HPB Pathology

Dr Jemimah Denson

University Hospitals Plymouth

Outline of this presentation

- Issues in referral/MDT practice
- Gall bladder common issues
- Targeted liver biopsies

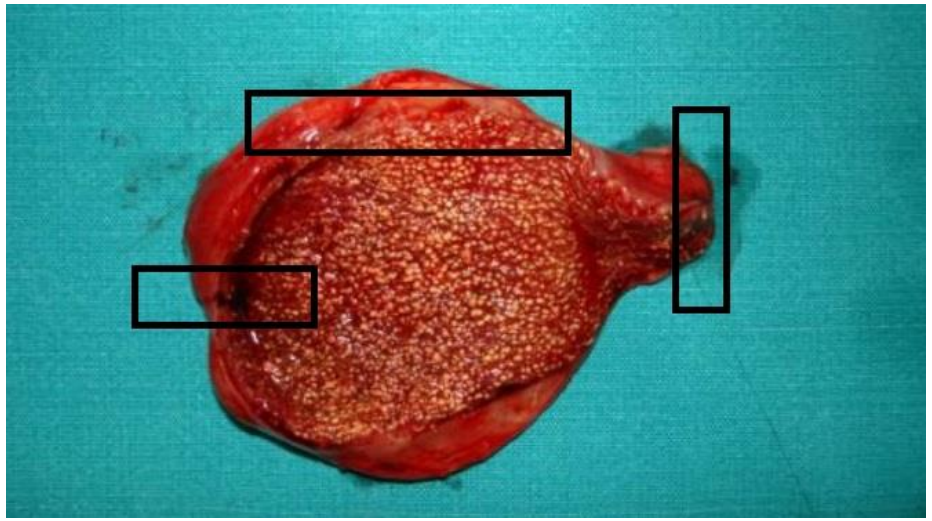
Gall bladder

- Macroscopy and sampling
- Approach to flat dysplasia & DD
- Polyps

GB macro & sampling

Issues in referral work:

- Site of lesion in GB not described
- Relationships to margins not described
- Margins not clearly defined/identifiable on microscopy
- CD margin not sampled properly
- Defects in specimen not described

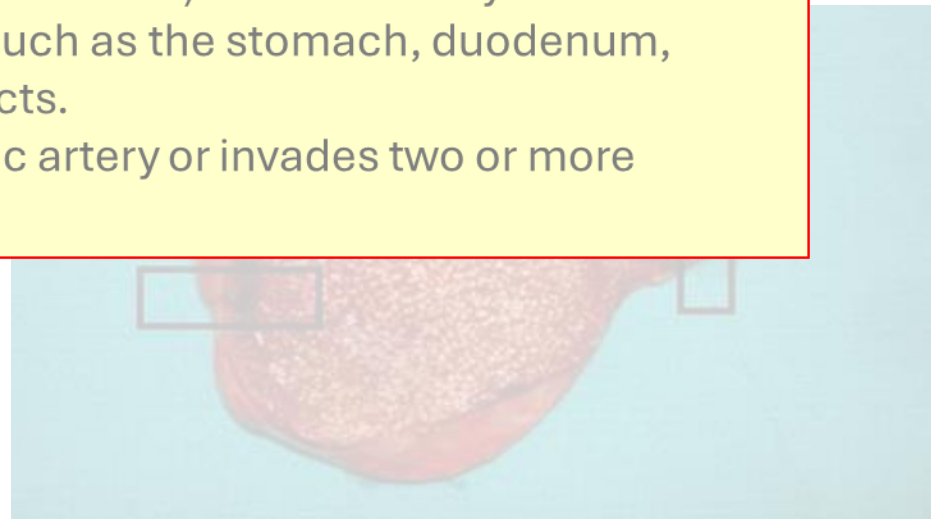


GB macro & sampling

pT0	No evidence of primary tumour
pTis	Carcinoma in situ, BillN3, high-grade dysplasia
pT1a	Tumour invades lamina propria
pT1b	**Tumour invades muscular layer**
pT2a	**Tumour invades perimuscular connective tissue on the peritoneal side with no extension to the serosa**
pT2b	**Tumour invades perimuscular connective tissue on the hepatic side with no extension into the liver**

pT3 Tumour perforates the serosa (visceral peritoneum) and/or directly invades the liver and/or one other adjacent organ or structure, such as the stomach, duodenum, colon, pancreas, omentum or extra-hepatic bile ducts.

pT4 Tumour invades main portal vein or hepatic artery or invades two or more extrahepatic organs or structures.



GB macro & sampling

- Mass present
  - Size, characteristics etc.
  - Relationships – which side of GB, serosal surface, margins:
    - Cystic duct
    - Gall bladder bed (liver)
    - CRM
  - Ink GB bed margin
  - Sample:
    - Mass
    - Serosa
    - Margins – GB bed, CD, CD CRM
    - Background

GB macro & sampling

- No mass seen macroscopically
  - Metaplasia – no need for further sampling
  - LG BilIN – 1 extra block per cm
  - HG BilIN – whole GB
  - ICPN - 'thorough sampling'
  - Hyalinising cholecystitis/porcelain GB - 'thorough sampling'
  - Carcinoma - 'thorough sampling’

  - NB: if history of PB mal-junction/other ‘risky biliary tree’ – embed entire GB
  - Check pot for free floating polyps

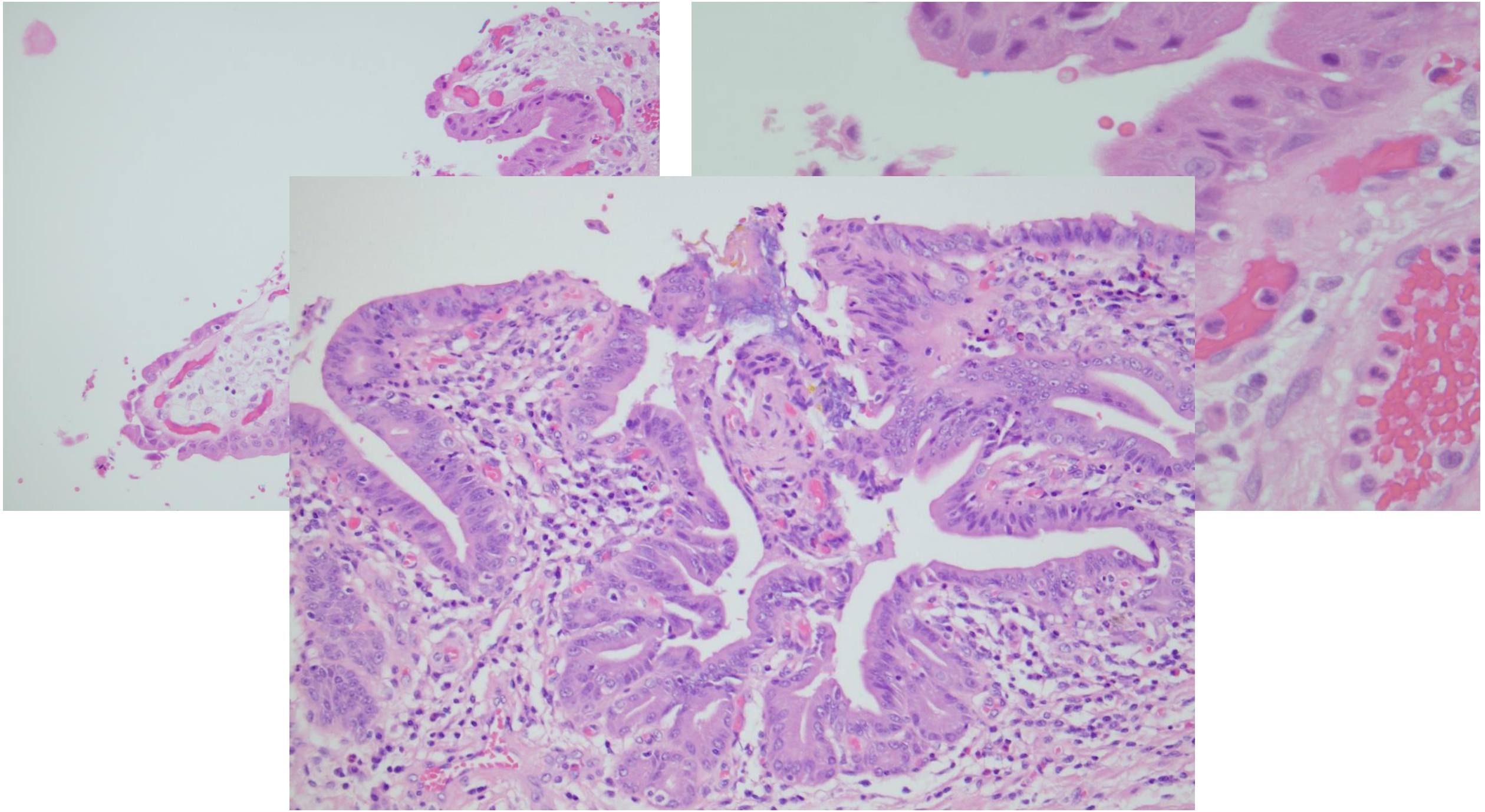
Flat dysplasia – common issues

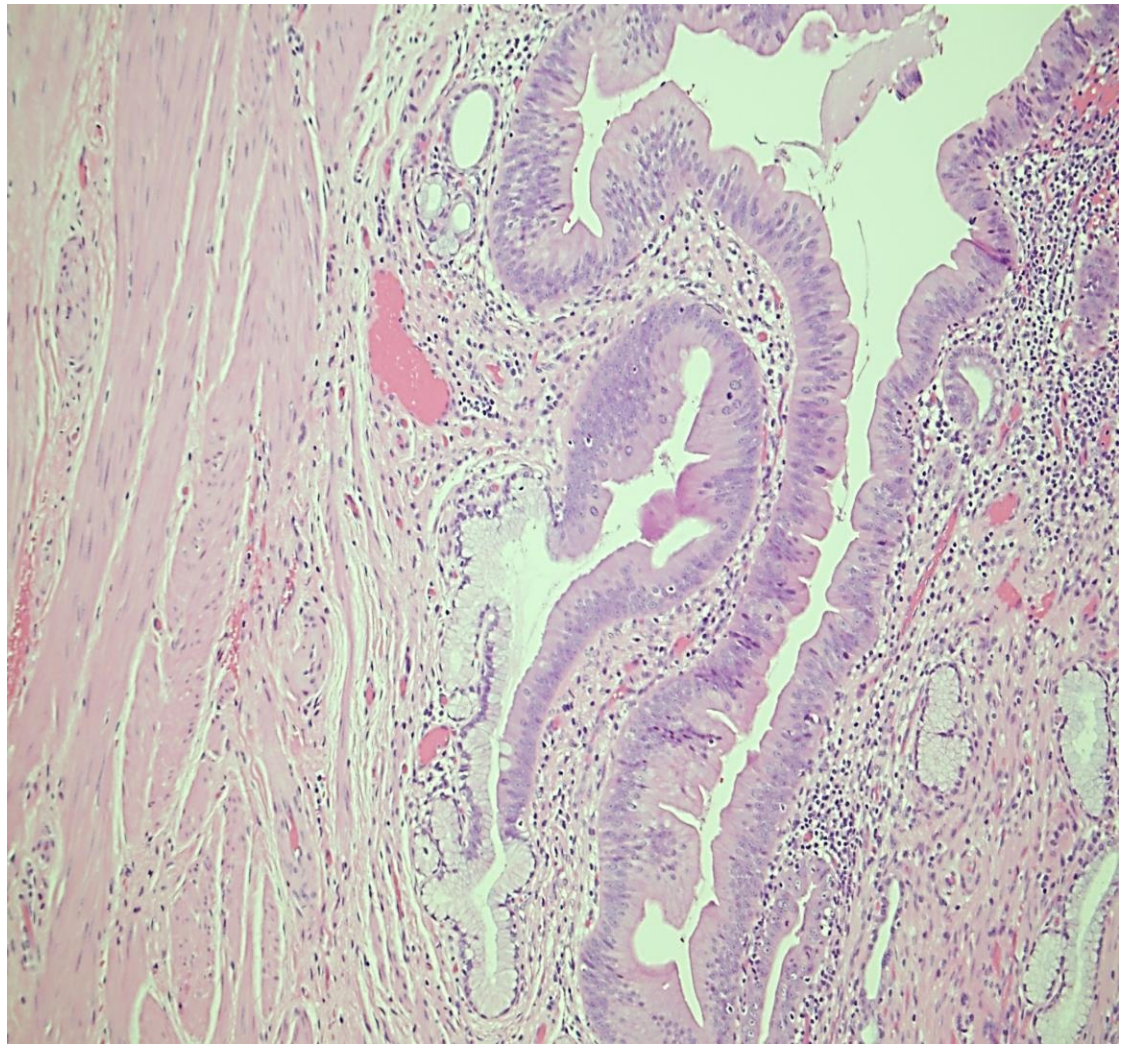
- Reactive vs low-grade dysplasia
- Low- versus high-grade dysplasia
- Dysplasia that can be missed
- High-grade dysplasia vs carcinoma

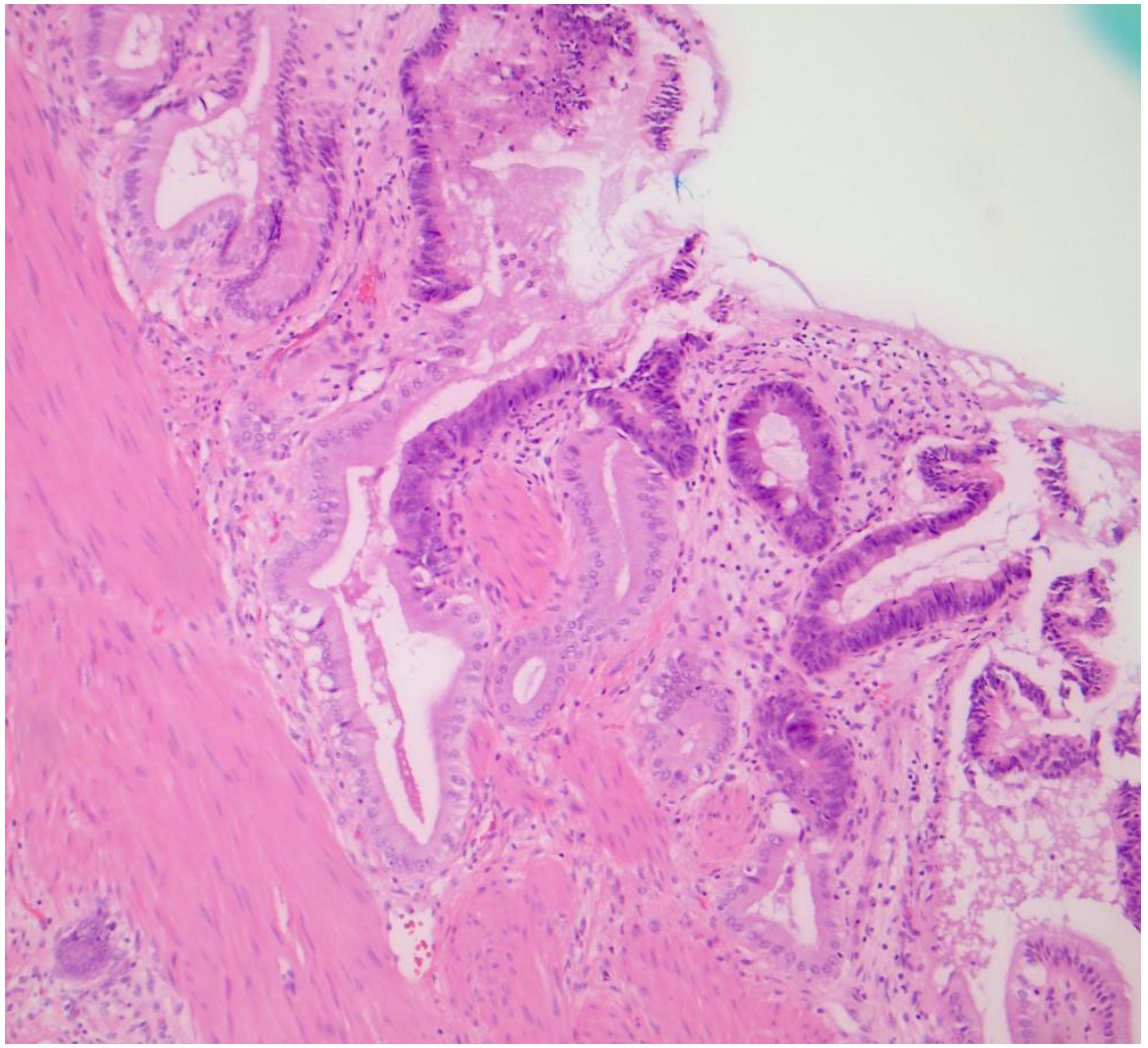
Reactive change vs low-grade dysplasia

Favours reactive	Favours dysplastic	Not helpful
• Inflammation • **Intercellular clefts** • Attenuated epithelium • Pale nuclei • Maturation • Blending into background • Signs of injury or repair	• Hyperchromasia • Stratification • Hyperchromasia, coarse chromatin, nucleoli • Present at surface • Abrupt cut-off • Metaplasia (IM or foveolar)	• Mitoses • IHC

