Early hepatocellular carcinoma: pathology and diagnosis

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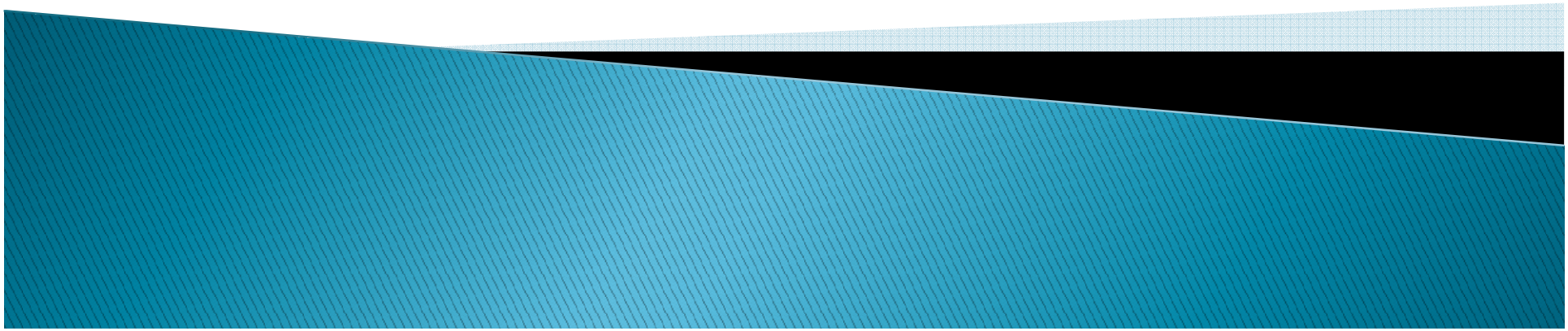


WHO classification 2010: hepatocellular neoplasms and malignancies of mixed or uncertain origin

- *Benign*
- Hepatocellular adenoma 8170/0
- Focal nodular hyperplasia

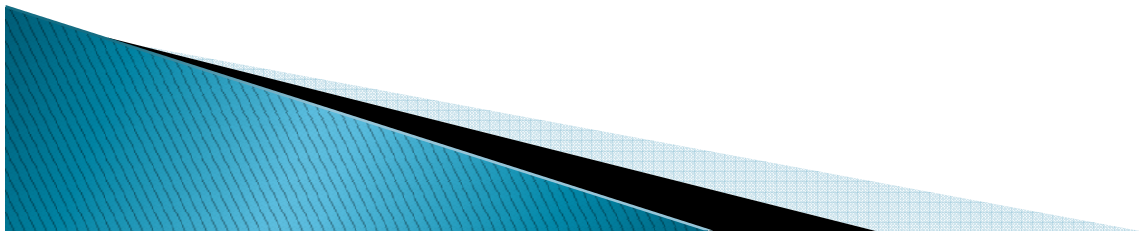
- *Malignancy-associated and premalignant lesions*
- Large cell change (formerly "dysplasia")
- Small cell change (formerly "dysplasia")
- Dysplastic nodules
  - Low grade
  - High grade

- *Malignant*
- Hepatocellular carcinoma 8170/3
- Hepatocellular carcinoma, fibrolamellar variant 8171/3
- Hepatoblastoma, epithelial variants 8970/3
- Undifferentiated carcinoma 8020/3

Calcifying nested epithelial stromal tumour 8975/1*
Carcinosarcoma 8980/3
Combined hepatocellular-cholangiocarcinoma 8180/3
Hepatoblastoma, mixed epithelial-mesenchymal 8970/3
Malignant rhabdoid tumour 8963/3

Aims of presentation

- Briefly review aspects of typical HCC
- Consider HCC outliers/variants
- Review concept of precursor lesions in the development of HCC
- Discus nodular lesions and their classification
- Consider the concept of early HCC and its diagnosis
- Put early HCC into context clinical staging
- Highlight difficulties and future direction



HCC: a changing picture

- 3rd leading cause of cancer related death in the world
- 2nd most common cancer in Asia
- Rates highest in Mongolia: 116 per 100,000 person years
- Recent decrease over past decade in high risk areas
- Conversely 80% increase in annual incidence in USA(++ African Americans) and similar trend in UK, Canada and Australia
- ? Effect of HCV infection & younger onset ALD
- Impact of screening in cirrhotics

Yang &Roberts (2010)

Typical hepatocellular carcinoma

- Nodular type
- Massive type
- Diffuse (cirrhoto-mimetic) type
- Multifocal
- Pedunculated
- Encapsulated

- Macroscopic patterns

Typical hepatocellular carcinoma

- Trabecular
- Pseudoglandular
- Compact

- Pleomorphic cells
- Clear cells
- Spindle cells
- Steatosis
- MD bodies
- Pale bodies
- Ground glass inclusions

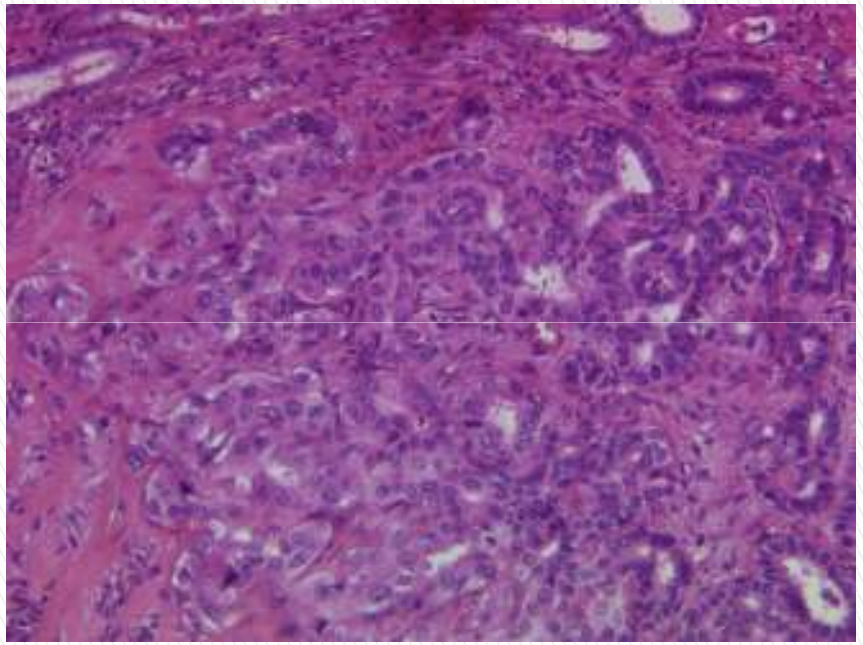
- Microscopic patterns

HCC: outliers

- Fibrolamellar
- Scirrhous
- Undifferentiated
- Lymphoepithelioma-like
- Sarcomatoid HCC

