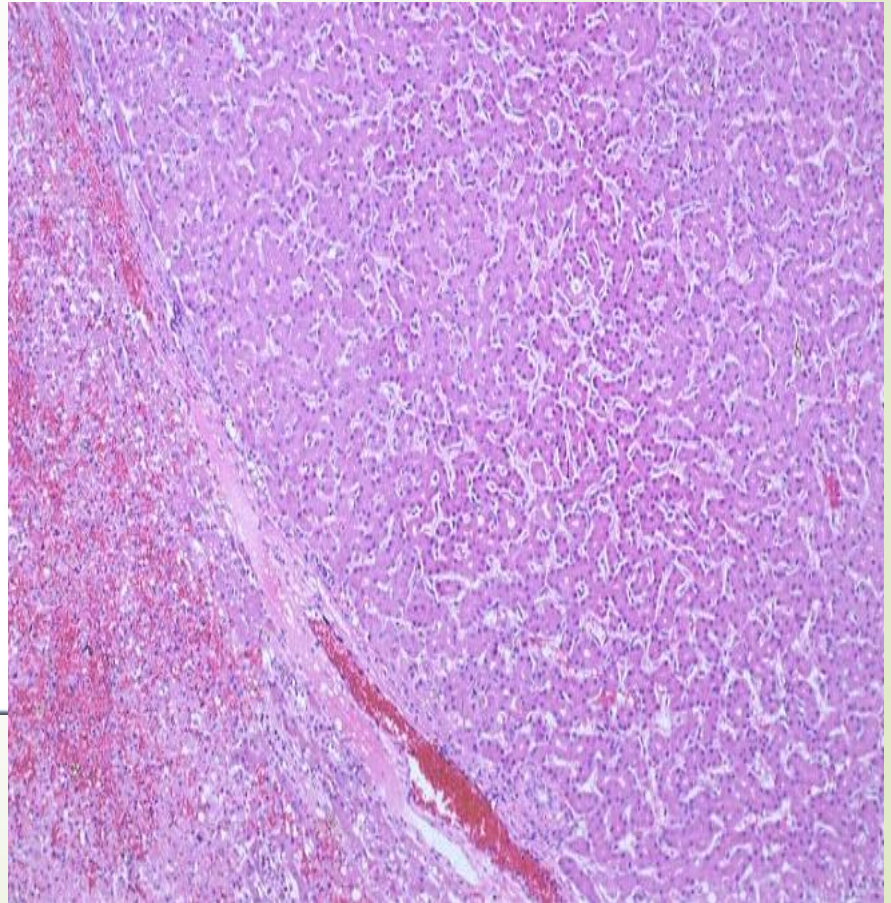
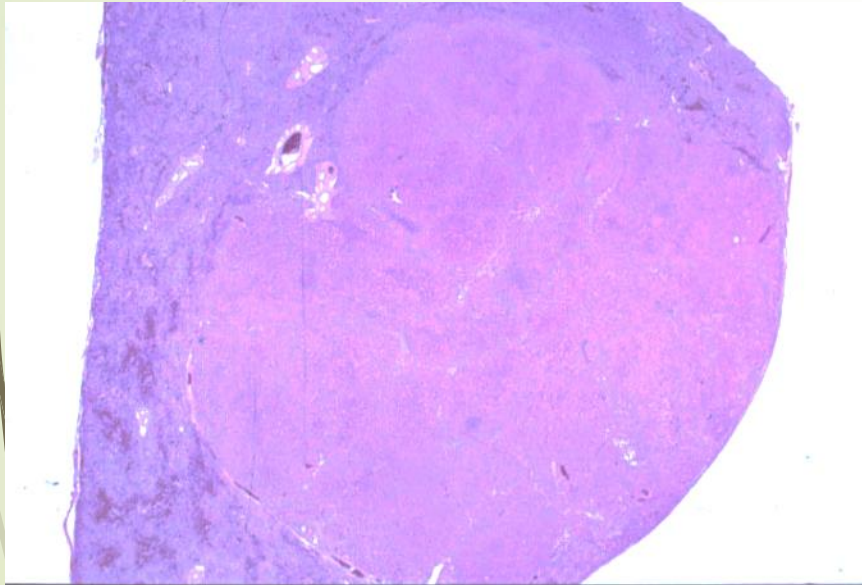
Hepatic Neoplasia: Hepatocellular adenoma

- Usually solitary
- Common
- Loss of lobular architecture
- Trabeculae uniform
- Some necrosis possible

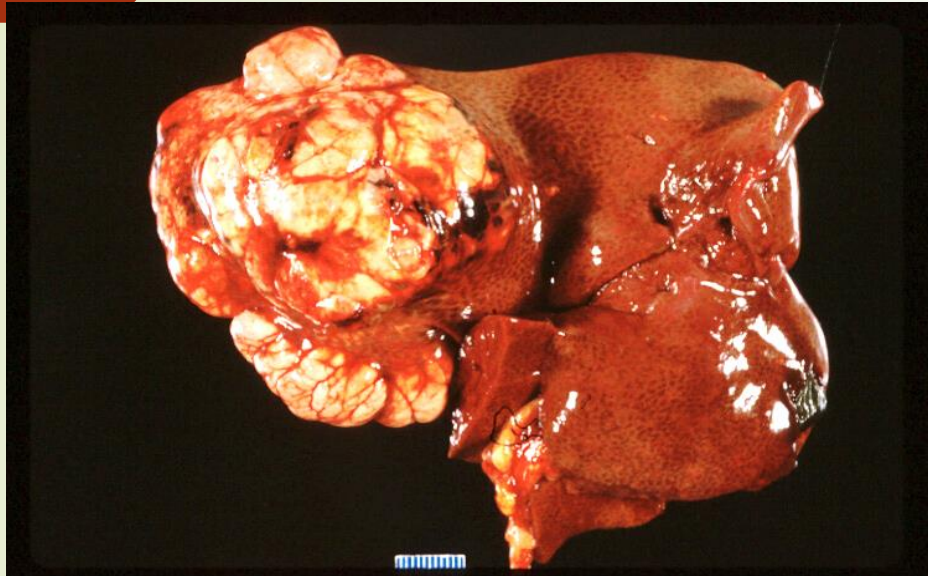
Hepatic Adenoma



Hepatic Adenoma



Hepatocellular carcinoma

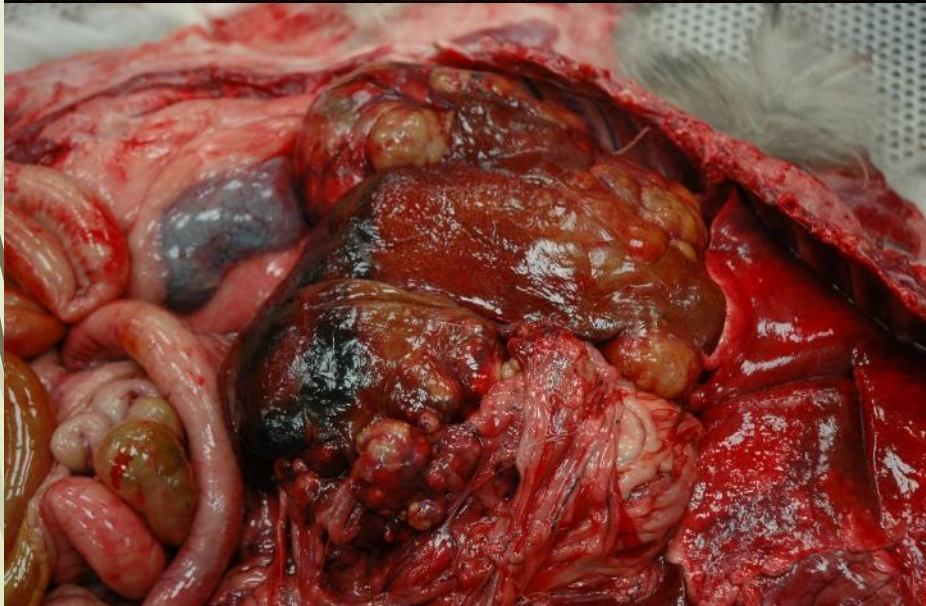


Uncommon in domestic species

Friable gray-yellow to red
Single nodule or multinodular

Necrosis

Metastasis uncommon generally



Hepatocellular Carcinoma

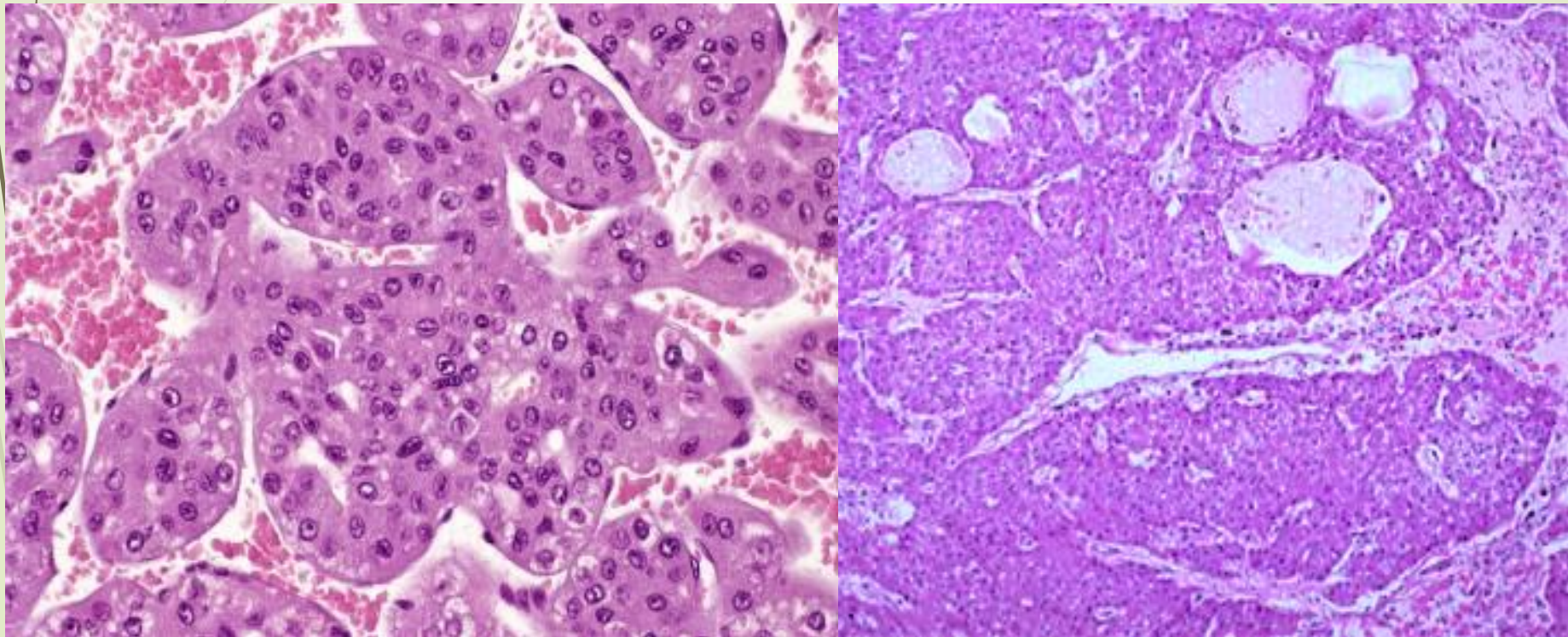
- Histologic Variants
 - Trabecular
 - Glandular
 - Solid
 - Clear Cell
- Often mixed forms
- No relationship between histologic appearance and behavior (one exception)



Hepatocellular Carcinoma

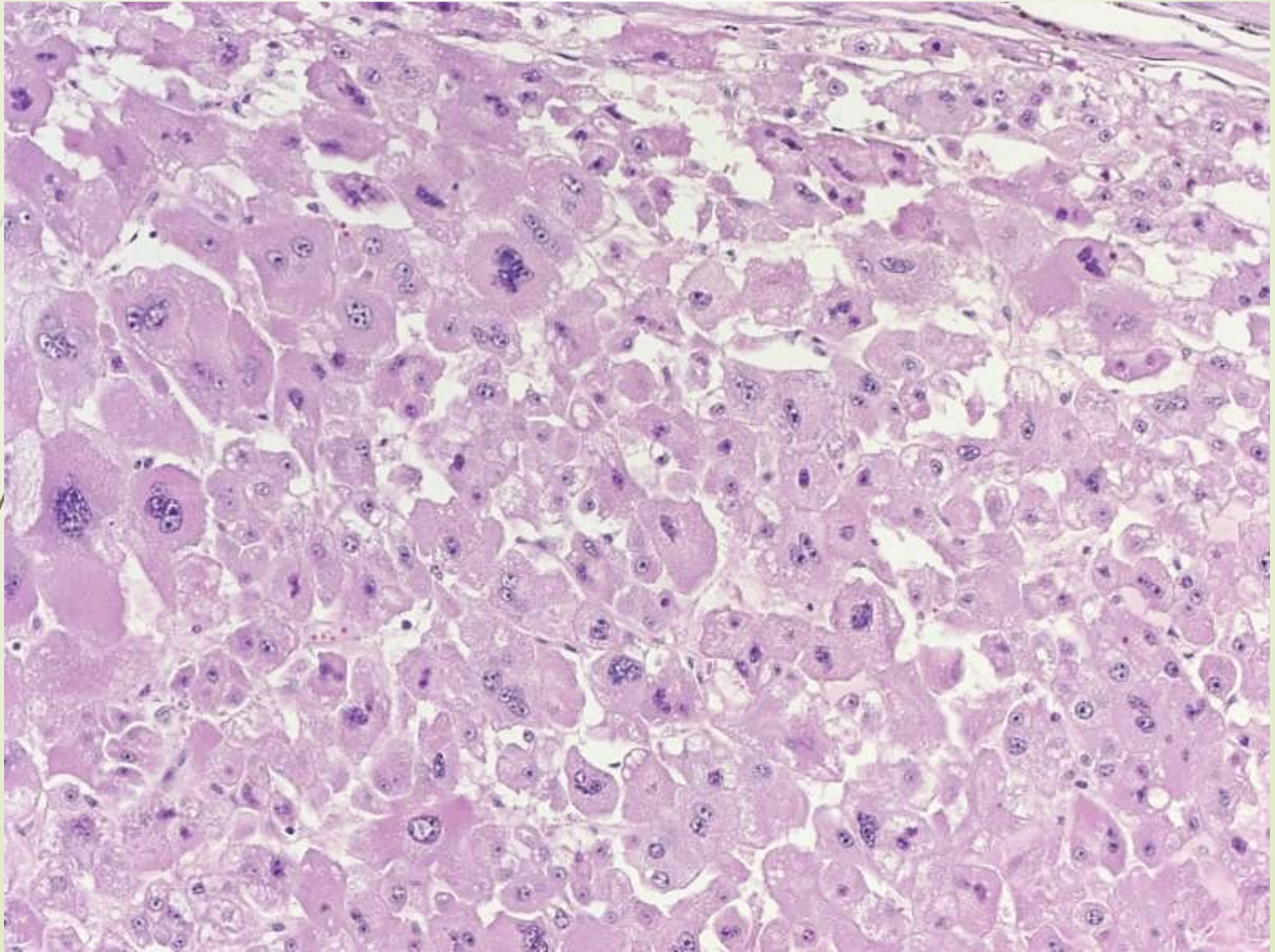
- **Key Features for Diagnosis of Malignancy**
 - Pleomorphism
 - Mitoses
 - Invasion
 - Local
 - Intravascular
 - IHC (K19)