Does it matter? - focal vs diffuse. Sampling. Resection margin

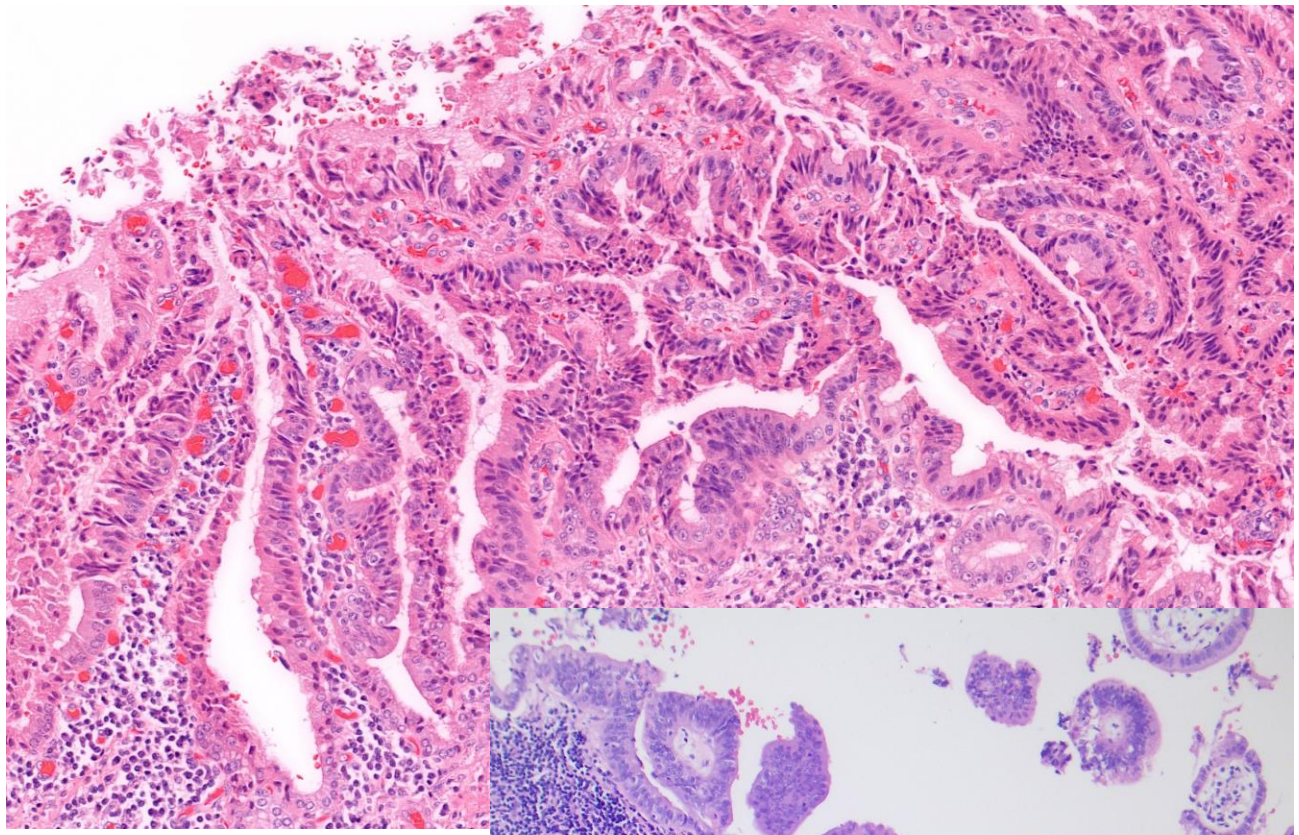


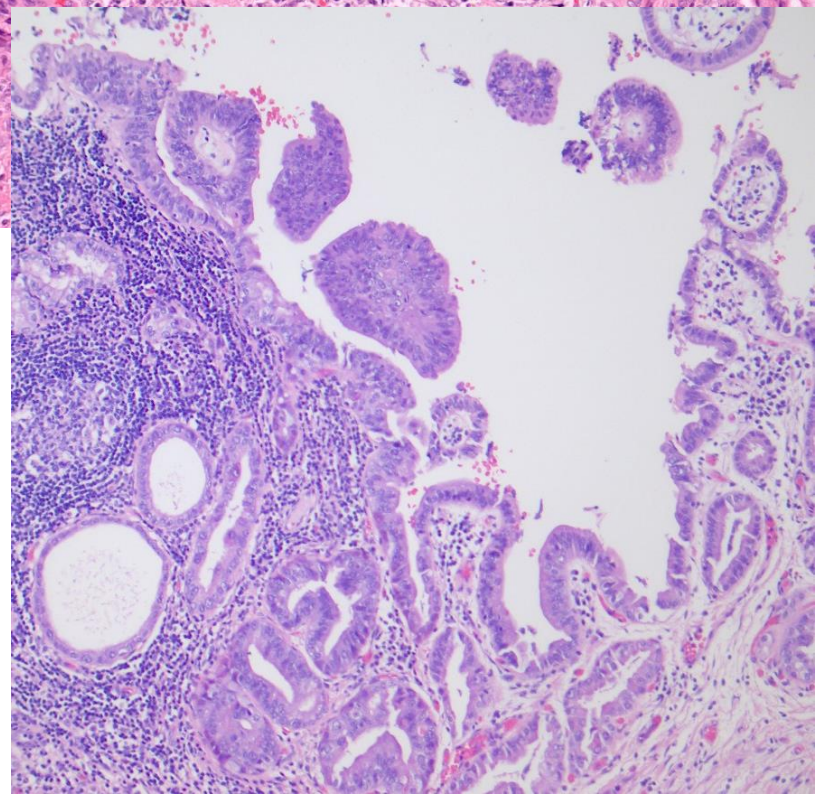


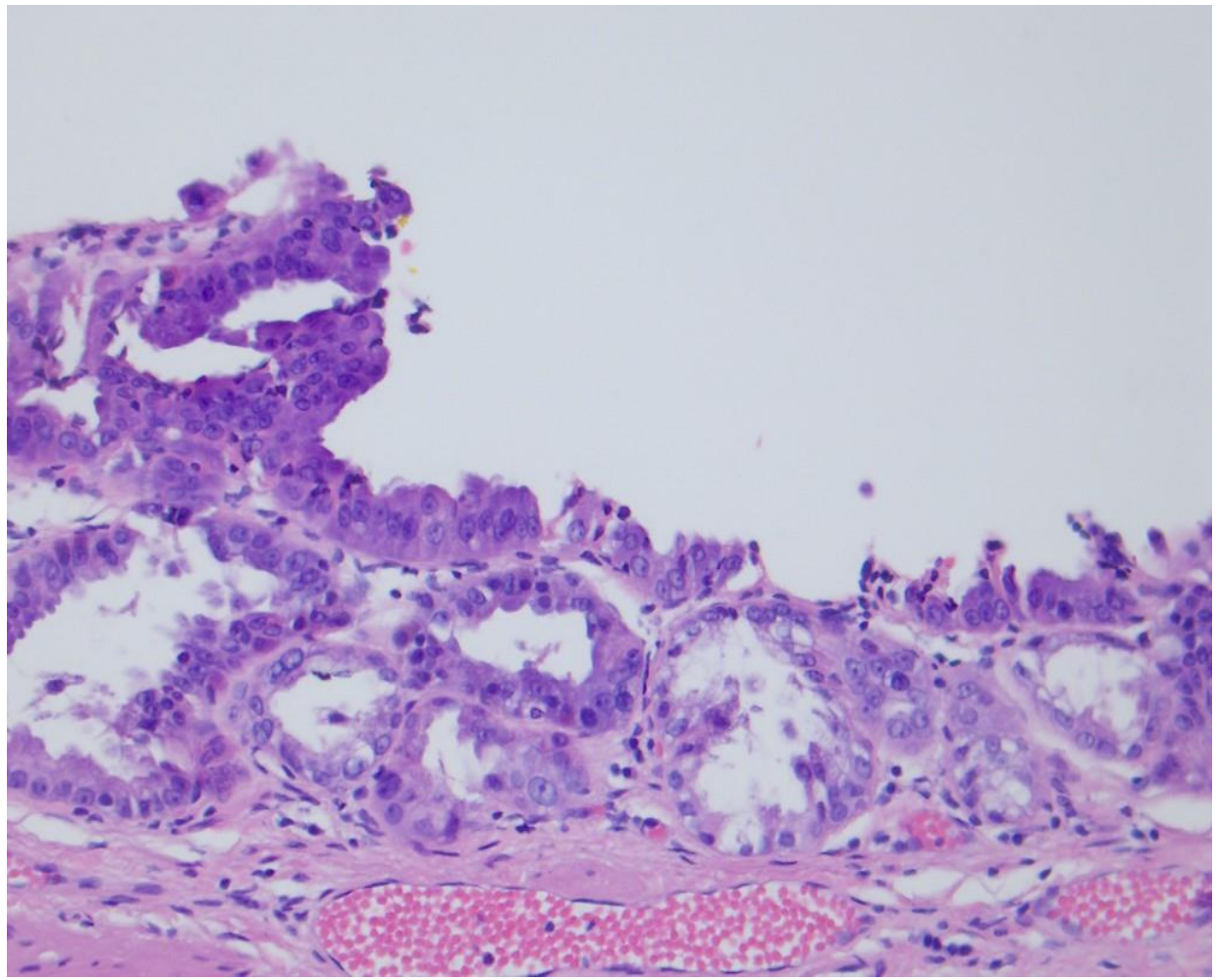


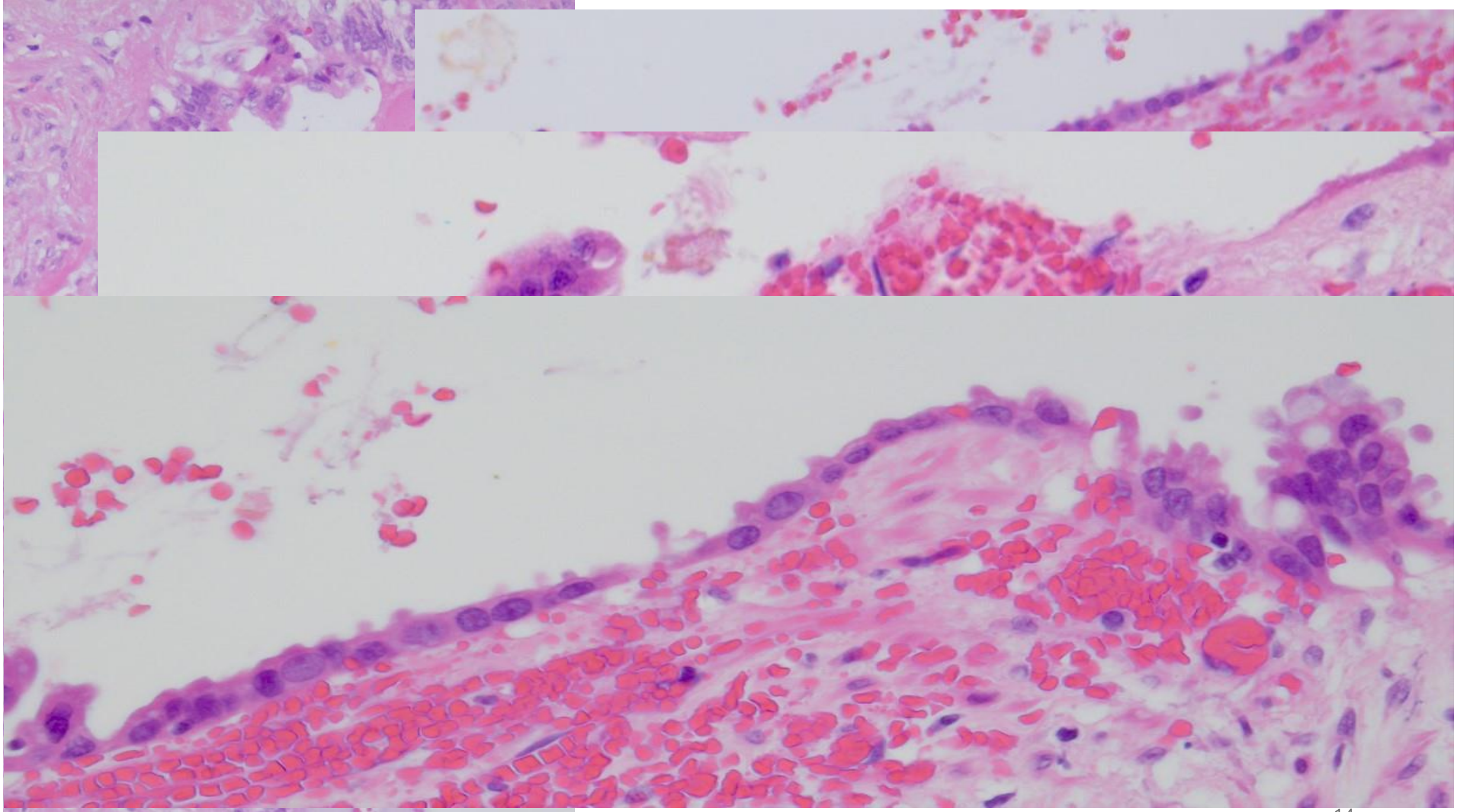
Low-grade dysplasia vs high-grade dysplasia

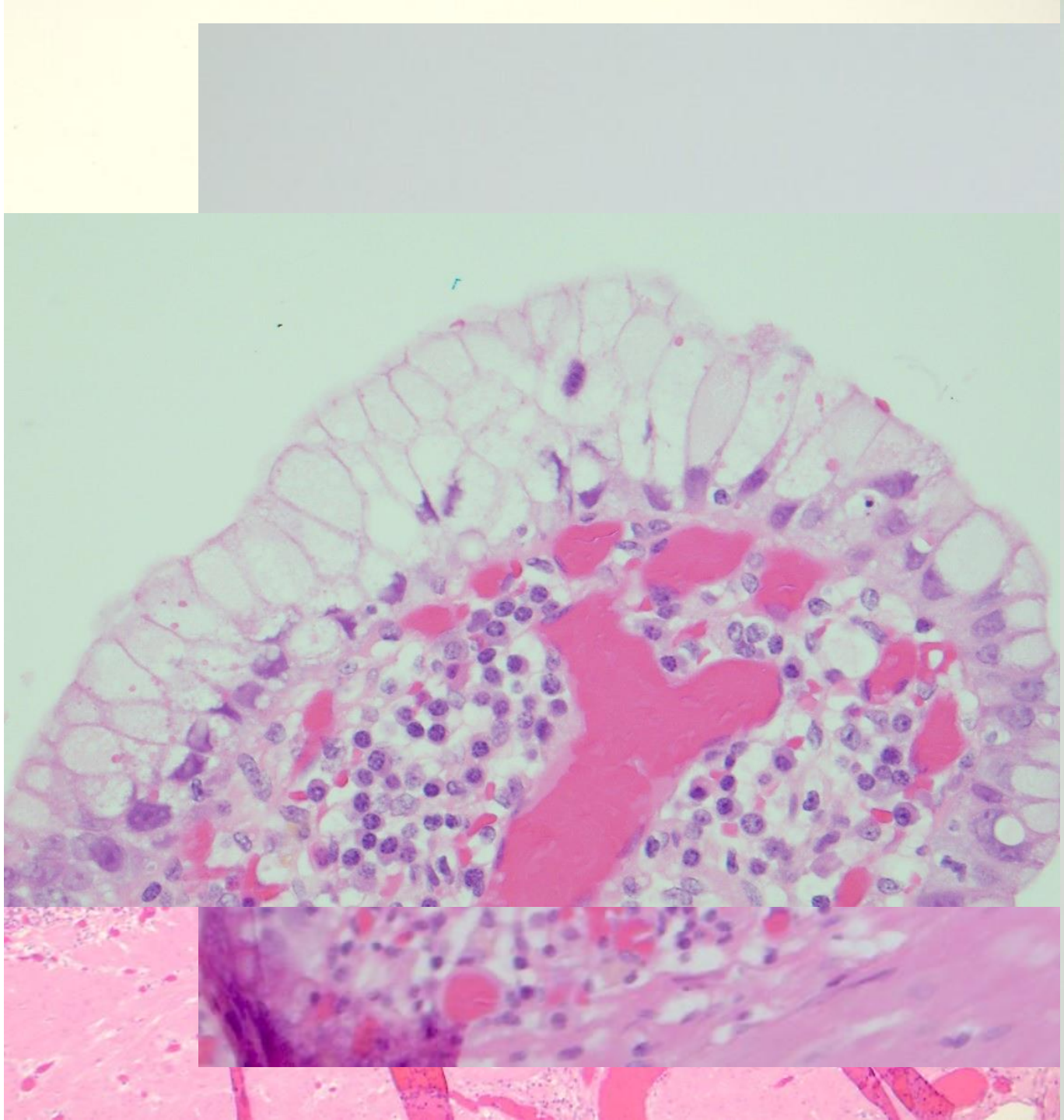
- Sample widely!
- HGD is more likely to be widespread
- More architectural complexity
- More stratification, atypia, mitoses etc.