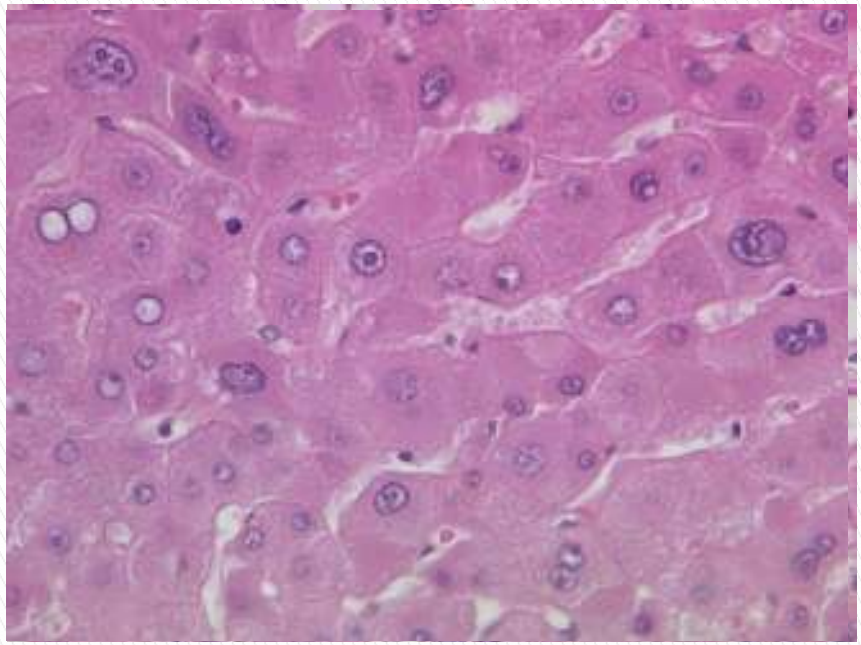
Combined hepatocellular-cholangiocarcinoma

- Incidence depends on definition!!
- Classical combined tumour shows distinct areas of classical HCC and typical CCC
- Some show stem cell features (NCAM; KIT;EpCAM positive)
  - 'Typical'
  - Intermediate cell type
  - Cholangiolocellular type
- Note expression of CK19 by 'classical' HCC: of prognostic importance if > 5%
- Concept of continuum: mixed tumours



Hepatocellular dysplasia and atypia

- Small cell change
  - Previously : small cell dysplasia
  - Increased proliferative index
  - Increased N:C ratio
  - Telomere shortening and p21 checkpoint inactivation
  - Chromosomal gains
- Large cell change
  - Preserved N:C ratio
  - Nuclear pleomorphism and multinucleation
  - ? Senescent cells: may vary with aetiology
- Iron free foci



Observed in nodular lesions within cirrhotic livers: more frequent in those with HCC

Liver nodules and HCC precursor lesions

- Multi-step hepatocarcinogenesis
- Improved imaging and development of surveillance protocols highlighted spectrum of nodules in cirrhotic livers
- Defined histologically but emerging molecular signatures
- International Working Party of World Congress of Gastroenterology 1995 classification
  - Large regenerative nodule
  - Low grade dysplastic nodule
  - High grade dysplastic nodule
  - Small hepatocellular carcinoma

Molecular changes in dysplastic nodules and HCC

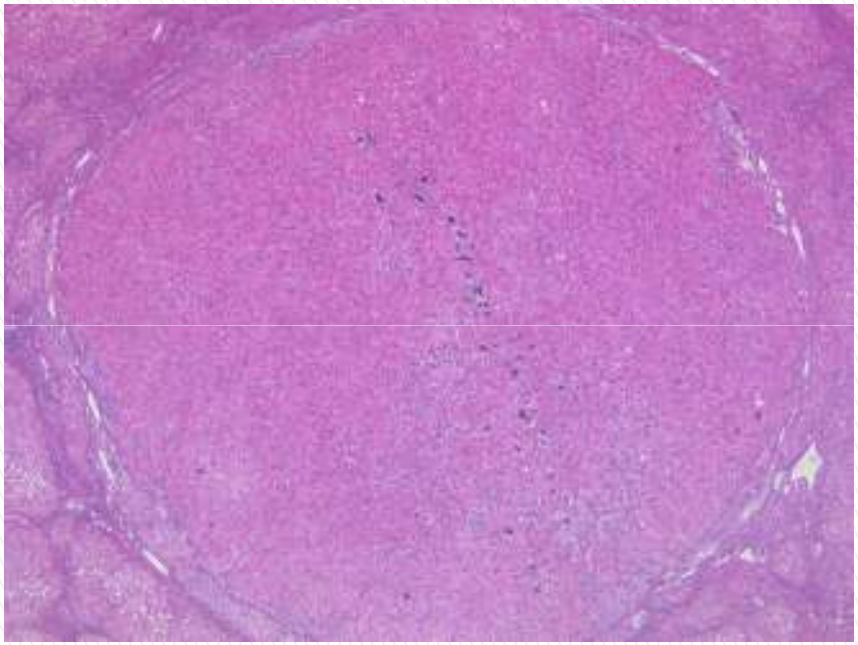
- Accumulation of genetic and epigenetic insults with clonal expansion of liver cells and progenitors in context of chronic liver disease
- Early over-expression of TGF α and IGF-2
- Gene activation by promoter methylation
- Additional effects in HBV with genomic instability
- Telomerase activation with decreased apoptosis

Molecular changes in dysplastic nodules and HCC

- Chromosomal amplifications
- LOH
- Global DNA hypomethylation
- Promoter hypermethylation
- Wnt/β catenin pathway commonly disrupted either by mutation or epigenetic silencing
- p53 and Rb1 pathways also altered
- PI3K/Akt/mTor pathway disrupted by activation of tyrosine kinase receptors or PTEN loss of function