Trabecular Hepatocellular Carcinoma

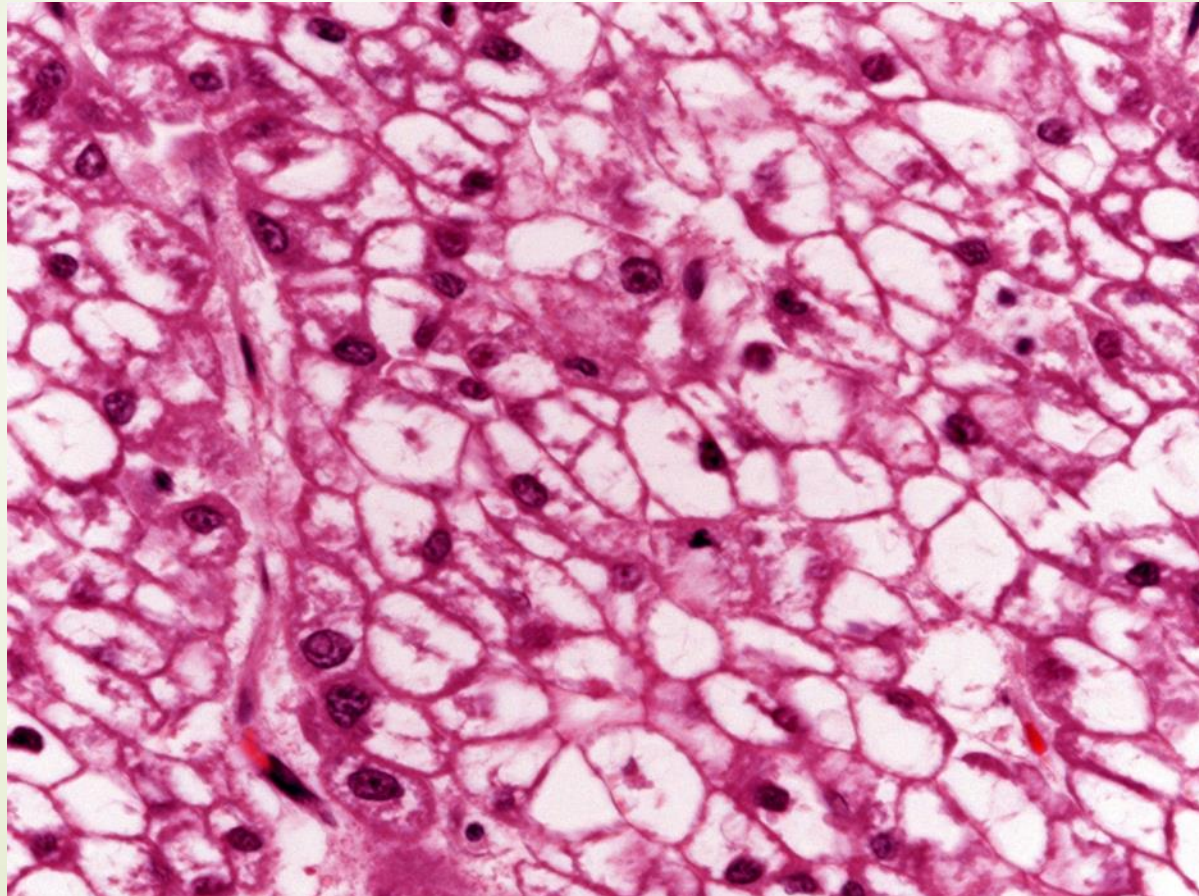


Irregular thickness

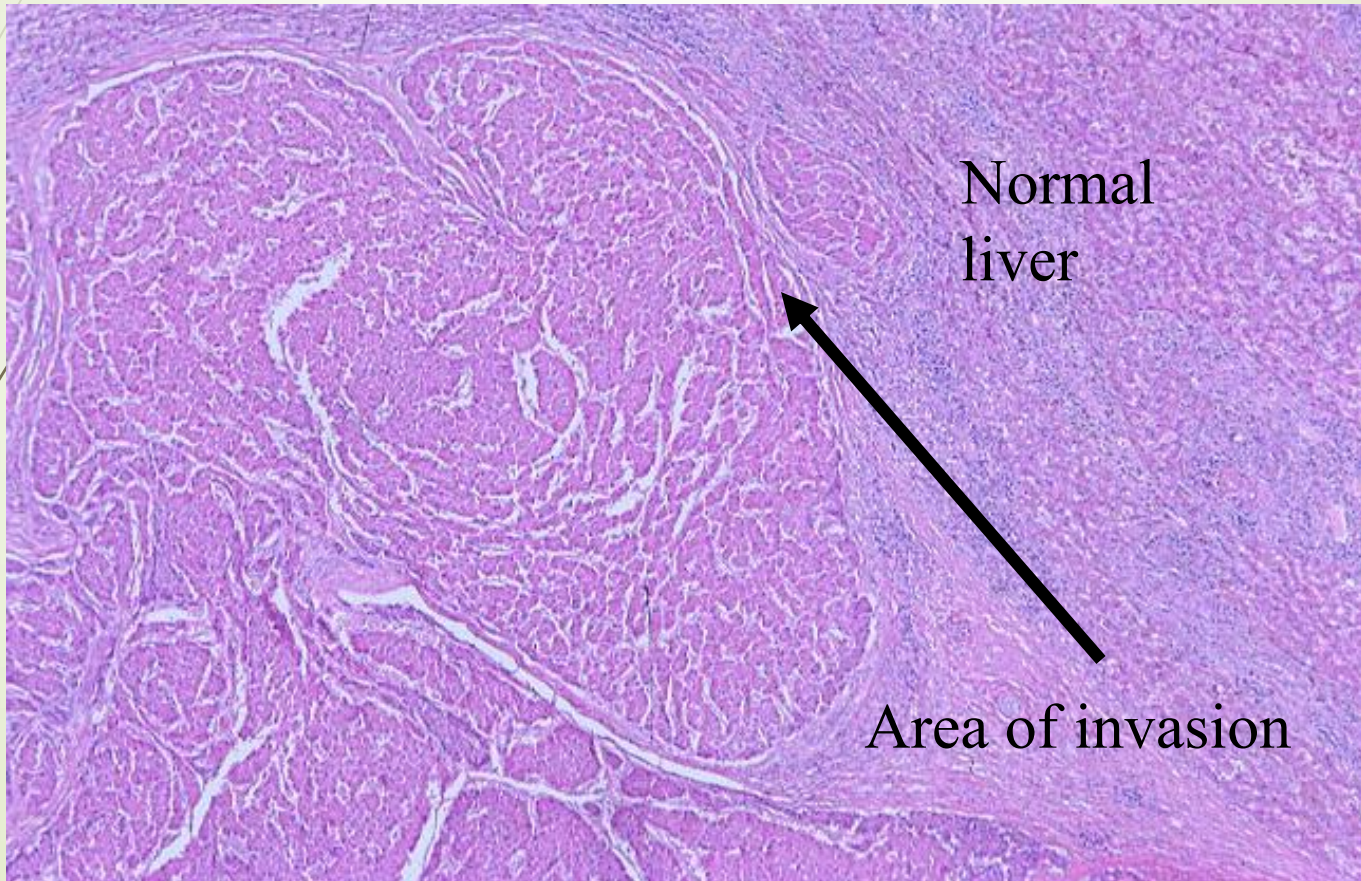
Solid-Pleomorphic



Clear Cell HCC



Invasion of HCC





Dogs

Can we predict the risk of metastasis in primary hepatocellular carcinoma?

- Take your pick!
- Reported Frequency
 - 61% (Patnaik AK et al. 1981, *Veterinary Pathology* 18:427)
 - 25% (Trigo FJ, et al. 1982, *J Comp Pathol* 92:21)
 - 4.8% (Liptak JM et al. 2004, *JAVMA*, 225:1225)
 - Quite uncommon-WSAVA working group

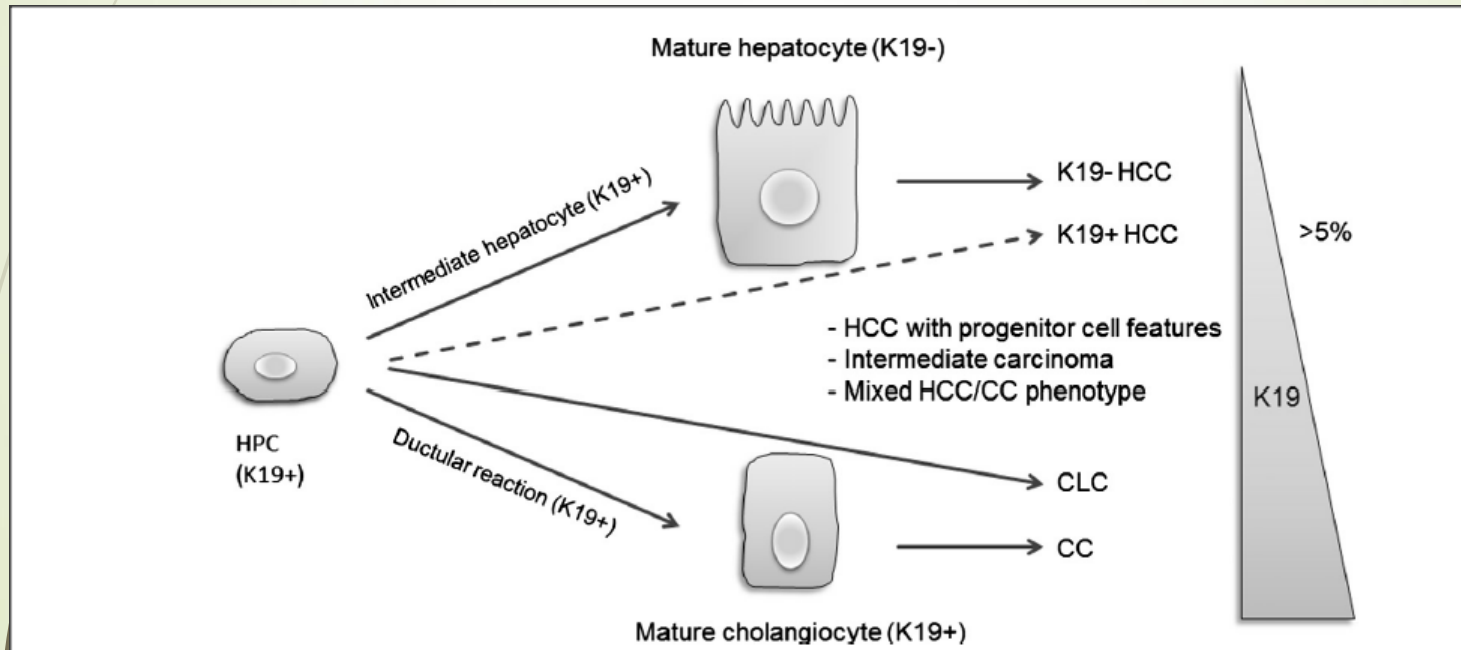
IHC markers can predict the risk of metastasis in dogs.

- Markers
 - HepPar1
 - Cytokeratin 7
 - Cytokeratin 19
 - Glypican-3
 - Muc-1
 - CD-10

Classification of primary hepatic tumours in the dog

Renee G.H.M. van Sprundel^a, Ted S.G.A.M. van den Ingh^b, Franco Guscetti^c, Olivia Kershaw^d, Hideyuki Kanemoto^e, Henrika M. van Gils^a, Jan Rothuizen^a, Tania Roskams^f, Bart Spee^{a,*}

Origin and Classification of Primary Hepatic Tumors in Humans

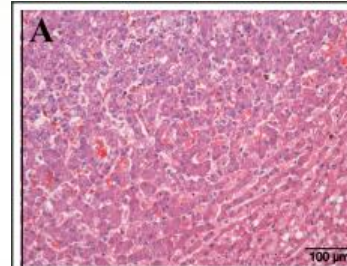


van Sprundel et al. Vet J. 197:2013

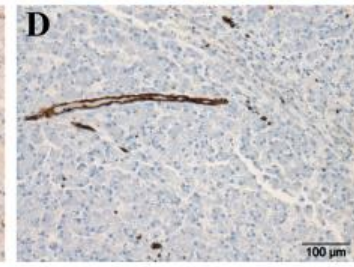
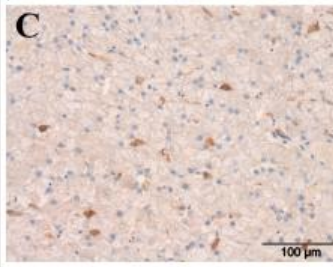
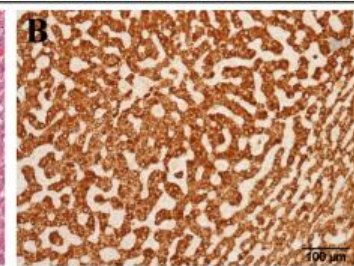
Canine Nodular Hyperplasia



H&E



HepPar1



CD 10

Cytokeratin 19

Van Sprundel
Vet. J 2013

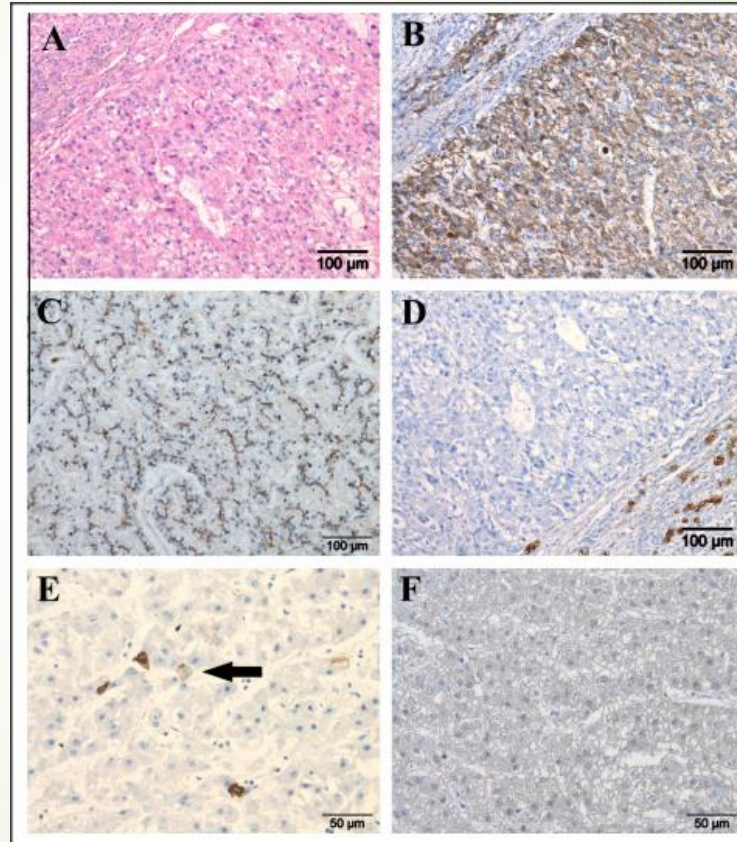
Canine hepatocellular tumor with low risk of metastasis



H&E

CD-10

Cytokeratin 19



HepPar-1

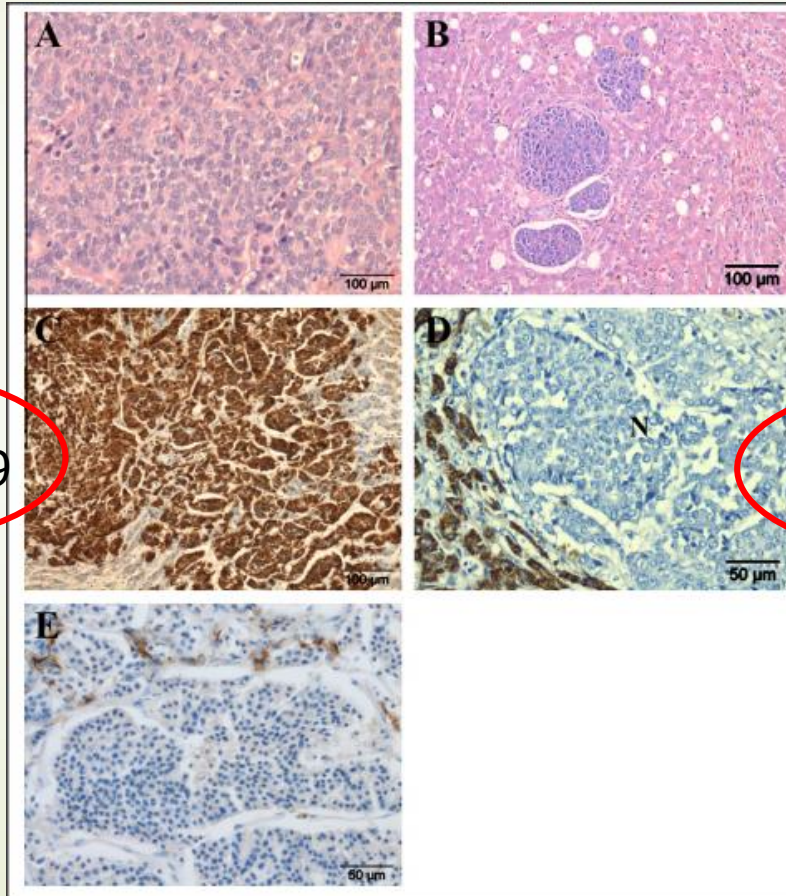
Cytokeratin 19

MUC-1

Van Sprundel, 2013

Canine HCC with high potential for metastasis

H&E



H&E

Cytokeratin 19

HepPar-1

CD-10

Table 1 Overview of the canine histological classification.

Groups	K19 expression	Grading 0 to 3	Staging 0 to 2	K7 expression	Glypican-3 expression	HepPar-1 expression
Normal liver (n = 5)	0%	0	0	0%	0%	100%
Nodular hyperplasia (n = 4)	0%	0	0	0%	0%	100%
Hepatocellular tumour K19 negative (n = 30)	0-5%	1 (n = 24) 2 (n = 6)	0	0% (n = 29) 5% (n = 1)	0%	50-75% (n = 2) 90-100% (n = 28)
Hepatocellular tumour K19 positive (n = 4)	10-90%	3	1 - 2	0% (n = 2) 5% (n = 2)	30-100%	0%

Grouping based on histology and K19 expression in hepatocytes compared with the results of the grading, staging, and clinicopathological markers

Table 2
Histological classification and immunohistochemistry of canine hepatocellular tumours.

	K19	Grading	Staging	HepPar-1	NSE	Cg-A	CD10	EMA/MUC-1
HCT 0-5% K19+	0% (n = 46) 1-5% (n = 16)	0 (n = 10) 1 (n = 35) 2 (n = 17)	0 (n = 62)	100% (n = 54) 60-90% (n = 8)	0% (n = 52) 5-20% (n = 10)	0% (n = 61) 5% (n = 1)	30-100% (n = 62)	0% (n = 62)
HCT >5% K19+	40-100% (n = 17)	1 (n = 3) 2 (n = 6) 3 (n = 8)	1 (n = 4) 2 (n = 13)	0% (n = 15) 5-20% (n = 2)	0% (n = 15) 20-40% (n = 2)	0% (n = 16) 5% (n = 1)	0% (n = 17)	0% (n = 17)
sHCT	Ductular 100% Trabecular 0% Solid 100% (n = 3)	0 (n = 1) 1 (n = 2)	0 (n = 2) 1 (n = 1)	Ductular 0% Trabecular 100% Solid 0% (n = 3)	Ductular 100% Trabecular 0% Solid 80% (n = 3)	0% (n = 3)	Ductular 0% Trabecular 50% Solid 5% (n = 3)	0% (n = 3)

Cg-A, chromogranin-A; EMA/MUC-1, epithelial membrane antigen/mucin-1; HCT, hepatocellular tumour; K19, keratin 19; NSE, neuron-specific enolase; sHCT, scirrhous hepatocellular tumour.



