

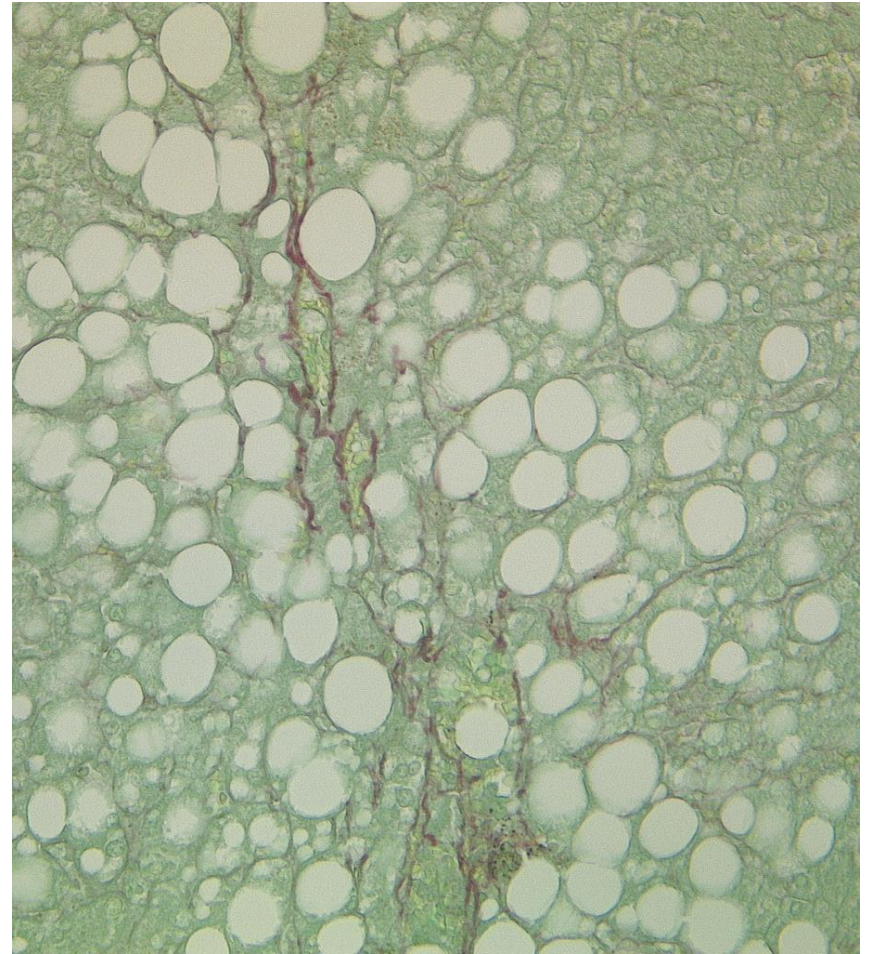
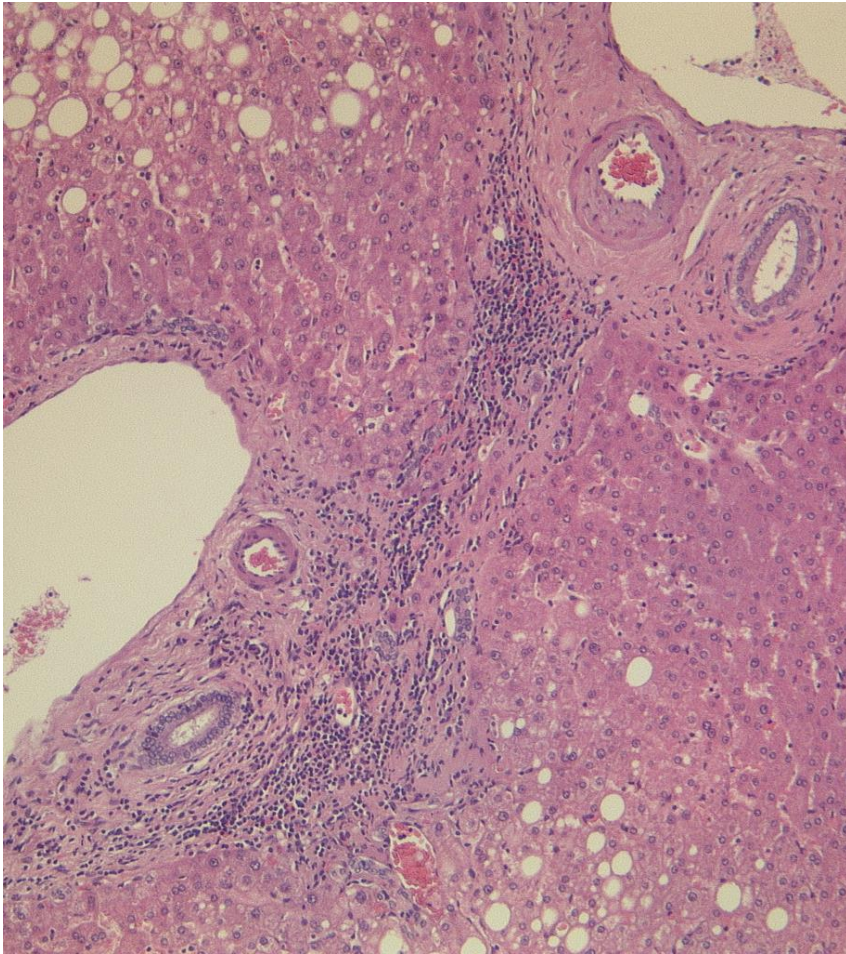


Gnomes 2013: HepaLUMPs down under

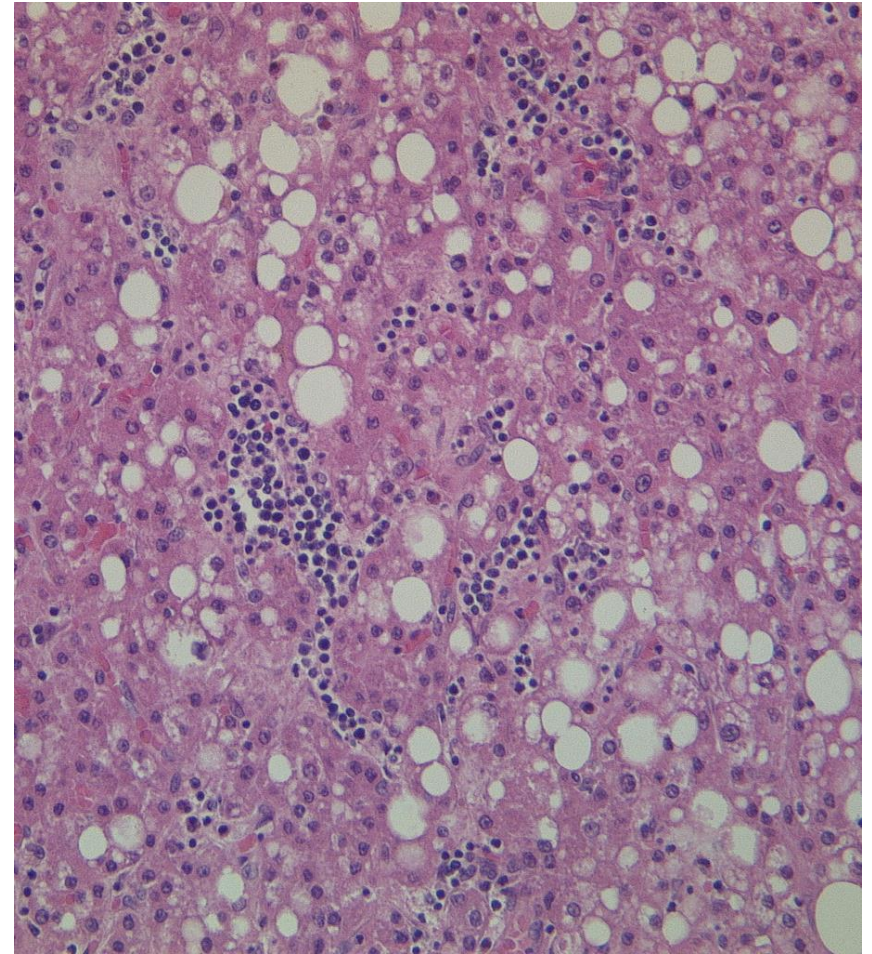
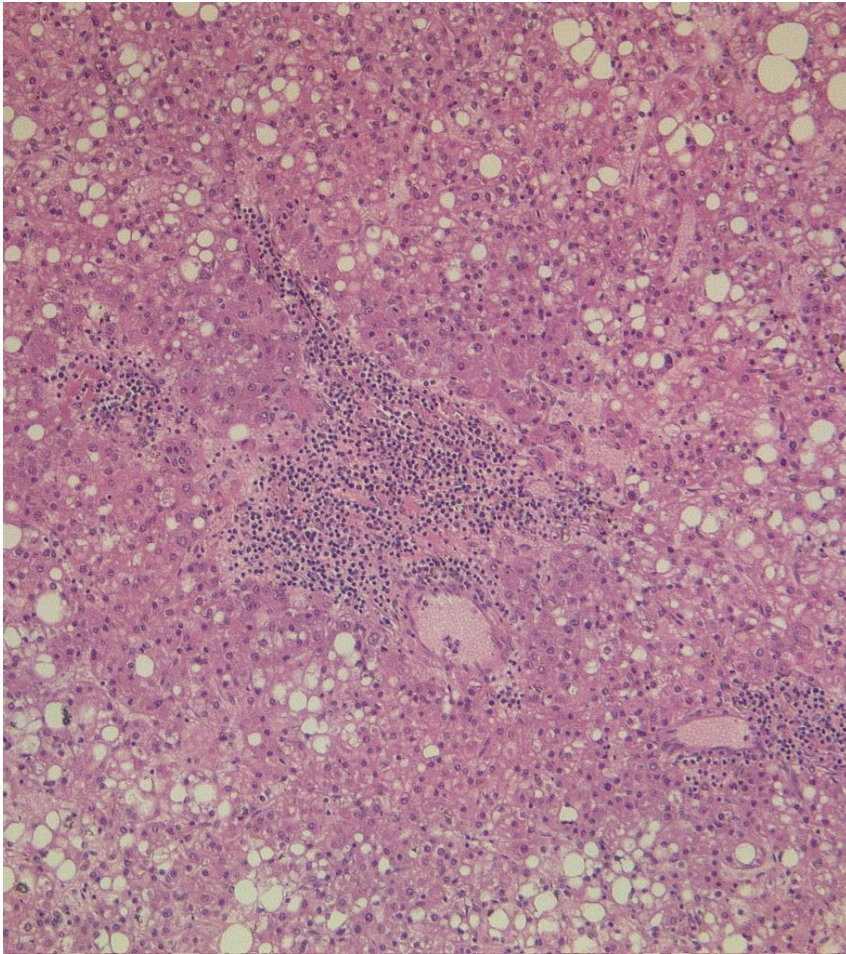
Adelaide A

- 71 year old male; known metabolic syndrome
- RUQ pain: US identified 9 cm mass
- Right hepatectomy
- Specimen weighed 716g and measured 152x140x102mm
- Capsule intact although tumour abutting capsule
- Well circumscribed lesion; pale firm cut surface with central scar
- No macroscopic evidence of vascular invasion