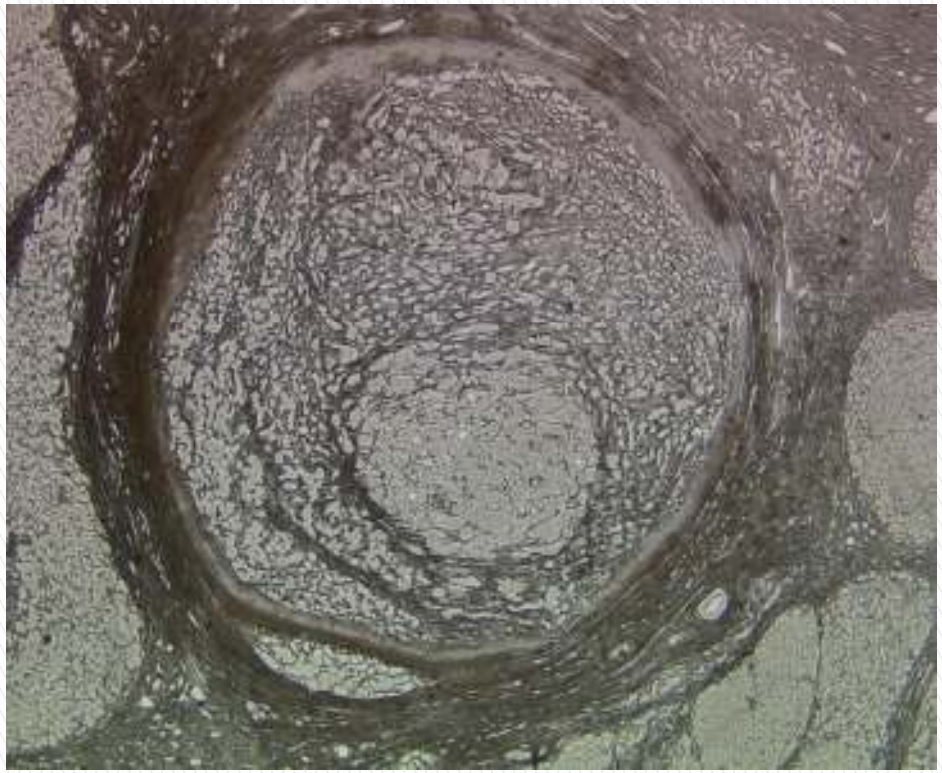
Low grade dysplastic nodules

- Hypercellular with expansile growth pattern: may have peripheral scar
- Evidence of clonality
- May be large cell change
- No pseudoglands or nodule in nodule
- May have siderosis or CAP
- Normally contain portal tracts: most blood from PV – rare aberrant arteries
- On imaging appear of normal vascularity or hypovascular
- ? Distinction from LRN



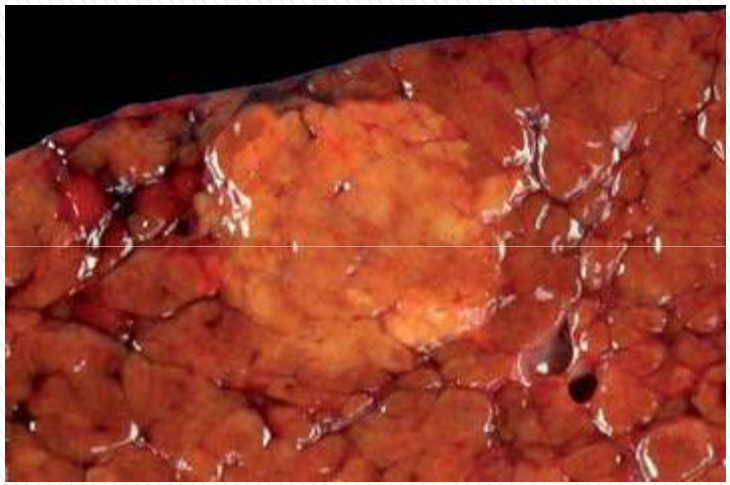
High grade dysplastic nodules

- Vaguely nodular
- Frequently show diffuse or focal small cell change
- Steatosis
- Clear cell change
- MD bodies/p62 inclusions
- Thickened liver cell plates
- Acinar structures
- Nodule-in-nodule: worrying feature: most are HCC evolution



Subdivision of small hepatocellular carcinoma

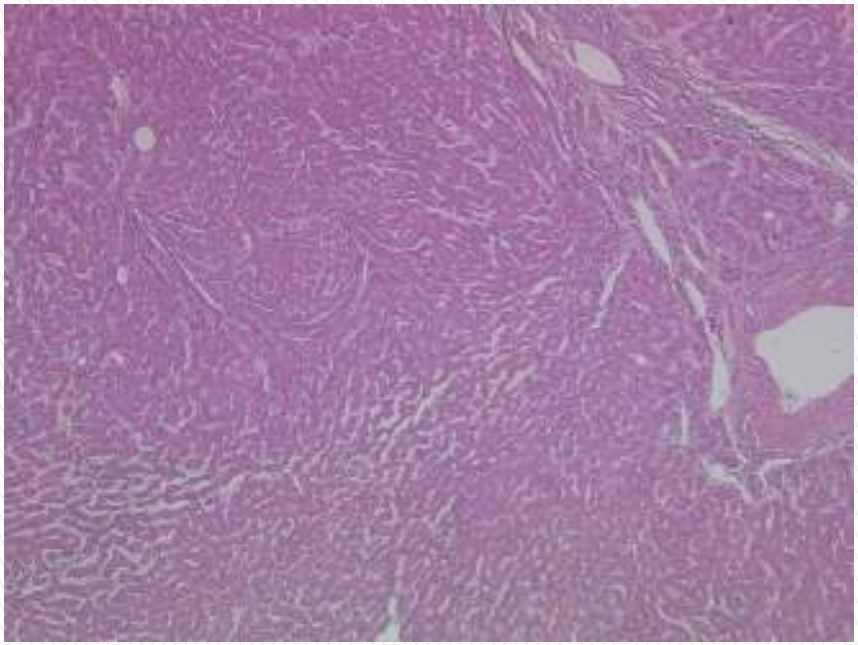
- Early HCC: vaguely nodular appearance; well differentiated
- Progressed HCC: distinctly nodular appearance; moderately differentiated; may be microvascular invasion
- Of prognostic significance: with eHCC 5YS = 89% cf. pHCC = 48%