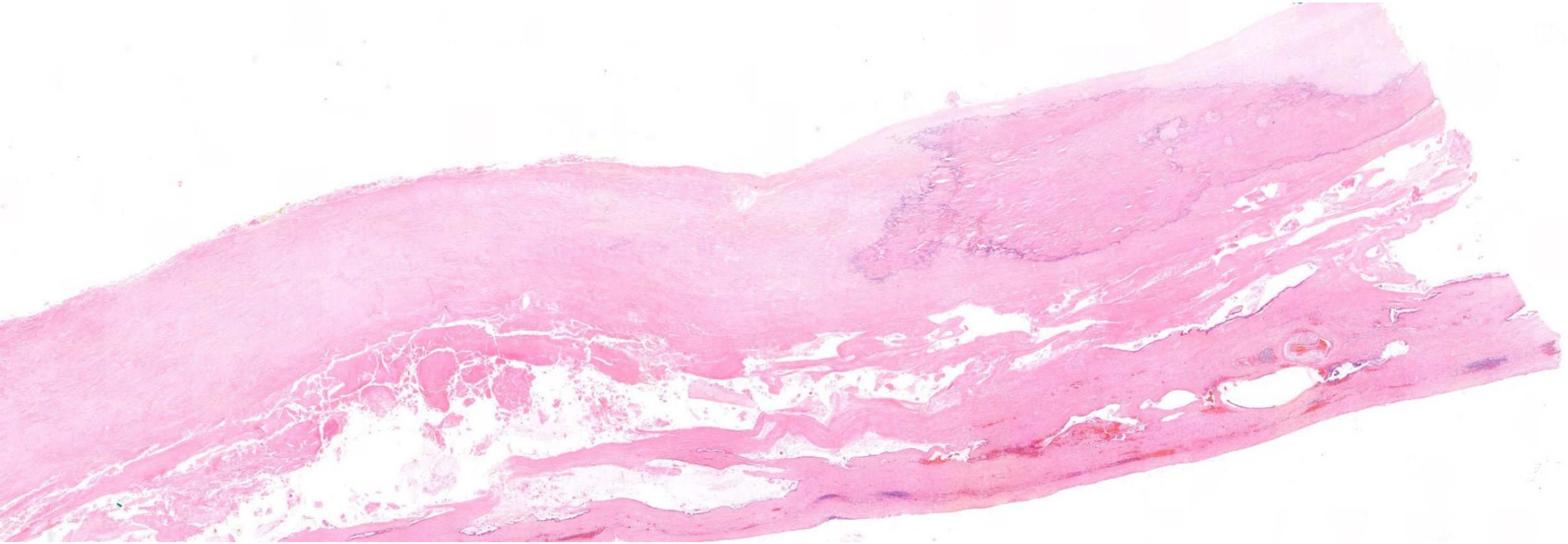






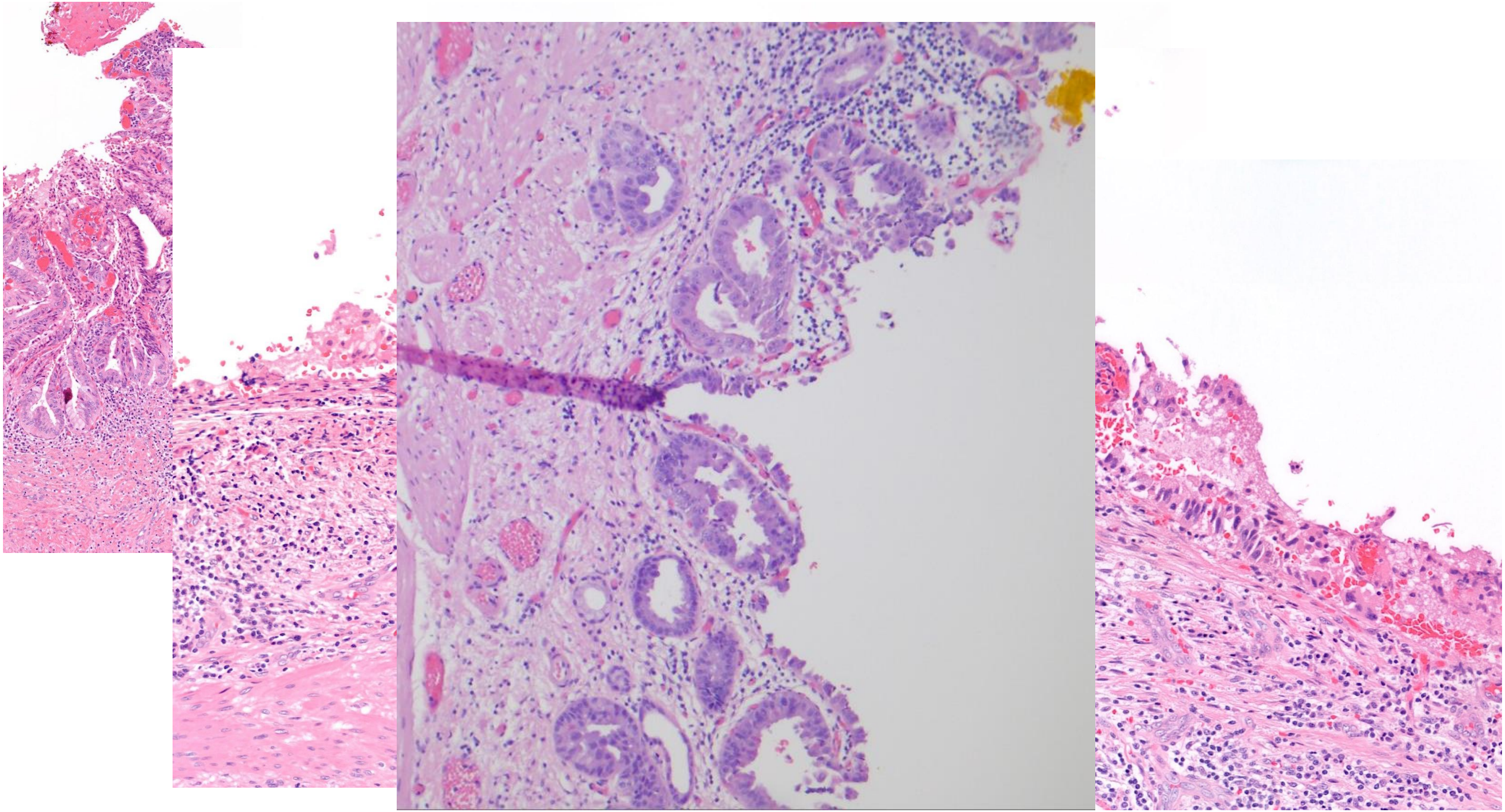


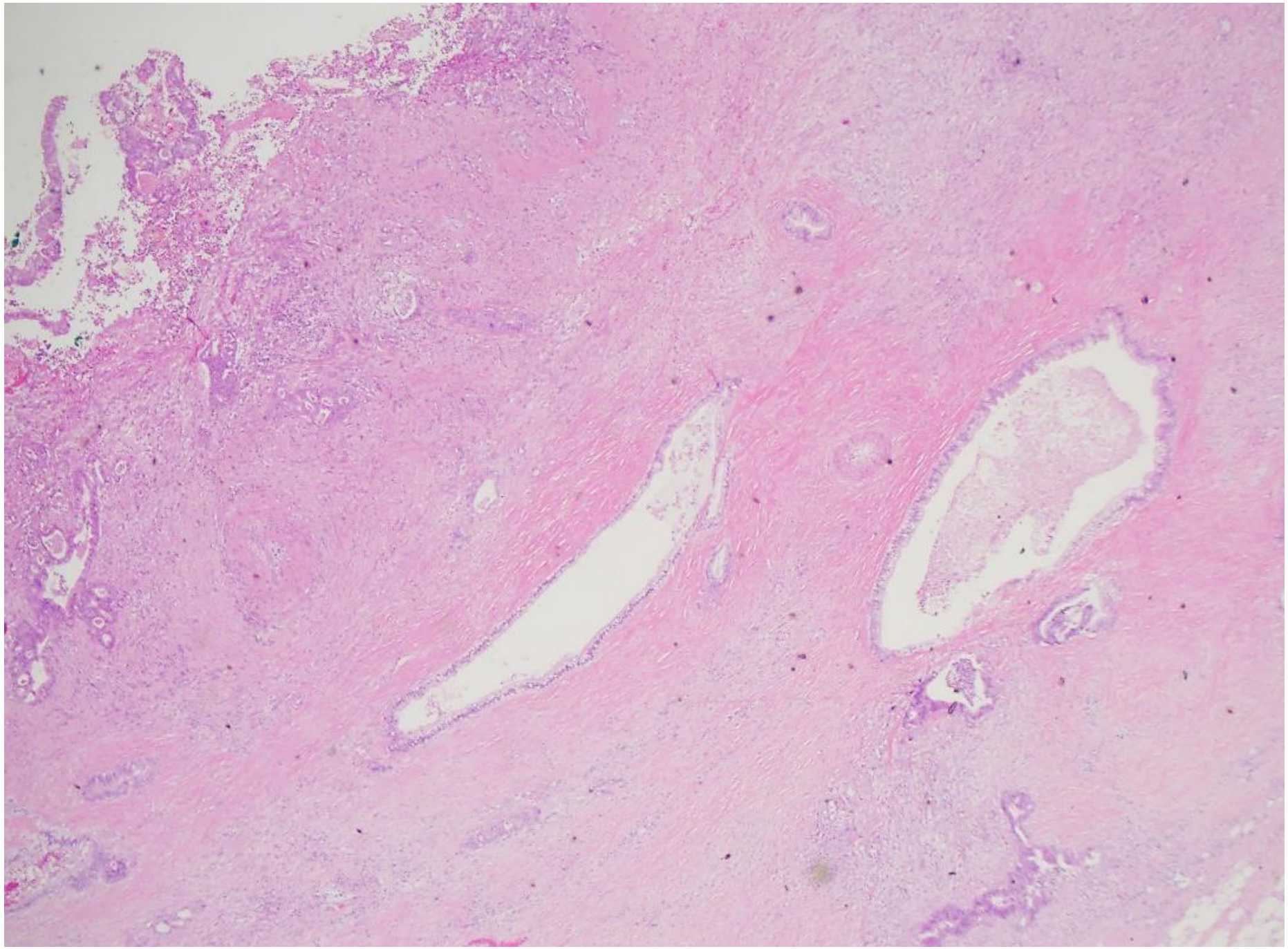


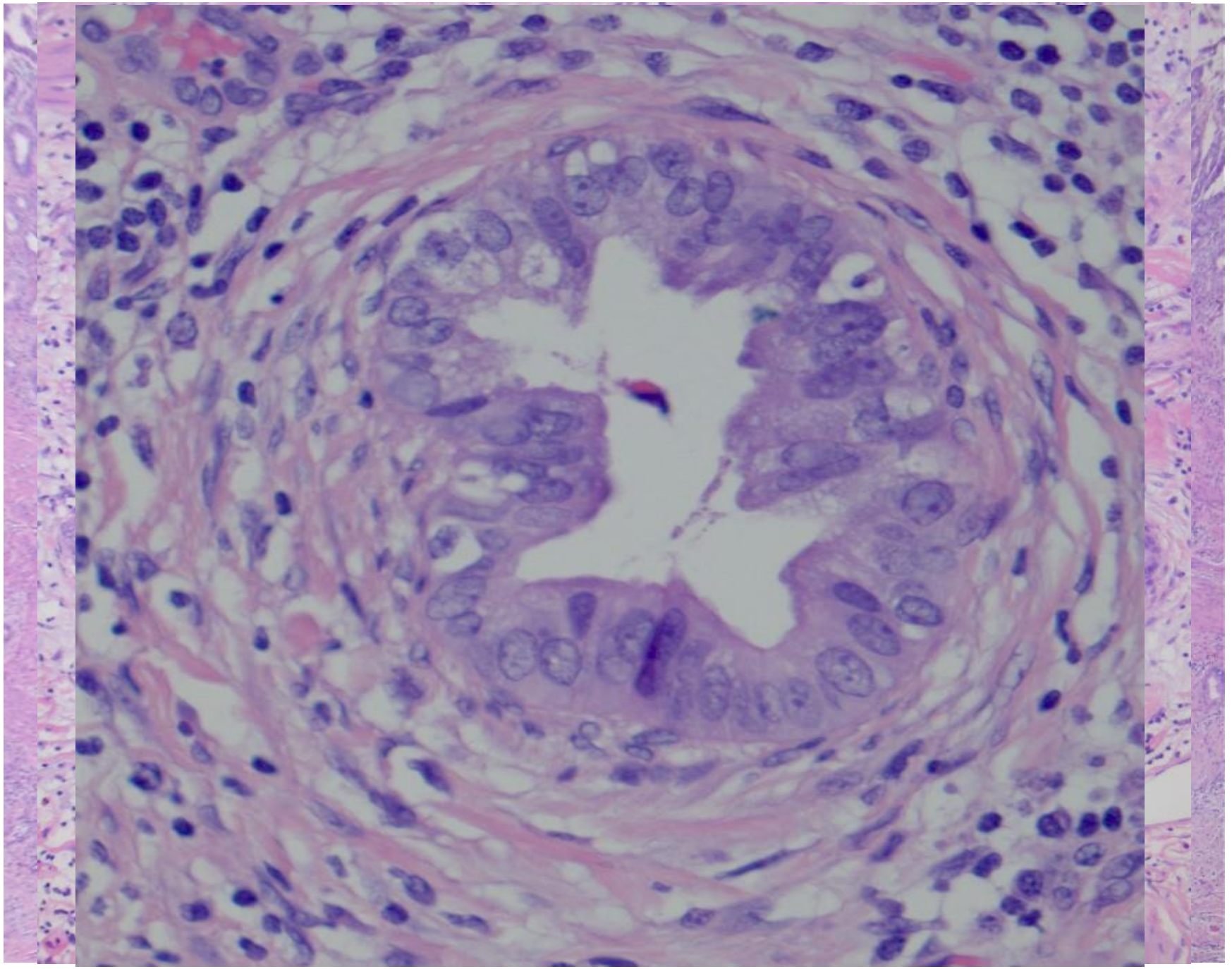


High-grade dysplasia vs carcinoma

- HGD vs pT1a
  - Difficult and debated – varies around the world.
  - Deeper glands which are very different to surface and very complex architecture favours pT1a
  - Natural history for HGD (pTis) and pT1 is very similar
- HGD in RA sinuses vs deeper carcinoma
  - Levels may help
  - Be aware of: horizontal RA sinuses, deeper atypical glands that can't be convincingly shown to connect to surface.
  - If not definitive carcinoma but still concerned, suggest imaging follow-up.
  - Even if fully excised, HGD does not have a 100% survival rate – field change, undetected cancer.
- Risks:
  - Presence at CD margin
  - Widespread
  - Extension into deep RA sinuses
  - 'risky biliary tree' - anomalous PD junction, PSC







Gall bladder polyps

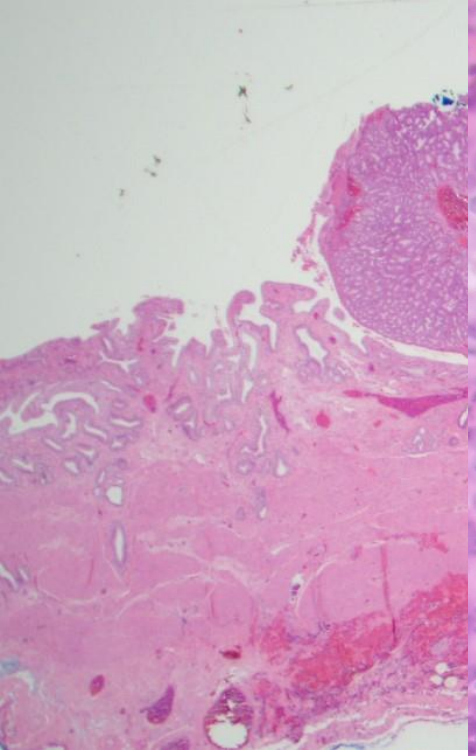
Cholesterol polyps, polypoid pseudopyloric metaplasia, inflammatory polyps etc.

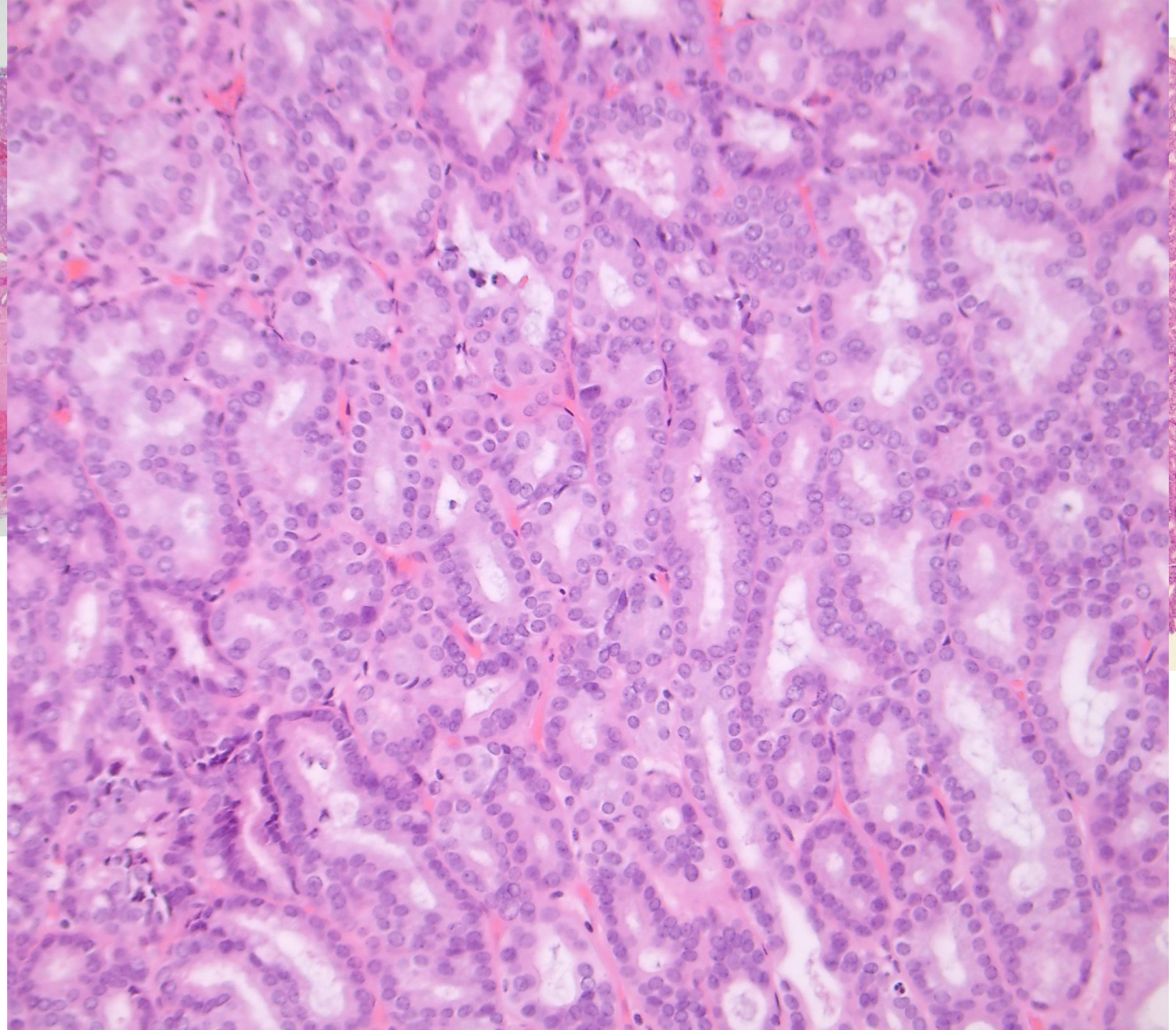
Intracholecystic neoplasms

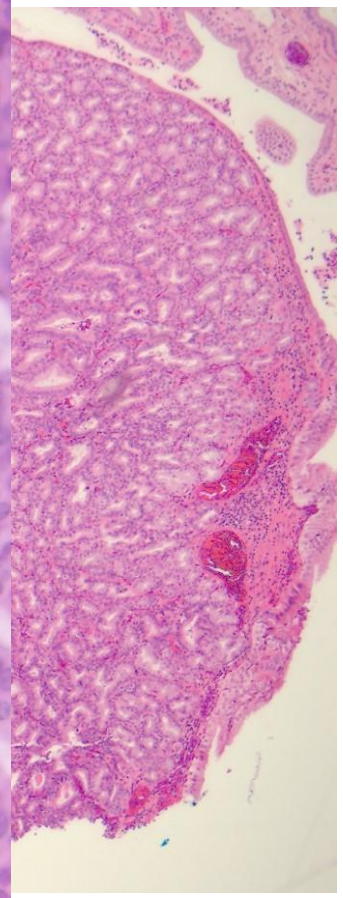
- Pyloric gland adenoma
- Intracholecystic papillary neoplasms (ICPN)
- Intracholecystic tubular non-mucinous neoplasm (ICTN)

Pyloric gland adenoma

- Not common
- Association with stones (also PJS and FAP)
- Usually less than 2cm
- Pyloric-type glands, closely packed, minimal atypia
- Background mucosa not neoplastic
- Very rarely can see dysplasia or Ca in large lesions



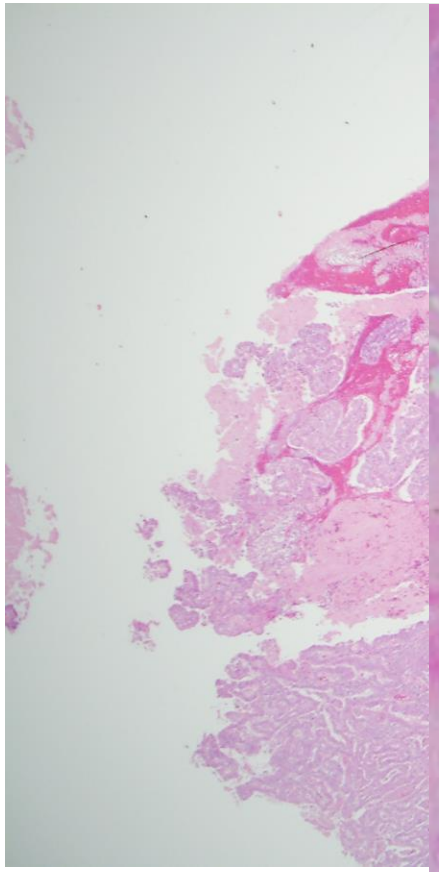


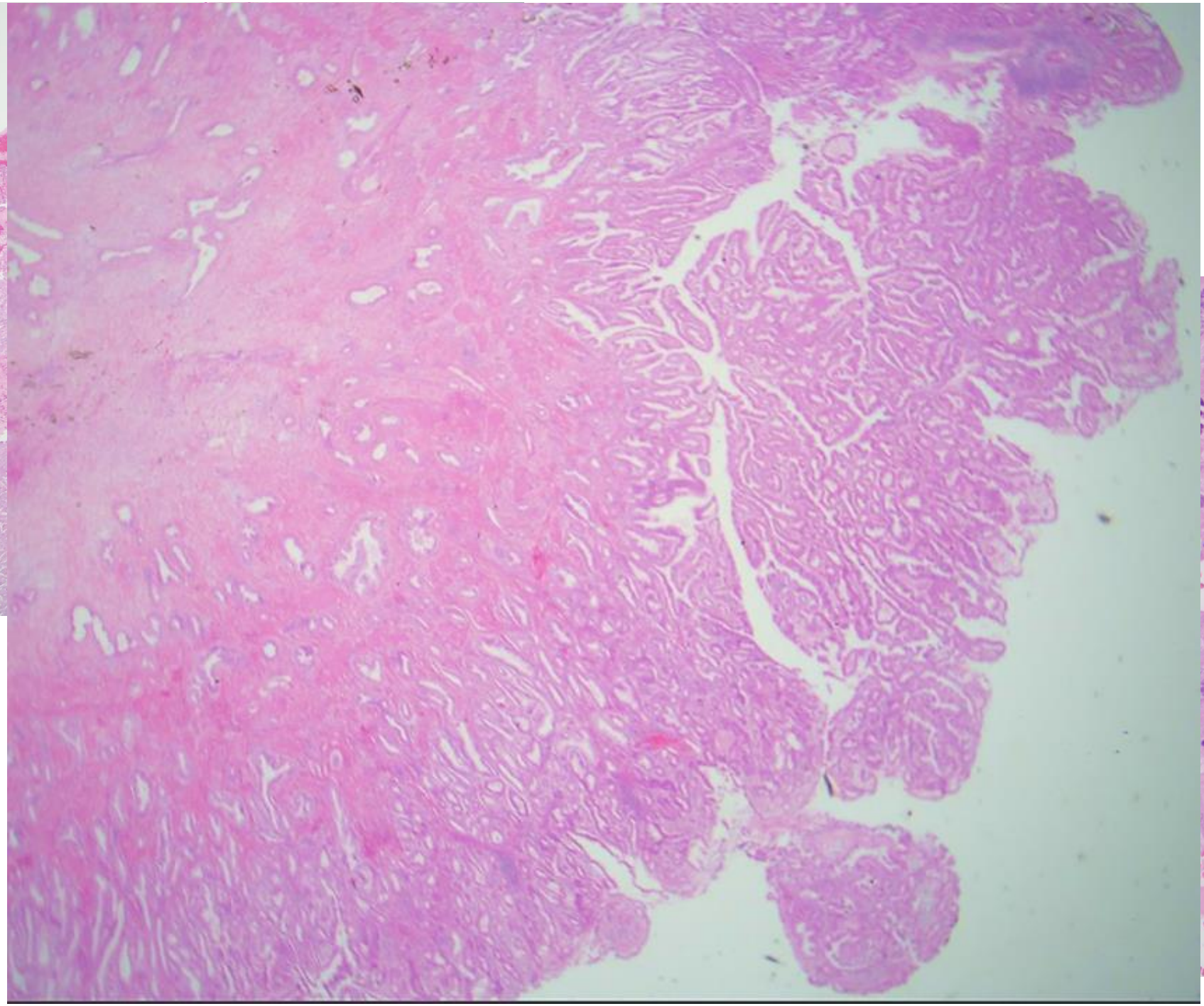


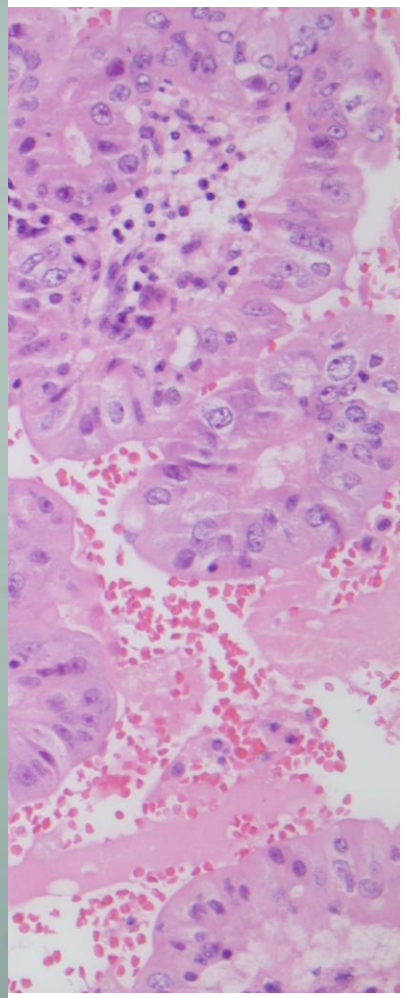
Intracholecystic papillary neoplasm

- Includes all neoplasms apart from PGA
- Usually over 10mm in size
- Can be multifocal
- Papillary or tubulopapillary growth
- Biliary, gastric, intestinal or oncocytic – often mixed
- Low- or high-grade dysplasia

- Strong association with invasion – sample widely as site of invasion isn't always at same site as polyp







Intracholecystic tubular non-mucinous neoplasms (ICTN)

- Not in WHO yet
- Tightly packed tubules lined by low-cuboidal (non-mucinous cells)
- Foci with nuclear features akin to papillary thyroid Ca
- Squamous morules can be present
- Due to architecture are graded as high-grade
- BUT – no field change effect and appear lower risk of Ca than ICPN

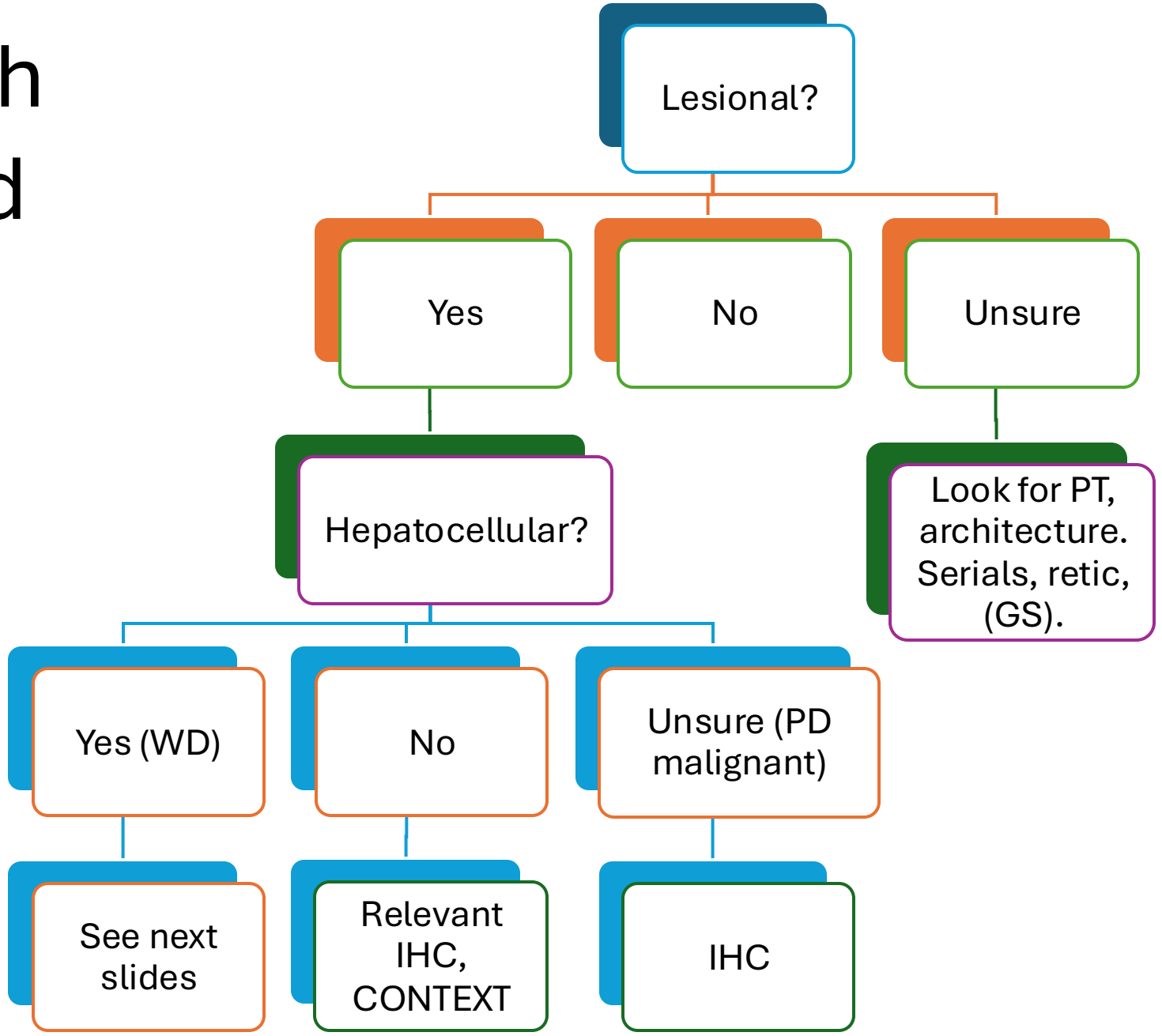
GB summary & tips

- Good macro description – educate all those doing cut-up
- Margins!
- ‘risky’ situations
  - HGD
  - Dysplasia in RA sinuses
  - Hyalinisation
  - Porcelain GB
  - Mucinous dysplasia
  - Neoplastic polyps