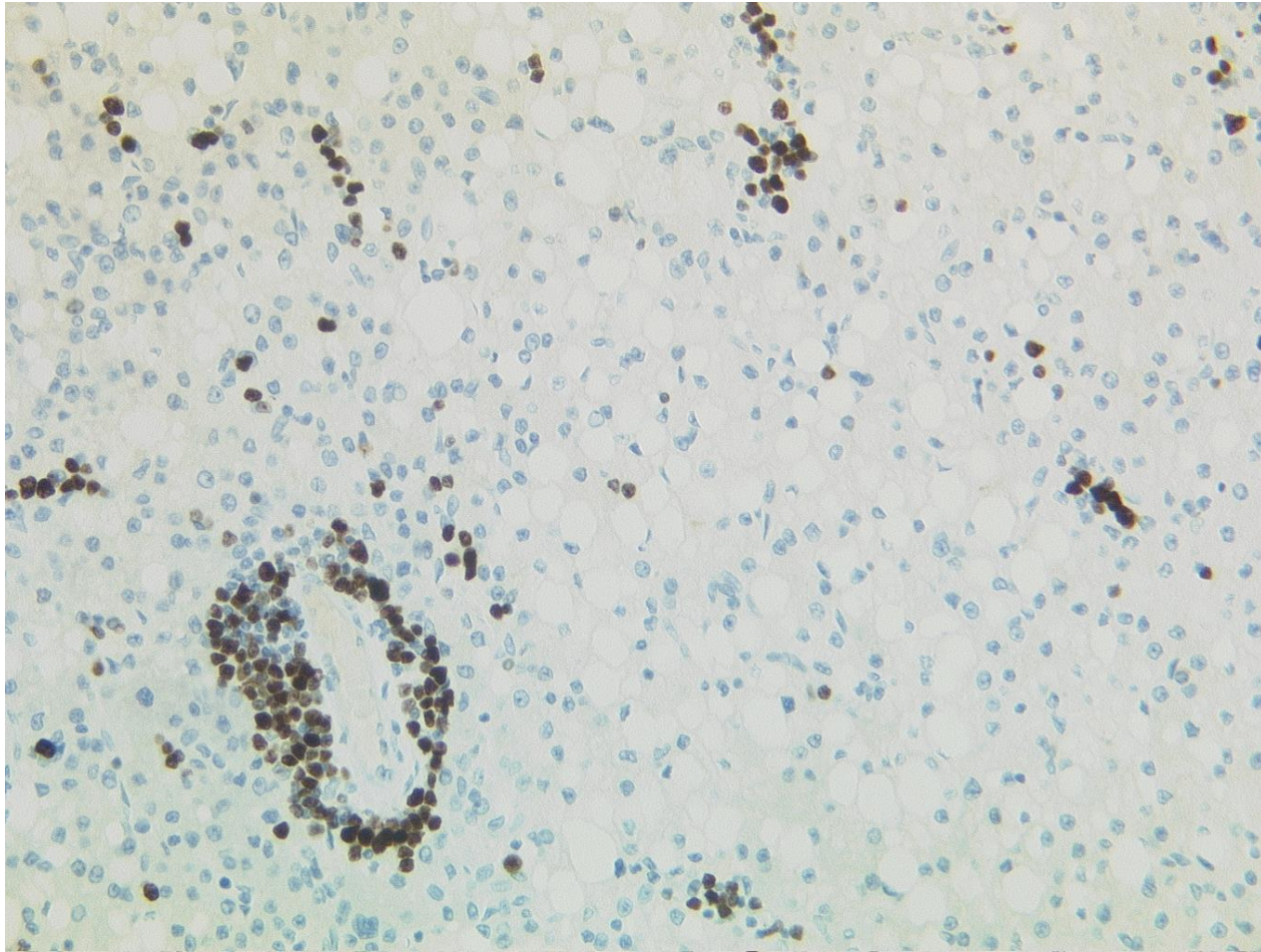
Adelaide A



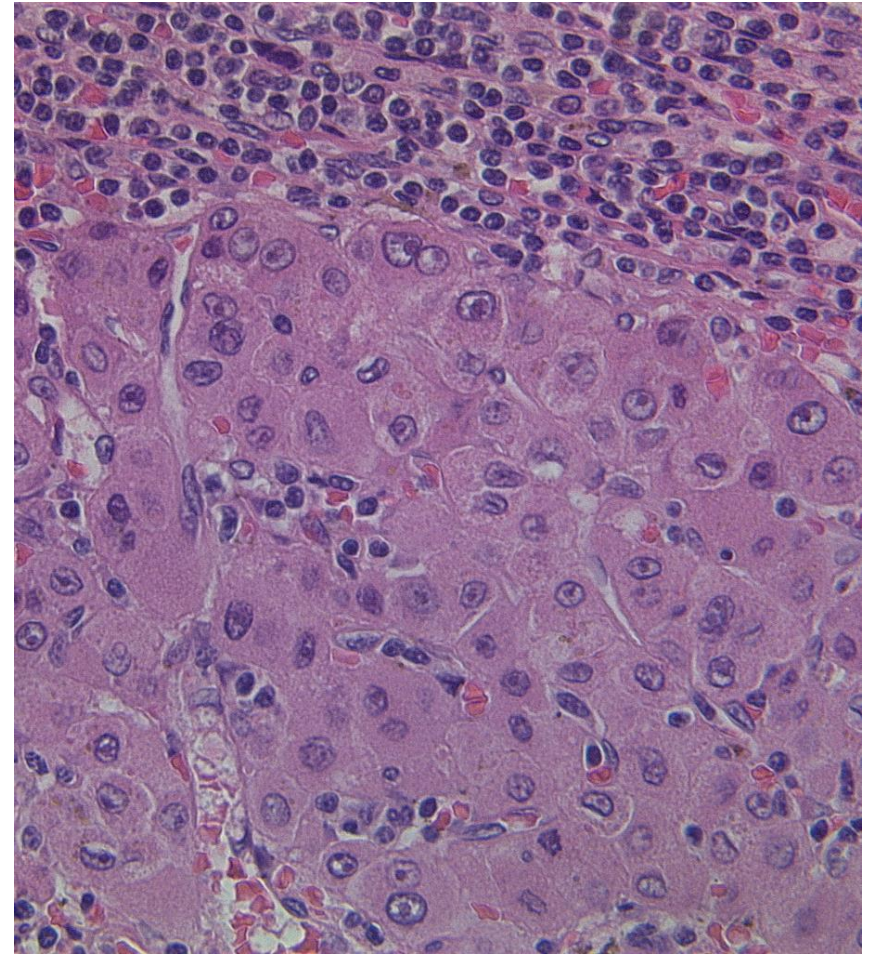
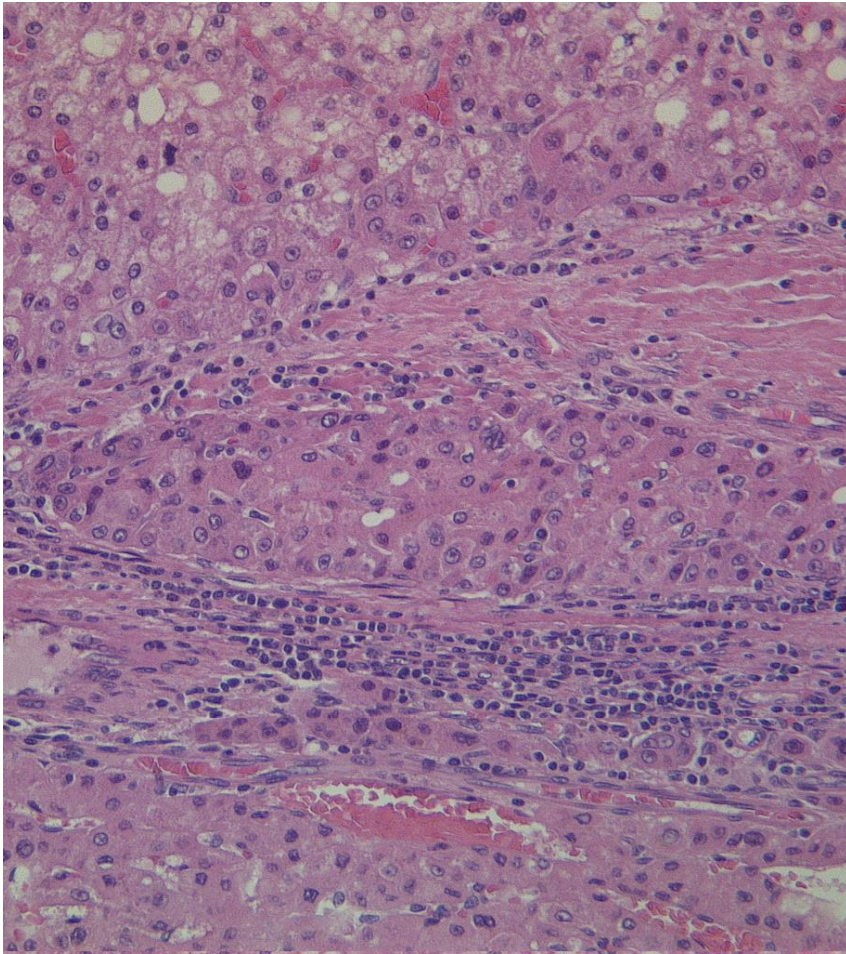
Adelaide A



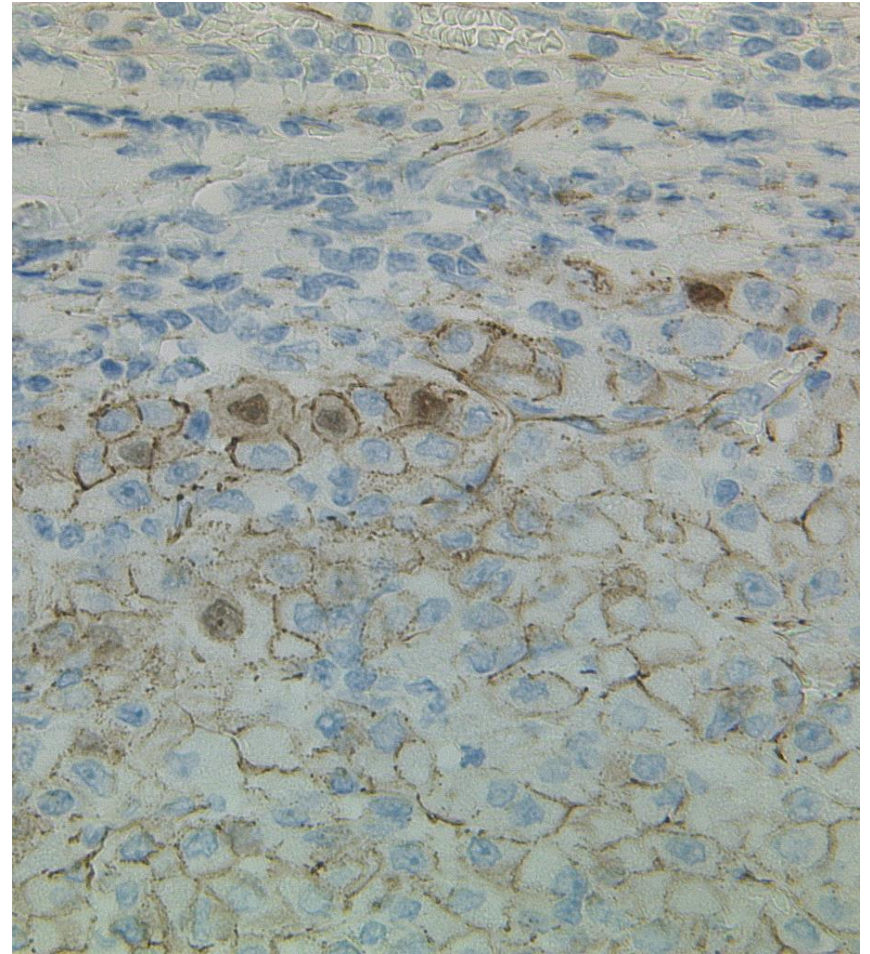
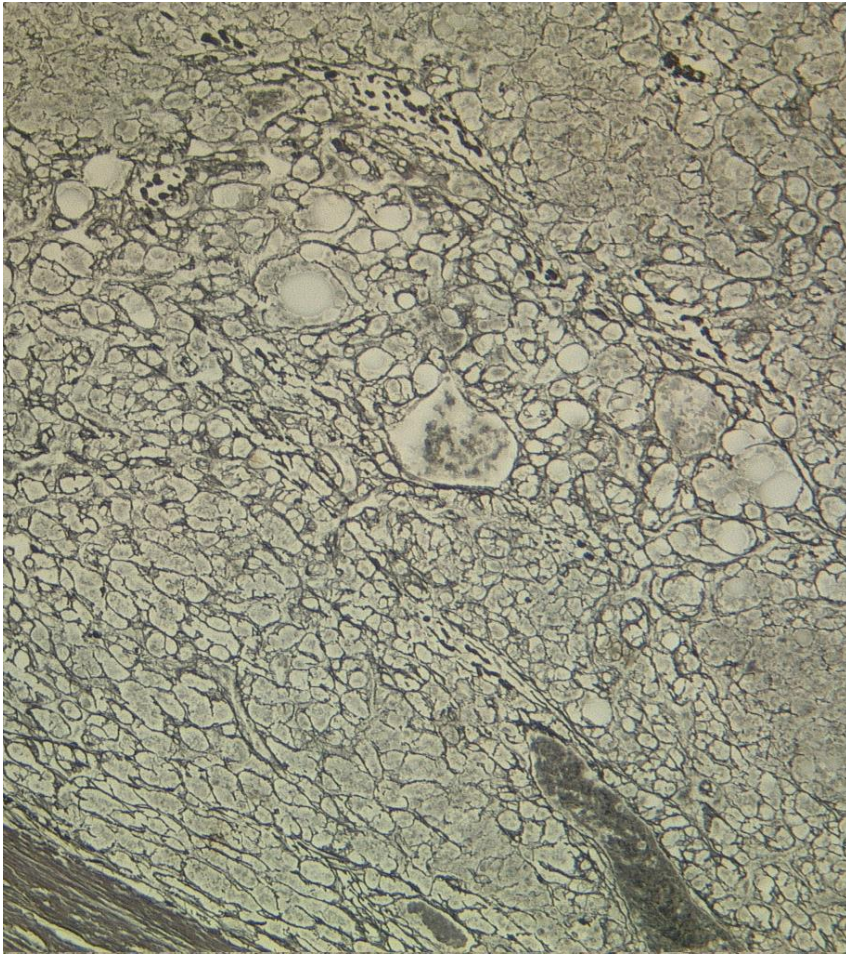
Adelaide A: Ki67