Takayama et al (1998)

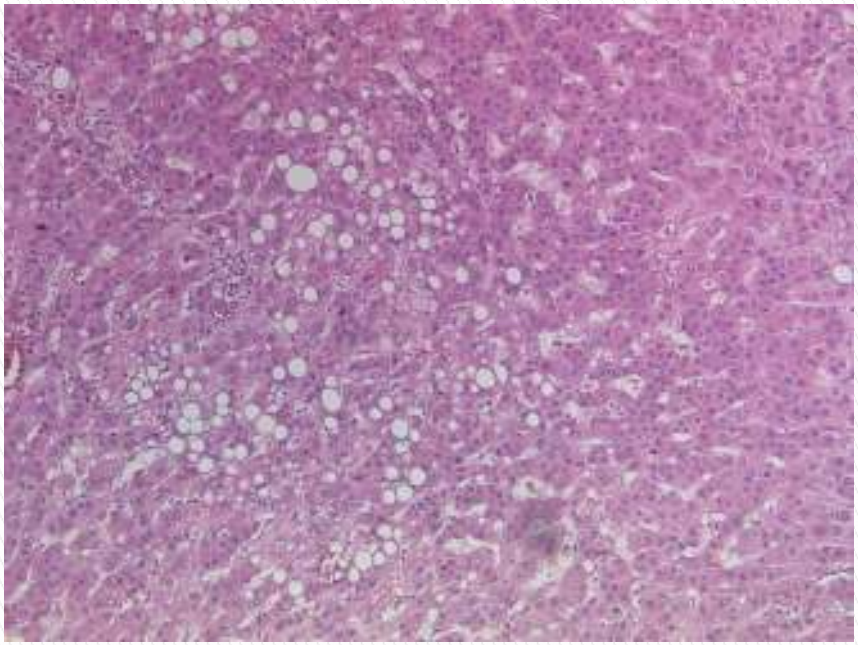
Early hepatocellular carcinoma

- Difficult to recognise macro and microscopically
- Recognised by Japanese for almost 25 years
- Now some (?) international consensus as to distinction from HGDN
- Small lesions (<2 cm diameter)
- Many of the cytological features of HGDN seen: merge with adjacent liver
- Stromal invasion required for diagnosis
- Absence of ductular reaction (cf. pseudoinvasion)



Early hepatocellular carcinoma

- Not all small HCCs represent ‘early HCCs’
- Classical HCC if trabecular architecture; pseudoacinar change; ++ aberrant arteries; presence of capsule
- Vascular supply differs between early HCC and classical HCC
- Portal tracts seen in former
- Reflected in imaging where early HCC may have normal vascularity but arterialised classical HCC is hypervascular

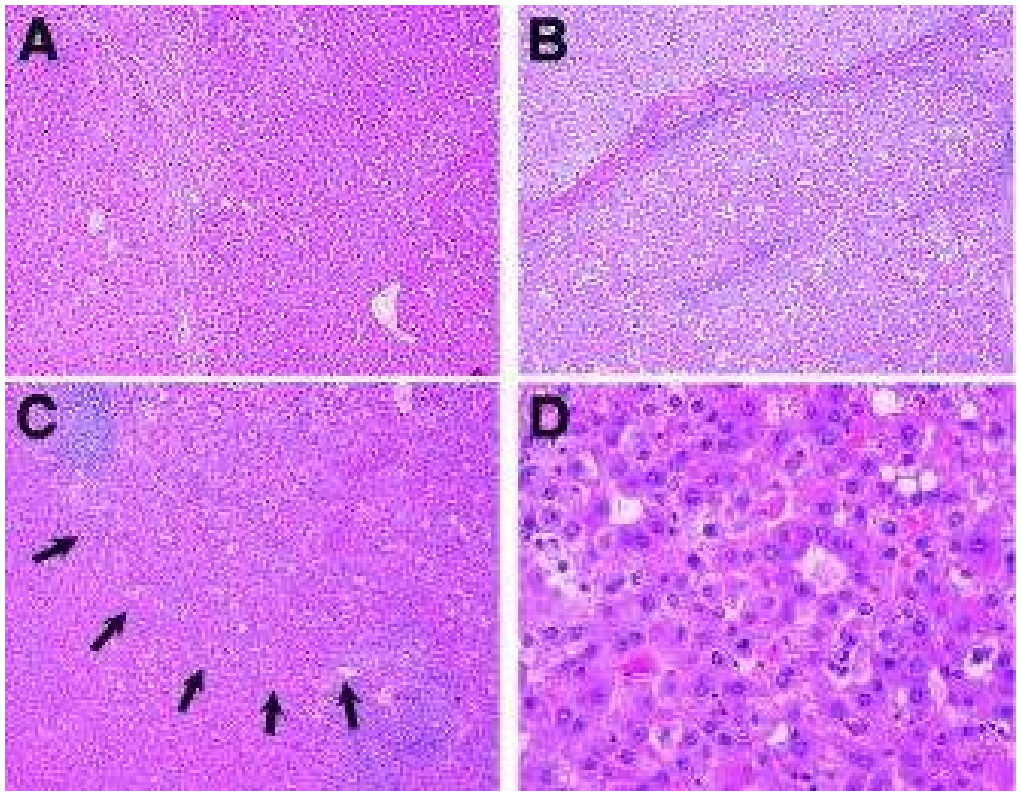


International consensus group for hepatocellular neoplasia

- 34 pathologists from 13 countries
- Several meetings 2002-7
- 26 cases
- All resected specimens with lesions < 2 cm: no transplants or biopsies
- Restricted to Japanese or Korean patients
- All HBV or HCV associated
- Highlighted East-West divide!
- Importance of stromal invasion for diagnosis of eHCC
- Kappa values of 0.49 (after tuning the violins!)