Liver – approach to targeted liver biopsies

FNH	
HCA	
HCC	
Non-hepatocellular	Adenocarcinoma - CC vs mets
	Other entities
Abscess/eosinophilic mass	

My approach to a targeted liver biopsy



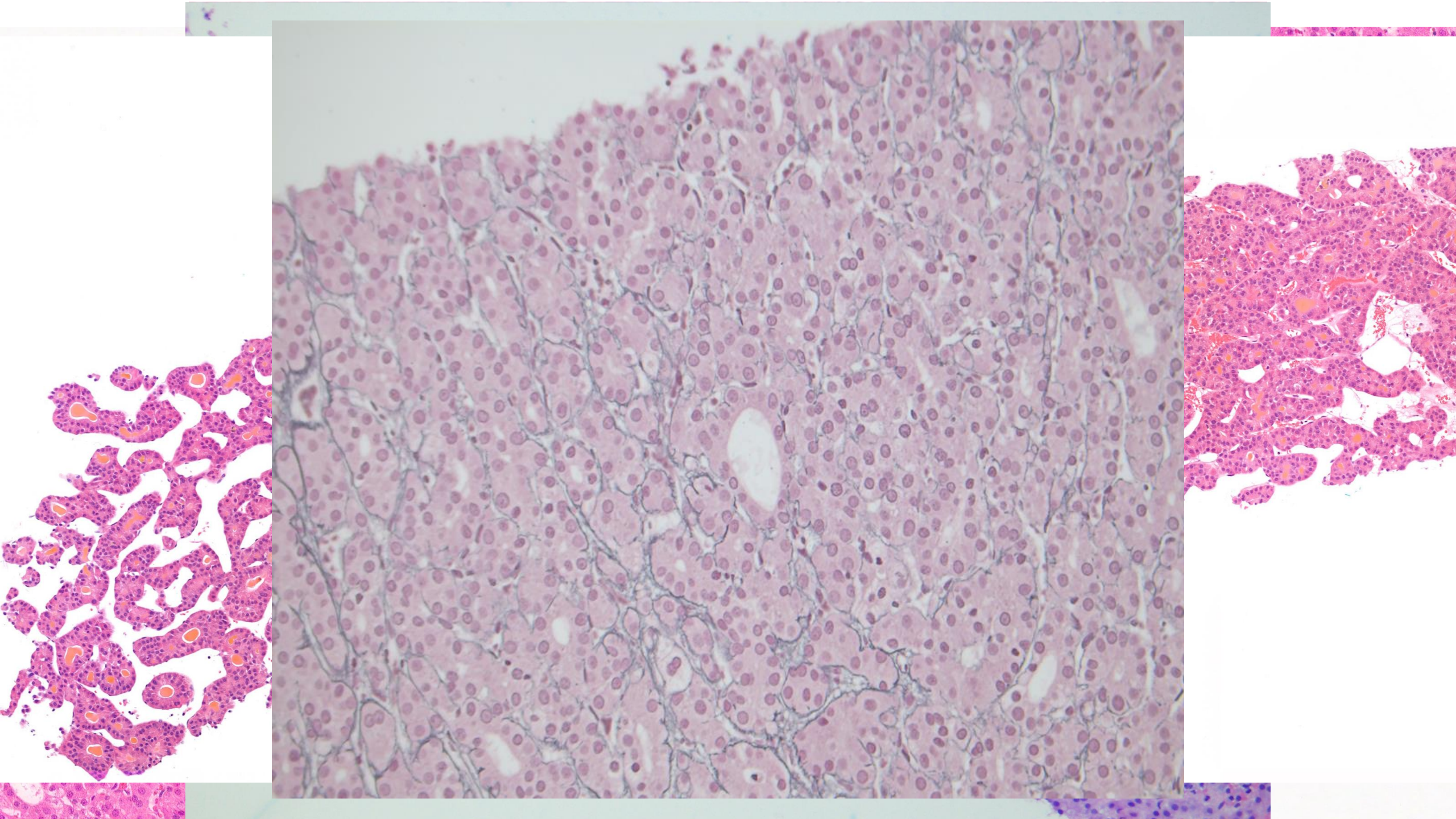
Looks well-diff hepatocellular – what are the options?

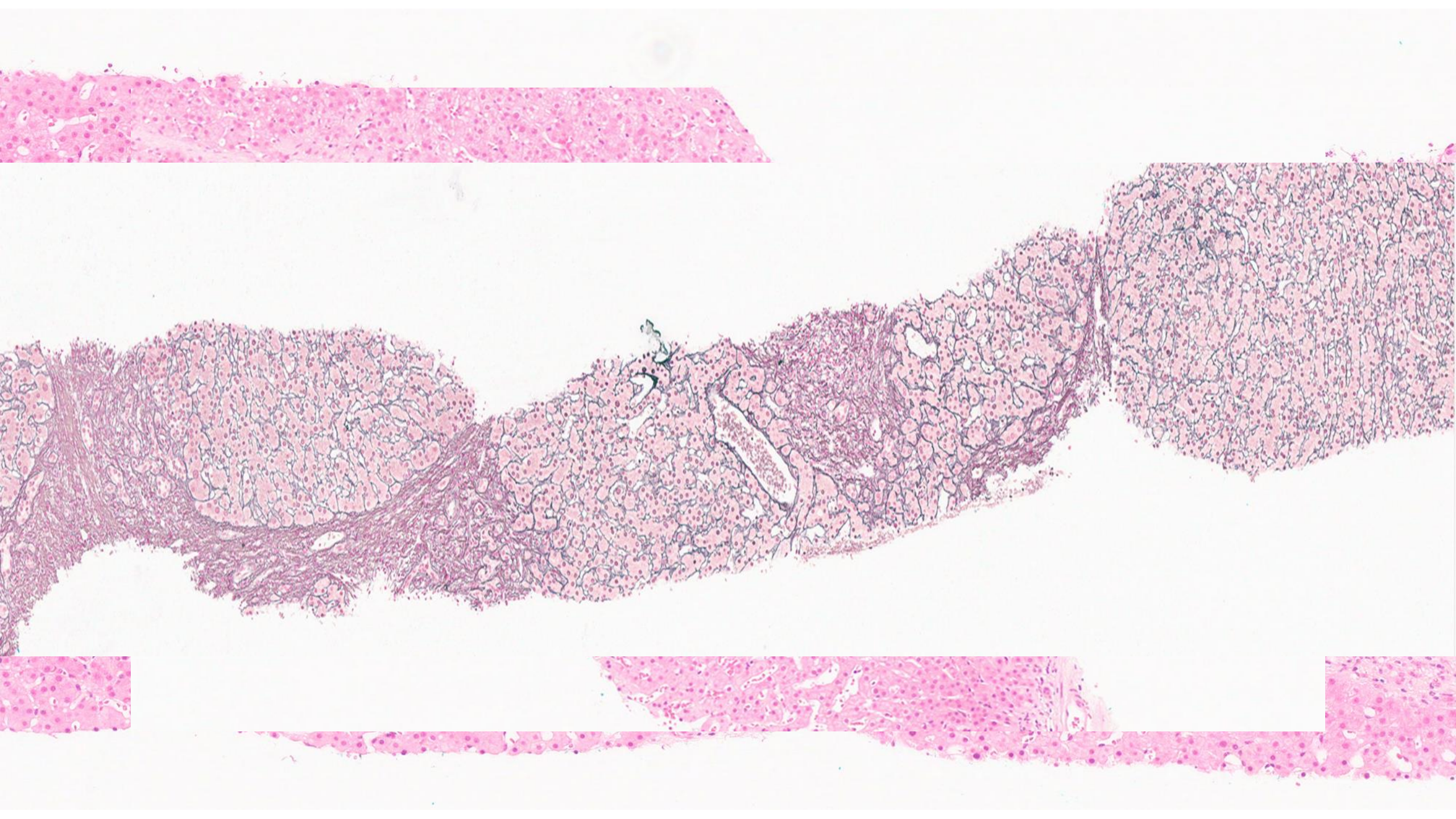
- Non lesional
- FNH
- HCA
- HCC
- (Other e.g. RHP, SAA pos nodule)

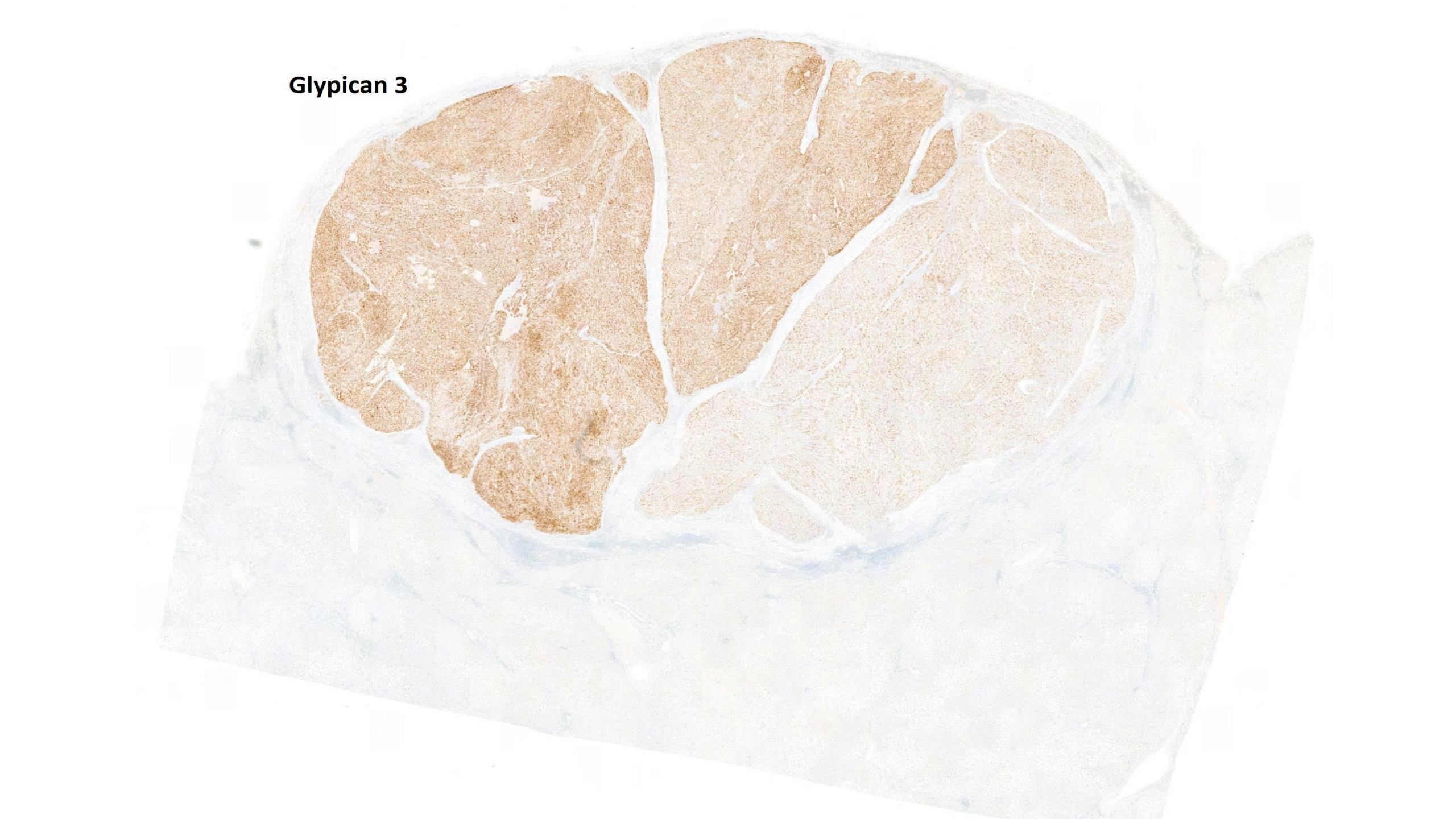
Why is this difficult??

Looks hepatocellular (well differentiated)

- CONTEXT
  - Age
  - Gender
  - PMHx
  - Drug Hx
  - Imaging appearances
  - Non-neoplastic liver – CLD, cirrhosis or not
- Morphology – lesion and background
- Reticulin
- Glypican 3, glutamine synthetase, HSP70
- Adenoma markers – SAA/CRP, LFABP, Beta catenin, GS






Glypican 3

Hepatocellular adenoma

HNF1A-inactivated

- More in females. 90% somatic mutation. Seatotic. Loss LFABP on IHC

Inflammatory

- More in females. Assoc with obesity, met synd, ETOH. Steatotic background liver. Sinusoidal diln. & inflammation. SAA/CRP positive.

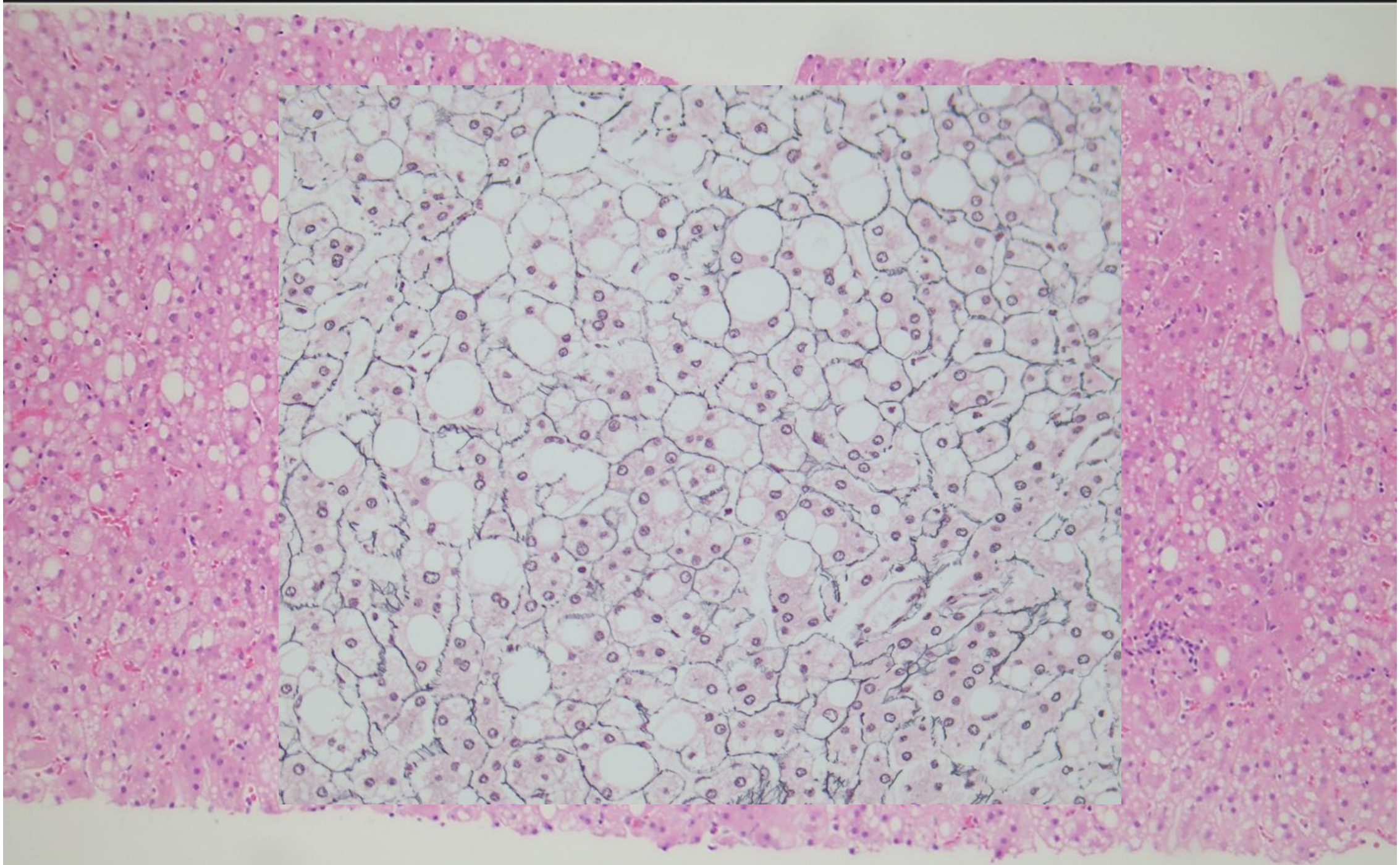
Beta catenin activated

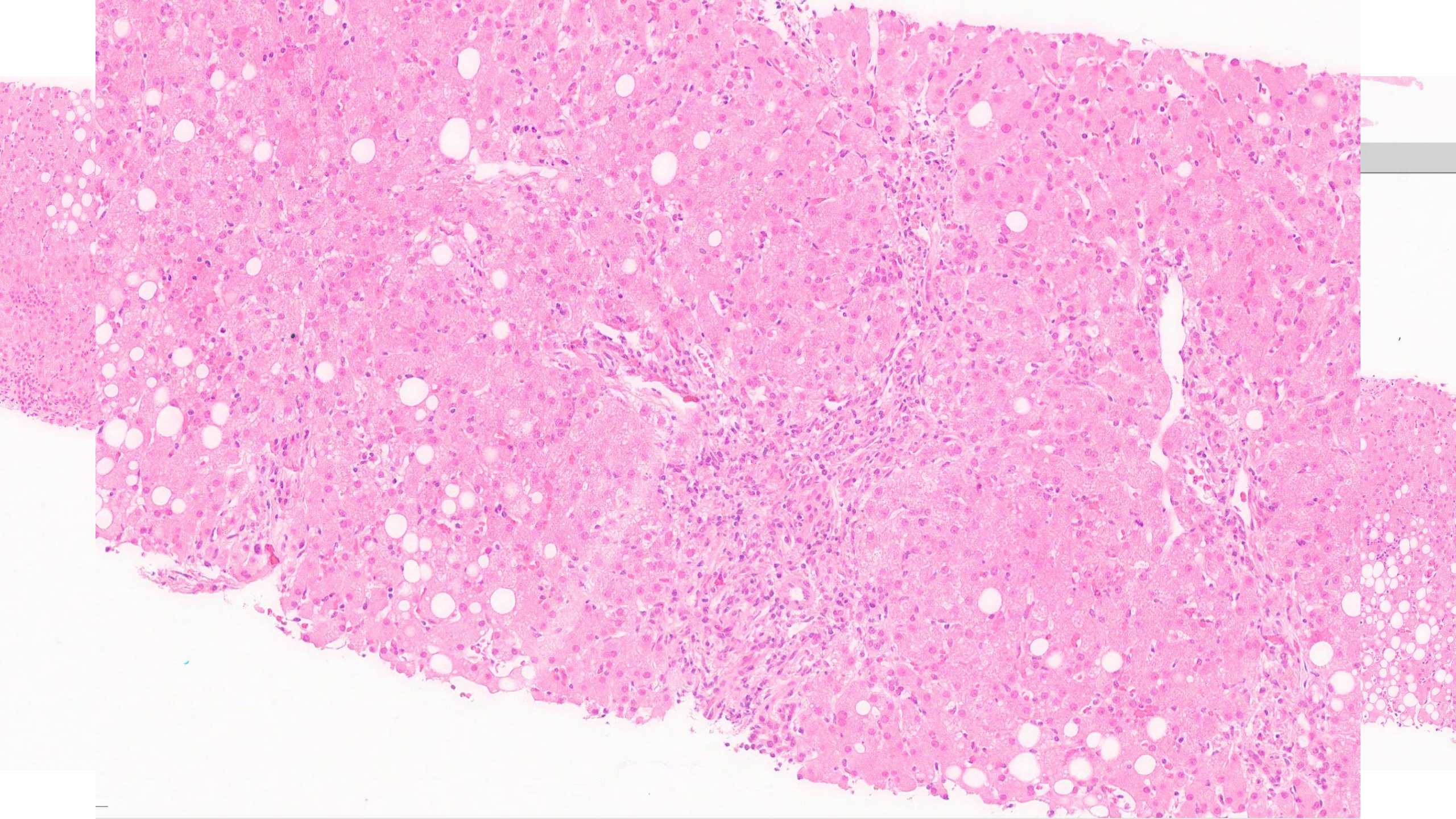
- Male & female, more atypia, nuclear BC, GS overexpression, highest risk of HCC