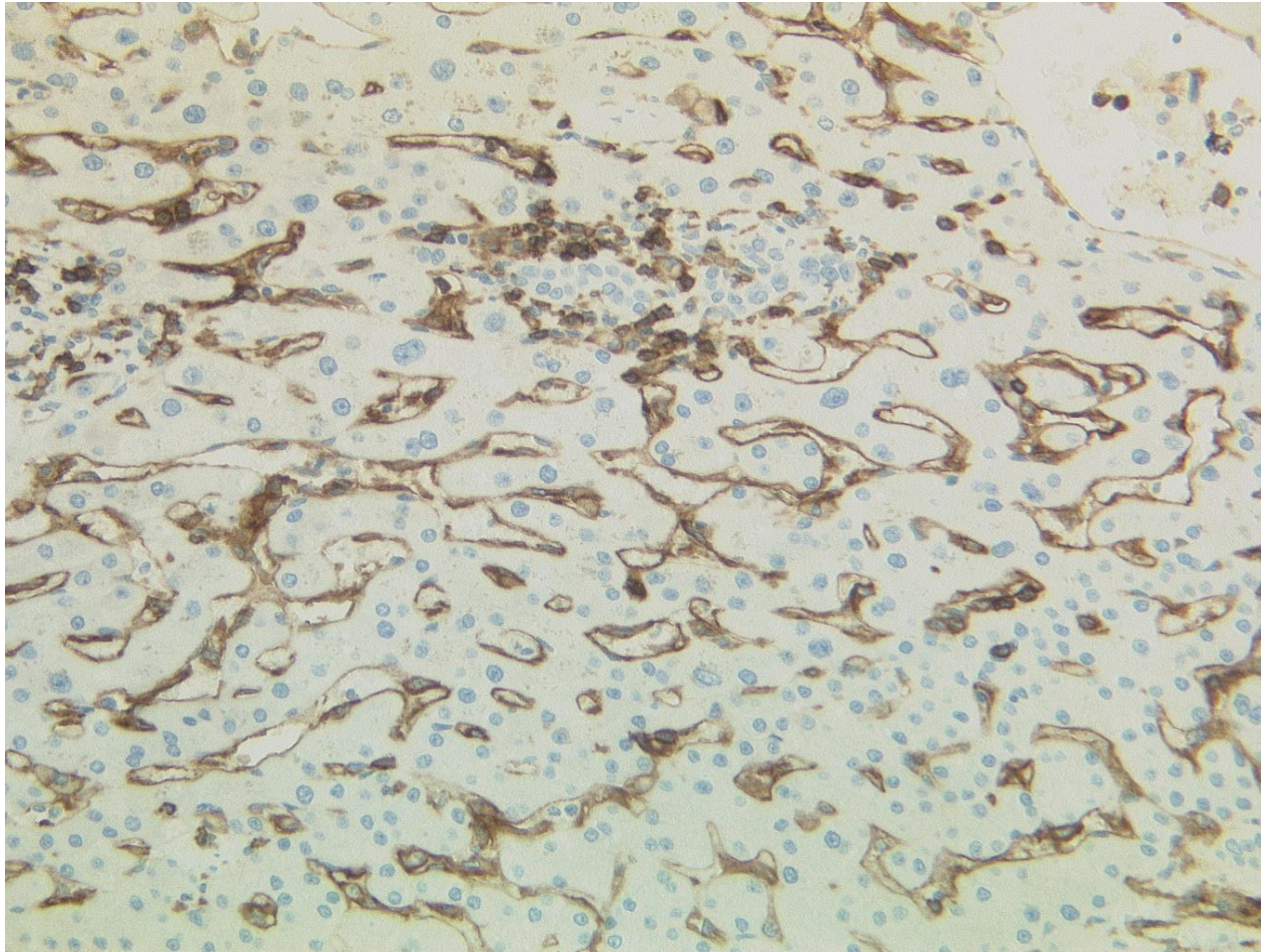
Adelaide A



Adelaide A



Adelaide A: CD31



Adelaide A

- Well differentiated hepatocellular carcinoma
- ?? ex hepatocellular adenoma

- How frequently does HCC evolve from HA?
- Pathway for HCC development in non cirrhotic livers (eg NASH)?
- How can we tell from morphology, IHC, molecular genetics, proteomics?
- Any pointers from animal models such as DEN-induced tumours?



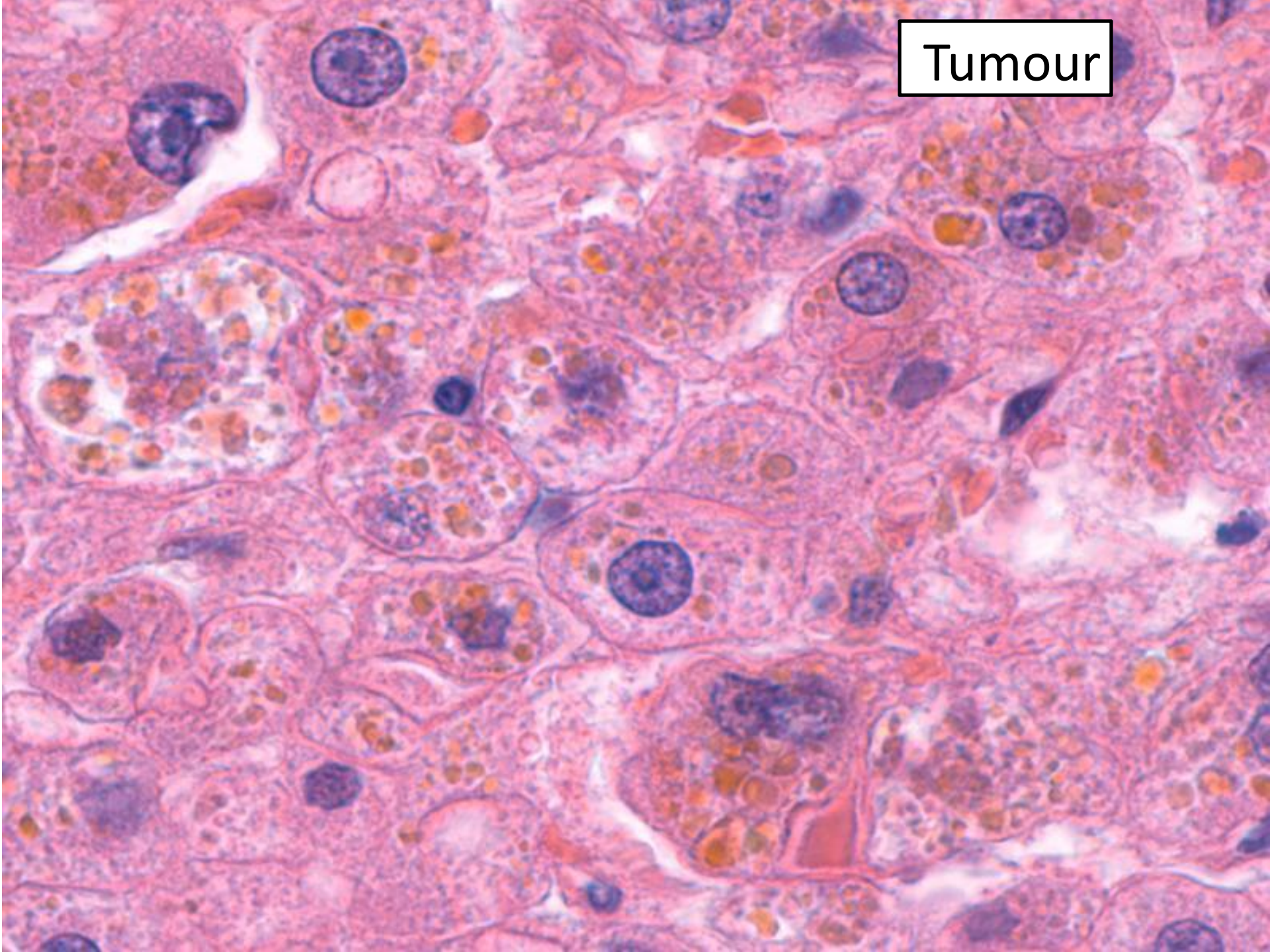
Baltimore Case B

- 20 year old male
- 4 months of early satiety and a 15 lb weight loss.
- Low grade fevers, light headedness and weakness.
- No past medical history
- Serum AFP levels normal
- CT: heterogeneously enhancing 11 cm mass in the liver with a central scar