Cell density in precursor lesions

LGDN

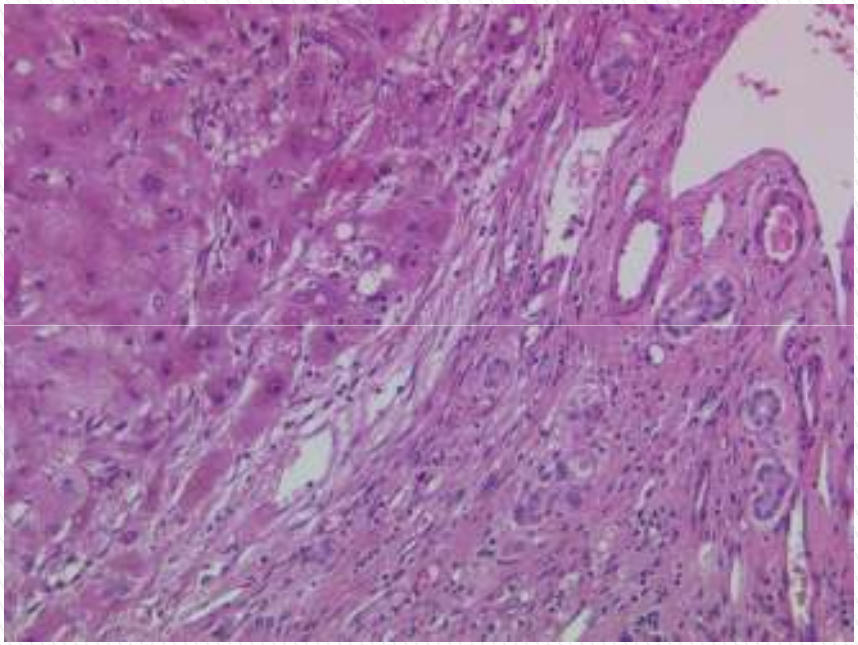


HGDN

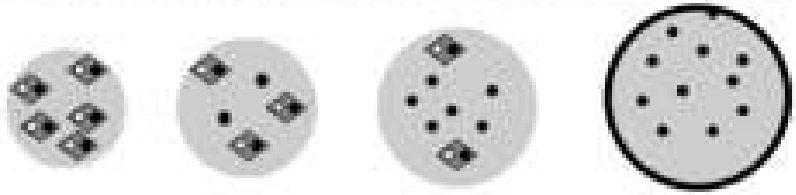
Early hepatocellular carcinoma

Stromal invasion

- Tumour cell invasion into portal tracts or fibrous septa in vaguely nodular lesions
  - Kondo et al (1994)
  - Nakano et al (1997)



International Consensus on Small Nodular Lesions in cirrhotic liver

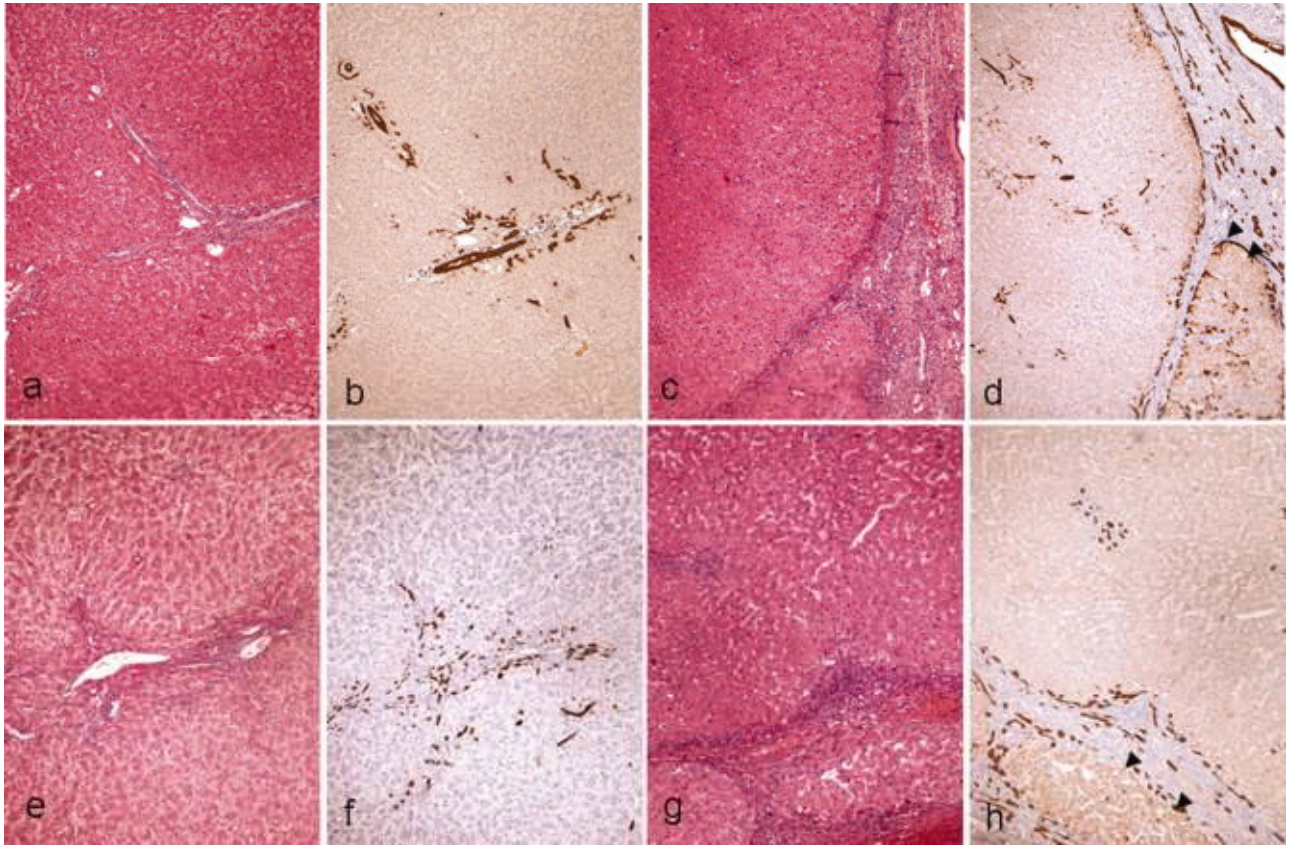


IWP classification	L-DN	H-DN	WD-HCC	MD-HCC
Pathological features				
gross appearance			vaguely-nodular	distinctly-nodular
stromal invasion	(–)	(–)	+ / –	+ / –
Clinical (imaging)				
arterial supply	iso / hypo	iso / hypo	iso / hypo rarely hyper	hyper
portal vein supply	+	+	+	—
Clinico-pathological	Premalignant		Early HCC	Progressed HCC