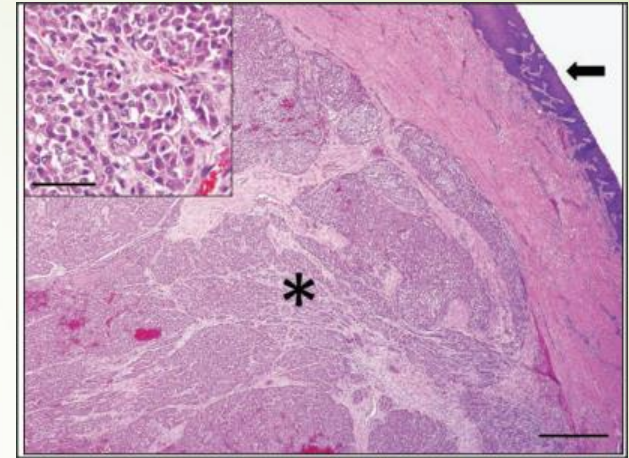
Canine Hepatocellular Carcinoma Risk

- A small subset of tumors stain with:
 - Cytokeratin 19 (>5% of surface area)
 - Glypican-3
- Do not stain with HepPar1
- These tumors are the most likely to metastasize
- Note: some tumors with HepPar1 do metastasize

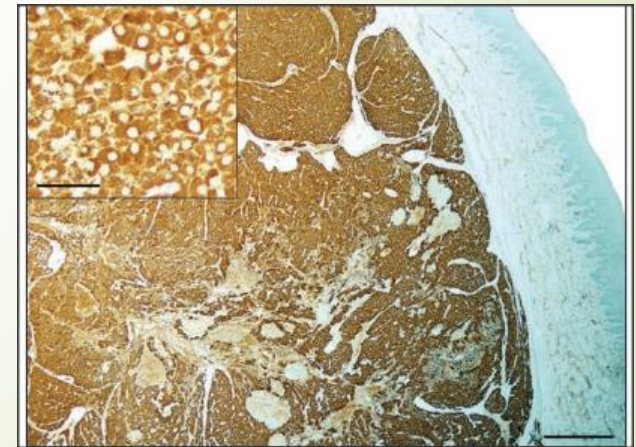
Some HepPar1+ HCC do metastasize



H&E

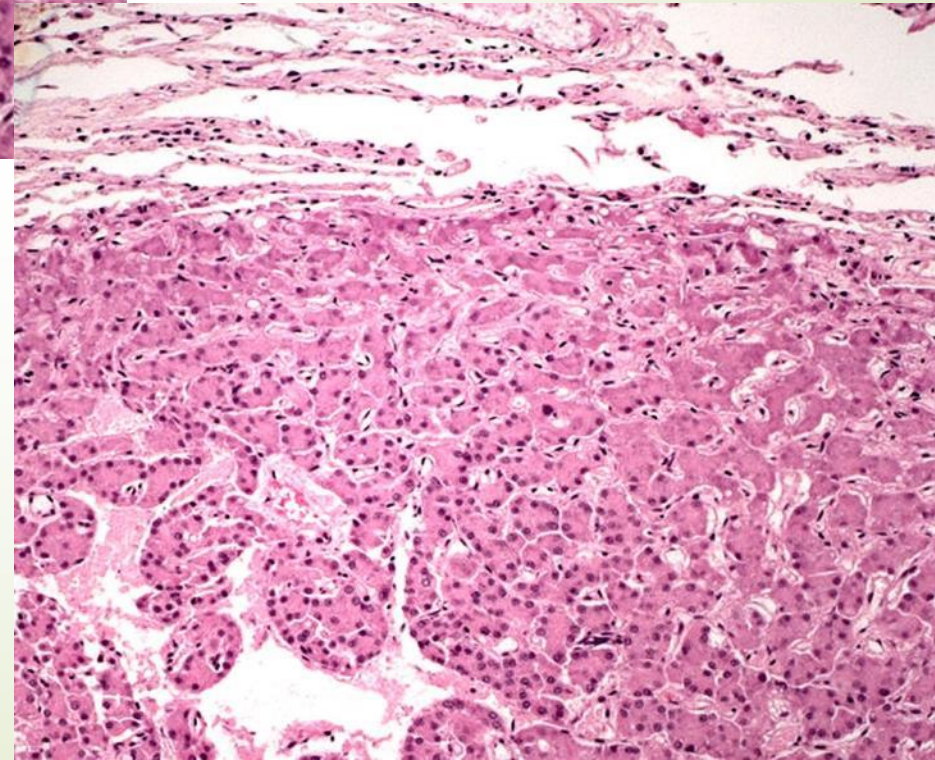
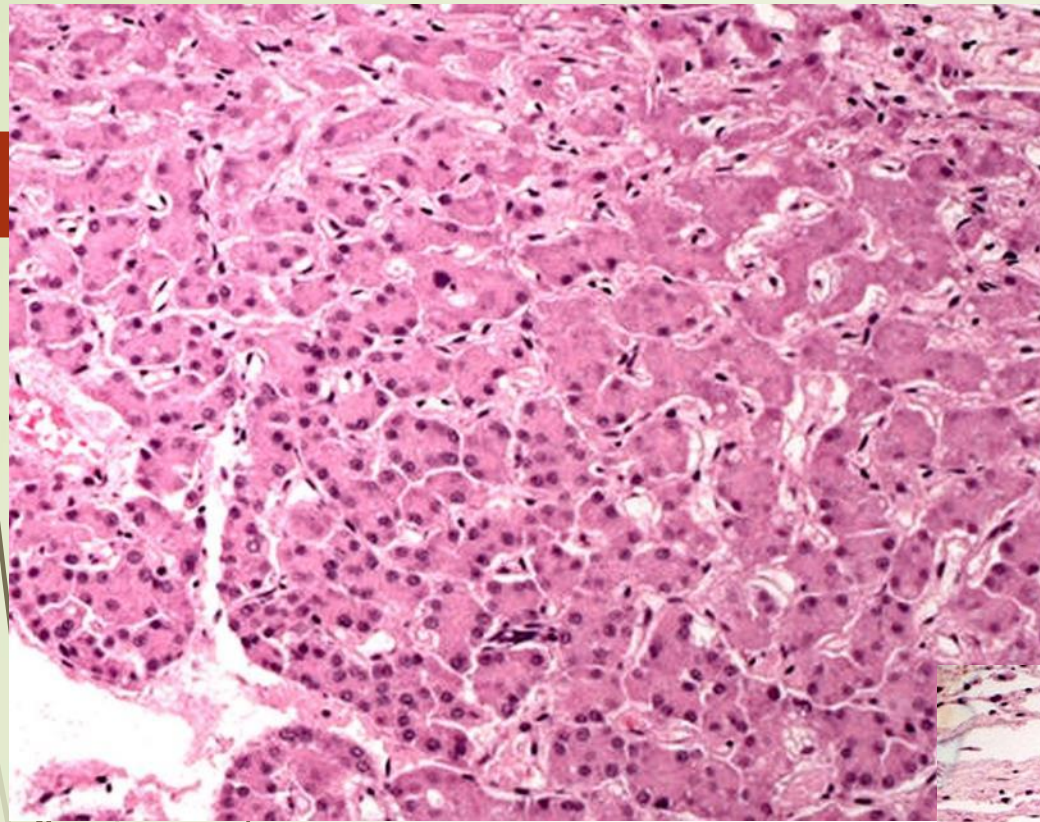


HepPar1



Lamoureaux, J. et al. JAVMA, Vol 241, No. 12, December 15, 2012

Benign or
Malignant?





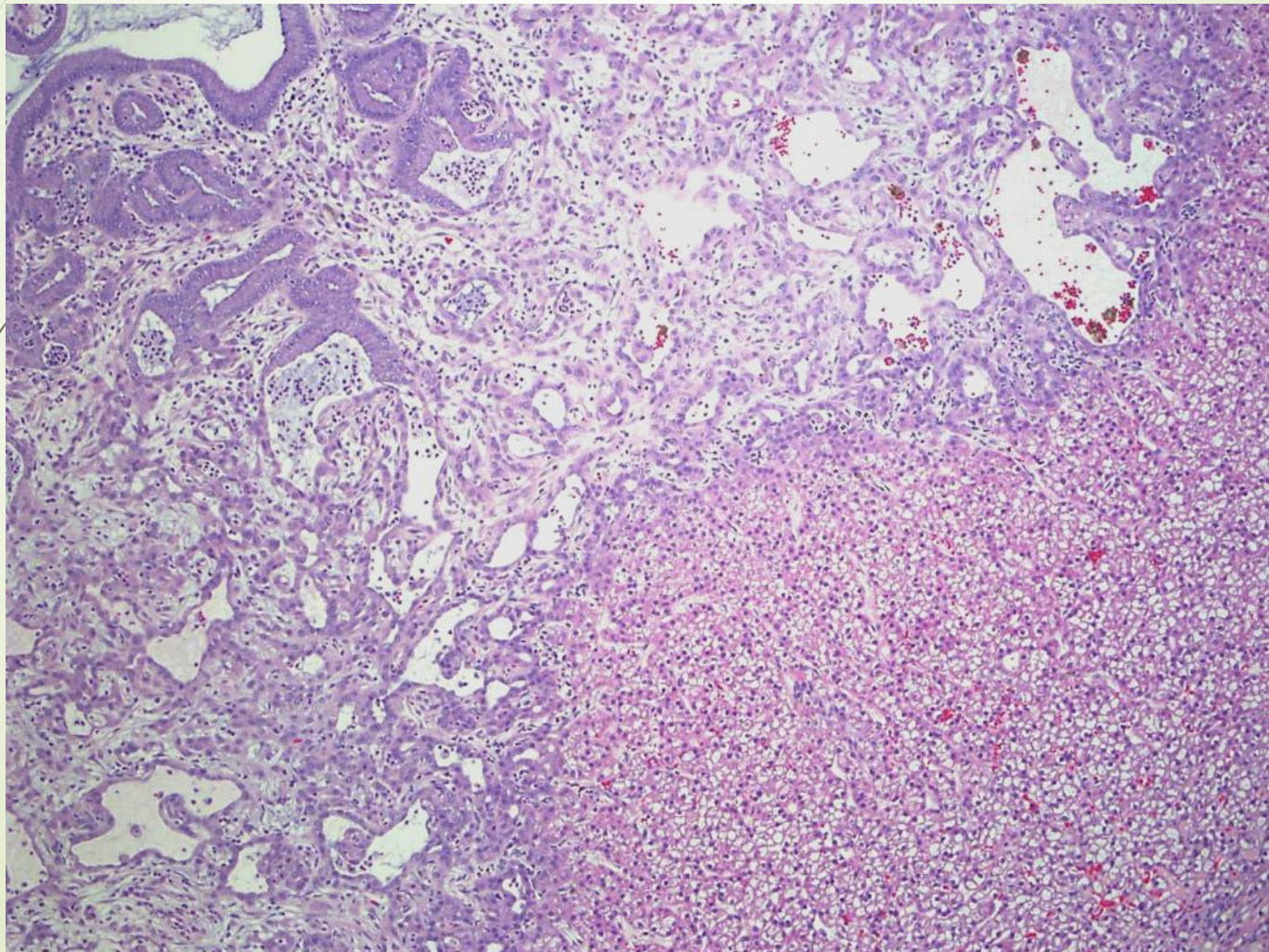
Mixed Hepatocellular- cholangiocellular carcinoma



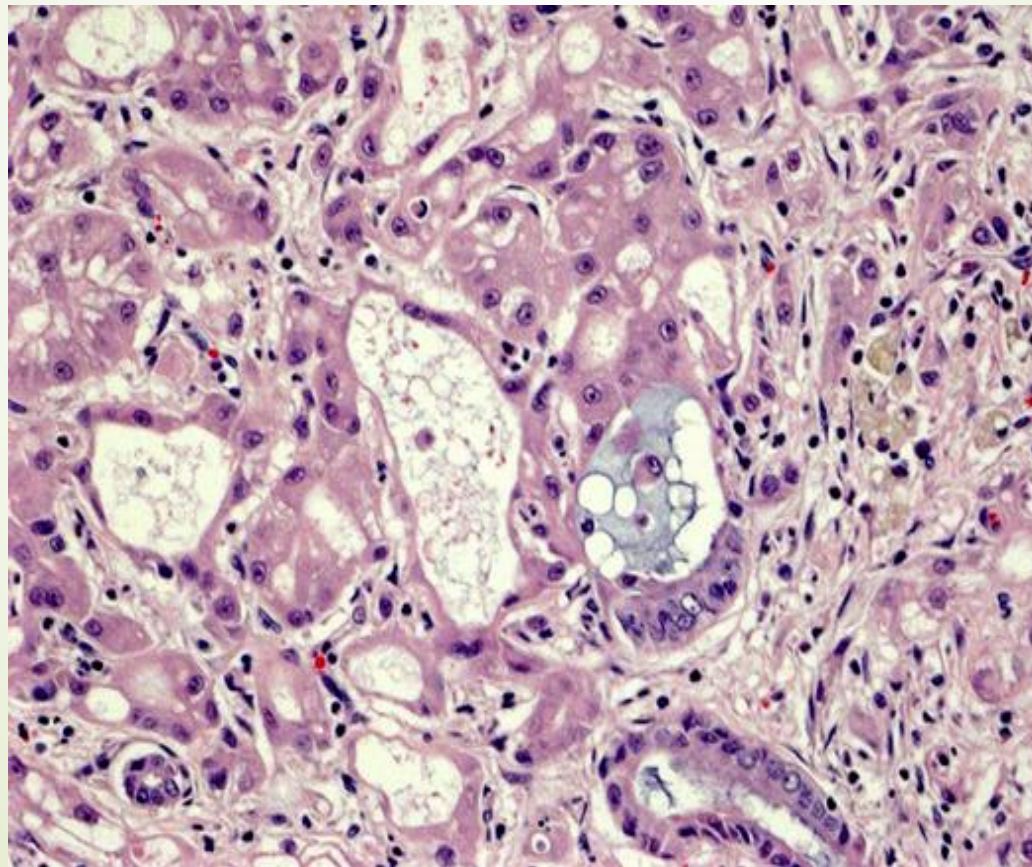
Uncommon

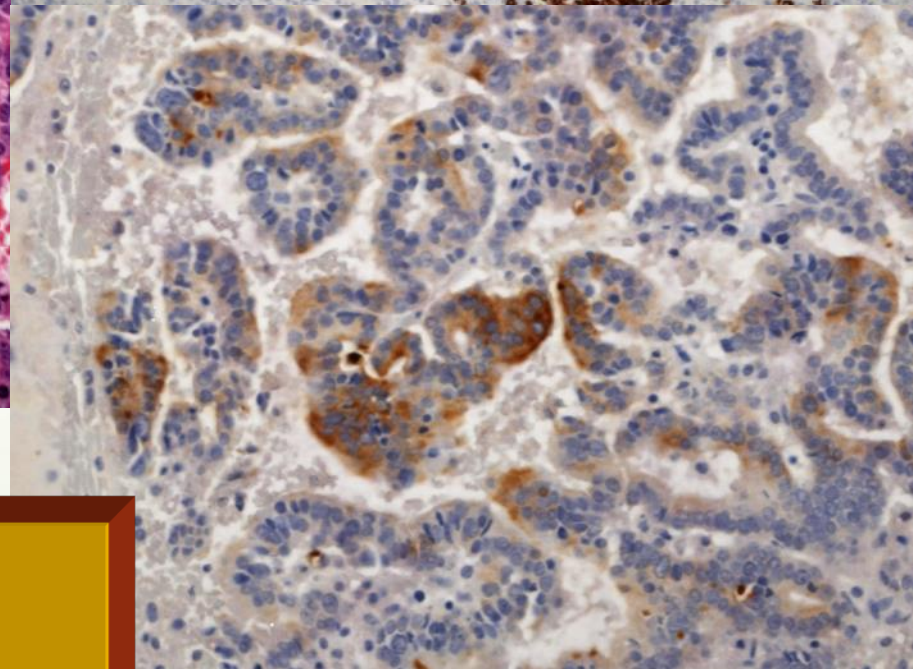
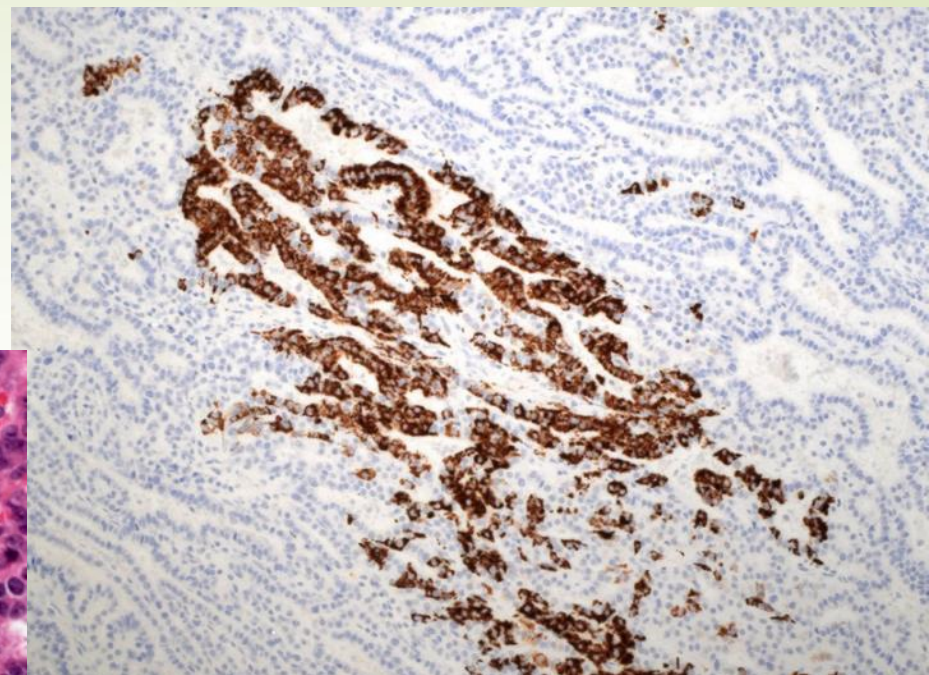
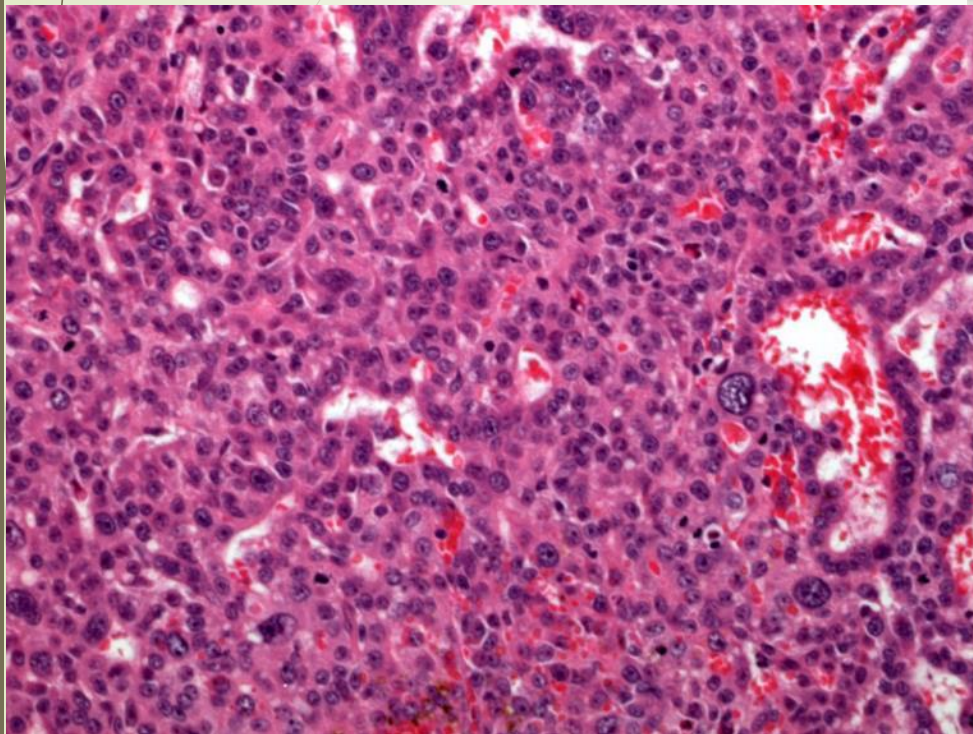