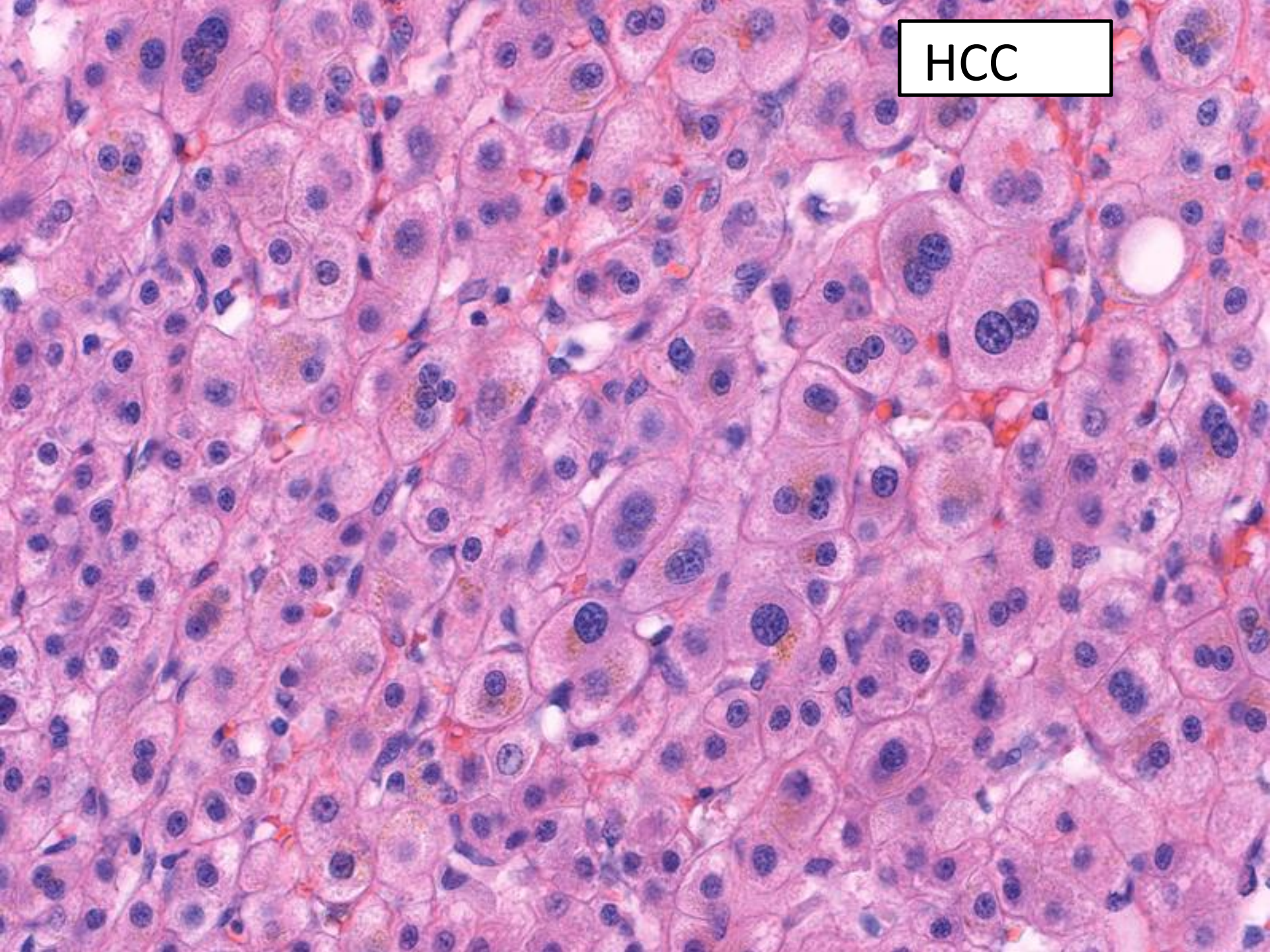
Baltimore Case B

- CT: heterogeneously enhancing 11 cm mass in the liver with a central scar.
- MRI performed a few days later 17 cm mass
 - also observes a central scar with radiating bands of fibrosis.
 - The scar is bright on T2 but not enhancing.
- Radiology differential:
 - fibrolamellar carcinoma (favored)
 - hepatocellular carcinoma,
 - atypical adenoma.

Tumour



HCC



Baltimore Case B

- Final diagnosis:

**Hepatocellular carcinoma developing
in a pigmented hepatic adenoma**

Pigmented adenomas

- Similar M:F ratio
- Reported ages: 32-65
- Reported in Asians and Caucasians
- Tumour sizes: 2.5 to 25 cm
- Dubin Johnson like pigment is Fontana Masson positive

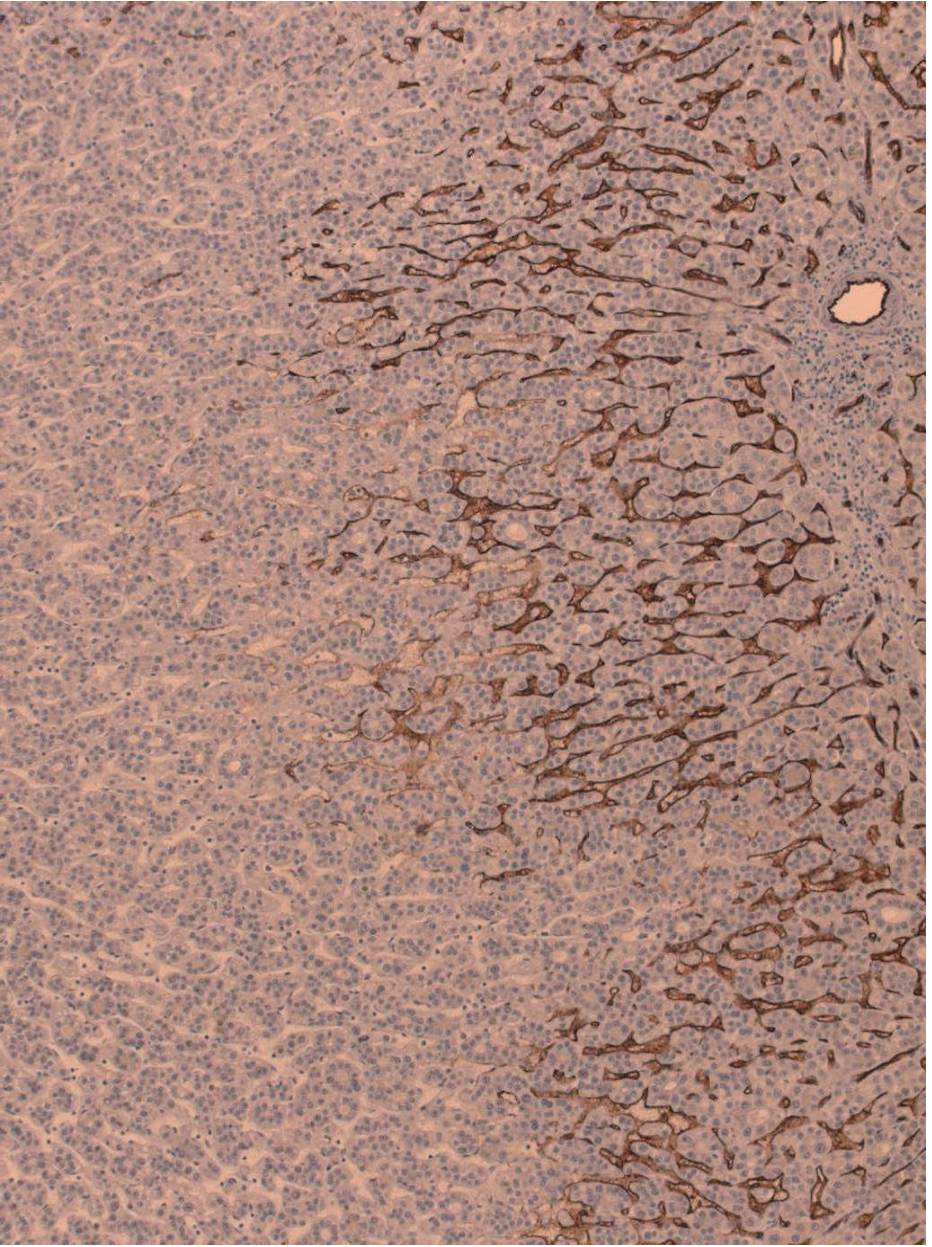
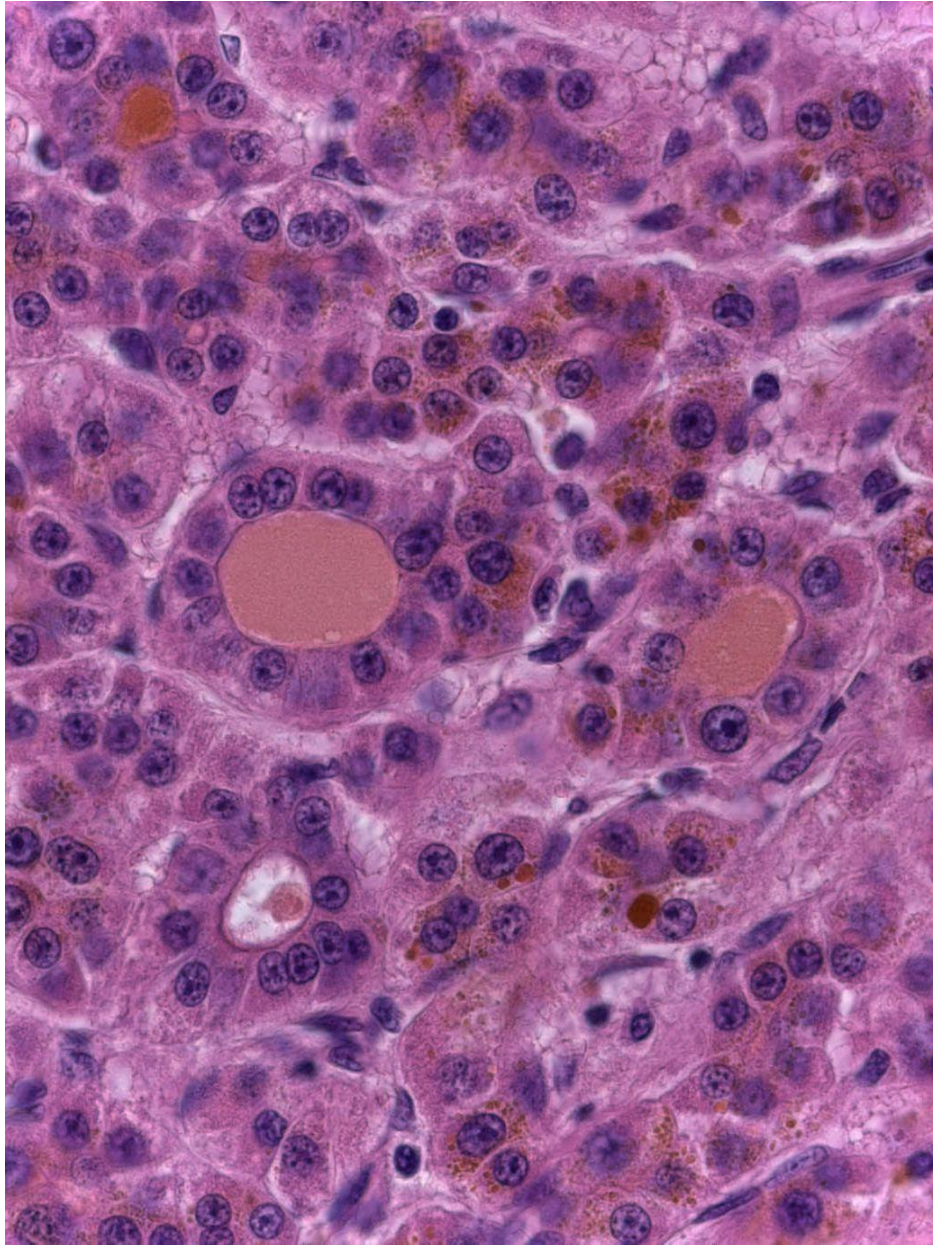
Roth et al, 1982, Ye et al, 1999; Hassan et al, 2000; Bernard et al 2000; Masuda et al, 2011; Hechtman et al, 2011; Vig et al 2012; Koea et al 2012

Malignant transformation of hepatocellular adenomas

- Micchelli et al (2008): 3 of 17 cases with progression to HCC; in 2 focal atypia in adenoma. No association with β catenin mutations
- Occasional single case reports: Hectmann et al (2011) : HCC arising in pigmented inflammatory adenoma – β catenin mutation
- Paradis et al (2009): 5 HCCs arising in series of metabolic syndrome-associated tumour were on background of adenoma
- Systematic review: 1600 adenomas – overall risk is 4.2% but <5% of these found in small adenomas (< 5 cm) Stoot et al (2010)
- Farges et al (2011): risk 10 times greater in men than women