◆ Intratumoral portal tract • Unpaired artery

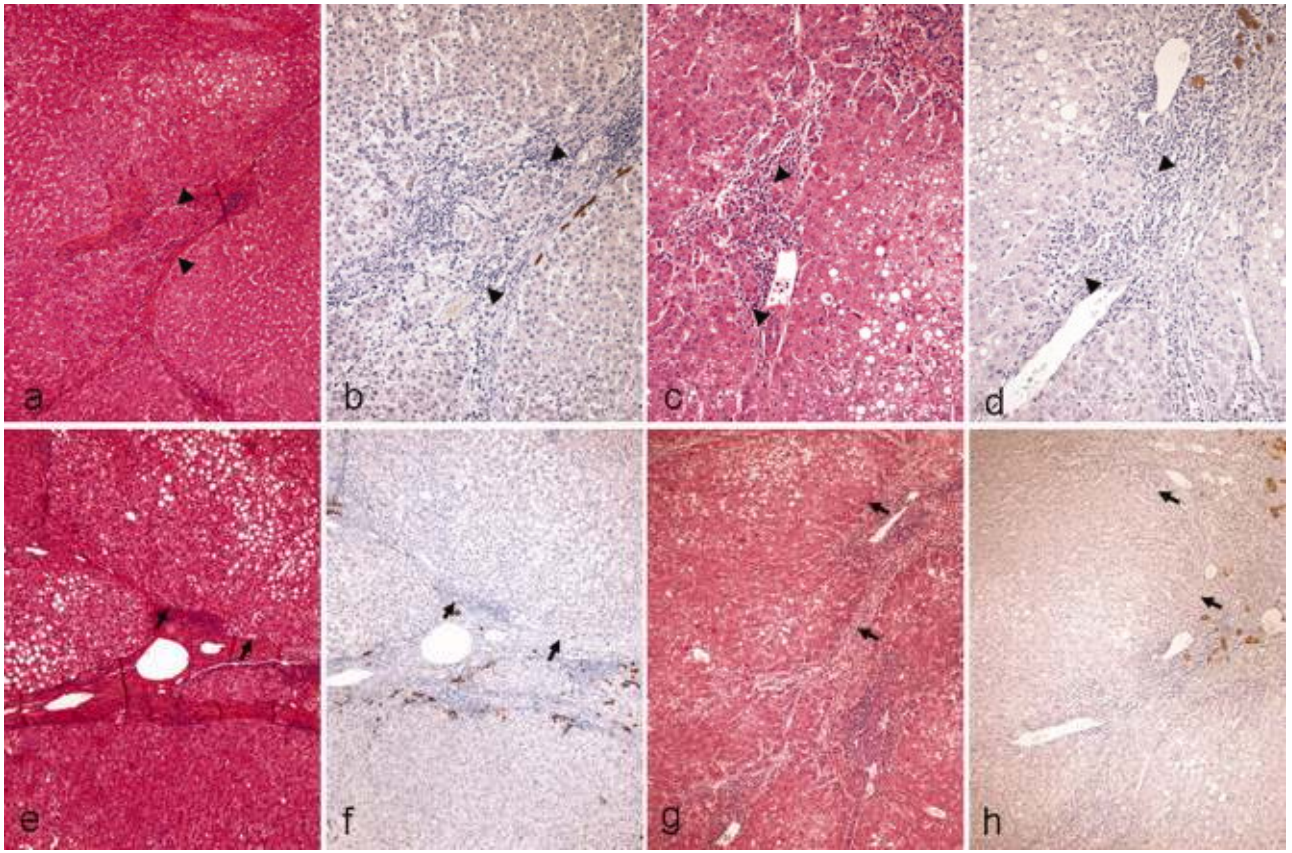
H-DN: High grade dysplastic nodule L-DN: Low-grade dysplastic nodule WD: Well-differentiated
MD: Moderately differentiated iso: isovascular hypo: hypovascular hyper: hypervascular

Ductular reaction in dysplastic nodules



Park et al (2007)

Lack of ductular reaction in early HCC in areas of stromal invasion



Park et al (2007)

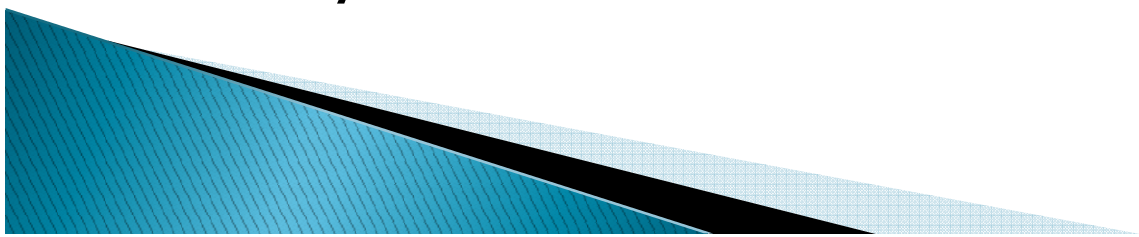
Candidate molecular markers for diagnosis of early HCC

- HSP 70
- CAP2
- Glypican 3
- Glutamine synthetase
- Epigenetic markers
- miRNAs

Llovet & Bruix (2008)
Sakamoto et al (2008)
Suriawinata & Thung (2010)

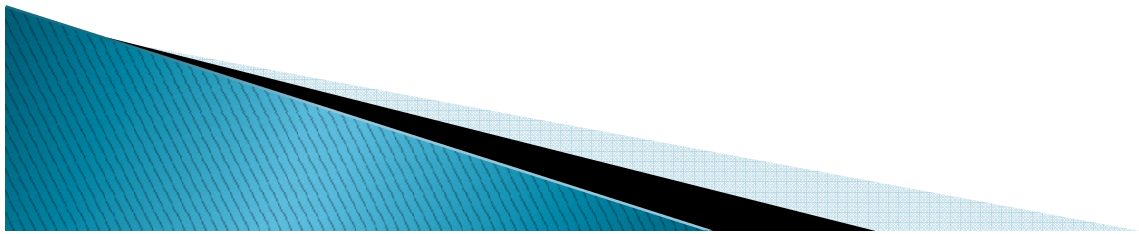
Molecular changes and early HCC

- Rarely positive with serum markers eg. aFP
- HSP70 upregulated: seen in majority of early HCC but rare in HGDN
- Glypican 3: expression higher in early HCC than HGDN: reported sensitivity of 77% and specificity of 96%
- Increased staining and abnormal distribution of glutamine synthetase also a feature (normal - < 10% hepatocytes
- Can these be used to make a diagnosis of early HCC in the absence of stromal invasion?