Mixed Hepatocellular- cholangiocellular CA



Mixed Hepatocellular-cholangiocellular carcinoma



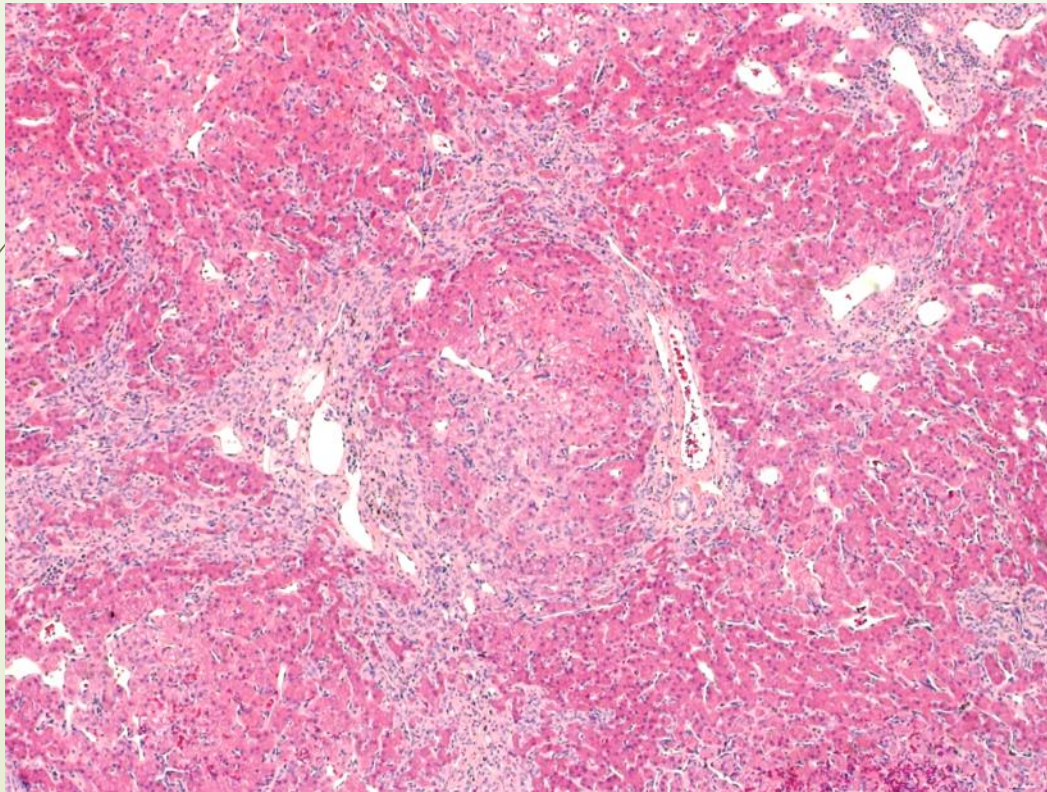


IHC: HepPar1 for hepatocytes
Cytokeratin 7 for biliary epithelium

Scirrhus Hepatocellular Tumor

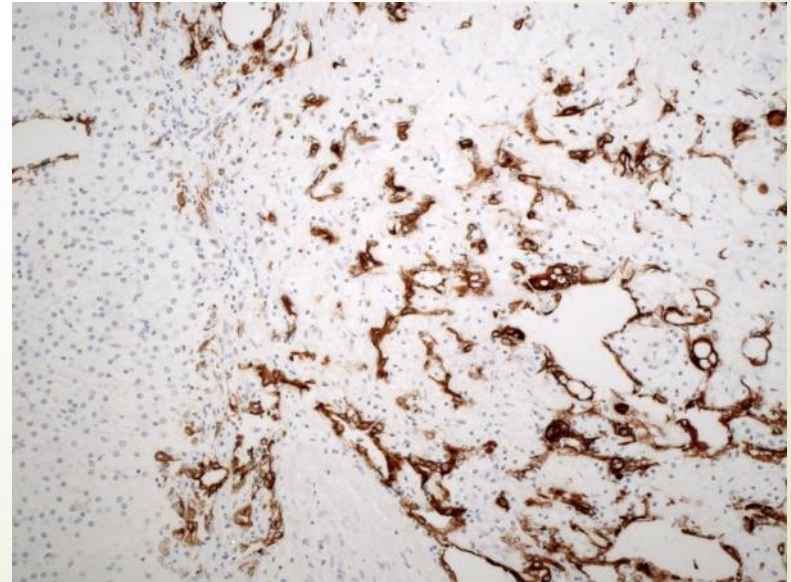
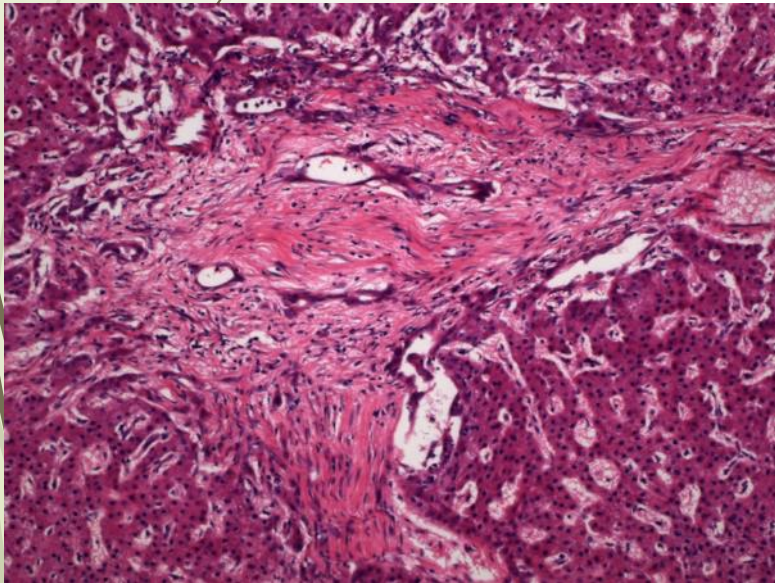


Canine Scirrhous Hepatocellular Carcinoma



Canine Scirrhous HCC variant: Metastasis risk not well characterized

Cytokeratin 19
staining of ductules



HCC in Cats



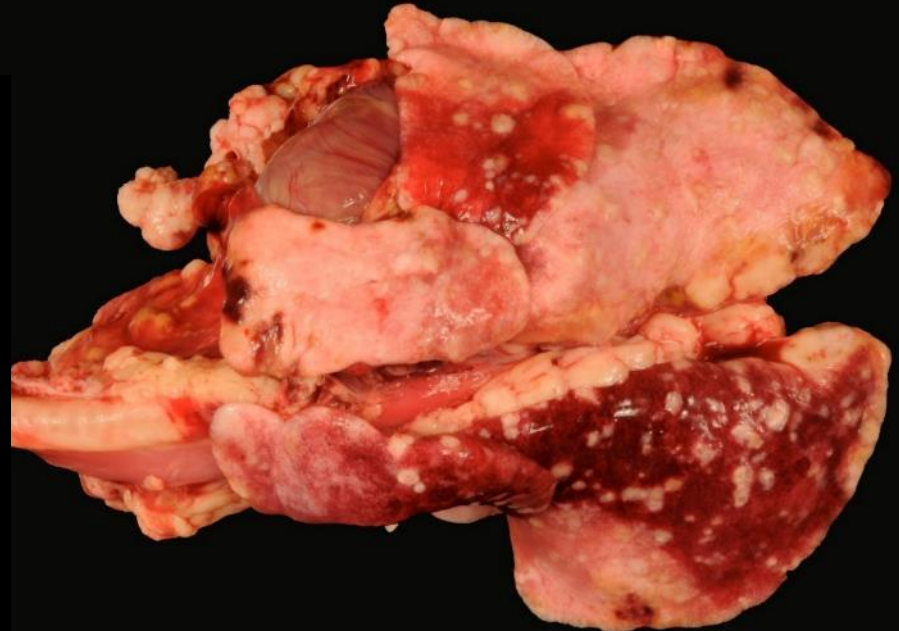
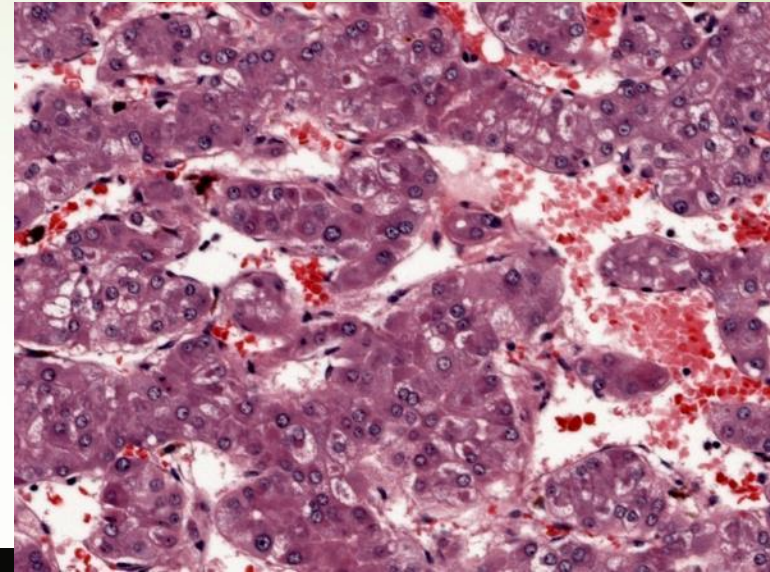
Metastasis

- Uncommon
- 3/18 with mets.

IHC

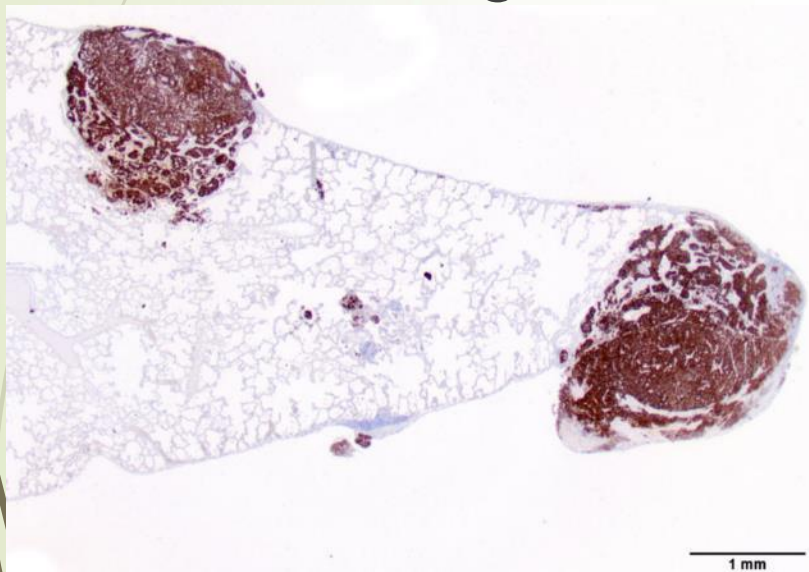
- All tumors express HepPar1
- None with >5% CK19

Feline HCC

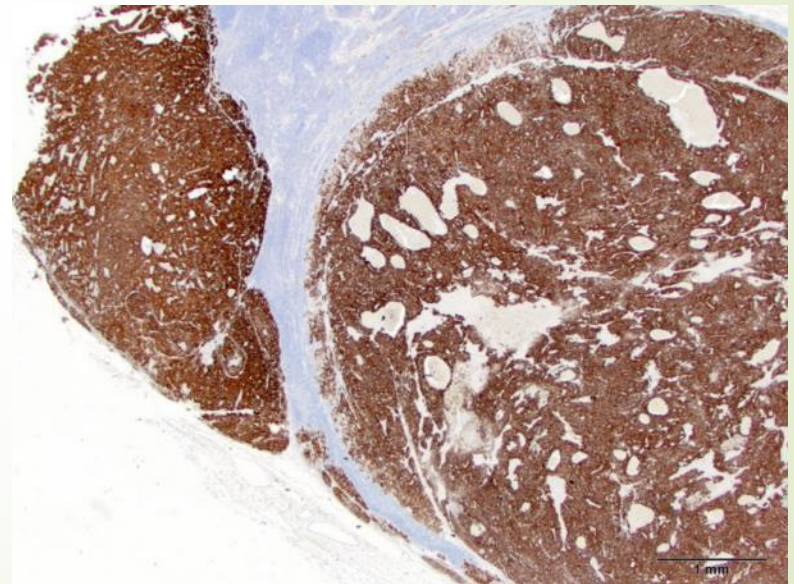


HepPar-1+ metastasis in cats

Lung



Hepatic Lymph
node



HepPar1

Hepatocellular Carcinoma in Lemurs

Metastasis

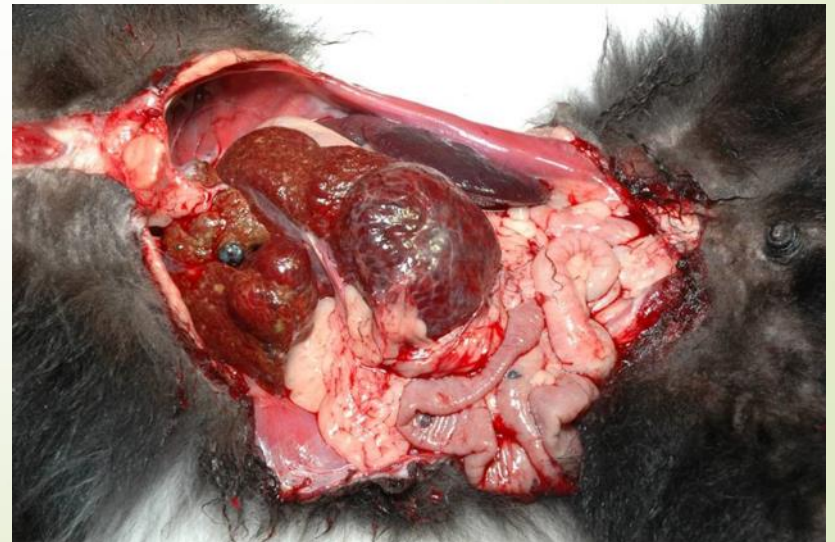
Relatively
common

Metastasis = 6/15

Iron?

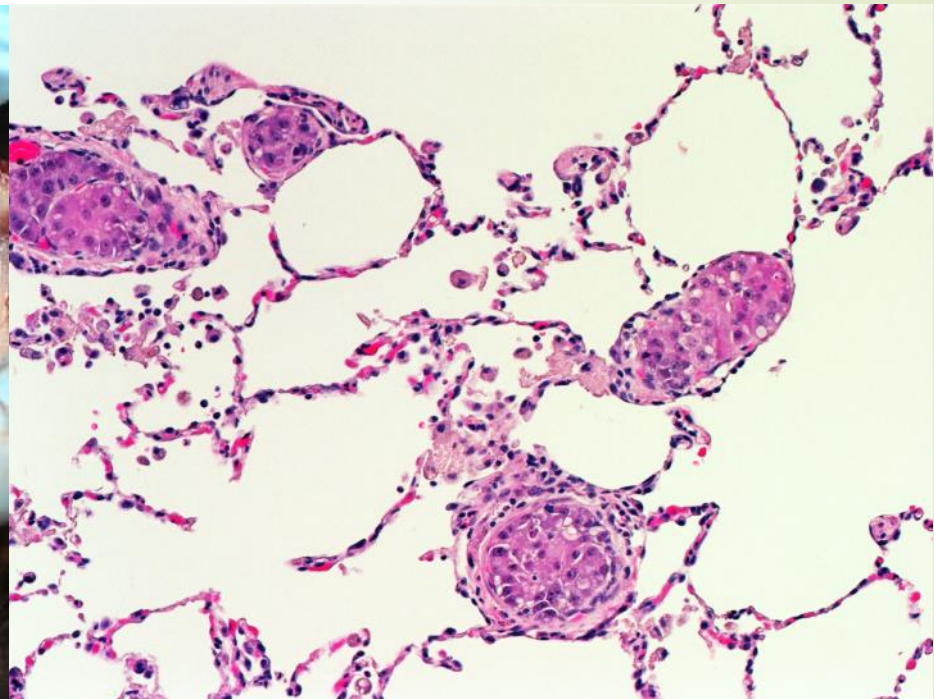
Virus?