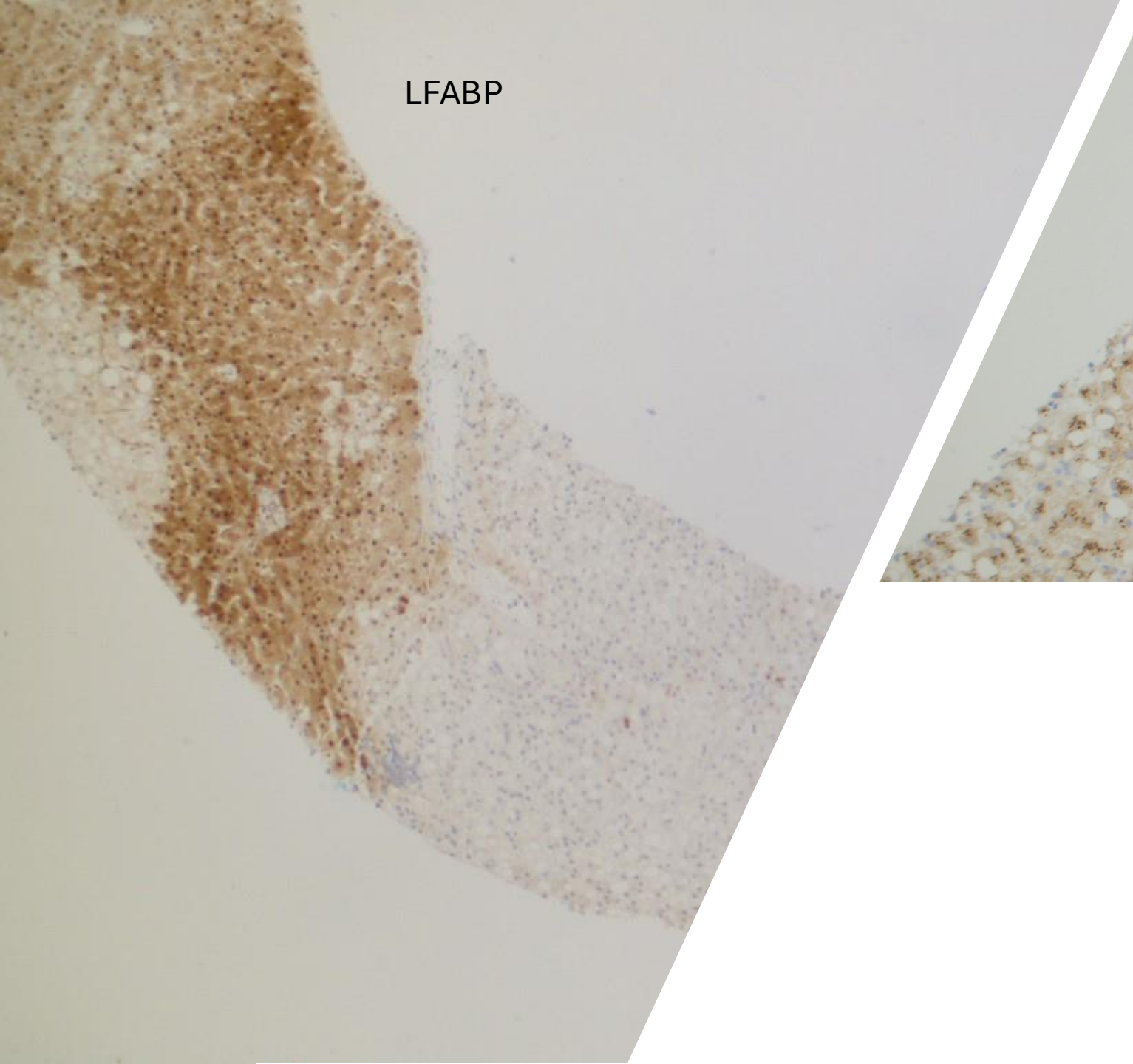
Sonic hedgehog activated

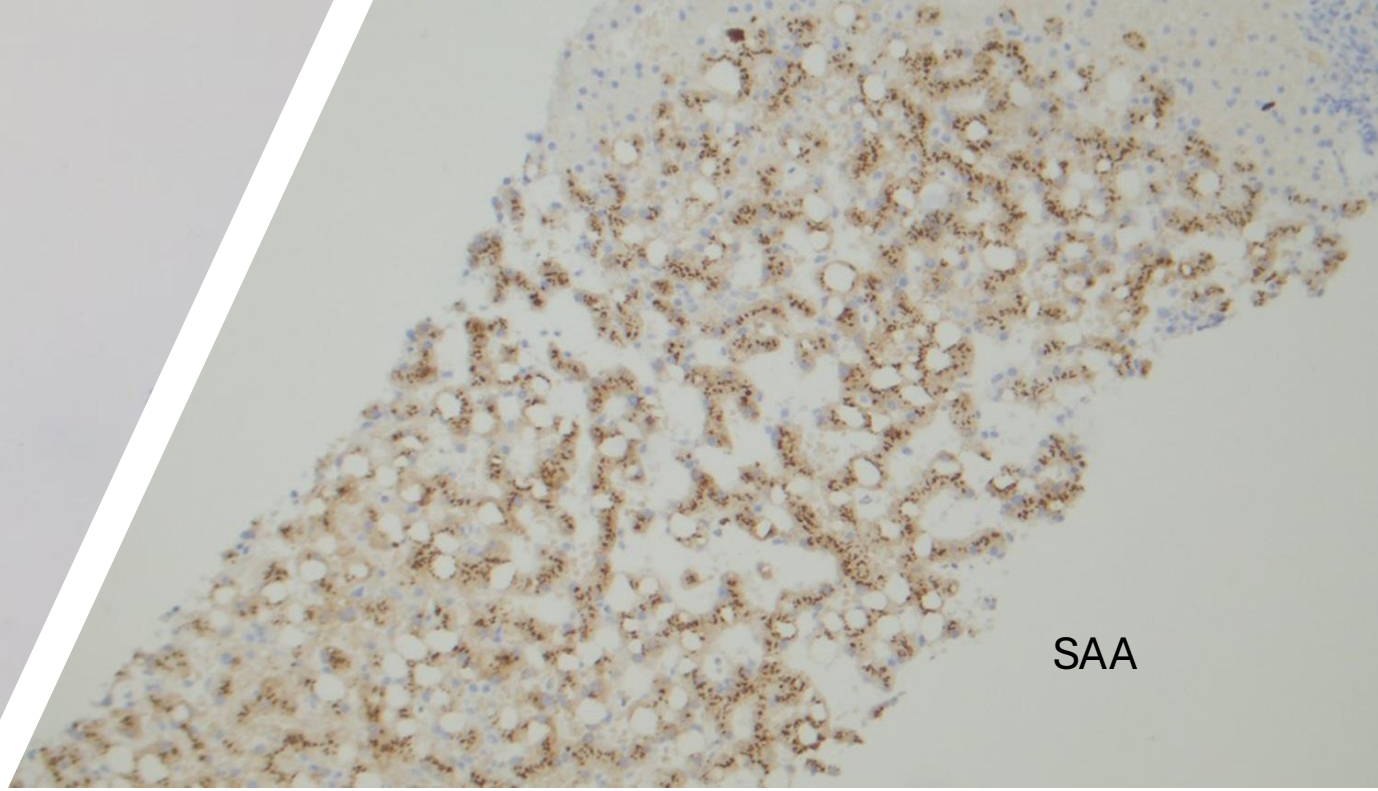
- Females. Assoc with obesity, met syndrome, adenomatosis. Haemorrhage risk

Unclassified






LFABP


SAA

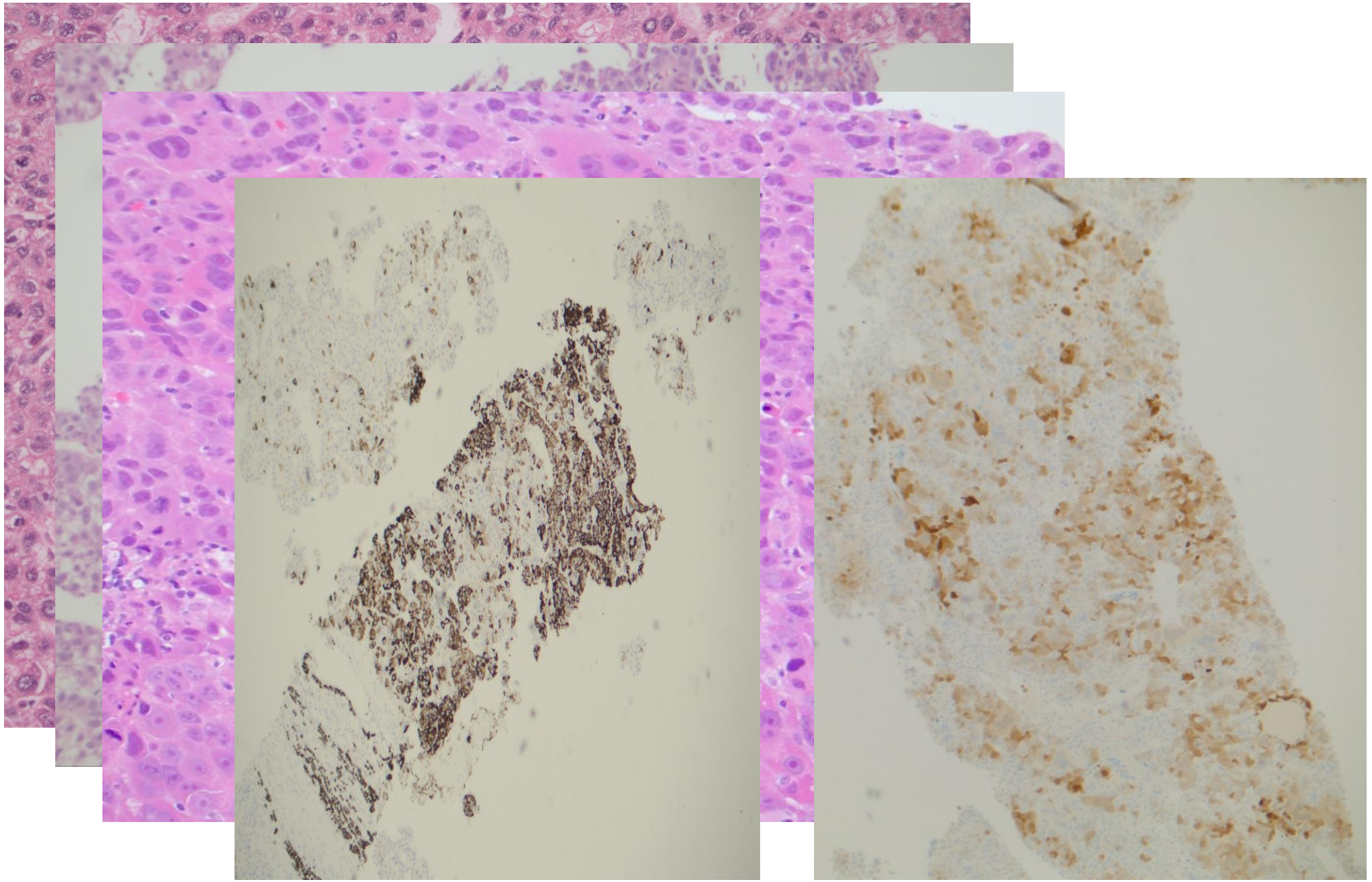
How definitive can you be on biopsy???

Looks malignant unsure if hepatocellular or not

Context

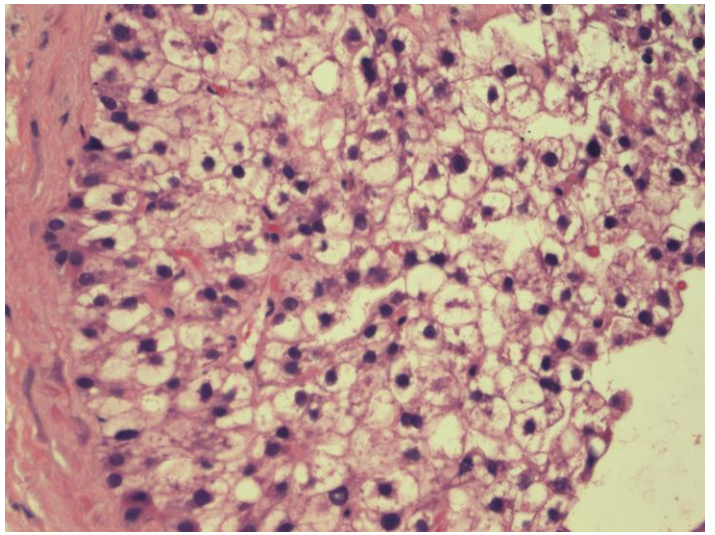
IHC panel to confirm HC origin:

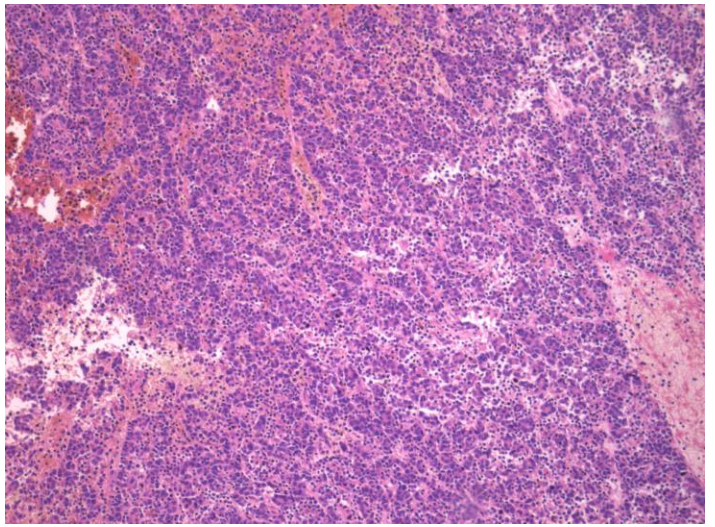
- HepPar1
- Arginase-1
- Glypican 3
- (AFP, CD10, pCEA etc.)



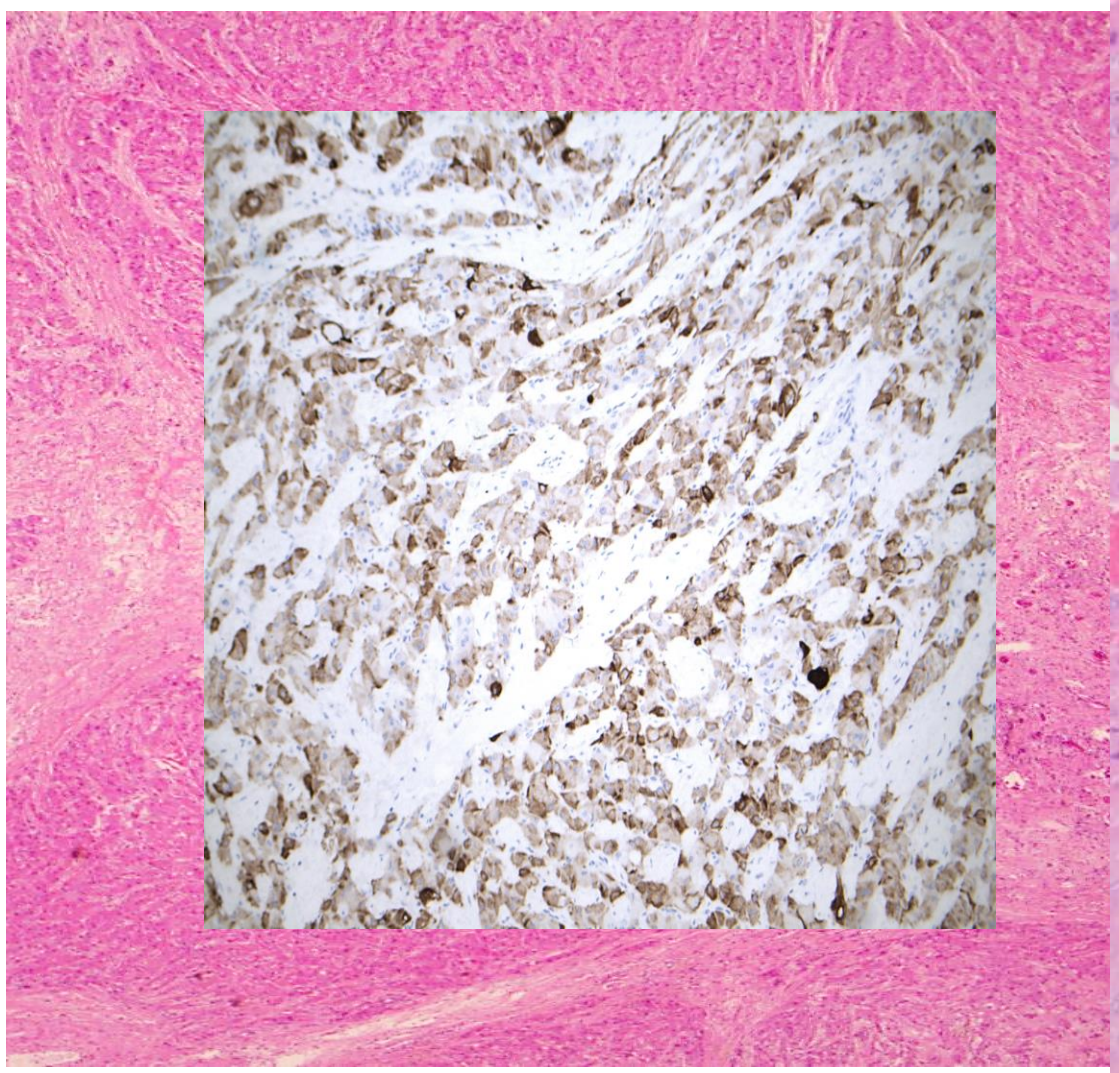
HCC subtypes

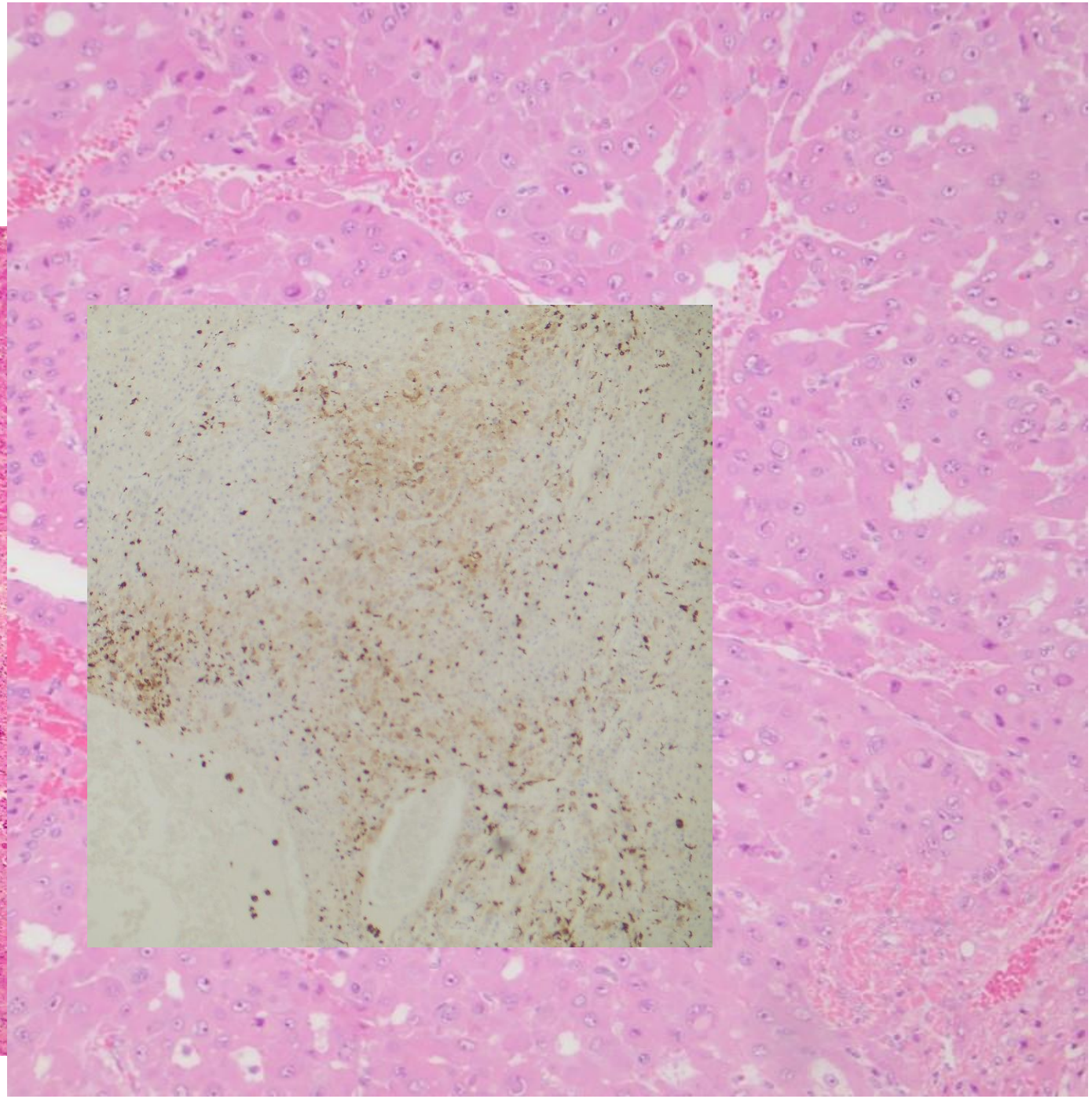
- Steatohepatitic
- Clear cell
- Macrotrabecular massive
- Scirrhous
- Chromophobe
- Fibrolamellar
- Neutrophil rich
- Lymphocyte rich





Fibrolamellar HCC





Obviously not hepatocellular

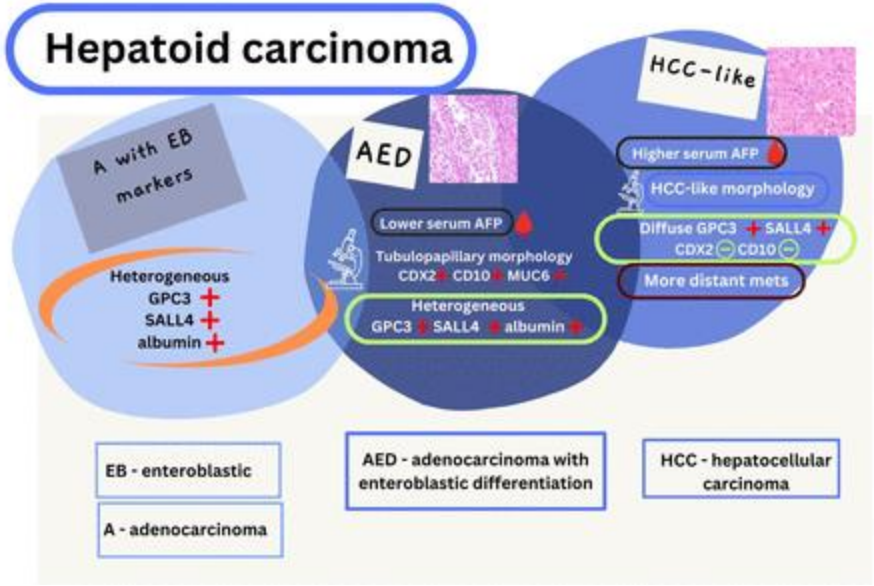
Context, history, imaging, tumour markers

If adenocarcinoma, NOS do very limited/no IHC

- Await MDTM
- Preserve tissue for molecular (IDH1 and FGRF2 etc.)