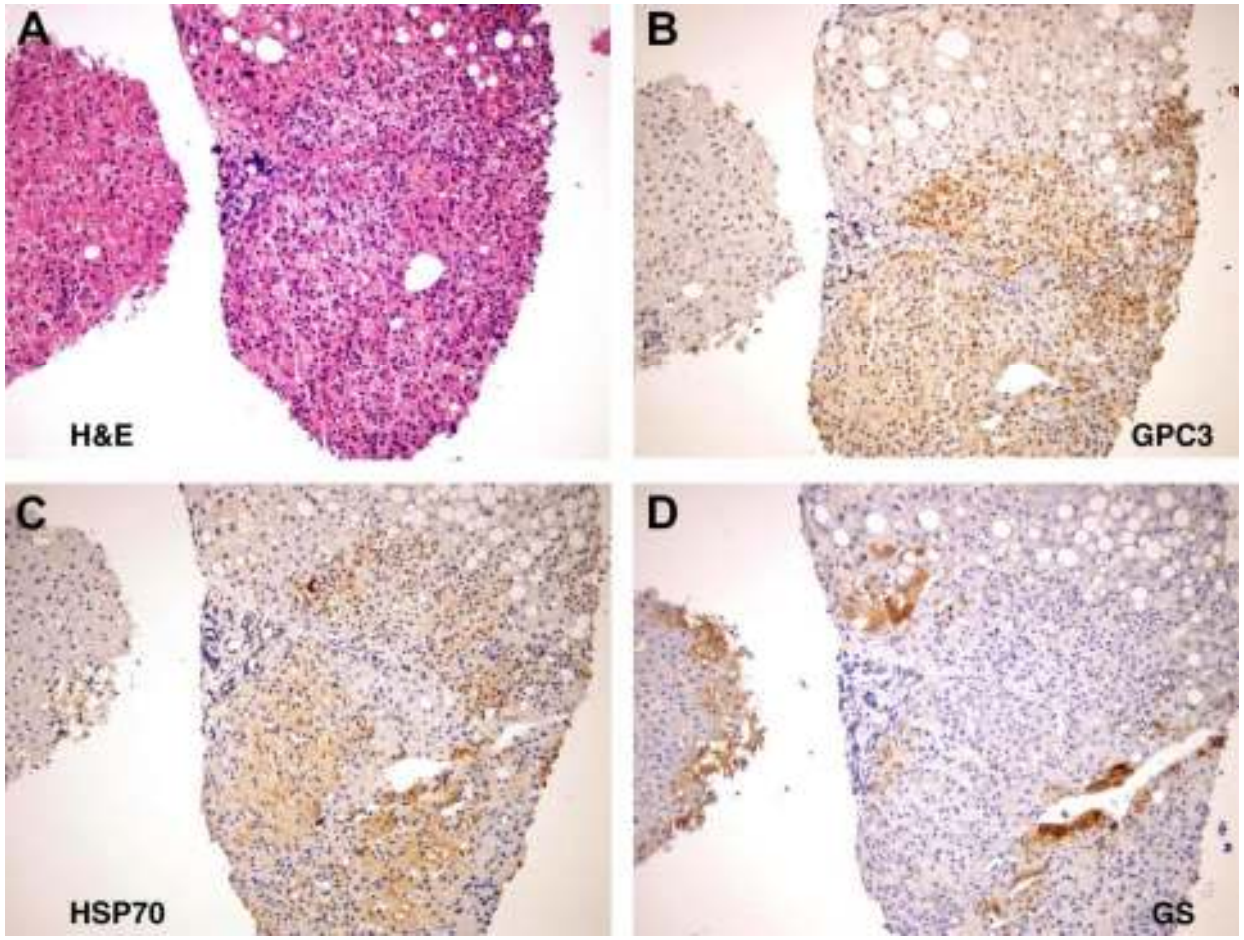


Candidate molecular markers for diagnosis of early HCC

- HSP 70
  - Anti-apoptotic
  - Most abundantly over-expressed gene in early HCC
  - Nuclear and cytoplasmic: may be focal
- Glypican 3
  - Cell surface heparan sulphate proteoglycan
  - Predominantly cytoplasmic (+/- membranous and canalicular)
  - May be focal and expressed in regeneration
- Glutamine synthetase
  - Ammonia metabolism: glutamine a source of energy for HCC
  - Normally expressed in PV hepatocytes
  - Diffuse in 50% of HCCs



Immunophenotyping of eHCC in biopsy specimens



Di Tommaso et al (2009)