Carcinogen?



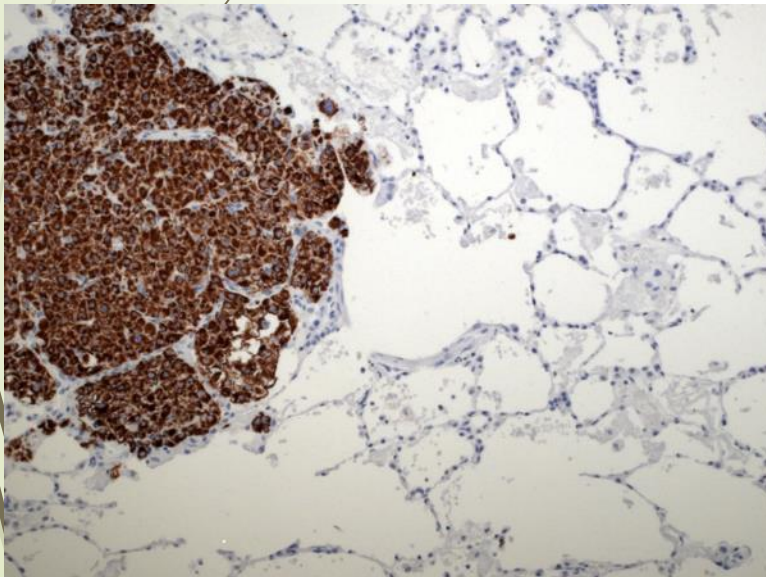
HCC in Lemurs

Pulmonary
metastasis

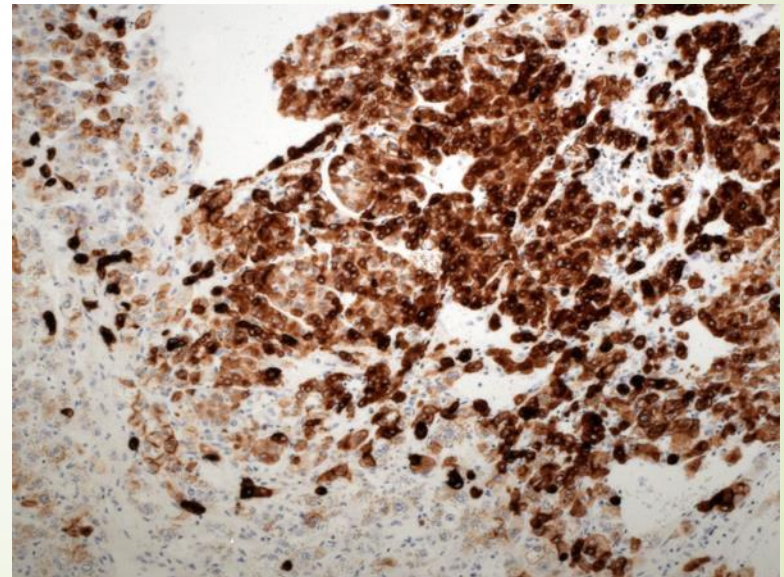


Lemur HCC metastasis markers: HepPar1 and Cytokeratin 7

HepPar1 in lung
metastasis

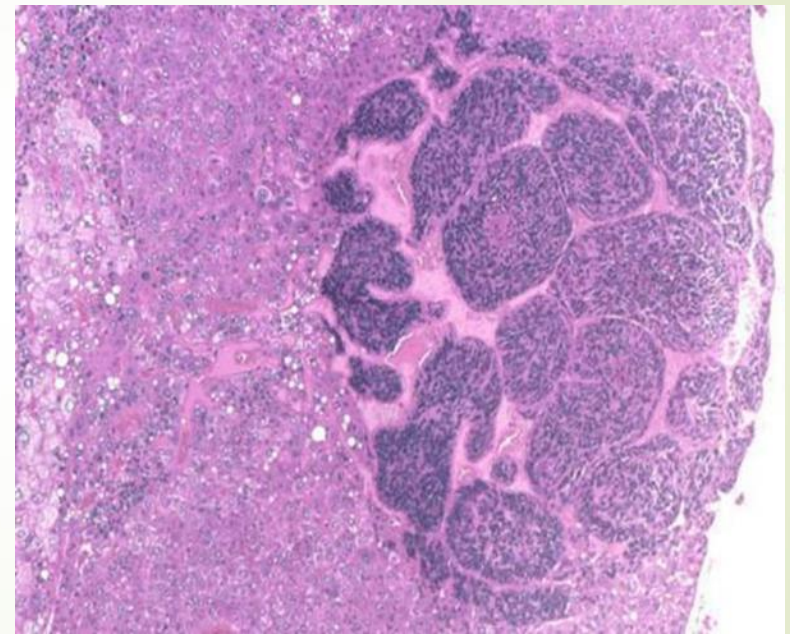
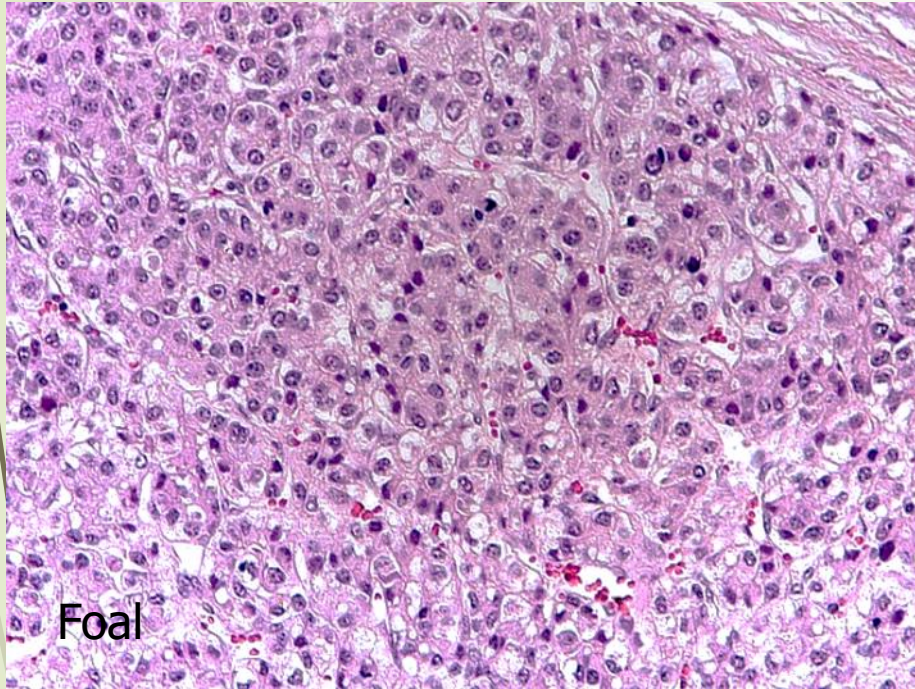


CK7 in lung
metastasis



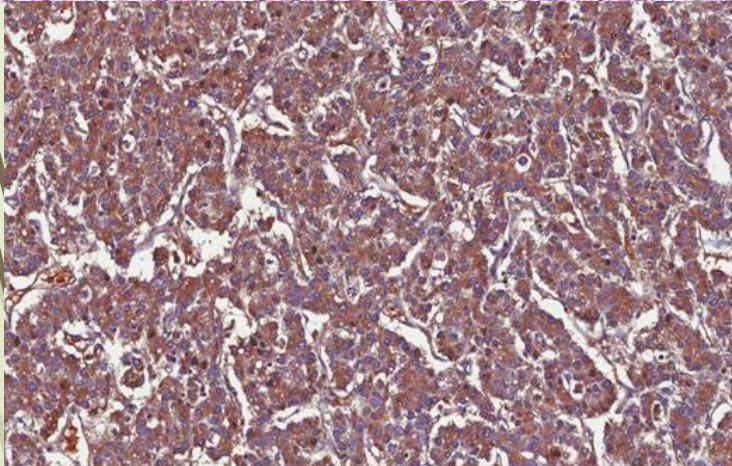
Hepatoblastoma

Rare!



Dr. D. Malarkey

Mouse



AFP stain



Old View?

Cholangiocellular adenoma

Most common in cats

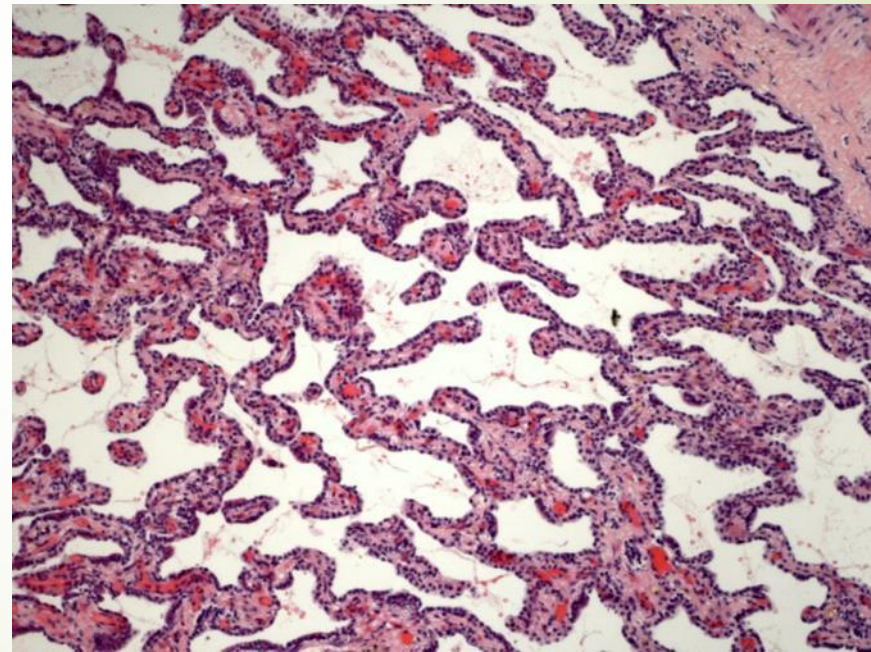
Ducts and cysts lined by well
differentiated biliary epithelium

Cystic variants-Biliary
cystadenomas

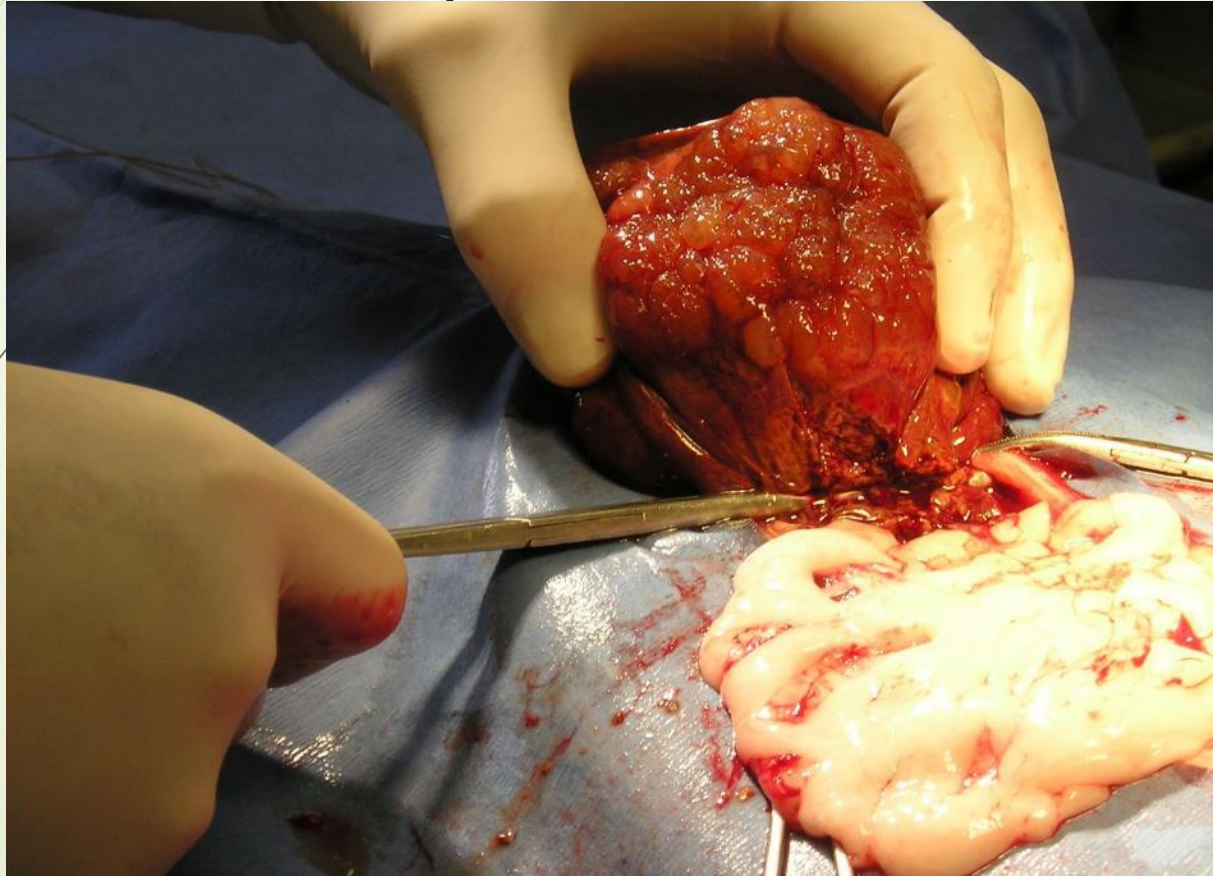
New View

Cholangiocellular adenoma

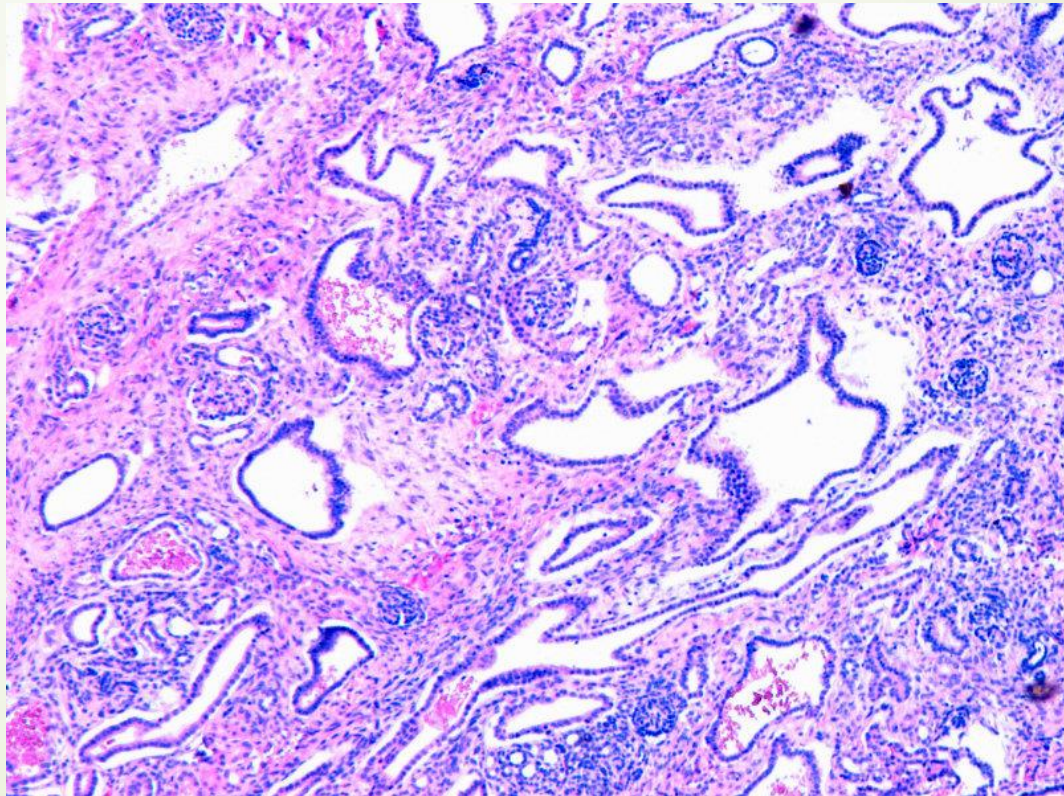
- Rare
- Solitary, well circumscribed
- Slightly dilated structures
- Cuboidal to flattened epithelium