Other tumours

- Angiomyolipoma
  - Can look like an odd HCC
  - Consider HMB45 etc.
- Vascular tumours – esp EHE
- Mets:
  - NET
  - MM
  - GCT
  - Acinar cell carcinoma
  - Hepatoid tumours



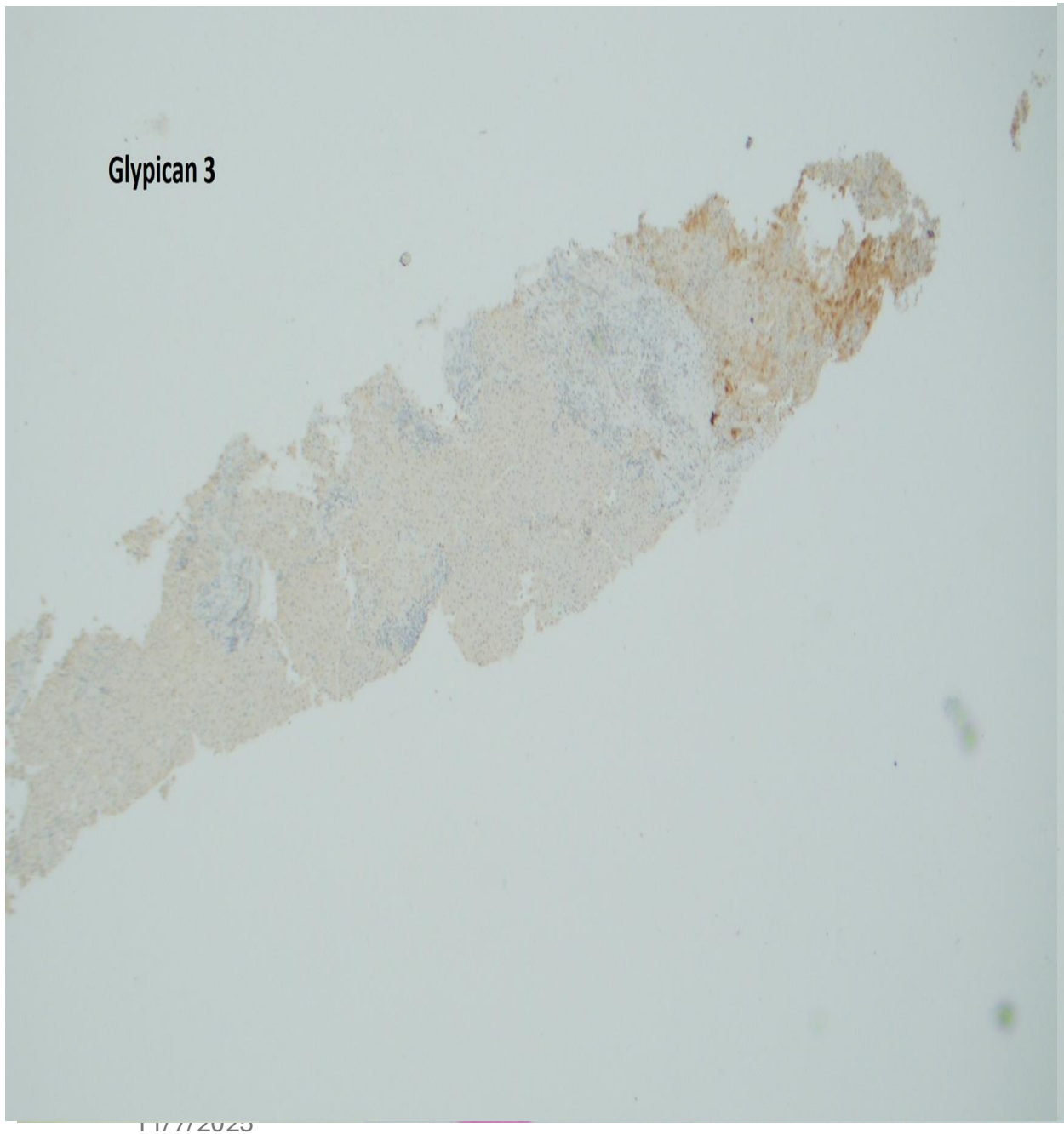
Deshpande V, Bal M. Enteroblastic gastric cancer subtype holds therapeutic clues. *Journal of Clinical Pathology* 2024;**77**:605-607.

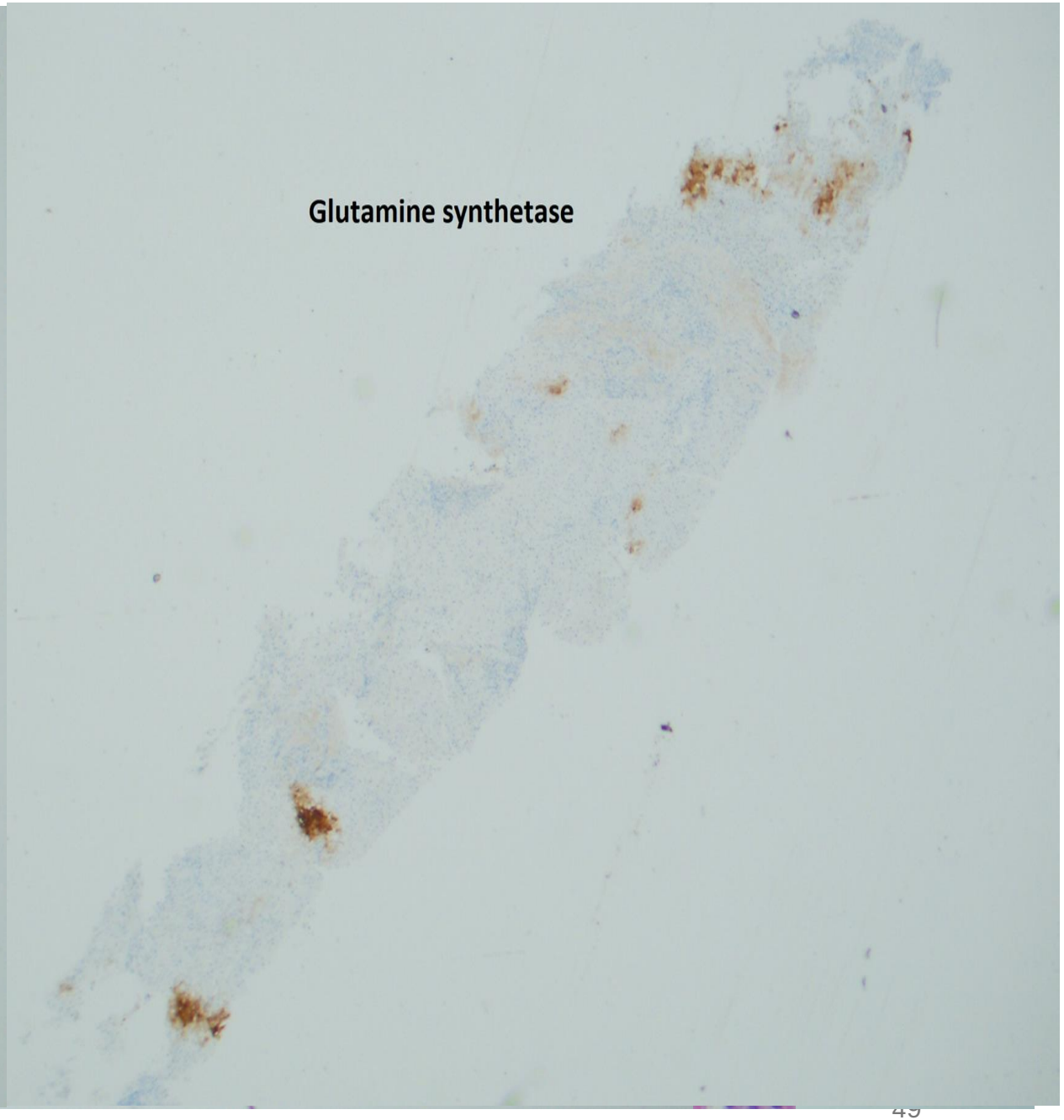
Practical tips for targeted liver biopsy

- History, gender, imaging (inc background liver), medications
  - If cirrhotic then adenomas and mets are unlikely
  - If male then risk is higher
  - OCP associations
- Get spares and/or split biopsies into separate blocks
- Think of algorithm before doing extra work
  - Hepatocellular benign vs malignant
  - Hepatocellular or non-hepatocellular
- Reticulin – for a hepatocellular neoplasm
- If in doubt (& you don't have the relevant IHC) send it for opinion.

What not to do…

- Tons of immunohistochemistry
- If it looks like liver, don't waste tissue proving it
- If it is an adenocarcinoma with no hx of other primaries, do minimal/no IHC at least until MDTM to preserve tissue for molecular.


Glypican 3


Glutamine synthetase

Eosinophilic necrotic mass

Necrotic tumour

- Consider IHC eg MNF-116

Helminth

- Fasciola or Enterobius in UK

Drug effect

Vasculitis

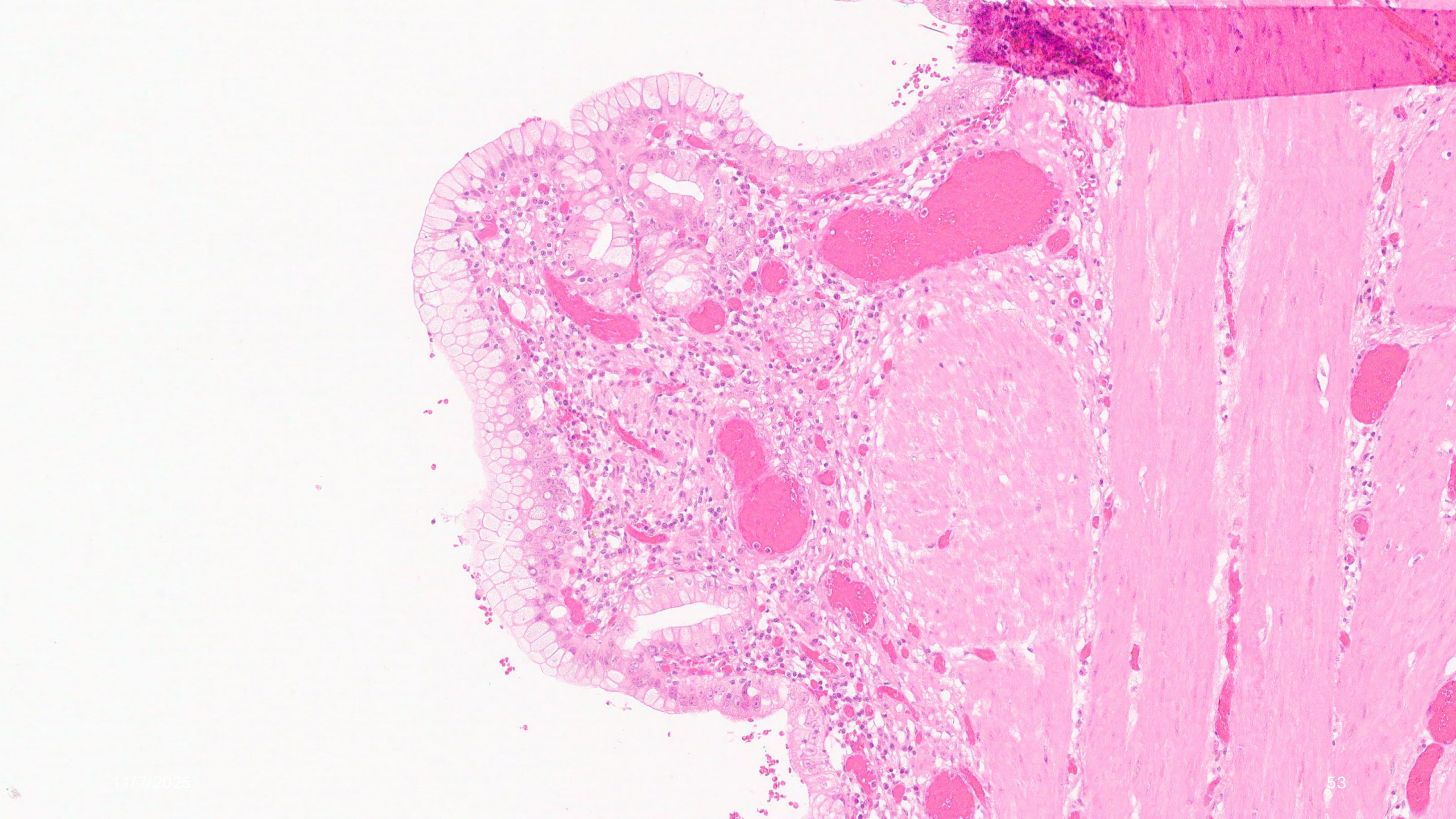
LCH

References

- WHO Classification of Tumours 5th Edn. Digestive System Tumours.
- Baker G & Kelly P. Preinvasive neoplasia of the gallbladder: flat and tumoral dysplasia. Diagnostic Histopathology 2024 April; 30: 252-267.
- Burt AD, Ferrell LD, Hubscher SG. MacSween's pathology of the liver. 8th Edn. Elsevier, 2023.

Case 1

42 year old female. PMHx of UC and PSC. Cholecystectomy as part of Whipple's for ?bile duct carcinoma. Gall bladder macroscopically oedematous but otherwise unremarkable.

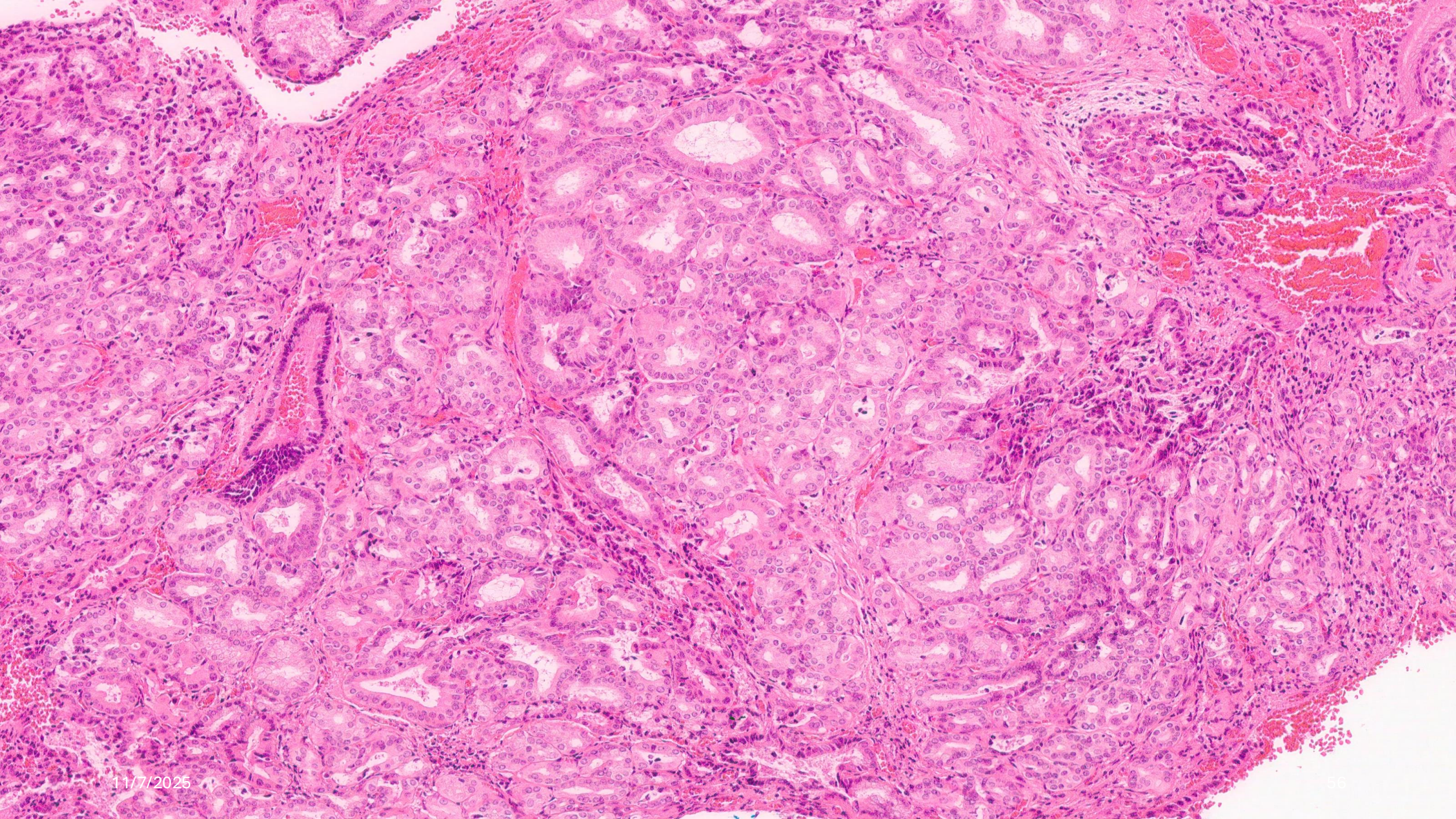


EQA responses

Diagnosis	%
Metaplasia/reactive	76
Dysplasia	17
Clear cell carcinoma	3.5
Mucinous cystic neoplasm	3.5

Case 2

71 year old female. Cholecystectomy for gall stones. Macroscopic description: An intact gallbladder measuring 90 x 20 x 18 mm. No paracystic lymph node identified. On opening, the specimen contains a single grey stonelike object, 7 mm in maximum dimension suspended within thick mucus but also includes fleshy fragments up to 6 mm in maximum dimension. The mucosa has an inflamed and partly haemorrhagic appearance showing raised areas up to 7 mm across. One raised area is sited in the neck and is 8 mm from the common bile duct margin. The wall is up to 3 mm thick in places.