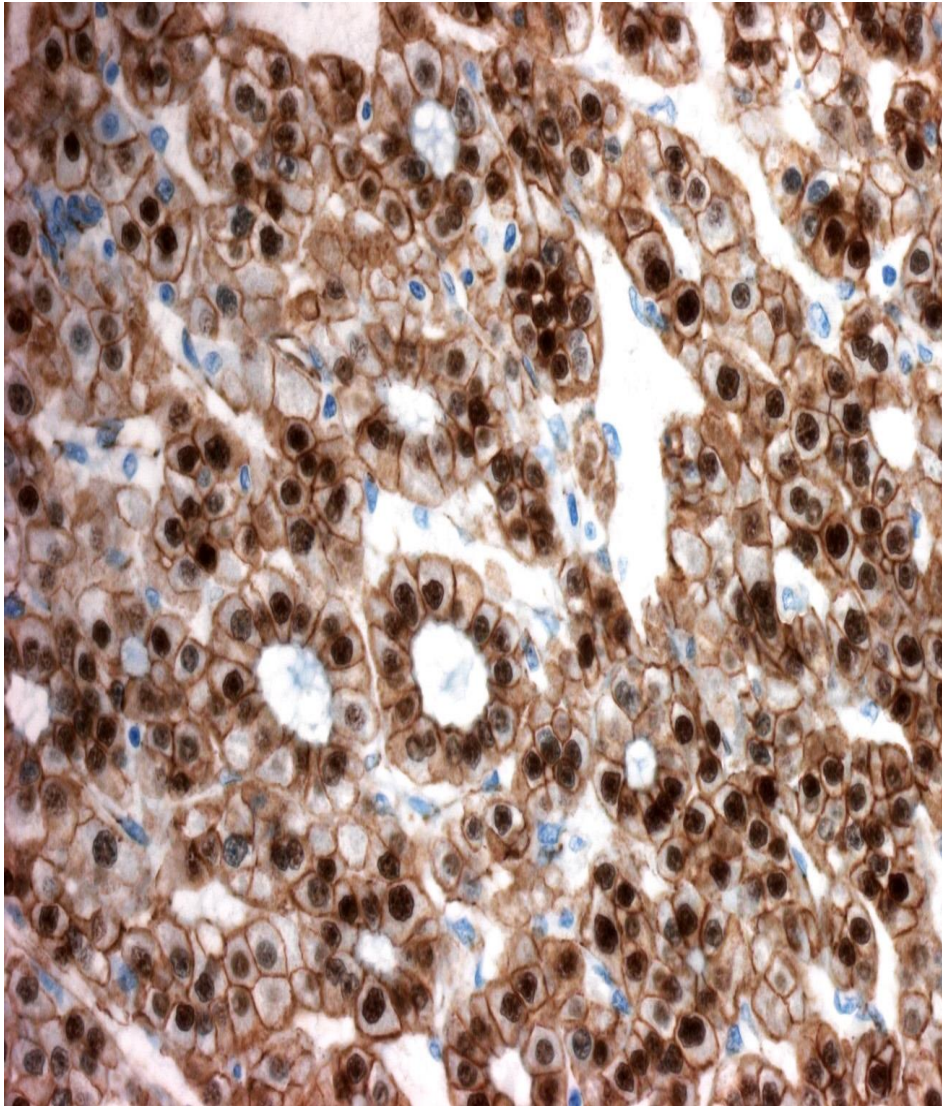
BASEL-A, 2013

- Male, 35 c/o chest pain, cough and mild RUQ tenderness
- Anabolic androgenic steroid (AAS) intake (body builder) at high doses over the last 5 years (> Testosterone propionate, i.m. and stanozolol,oral)
- Normal AFP; slight increase transaminases. Viral markers and autoantibodies: negative
- US: liver mass, left lobe, II-III segment, 6.5 cm.
- Hepatic resection: 16 cm size left lobe with green-dark well-demarcated nodule, 6.5 \ominus cm, close to resection margins

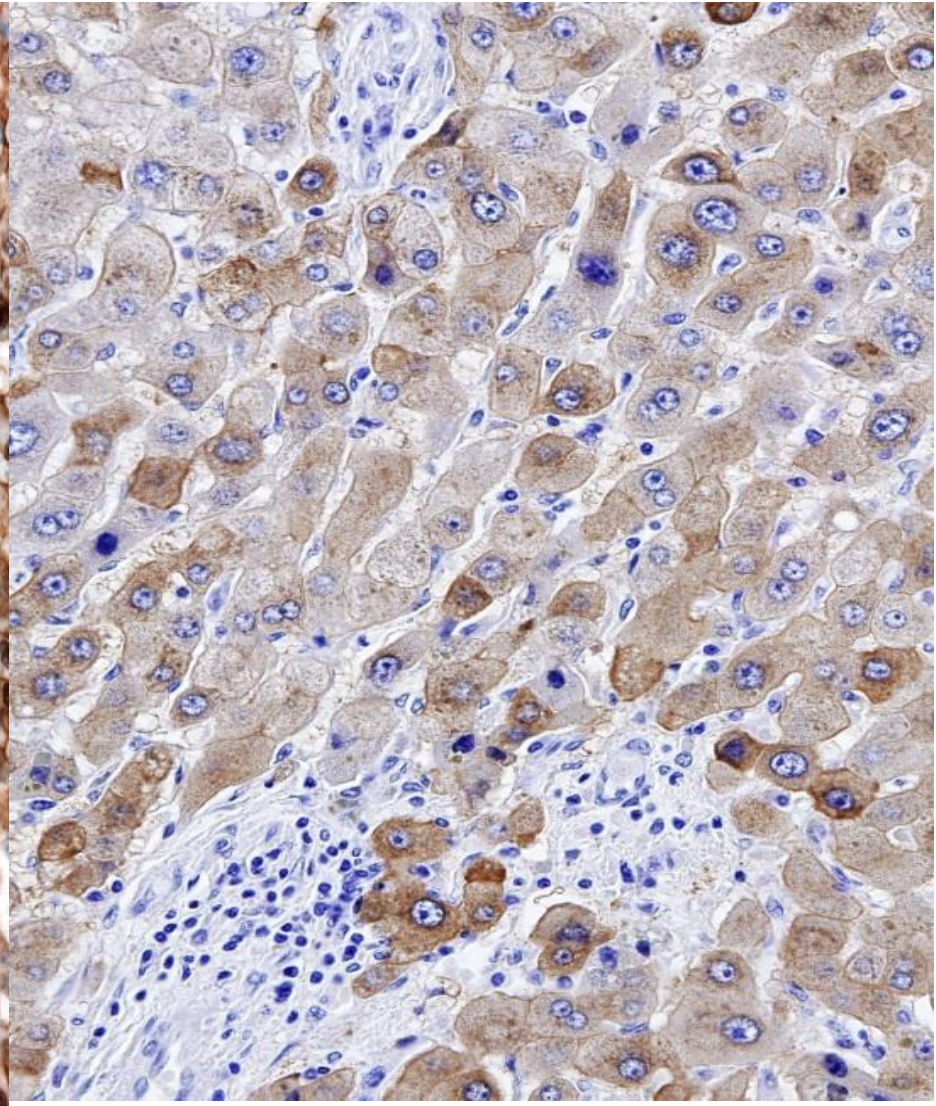


CD34

B04.11594

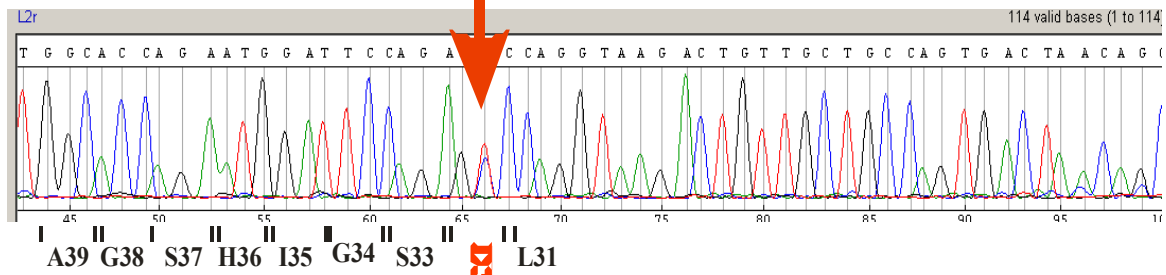
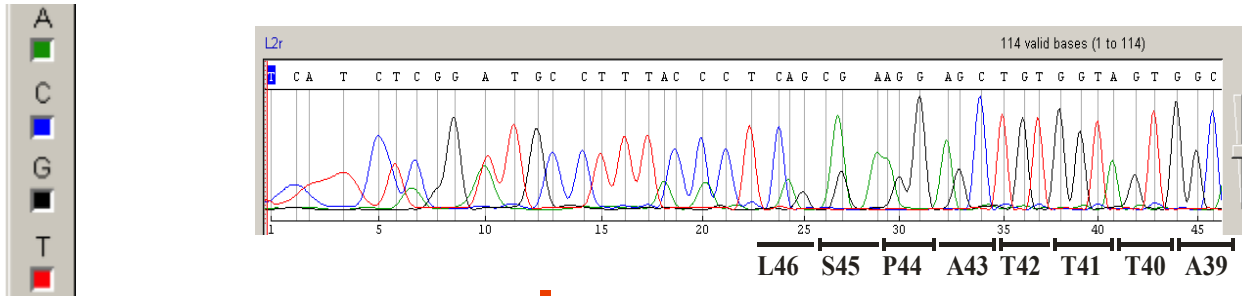


b-catenin



Glutamine synthetase

Sequence of sample B04.11594 = L2: **Mutation in b-catenin = D32G**
 (reverse sequence is showed in this document)



```

701 | gctgatttga tggagttgga catggccatg gaaccagaca gaaaagcggc
751 | tgttagtcac tggcagcaac agtcttacct gogactctgga atccattctg
801 | gtgccactac cacagctcct tctctgagtg gtaaaggcaa tcttgaggaa
851 | gaggatgtgg atacctccca agtccctgtat gagtgggaac agggattttc
901 | tcagtccttc actcaagaac aagtagcttg taagagtatt atttttcatt
951 | gccttactga aagtcagaat gcagttttga gaactaaaaa gttagtgtat
1001 | aatagtttaa ataaaatggt gtggtgaaga aaagagagta atagcaatgt
    
```

- T41 and S45
- nested primers
- exon 1
- exon 2
- exon 3

Present case

Favour HCC:

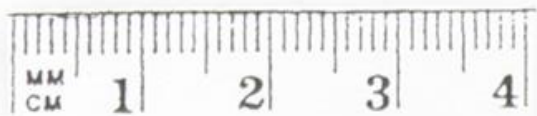
- Morphology
- Size: > 5cm
- Sex: Male

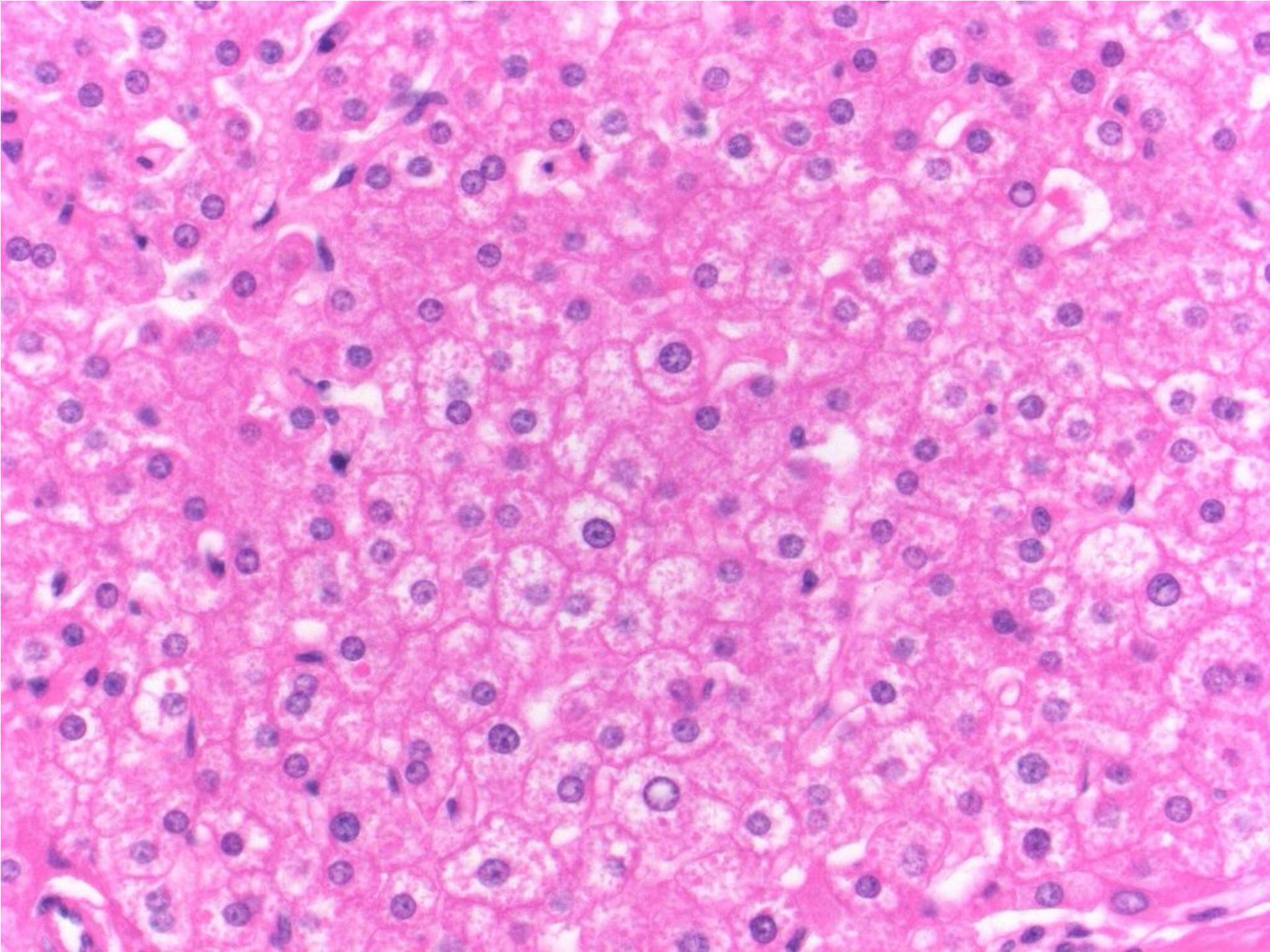
Favour adenoma:

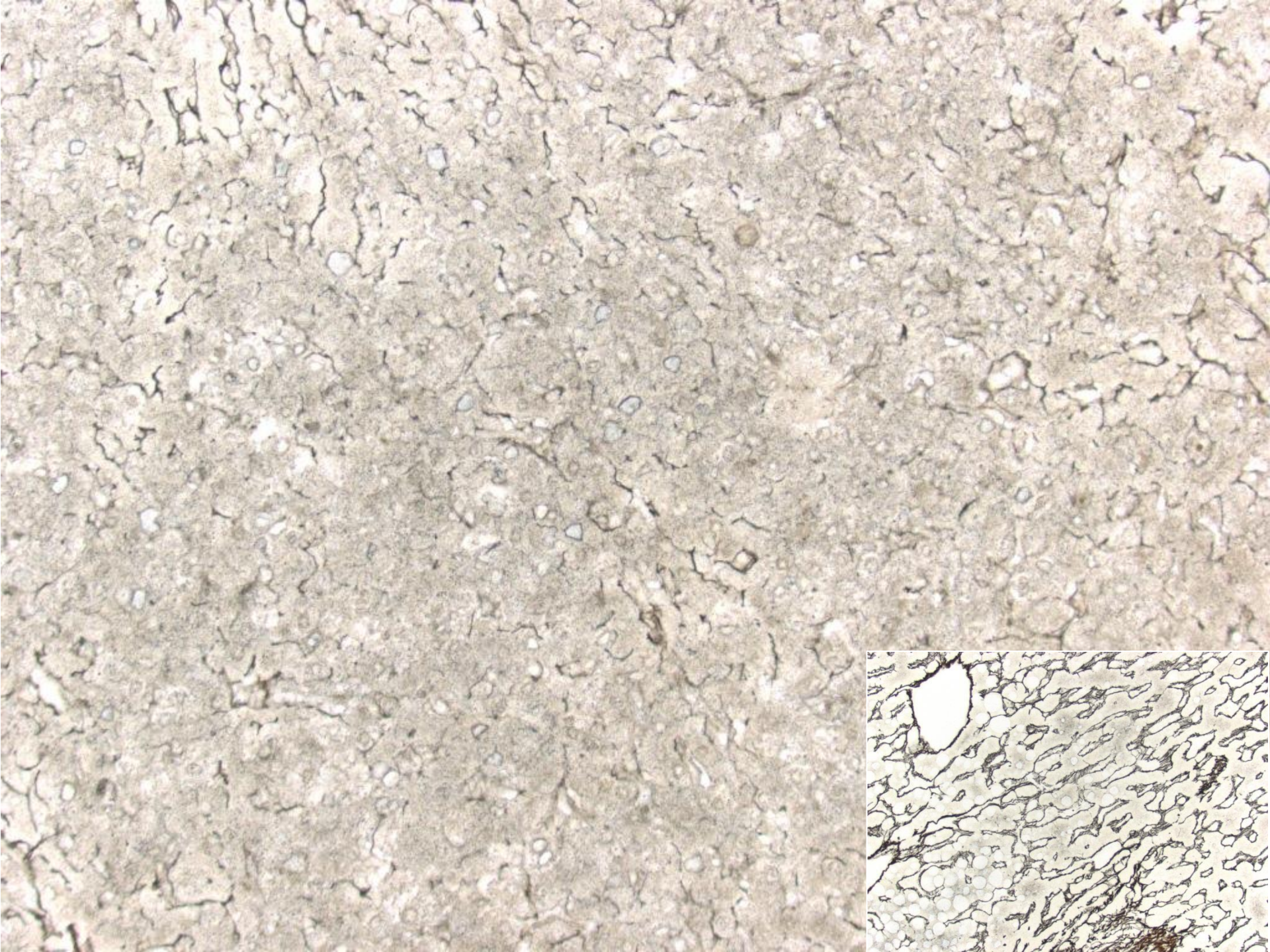
- Absence of chromosomal aberrations
- Negative GPC3 and HSP70 stainings, preserved reticulin, focal CD34 staining
- Behaviour (no relapse/mts after 6 yrs)

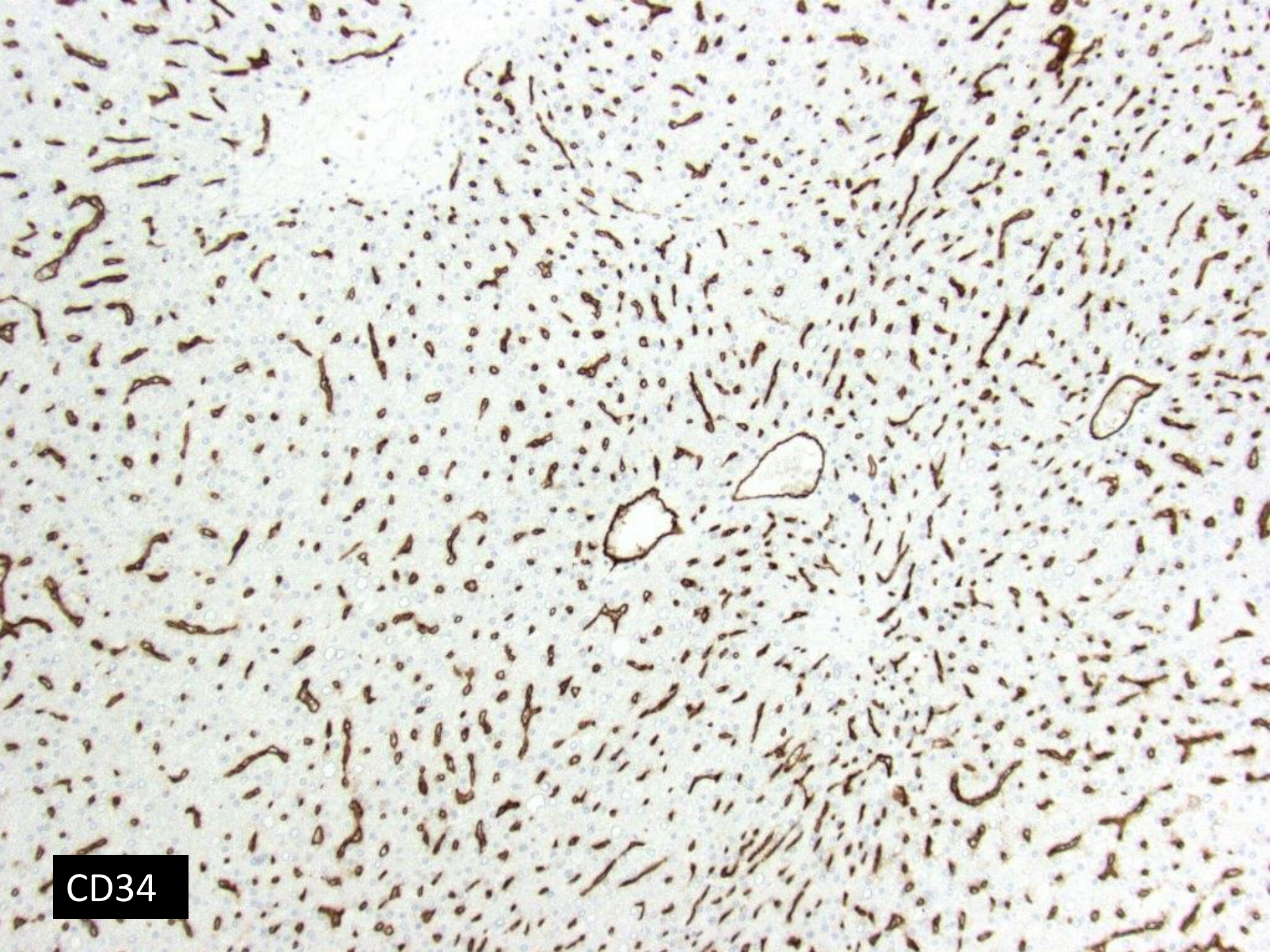
Brisbane A

- Female 30 - epigastric pain
- US followed by CT and MRI showed multiple arterially-enhancing lesions consistent with adenomas in both lobes of liver
- 8cm pedunculated lesion segment 2
- >> evidence of internal haemorrhage / necrosis.
- removed by sectionectomy