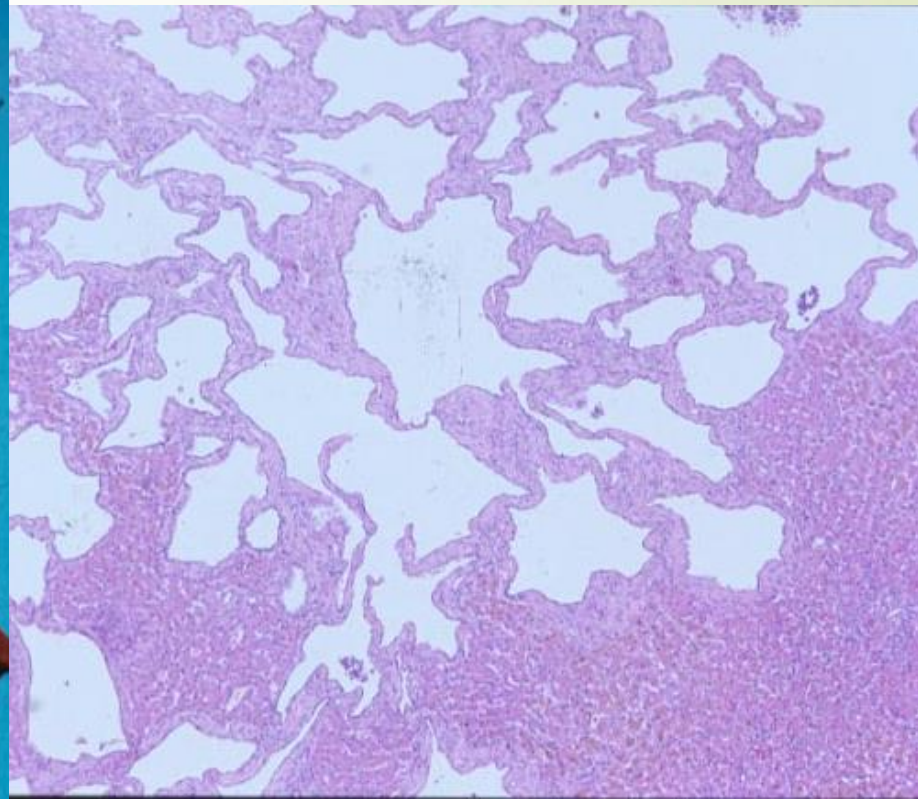
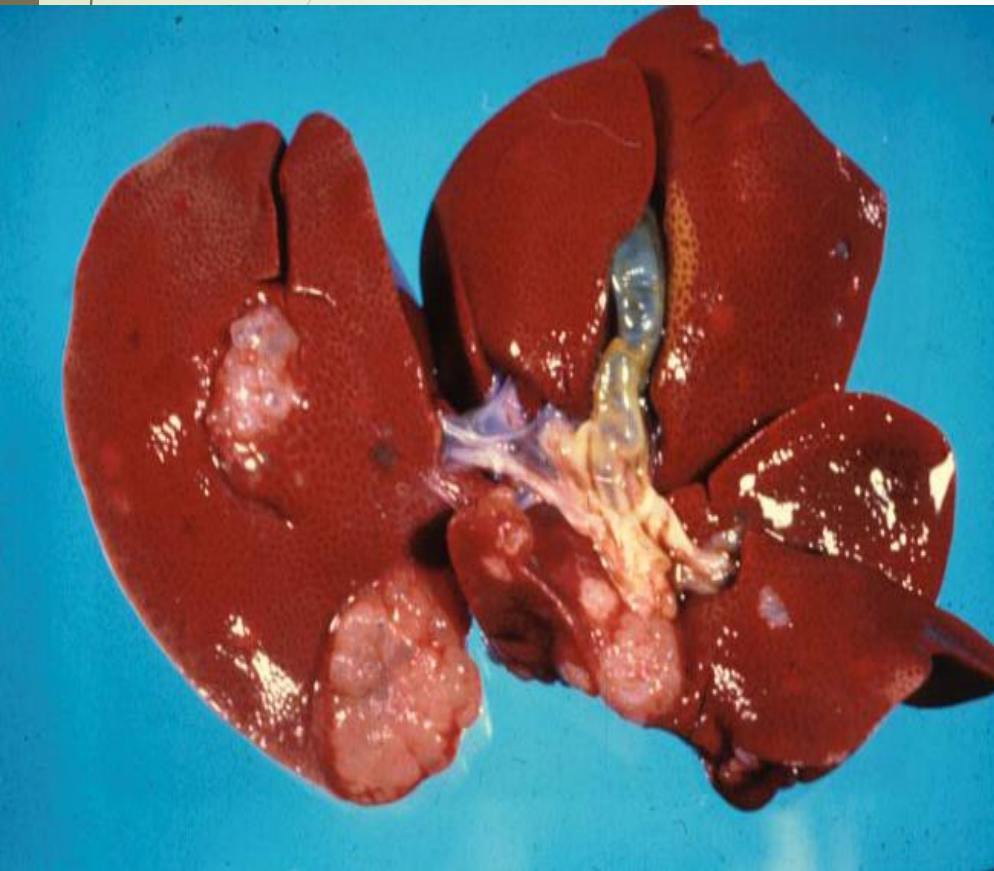
Cat: Biliary Adenoma vs. Anomaly



Kidney



Biliary Adenoma or Polycystic Disease





Hepatic Neoplasia: Cholangiocellular (biliary) carcinoma

- Single or multinodular masses
- **Firm, umbilicated, whitish**
- Histo: ducts or acini lined by poorly differentiated cuboidal biliary epithelium
 - Mucin
 - Mitoses
- Metastasis very common



Cholangiocellular Carcinoma

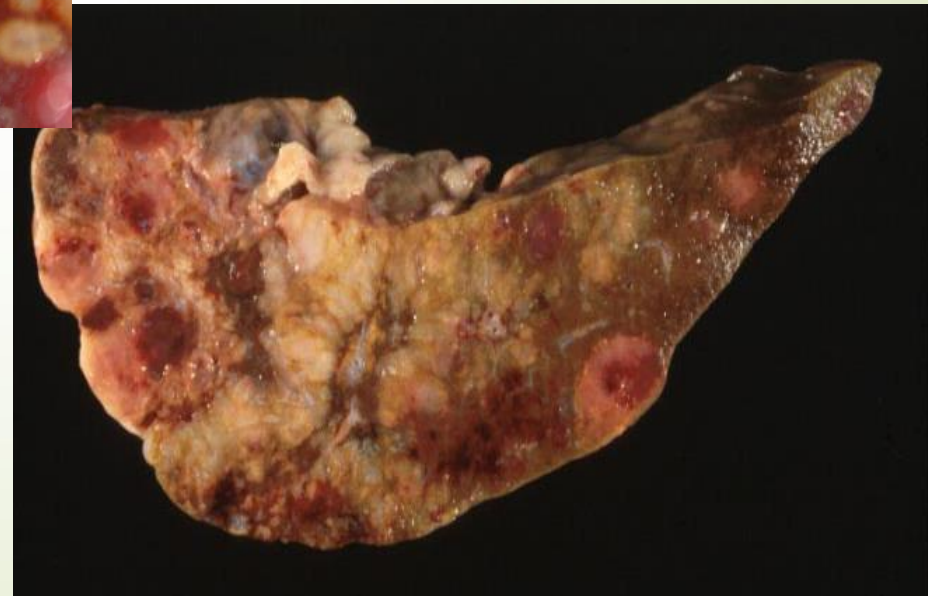
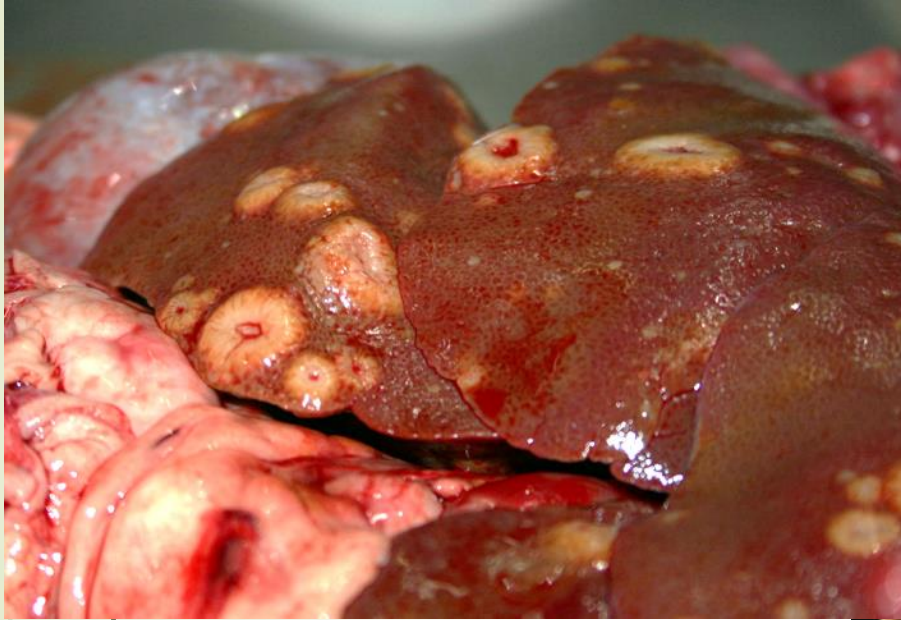
Dog

- Metastasis common
- 10/10 cases

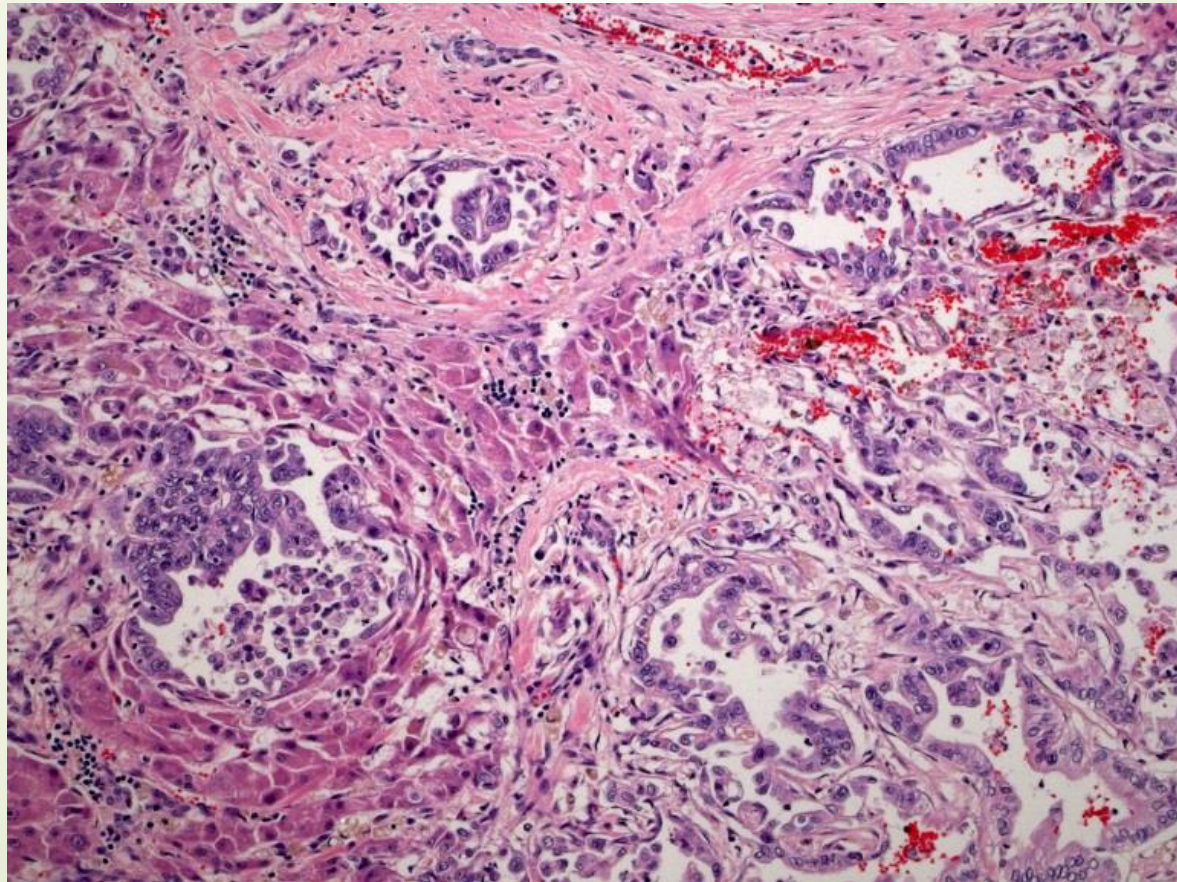
Cat

- Metastasis common
- 25/25

Cholangiocarcinoma



Cholangiocarcinoma/Biliary Carcinoma

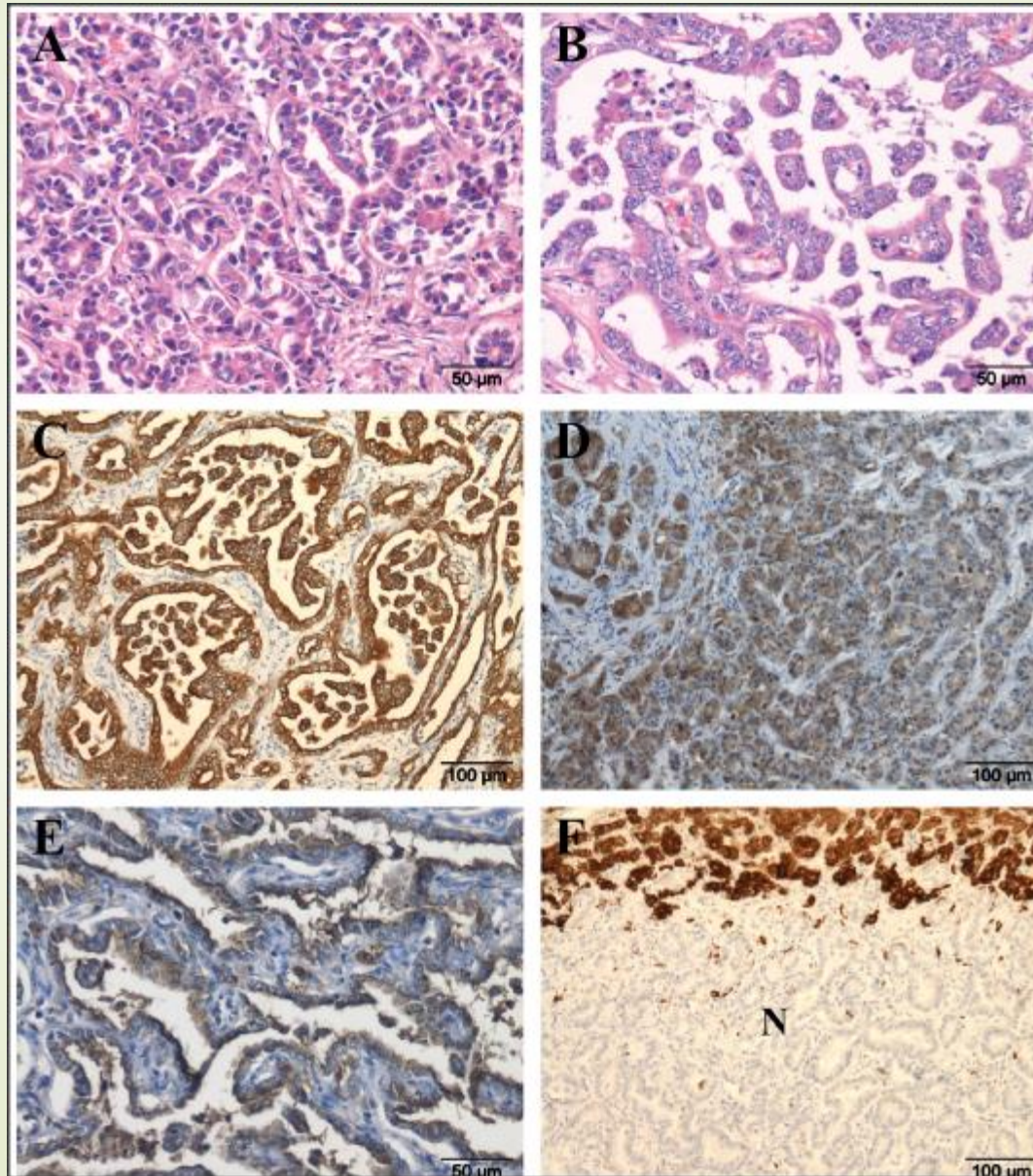




IHC Cholangiocarcinoma

- All Cytokeratin positive
- Muc-1 positive
- NSE +/-

Cholangiocarcinoma



Cytokeratin 19

Muc-1

Muc-1

HepPar1

Gall bladder Neoplasia

Epithelial

- Gall bladder adenoma
- Gall bladder carcinoma

Others

- Carcinoid
- Mesenchymal tumors



Carcinoids

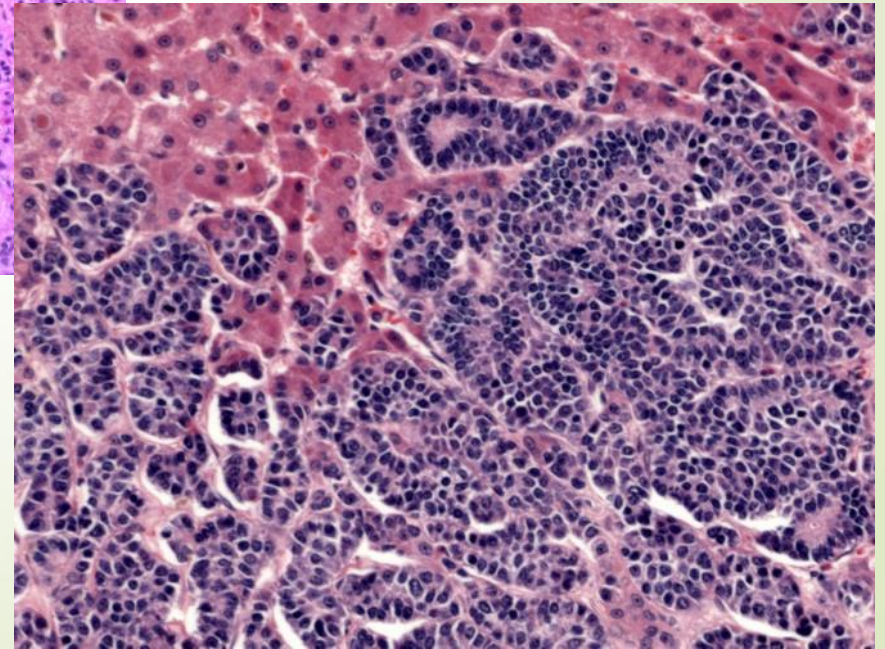
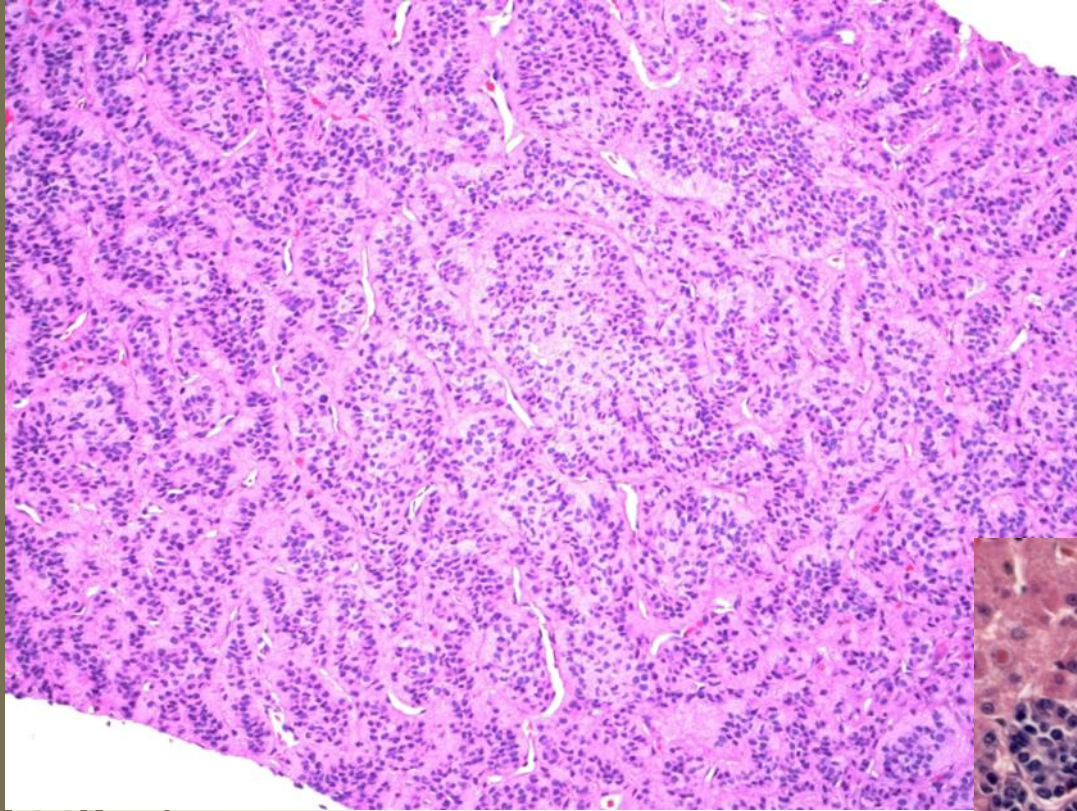
- Canine and feline
- Neuroendocrine cells in biliary tree
- High rate of metastasis
- IHC: chromogranin A and neuron-specific enolase