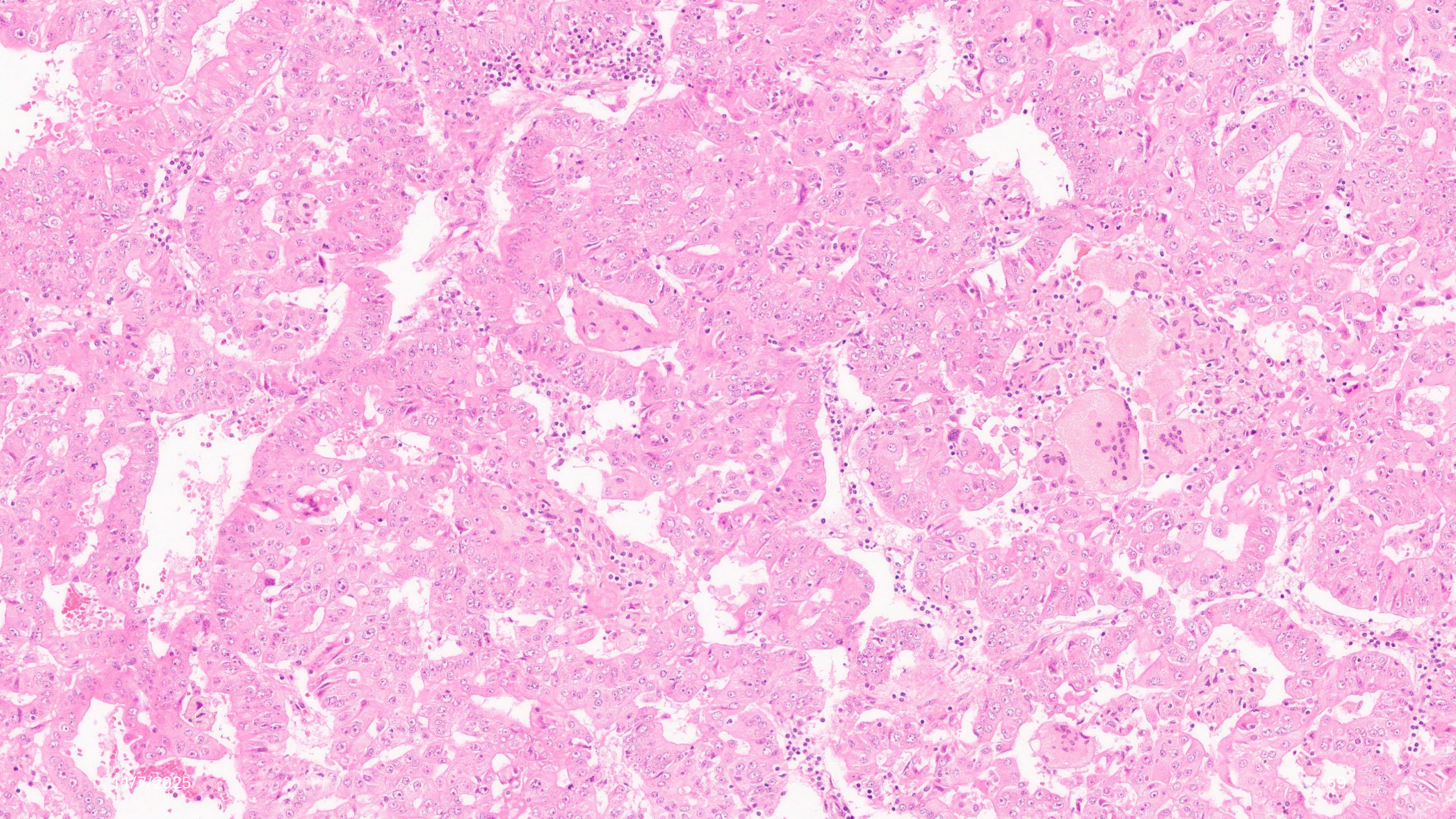


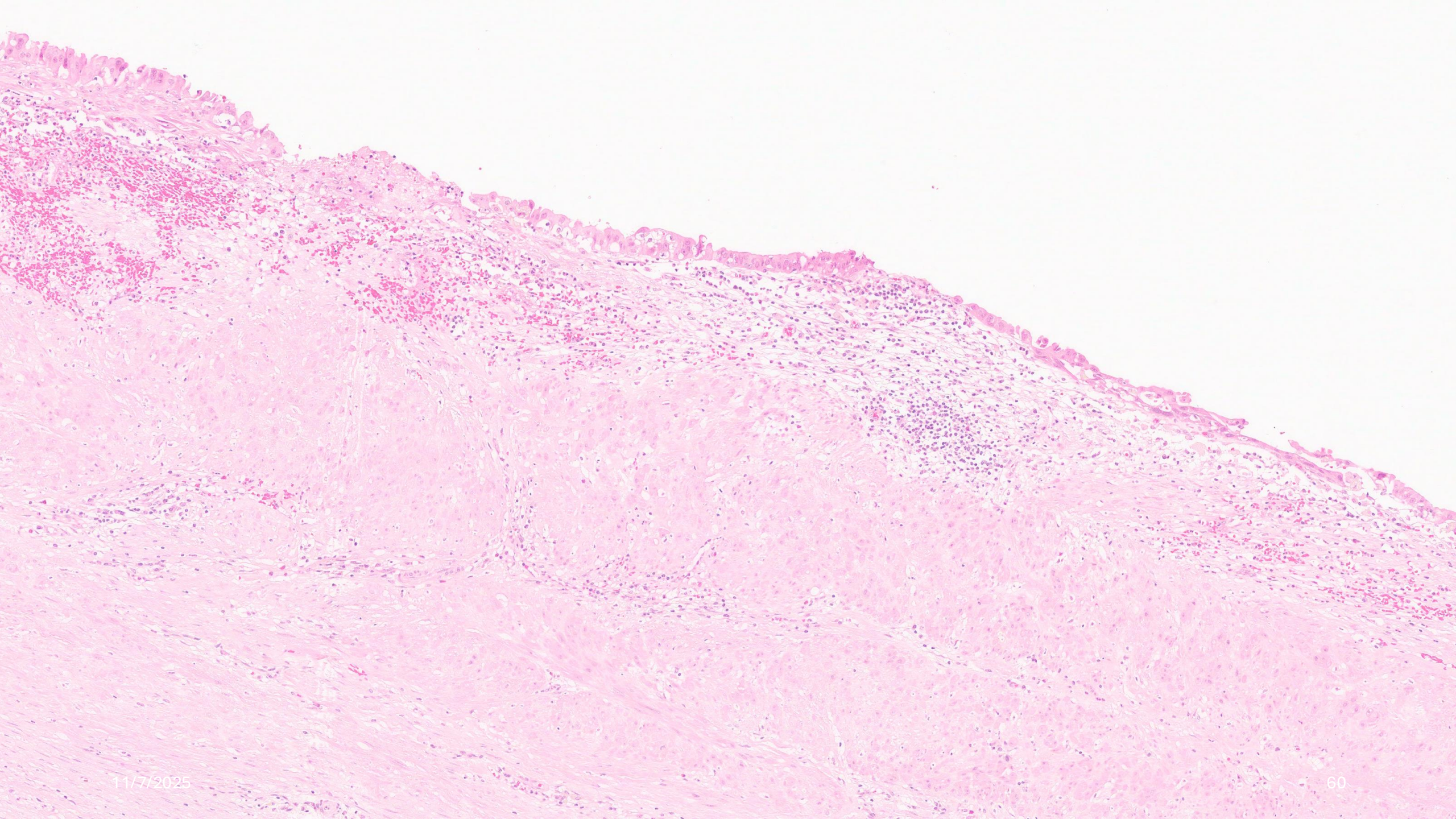
EQA responses

Diagnosis	%
Pyloric gland adenoma	56
ICPN/other neoplasm	41
Adenomyoma	3

Case 3

52 year old female. Gall bladder ?adenoma on imaging. Previous history of ovarian cancer. Macroscopic description: Intact gallbladder measuring 180 x 40 x 35 mm, no paracystic lymph nodes identified. The external surface has a mottled grey appearance with haemorrhagic areas up to 30 mm across. On opening the specimen is filled with soft brown, jellylike contents containing suspended yellow, cauliform stones up to 20 mm in maximum dimension. The wall is up to 3 mm thick in places. The mucosa appears entirely fibrosed and denuded. Contained within the brown jelly there is polyp like tissue 12 x 10 x 10 mm with a black exterior and grey interior. 1B = background mucosa and wall. 1C = free-floating polypoid tissue.



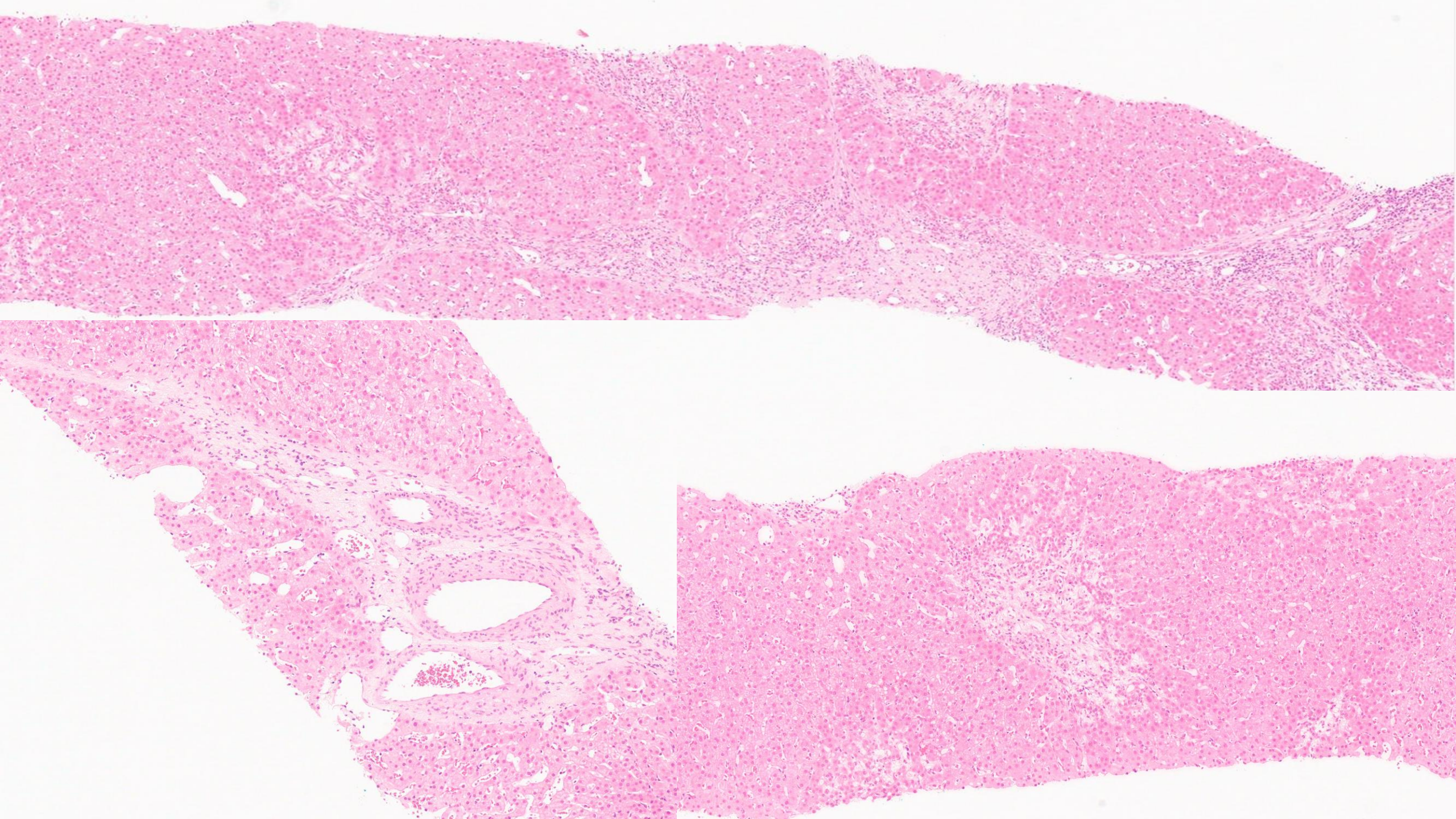


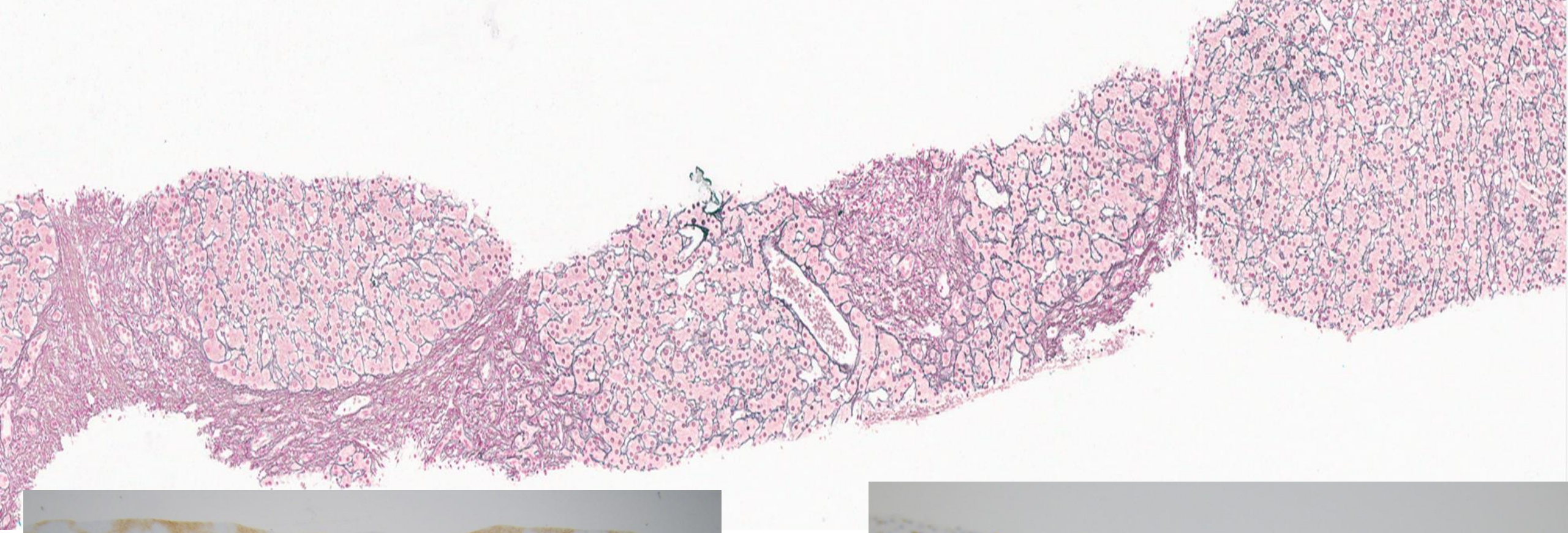
EQA responses

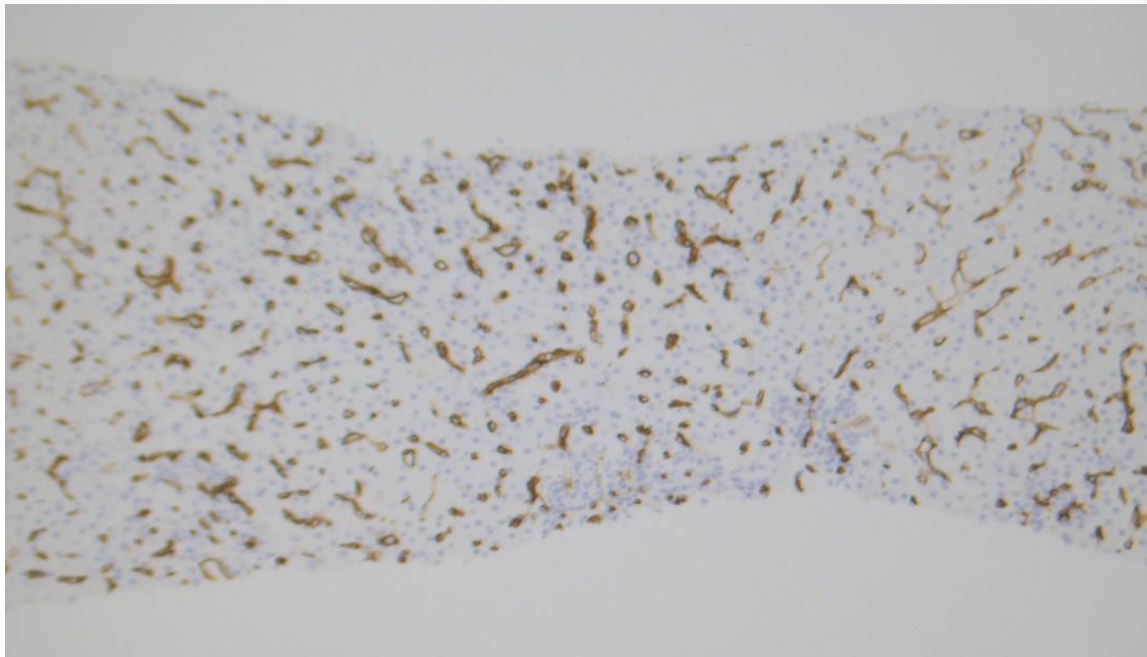
Diagnosis	%
ICPN	40
Adenoma/other terminology	32
Invasive carcinoma	20
Metastasis	8

Case 4

51 year old female. Three lesions in liver: one a haemangioma on imaging, seg 6 lesion previously biopsied at time of cholecystectomy and showed hepatocellular adenoma, segment 6 lesion not defined by imaging. Current biopsy is of segment 6 lesion.