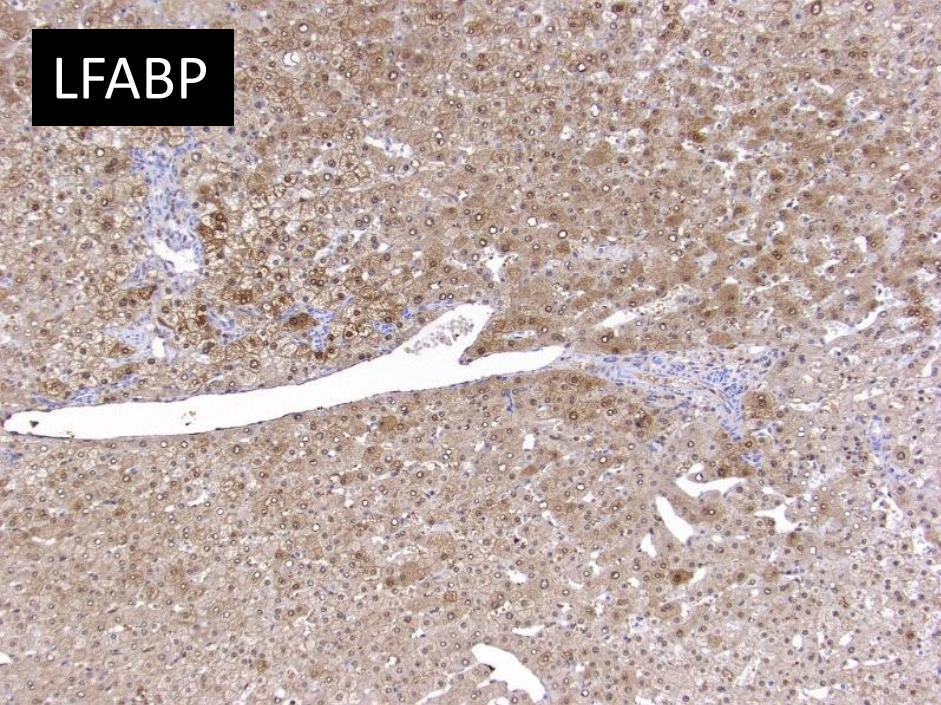




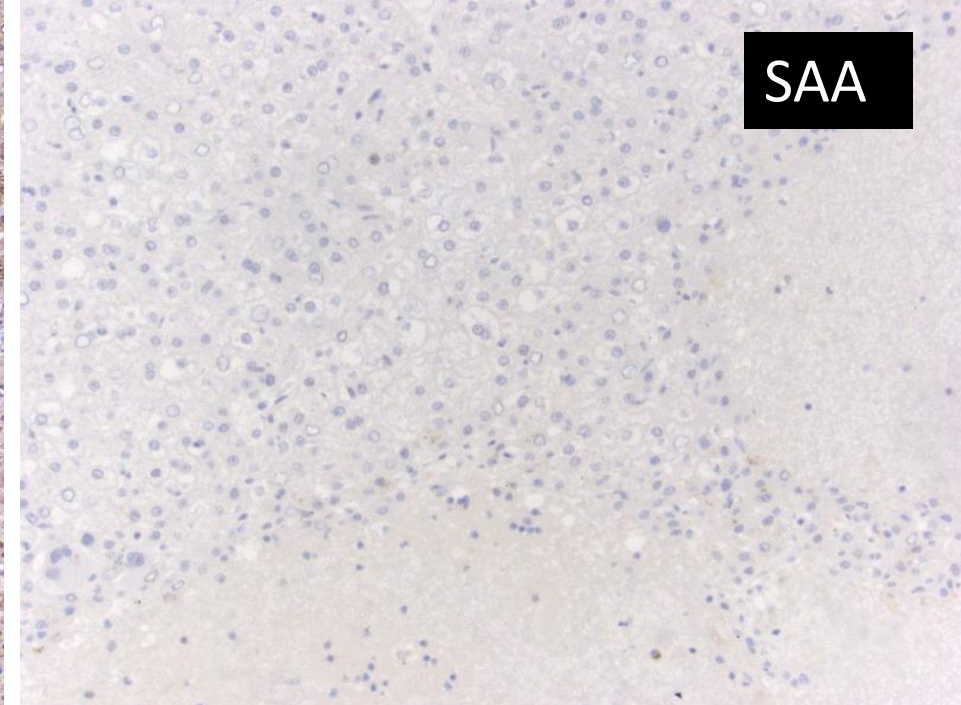


CD34

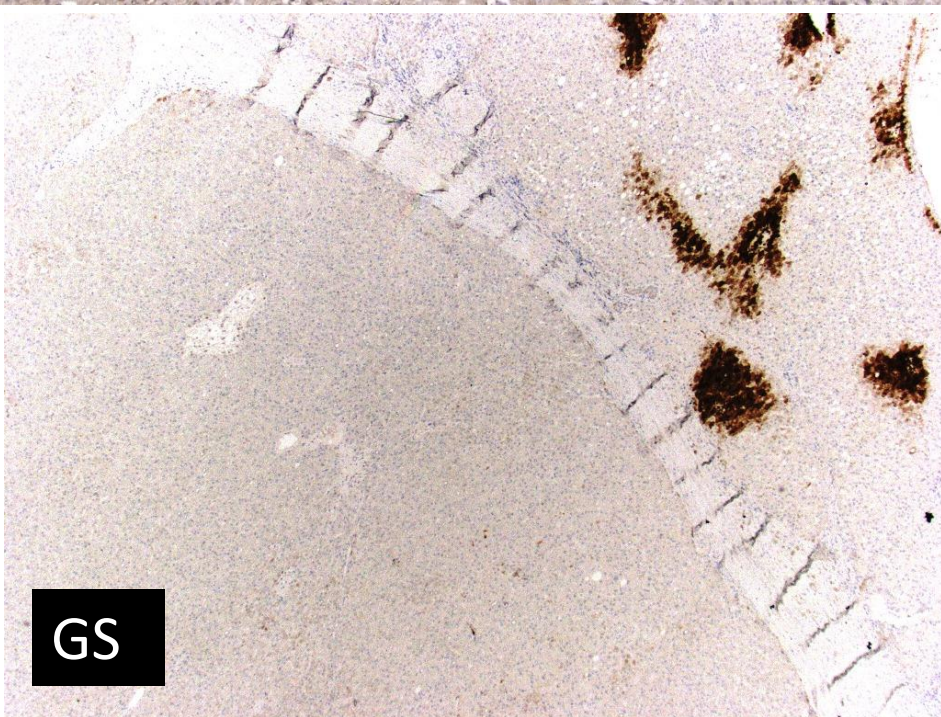
LFABP



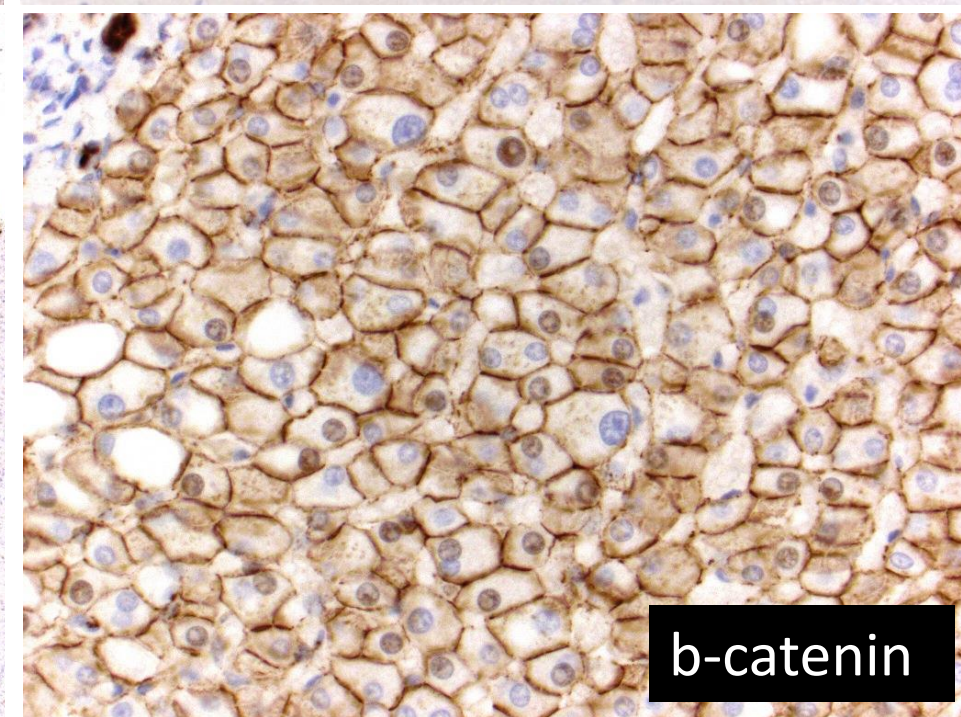
SAA



GS



b-catenin



CD34+ and reticulin loss in adenoma

Author	Year	Cases	CD34	Reticulin
deBoer	2000	5	0	0
Kong	2000	7	5 had >50%	“use retic”
Costan	2008	19	4 complete	-
Shefizadeh	2008	10 [HCC & gpc3]		“extremely well differentiated HCC”
Ahmed	2009	14	2	
Singhi	2012	14		Loss with fatty change
Bergman	1997	1 NAFLD		Retic loss
Scott	1996	1 HCC		Retic loss FL

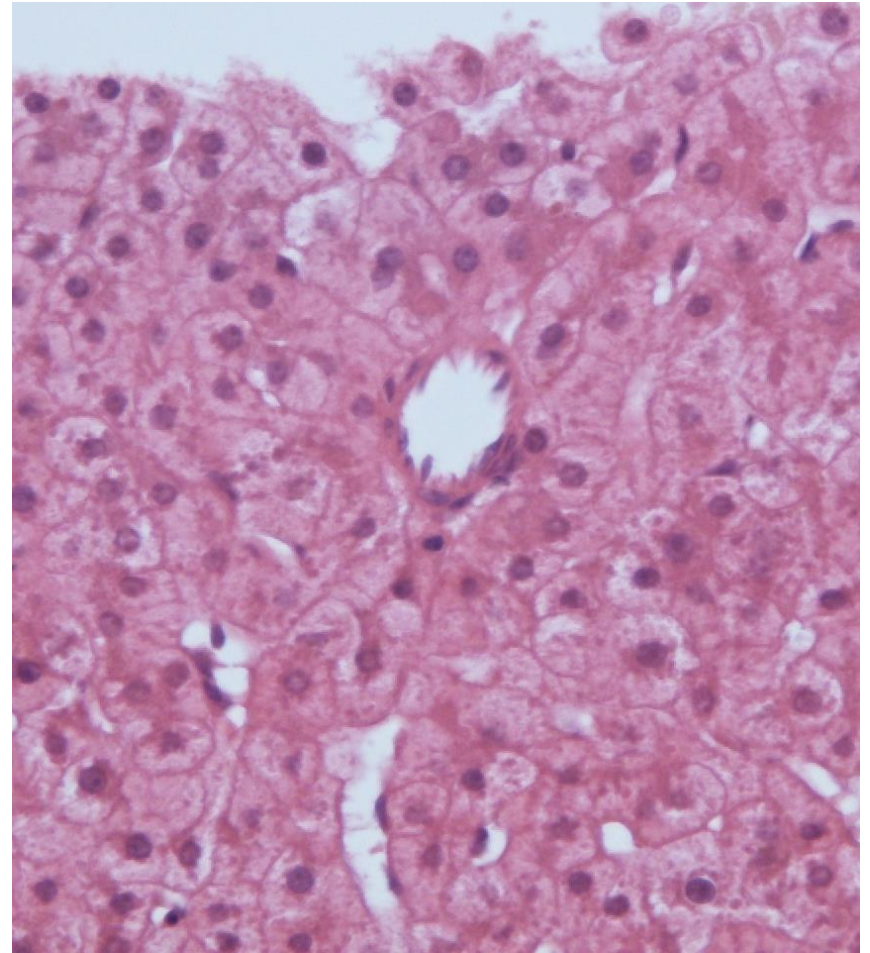
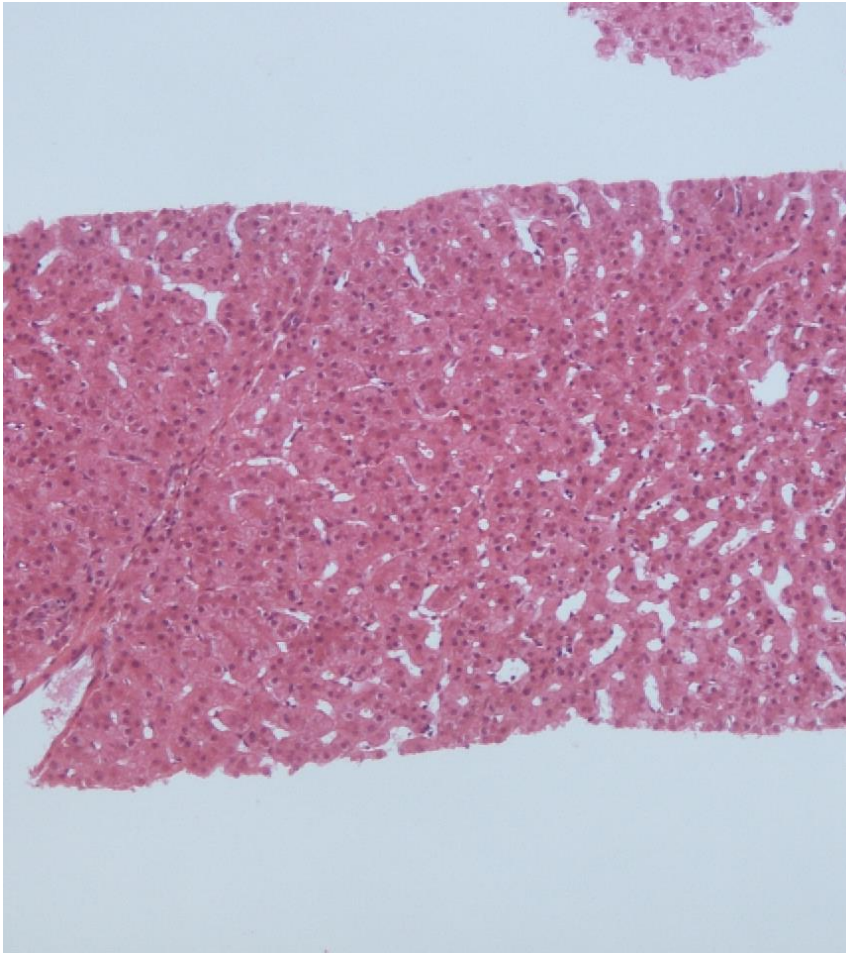
CD34+ and reticulin loss in adenoma

- both are described
- uncertain how often these occur together
- are there diagnostic thresholds for HCC?