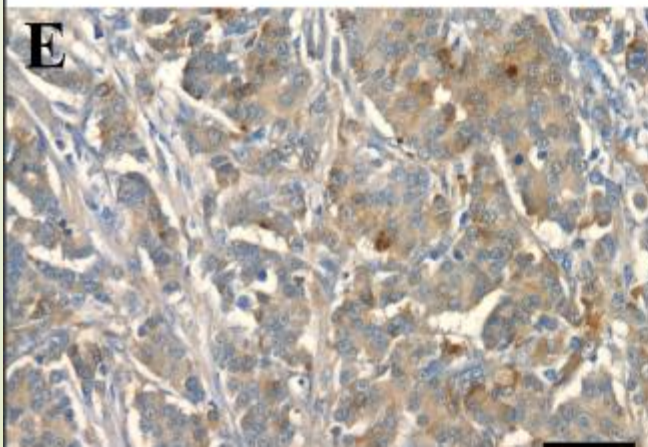
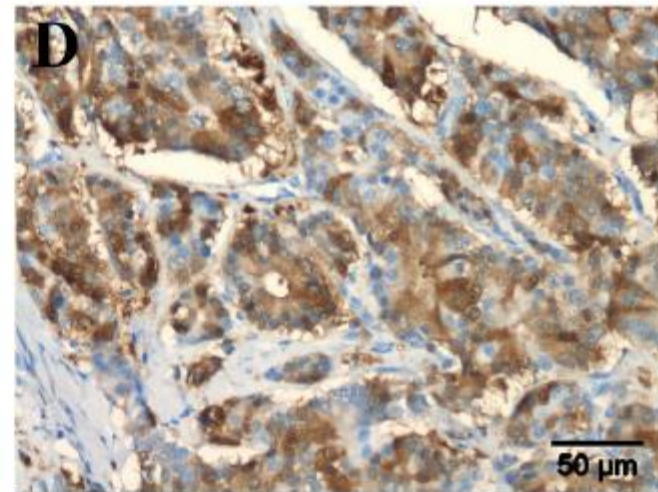
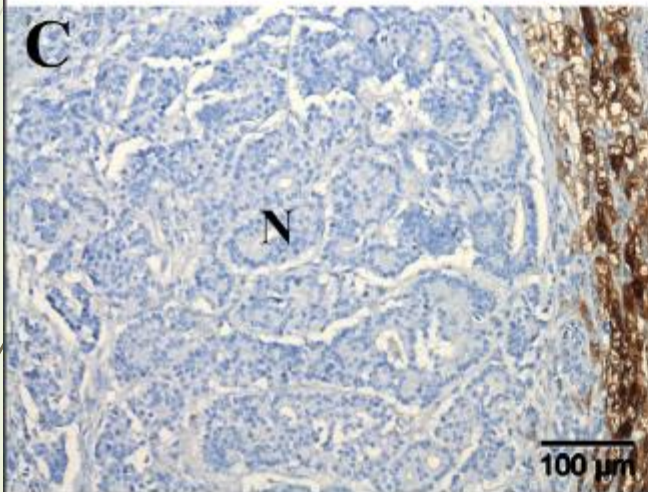
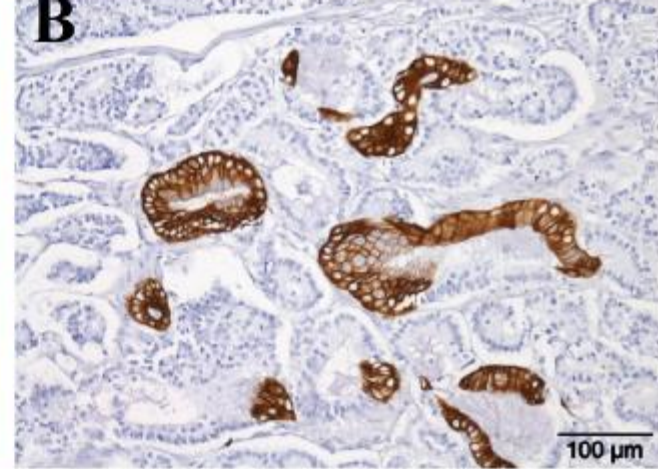
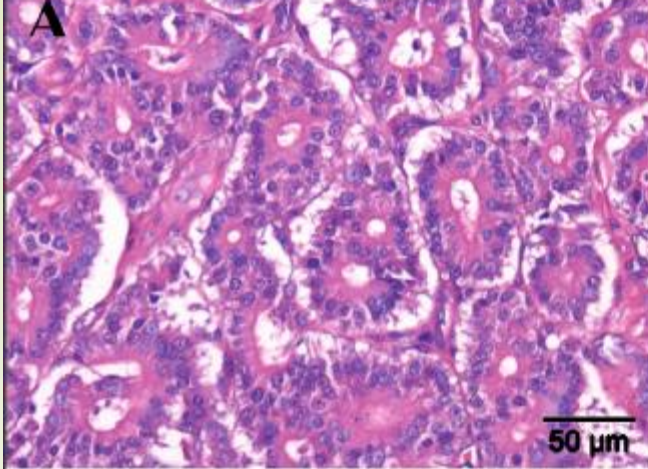
Cats

- +/- cytokeratin 19 (small cell carcinoma)



Hepatic carcinoid





synaptophysin

Canine hepatic carcinoid

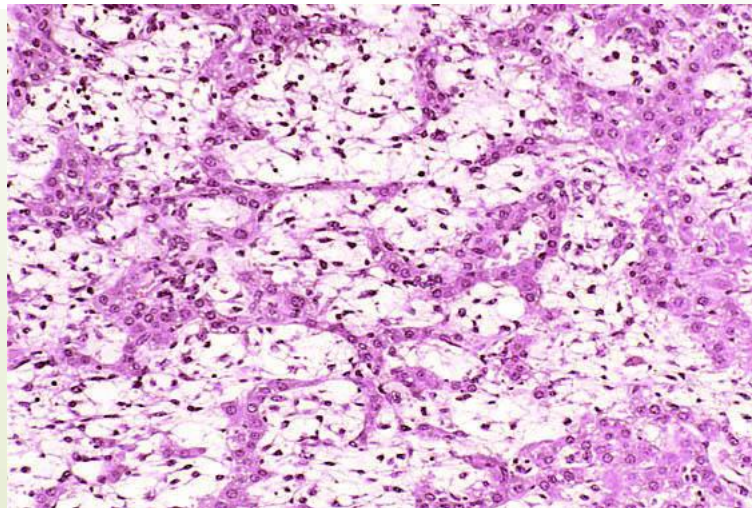
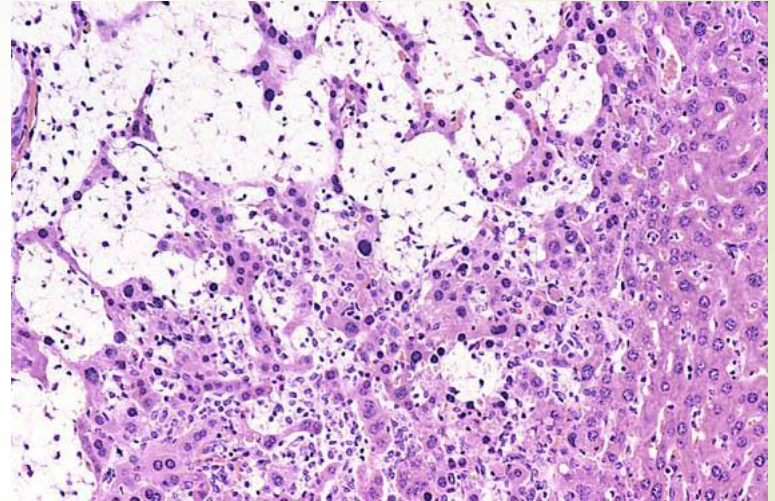
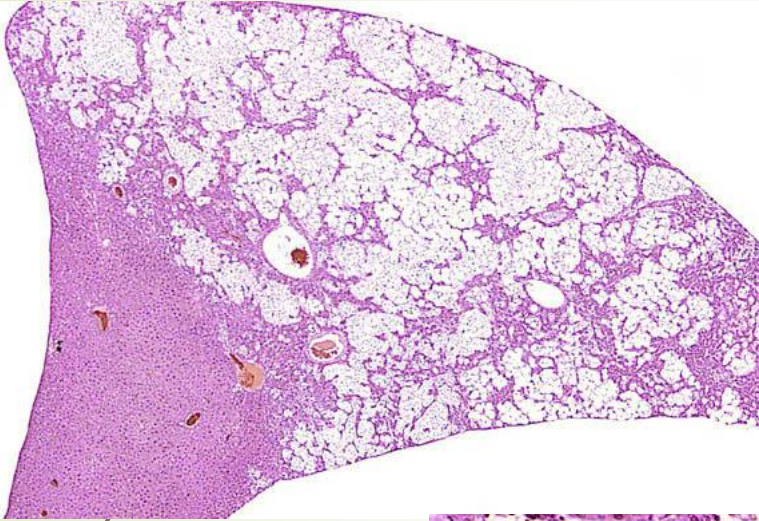


Hepatic Neoplasia

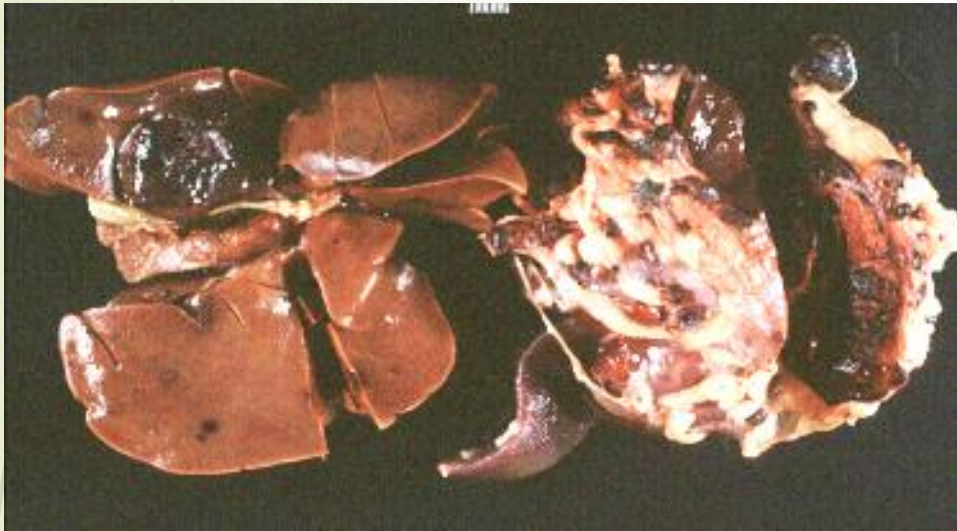
Miscellaneous

- Stellate cells
 - Rats
- Hemangiosarcoma
 - fibrosarcomas, osteosarcomas, leiomyosarcomas
- Myelolipoma