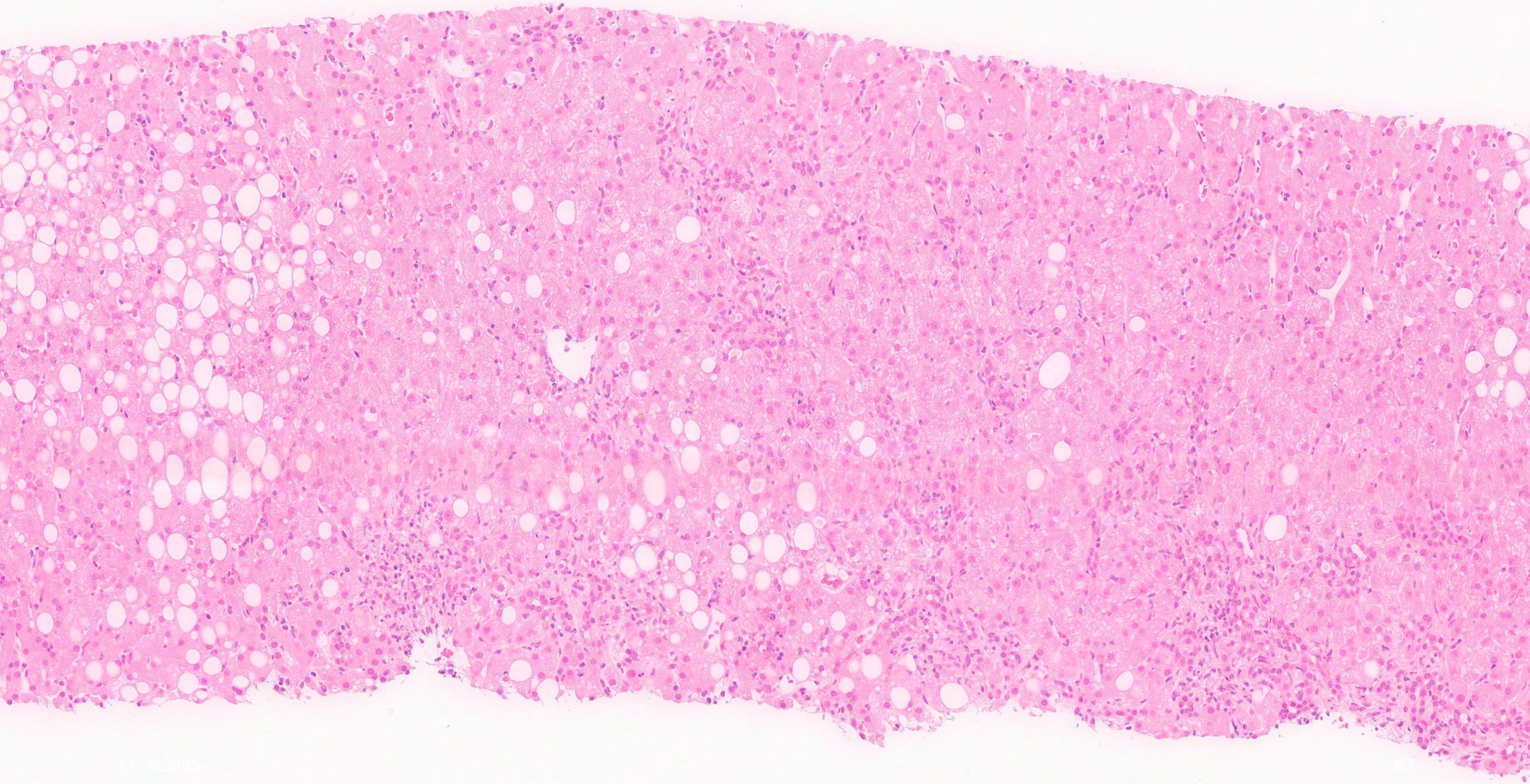


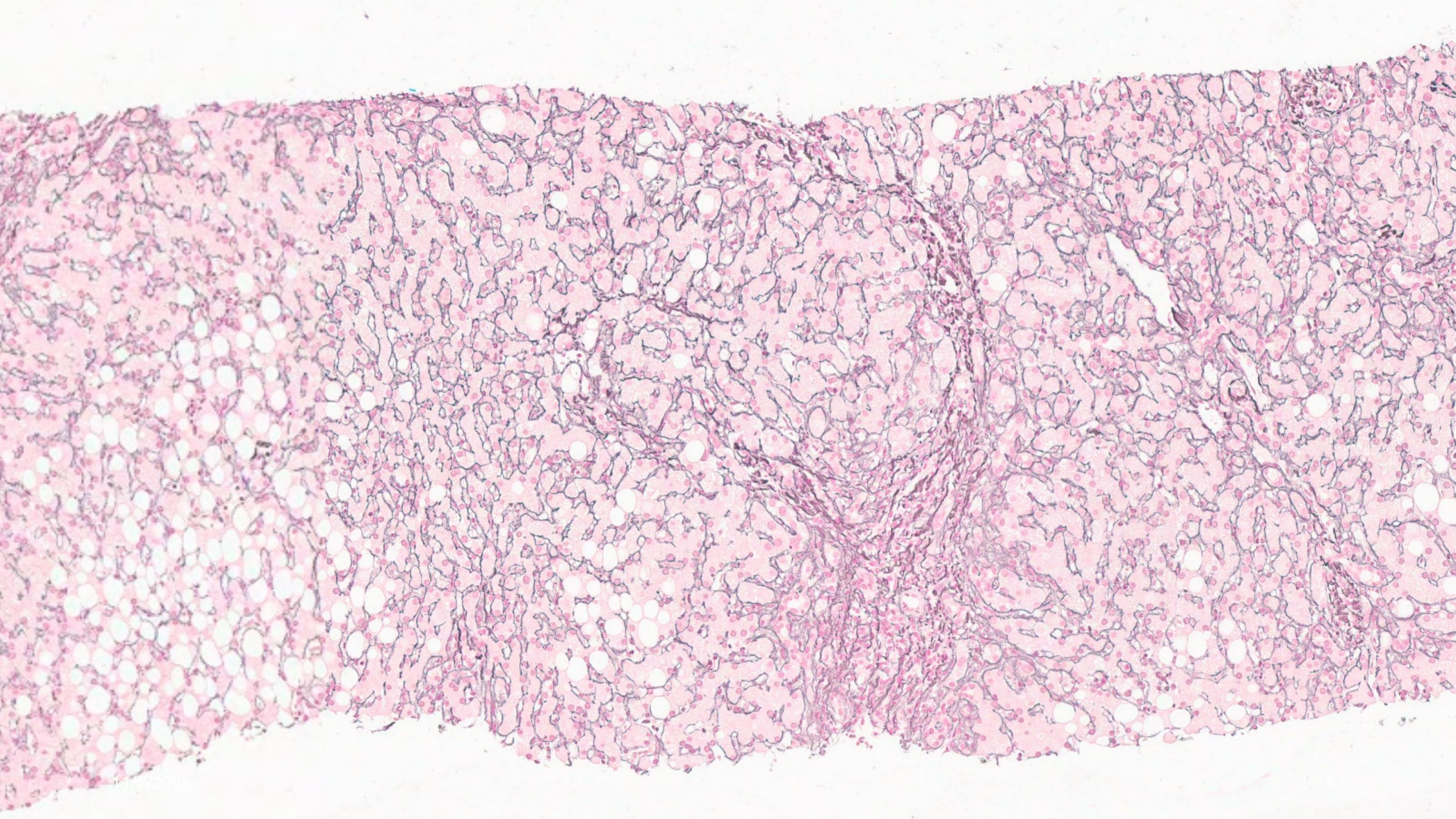
EQA responses

Diagnosis	%
FNH	43
HCA	32
CC	10
Cirrhosis/fibrosis	10
HCC	5

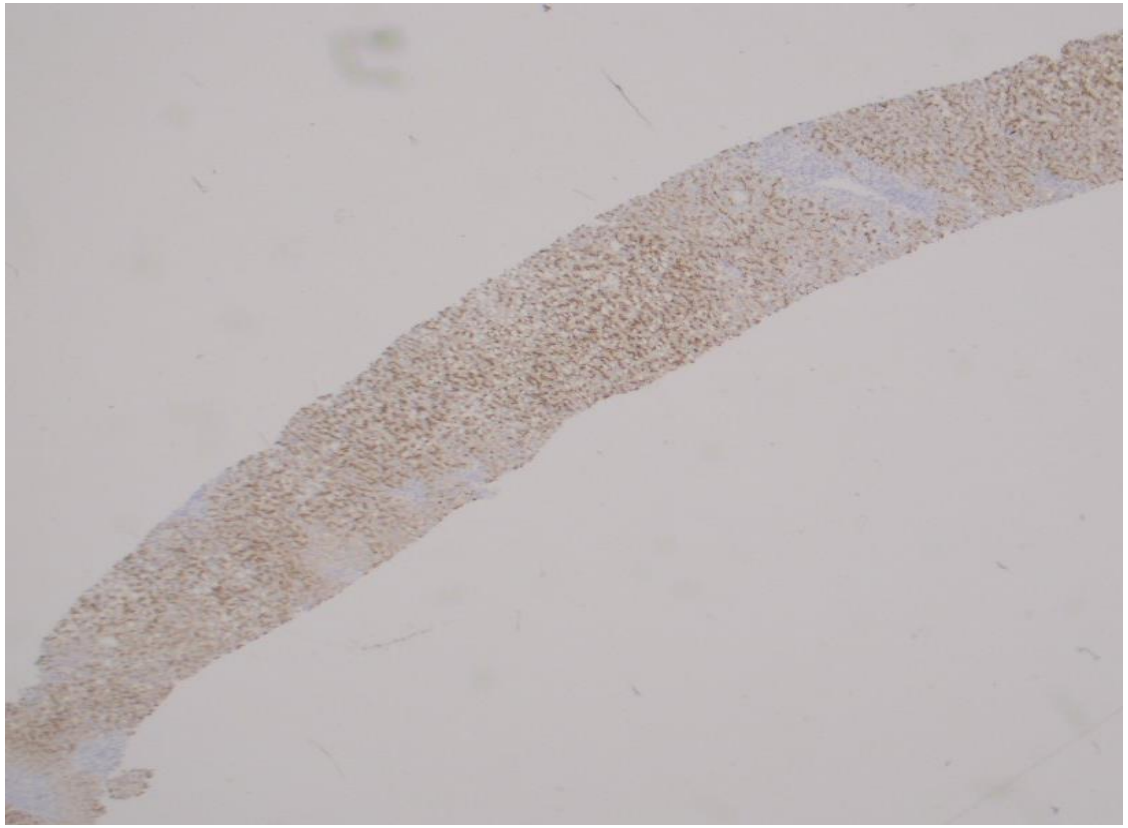
Case 5

54 year old female. Fatty liver, non-cirrhotic. Normal fibroscan. 2cm lesion adjacent to gall bladder. ?HCC

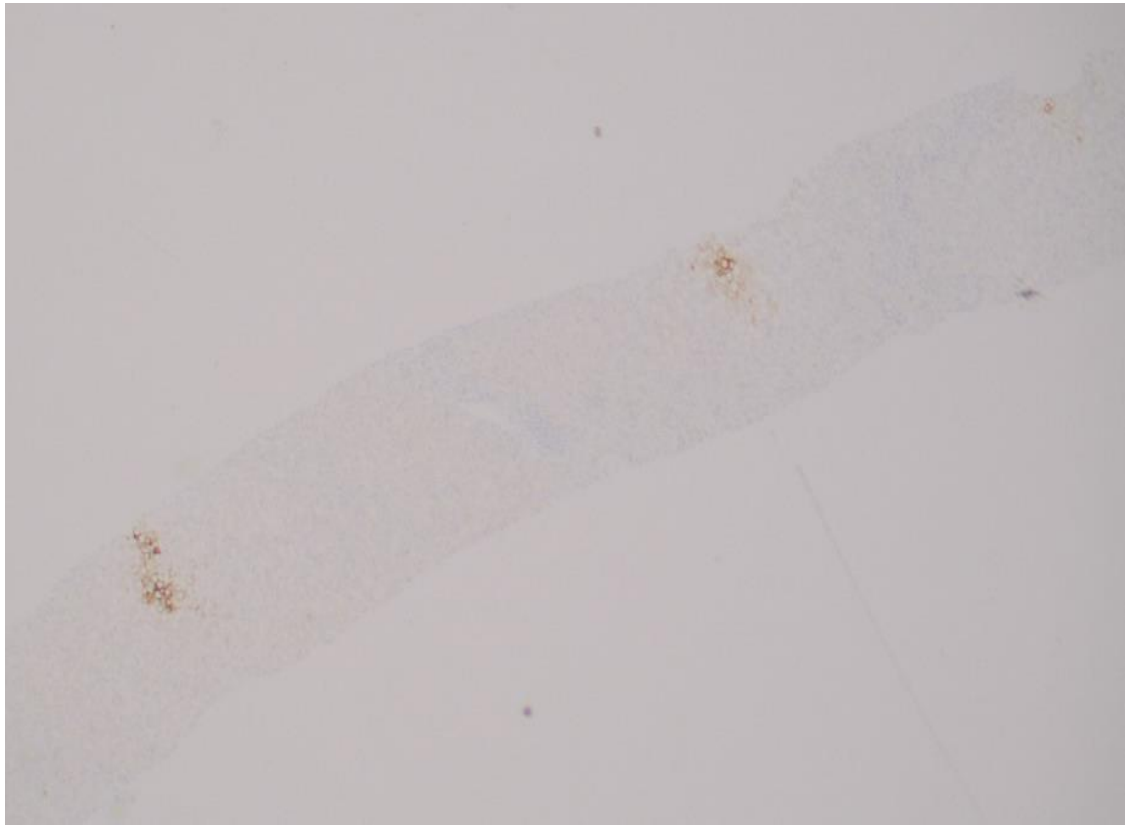




SAA



GS

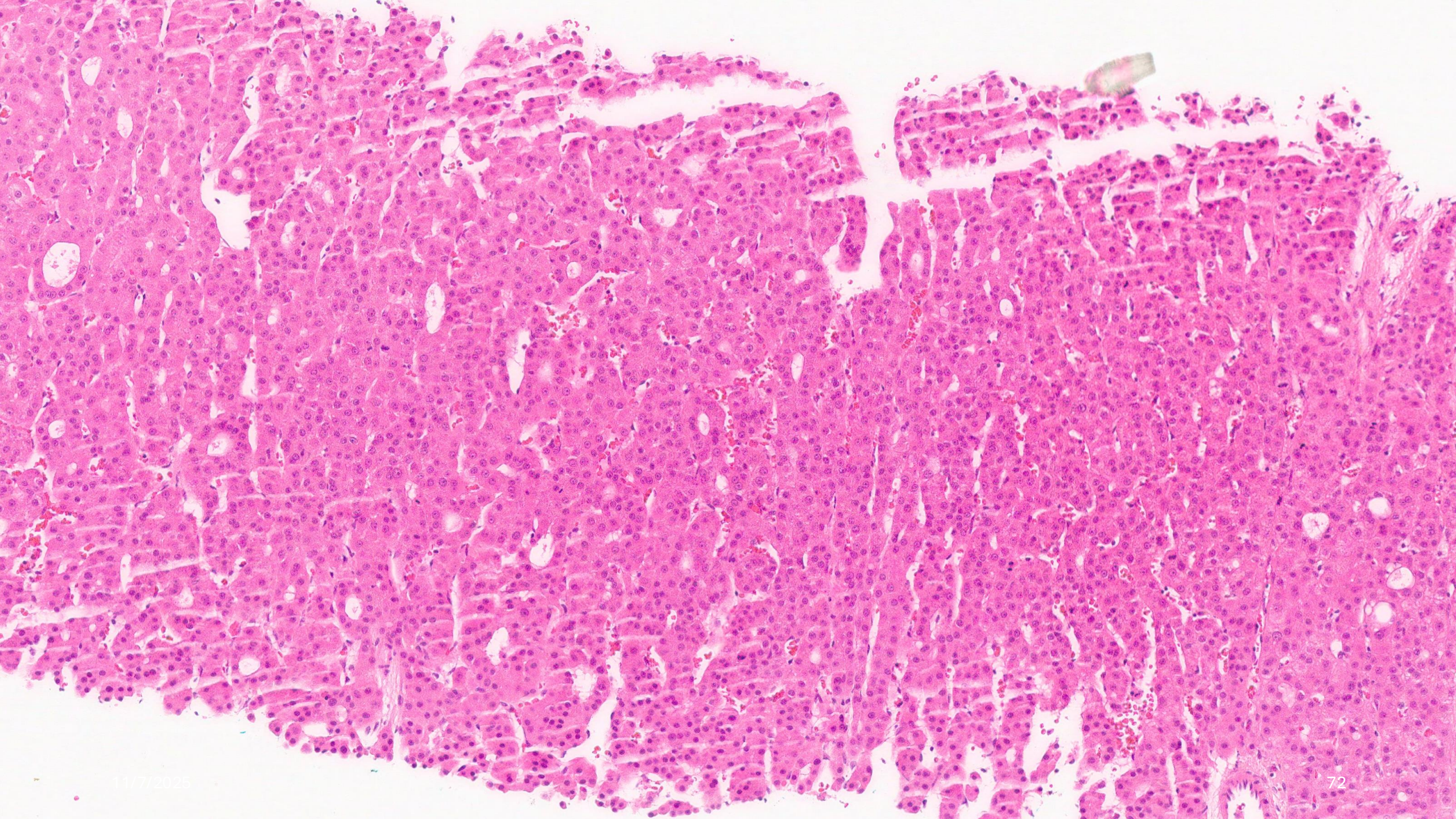


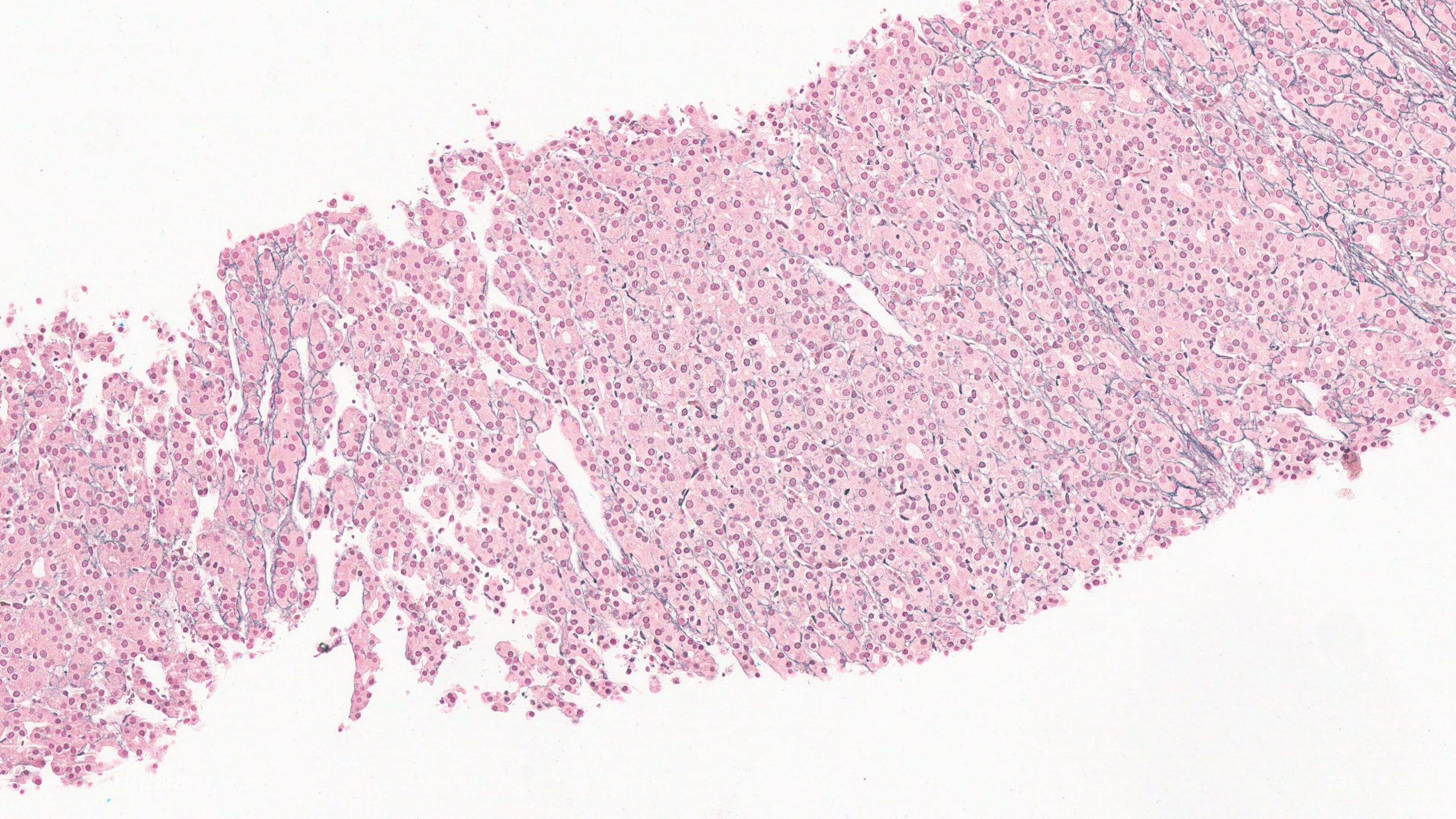
EQA responses

Diagnosis	%
HCA	57
Steatosis	26
HCC	13
FNH	4

Case 6

66 year old male. Metabolic liver disease. Cirrhosis. 3cm segment 3 nodule.





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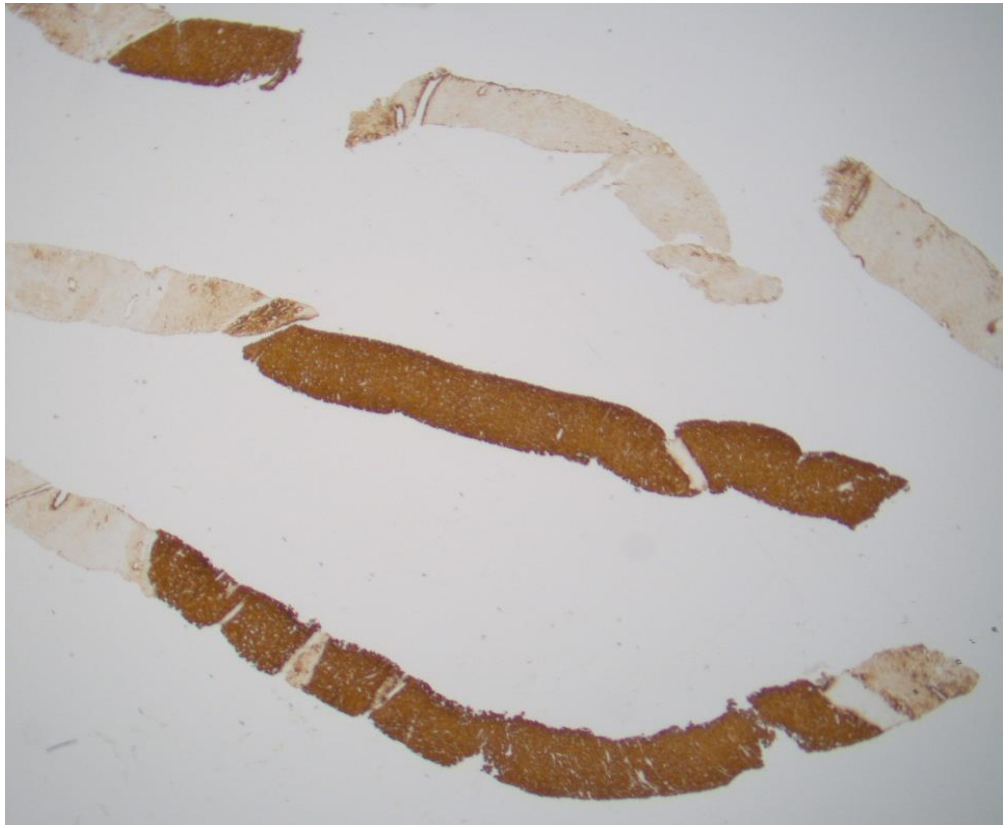
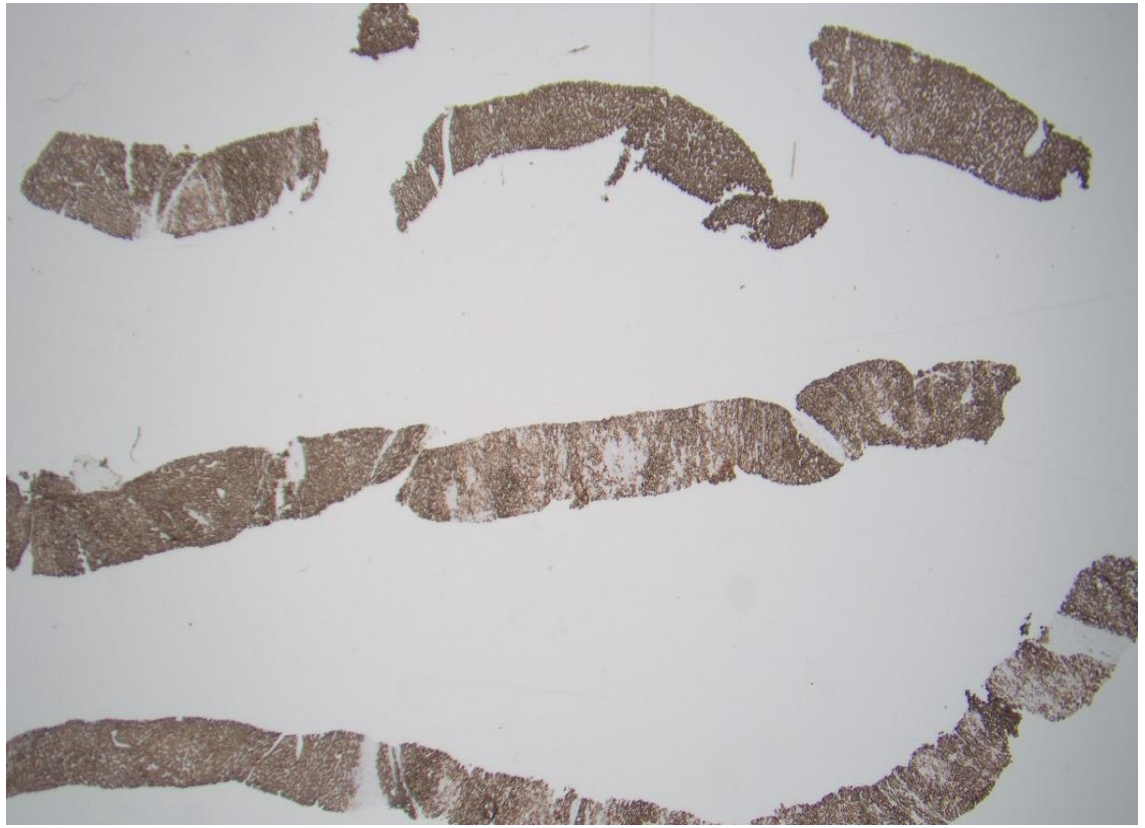


Hep Par 1



EQA responses

Diagnosis	%
HCC	90
HCA	5
Wilson's dx	5