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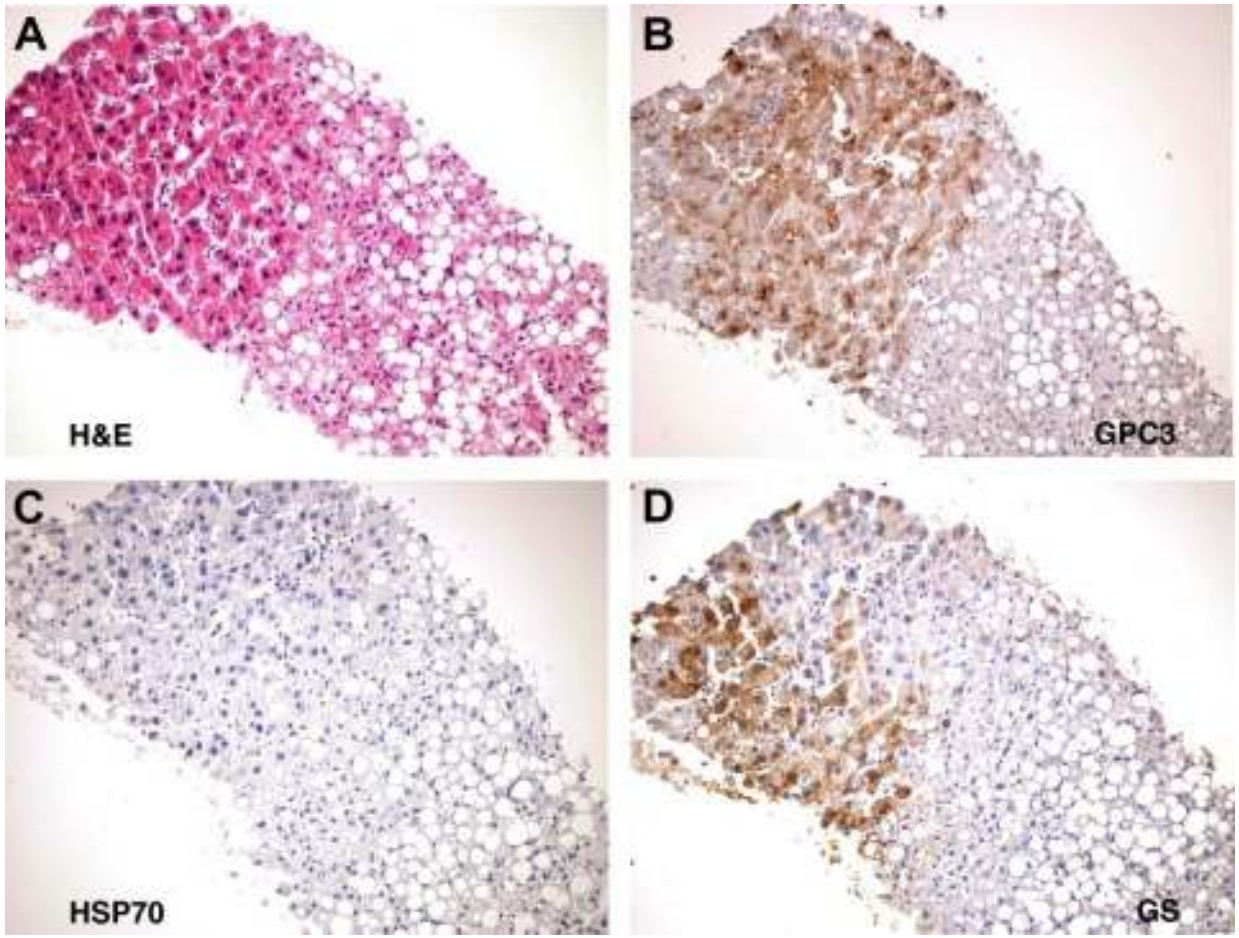

Di Tommaso et al (2009)

Distinction of HCC from benign hepatic mimickers using Glypican 3 and CD34 immunohistochemistry

- 88% hepatocellular cacinomas positive for GPC3
- Only 3% non-hepatic epithelial tumours GPC3 positive
- All adenomas and FNH: GPC3 negative
- Distinctive pattern with CD34 in HCC
- Incomplete vascular pattern in adenoma and FNH

Coston et al (2008)

TNM classification

- T – Primary tumour
- TX Primary tumour cannot be assessed
- T0 No evidence of primary tumour
- T1 Solitary tumour without vascular invasion
- T2 Solitary tumour with vascular invasion or multiple tumours, none more than 5 cm in greatest dimension
- T3 Multiple tumours any more than 5 cm or tumour involving a major branch of the portal or hepatic vein(s)
- T3a Multiple tumours any more than 5 cm
- T3b Tumour involving a major branch of the portal or hepatic vein(s)
- T4 Tumour(s) with direct invasion of adjacent organs other than the gall bladder or with perforation of visceral peritoneum

- N – Regional lymph nodes
- NX Regional lymph nodes cannot be assessed
- N0 No regional lymph-node metastasis
- N1 Regional lymph-node metastasis

- M – Distant metastasis
- M0 No distant metastasis
- M1 Distant metastasis

Stage I T1 N0 M0
Stage II T2 N0 M0
Stage IIIA T3a N0 M0
Stage IIIB T3b N0 M0
Stage IIIC T4 N0 M0
Stage IVA Any T N1 M0
Stage IVB Any T Any N M1

Barcelona Clinic Liver Cancer Staging System

- Stage A: very early/early HCC
- Stage B: asymptomatic mutinodular HCC
- Stage C: invasive/extrhepatic HCC
- Stage D: terminal HCC

- Linked to treatment pathways
- Endorsed by EASL and AASLD
- Does not take into account histology: not to be mistaken with histological concept of early HCC

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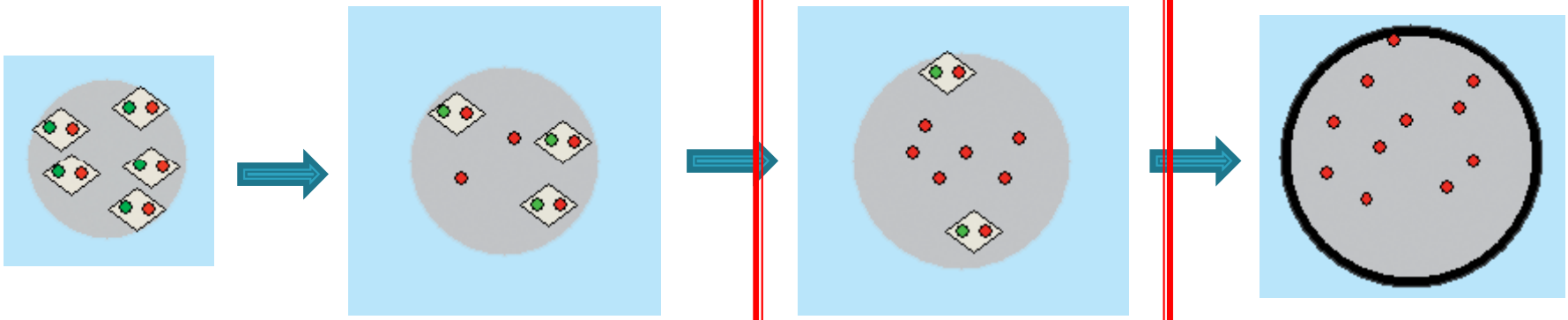
Cytological changes

Stromal invasion

Vascular changes



LGDN

HGDN

Early HCC

HCC

How important clinically?
How well can we identify this in ‘real life?’

"WE COLLABORATE. I'M AN EXPERT, BUT NOT AN AUTHORITY, AND DR. GELBAS IS AN AUTHORITY, BUT NOT AN EXPERT."