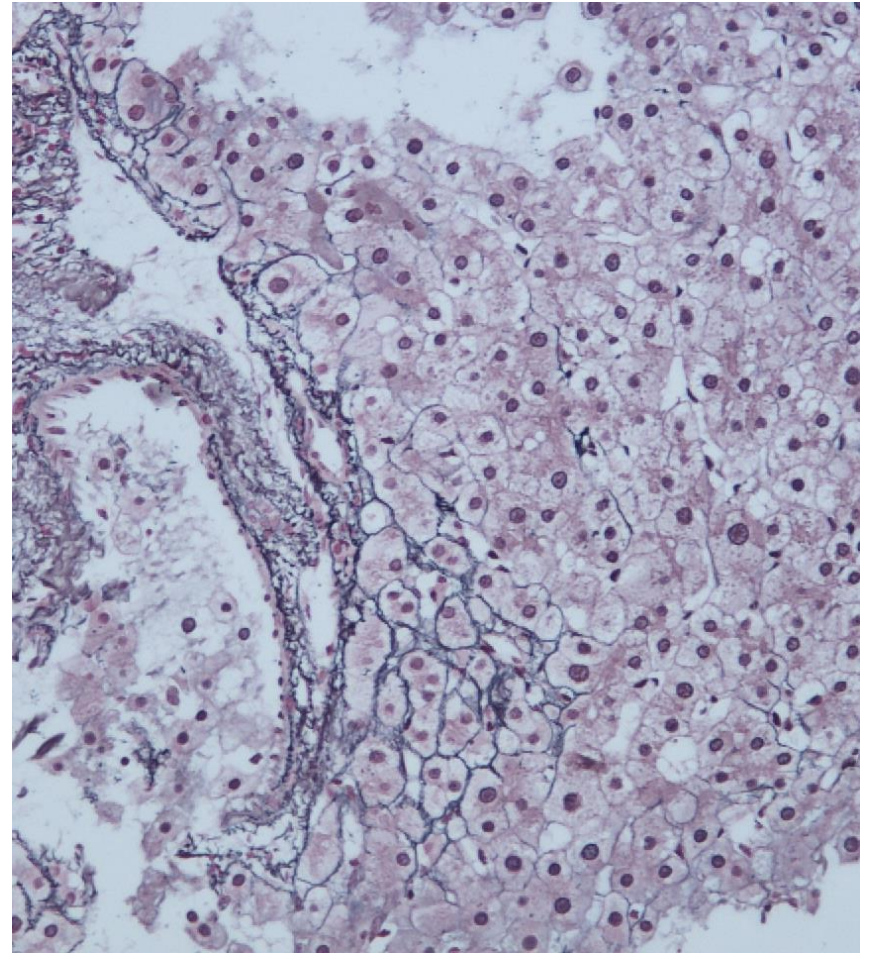
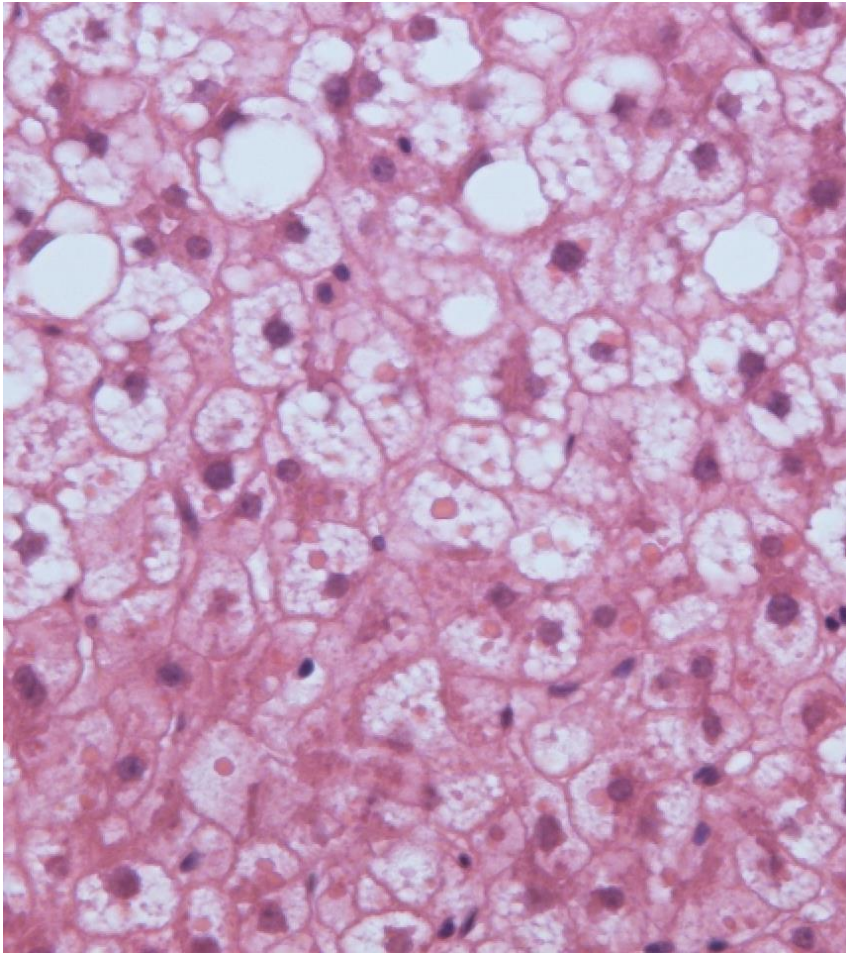
Birmingham A/2013

- Male 37
- Presented with acute abdominal pain in December 2012
- Imaging studies showed 11cm mass in right lobe of liver with portal vein thrombosis.
- Not suitable for resection or transplantation
- Biopsy February 2013 to confirm nature of tumour prior to possible further treatment.
- Three biopsies taken to include right lobe lesion and adjacent non-lesional liver (thought to be normal)

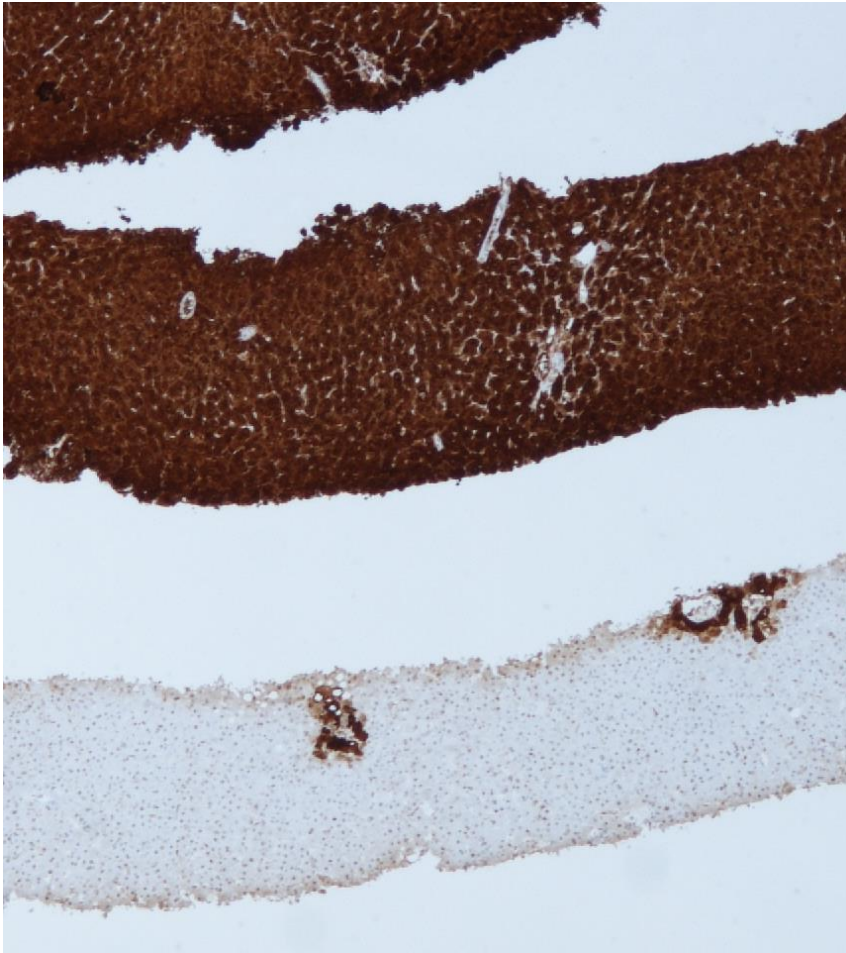
Birmingham A



Birmingham A



Birmingham A



Birmingham A-2013

Well-differentiated hepatocellular neoplasm

- Little/no cytological atypia
- Focal reticulin depletion
- Diffuse expression of glutamine synthetase
- Focal nuclear expression of beta-catenin
- Glypican 3 – focally positive
- CD 34 – diffuse sinusoidal immunoreactivity in places
- Ki 67 labelling – up to 5%
- negative for SAA and AFP
- weak focal positivity for CRP (less than in non-lesional tissue)

“Extremely well-differentiated HCC”

- 10 cases in their series were “extremely WD HCC”
- “focal small cell change, widened cell plates, stromal invasion, and / or reticulin loss”
- 50% expressed glypican 3

“Extremely well-differentiated HCC”

- “Atypical large well differentiated HCC with benign nature”
- cirrhotic liver (17 / 663 screened patients)
- large nodules >2cm, uniformly WD, no vascular invasion
- retain portal circulation
- indolent



Original contribution

Atypical hepatocellular adenoma–like neoplasms with β -catenin activation show cytogenetic alterations similar to well-differentiated hepatocellular carcinomas^{☆,☆☆}

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- Tumours that resembled HCA morphologically, but had one or both of the following atypical features:
 1. Atypical age/sex
 - Men (any age)
 - Women aged ≥ 50
 2. Atypical morphology
 - Focal cytologic or architectural atypia (small cell change, pseudogland formation, nuclear atypia) involving $<5\%$ of the tumour

Atypical hepatocellular adenoma-like neoplasms

(Evason, Human Pathology 2013; 44: 750-758)

Table 1 Morphologic, immunohistochemical, and cytogenetic features of HCAs and AHNs

	HCA, % (n)	AHN, % (n)	<i>P</i>
Age \geq 50 y	0 (0/28)	40 (14/35)	.00015 *
Male sex	0 (0/28)	29 (10/35)	.0020 *
Steatosis	45 (14/31)	55 (22/40)	.41
Inflammation	48 (15/31)	35 (14/40)	.26
Telangiectasia	45 (14/31)	33 (13/40)	.28
Ductular reaction	16 (5/31)	8 (3/40)	.25
Atypical morphologic features	0 (0/31)	70 (28/40)	<.00001 *
β -Catenin activated	10 (3/30)	35 (14/40)	.016 *
SAA positive	62 (18/29)	56 (20/36)	.60
Chromosomal abnormalities	0 (0/9)	59 (10/17)	.0034 *

- Other analyses showed further correlations between atypical morphology, β -catenin activation and chromosomal abnormalities.
- Limited follow-up data. 4/14 AHN cases had adverse outcomes suggestive of malignancy

Well differentiated hepatocellular neoplasm of uncertain malignant potential (HUMP)

- 28 circulated cases: 6 with histological features of HCA but with reticulin loss and nuclear crowding
- 3 pigmented adenomas; none steatotic
- 30-170 mm diameter
- None with increased mitotic activity, vascular invasion, recurrence or metastasis
- Reticulin loss can occur in steatotic adenomas and in fatty liver
- Poor concordance amongst group
- Current WHO classification fails to recognise these borderline lesions
- Recommend HUMP: needs careful follow up
- Detailed clinical and molecular profiling underway in larger cohort

Proposed entities considered to represent HUMPs

- Lesions with morphological features of HCA
 - Focally histologically atypical
 - Focal reticulin loss
 - Focal small cell change; nuclear atypia (<5% tumour)
 - Focal architectural atypia (pseudogland formation etc)
 - Genetically atypical
 - β -catenin activated tumours
 - Clinically atypical
 - Female > 50 or < 15
 - Male
- Lesions with features of HCC but which can regress with treatment of underlying disease
 - Anabolic steroid-induced tumours



Gnomes in Noosa 2013



Ravello

Villa Rufolo, Gnomes 2014