Rat Stellate (Ito) Cell Proliferation



Hepatic Neoplasia: Hemangiosarcoma

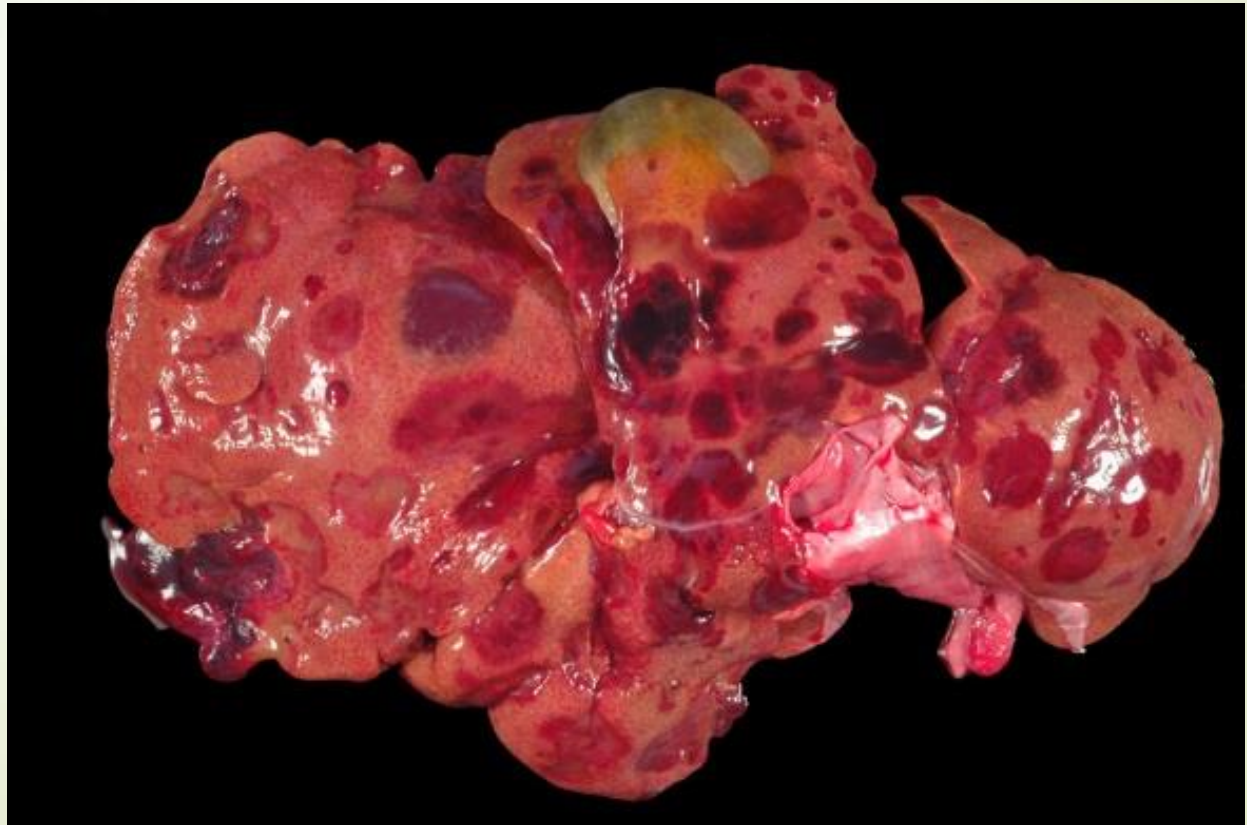


Dark red mass with hemorrhage and
omental adhesions

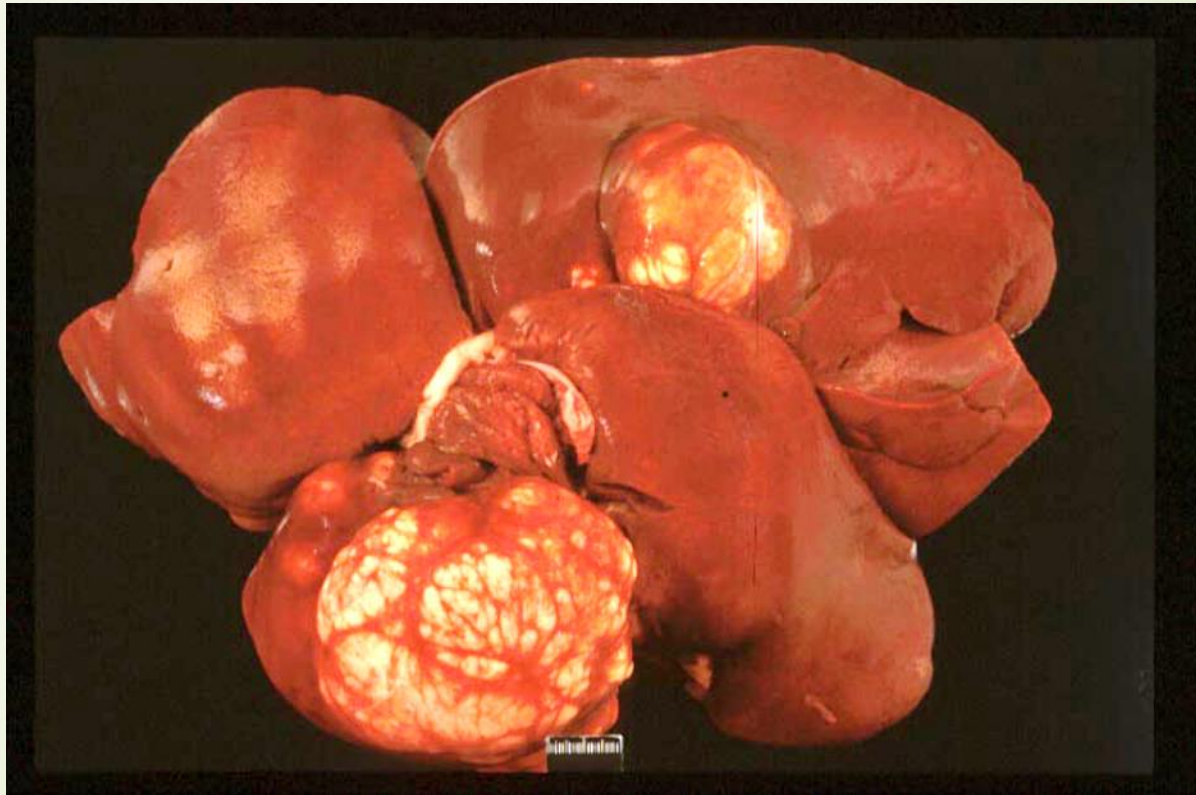
MUST CHECK WHOLE BODY



Corgi Telangiectasis

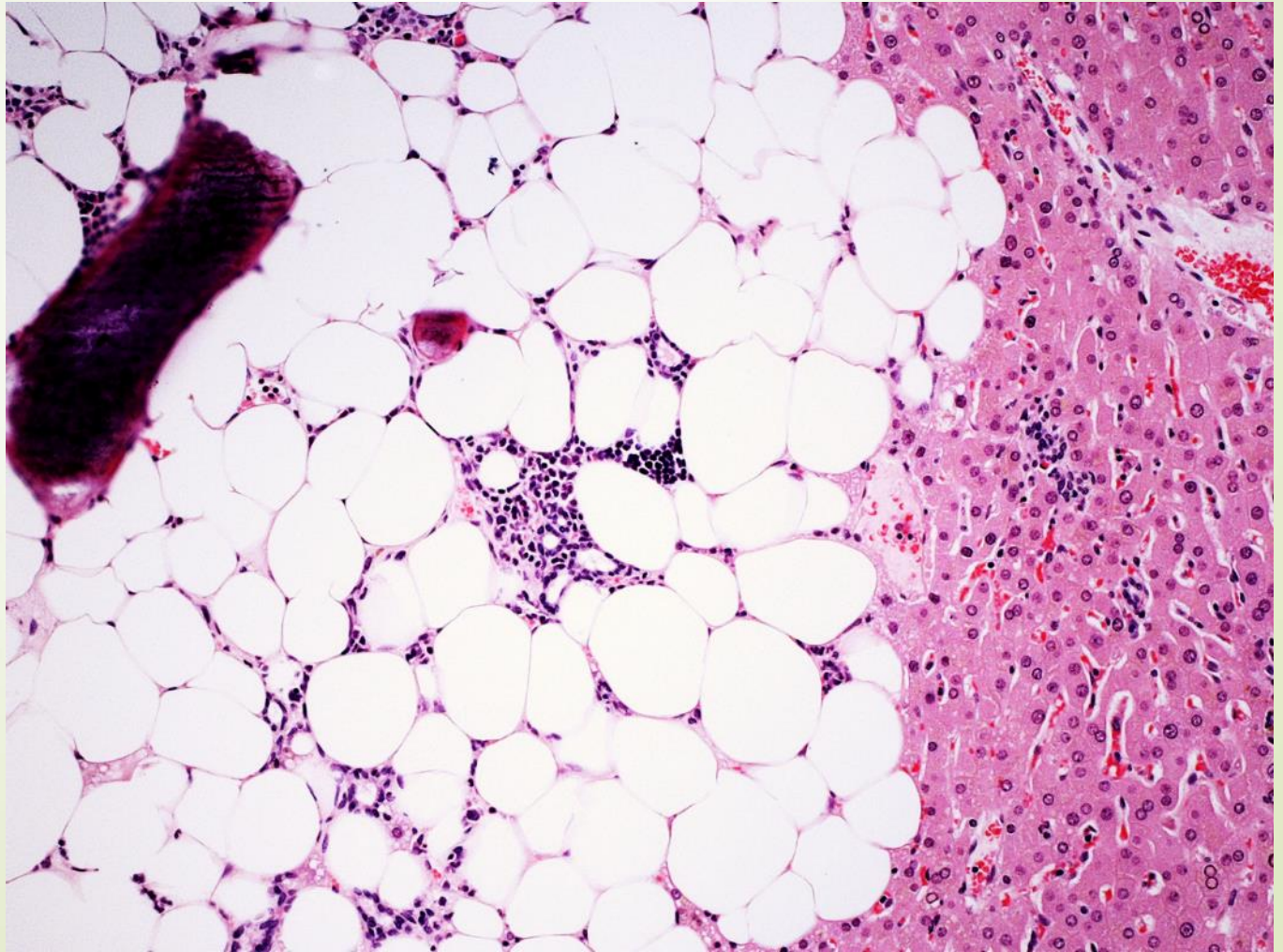


Leiomyosarcoma of the liver

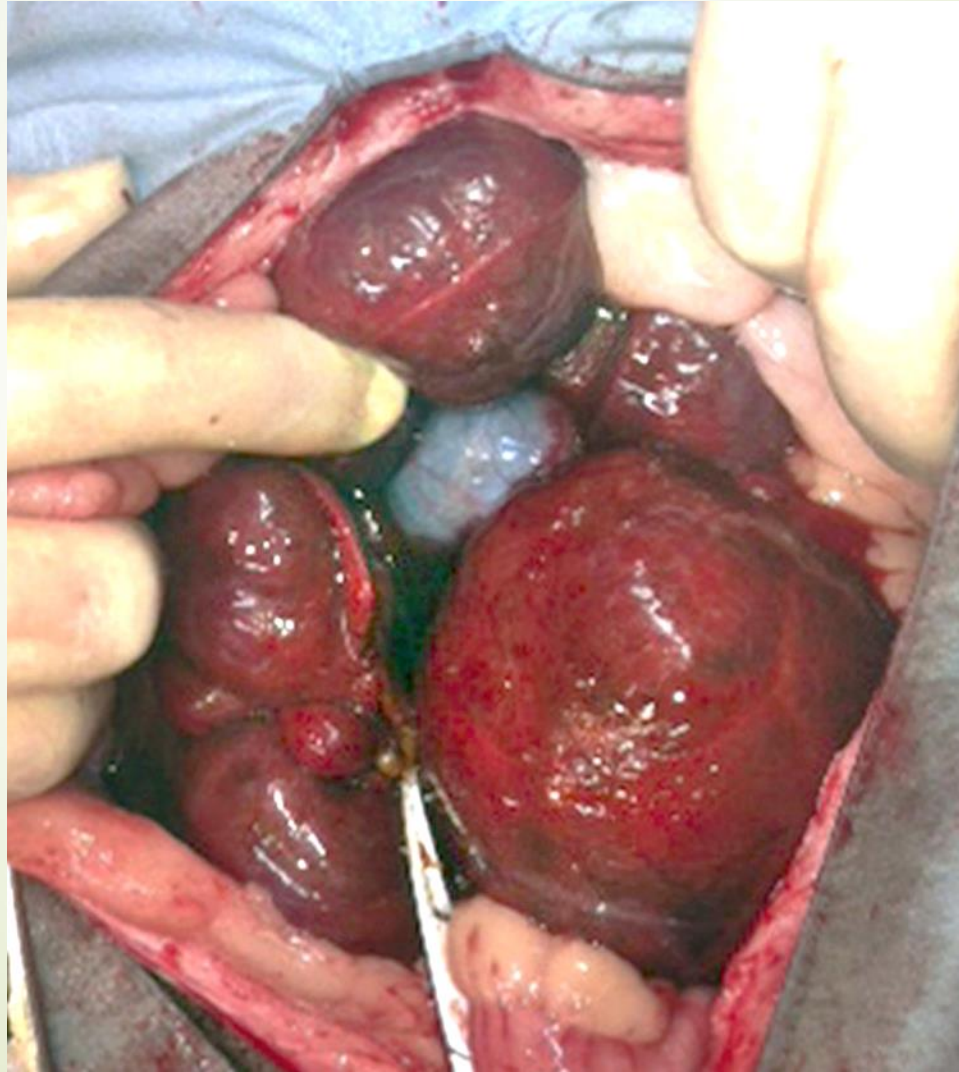


Myelolipoma

Cats > Dogs



Hepatic Splenosis



Metastasis

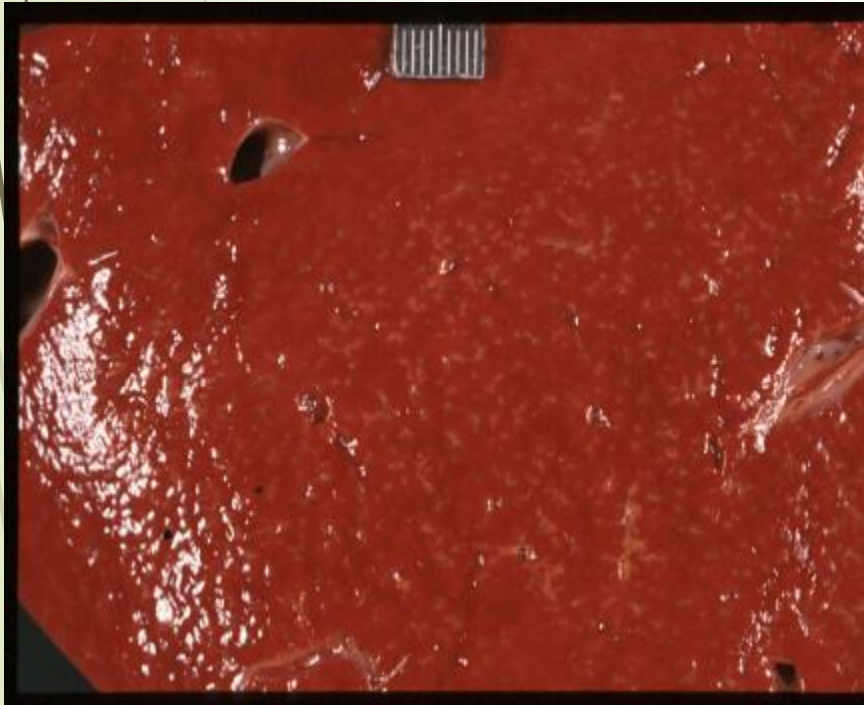
- Liver most common site of metastasis in most species

Hepatic metastasis of an intestinal carcinoma

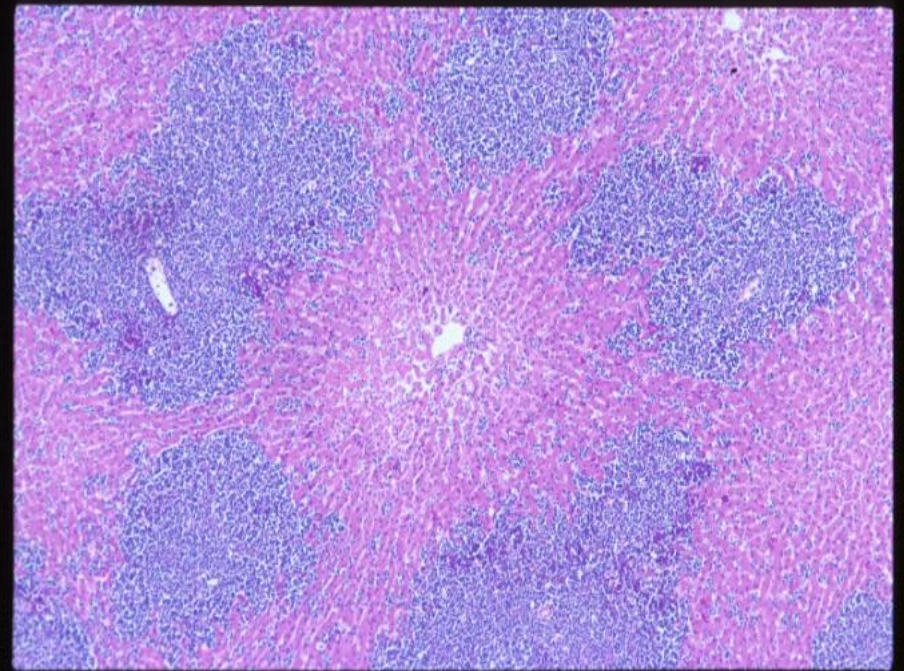


Hematopoietic Neoplasia

- Malignant lymphoma most common metastasis in most species



**Diffuse infiltration
at the gross level**



**Portal infiltration at
the histological level**



Hepatic Neoplasia: Conclusions

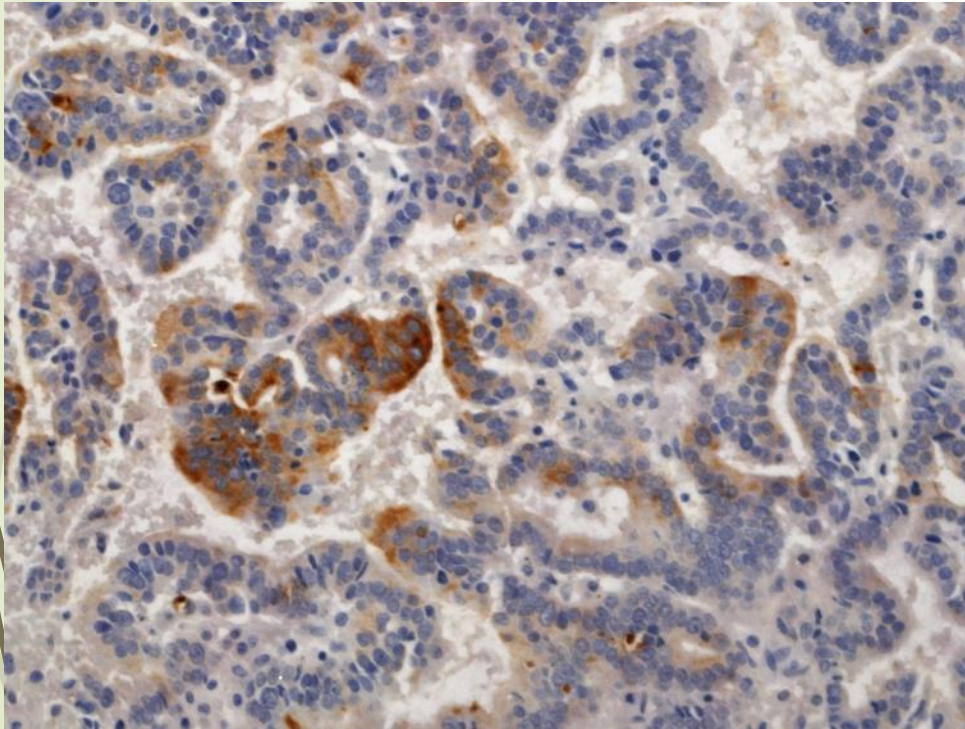
- ▶ Primary neoplasia of the liver is uncommon in dogs and cats.
- ▶ Metastasis from HCC is generally uncommon in dogs and cats, but occurs in about one half of lemur liver tumors.
- ▶ Metastasis from Cholangiocellular carcinoma is very common
- ▶ New markers associated with prognosis are being developed



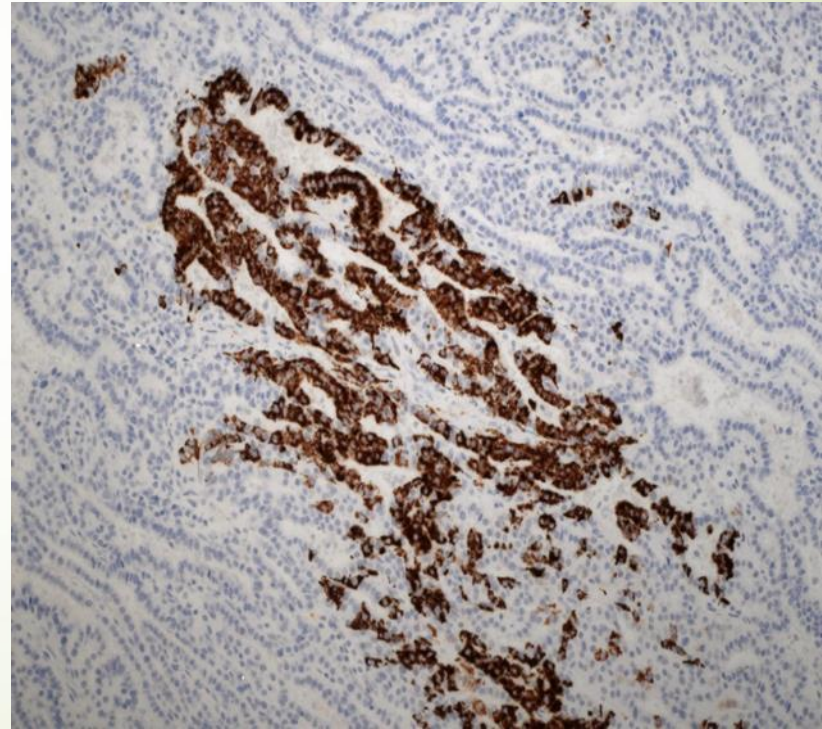
Thank You



Mixed Hepatocellular- choleangiocellular CA



Cytokeratin 7



Cytokeratin 19