Cholangiocarcinoma

Judy Wyatt

Dundee November 2010

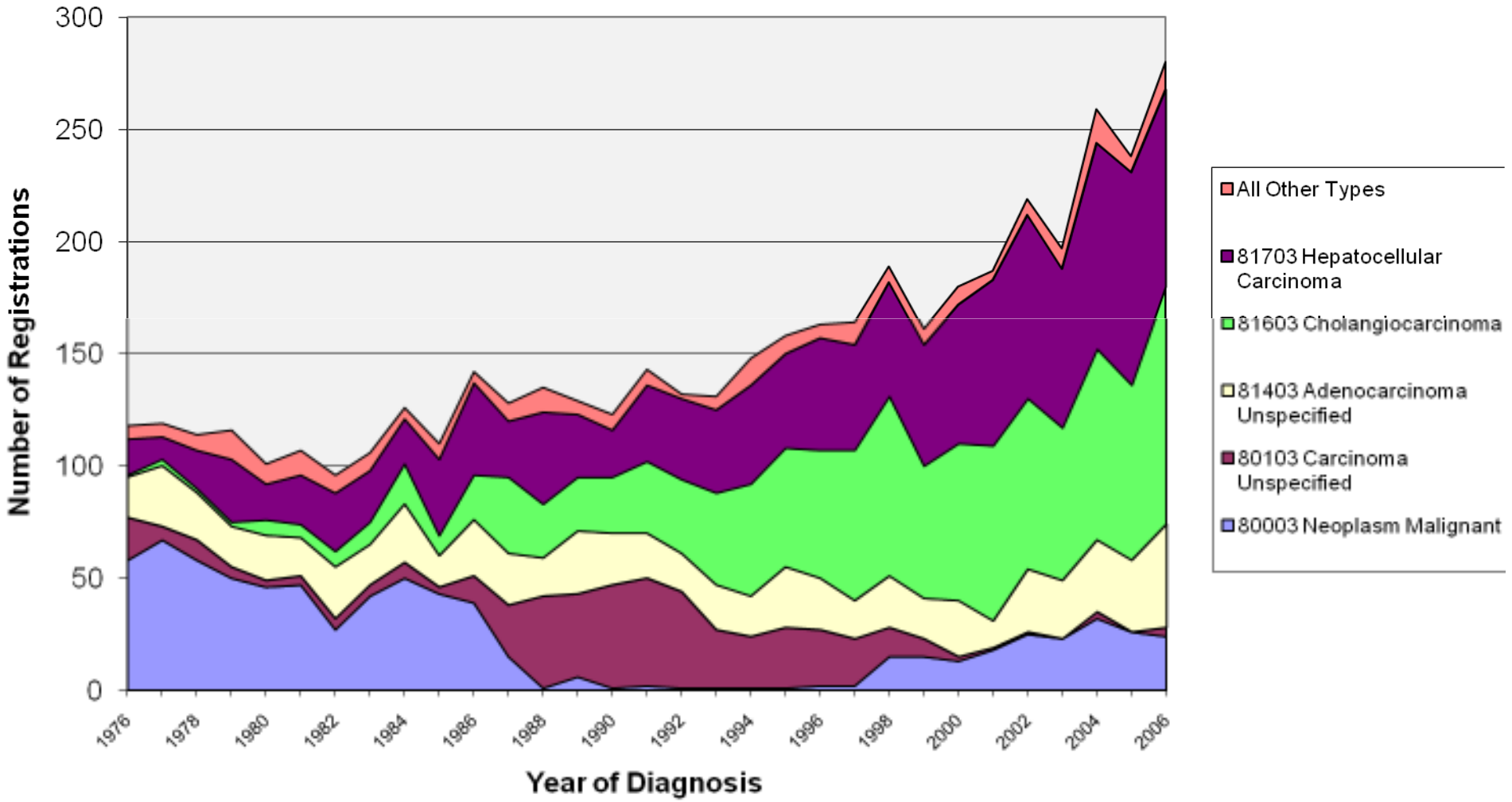
Making sense of cholangiocarcinoma

Difficulties with diagnostic criteria

How many entities within cholangiocarcinoma?

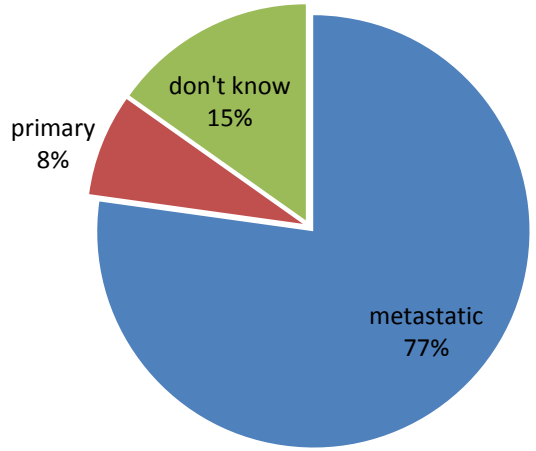
Rapidly evolving

Cancer of Liver (C22) and Other Biliary Sites (C24) in Yorkshire Region 1976-2006



Intrahepatic cholangiocarcinoma – encounters with the pathologist:

1. Liver needle biopsy diagnosis = adenocarcinoma
   158 biopsies July 2005 – Jan 2009



Challenge for pathologist =
distinction primary v. metastatic adenocarcinoma

2. Liver resection for cholangiocarcinoma:
   40 specimens July 2005 – Jan 2009

Challenge for pathologist =
Accurately detect and record prognostic features

1. Adenocarcinoma in liver biopsy – primary or metastatic?

Primary:

Cholangiocarcinoma

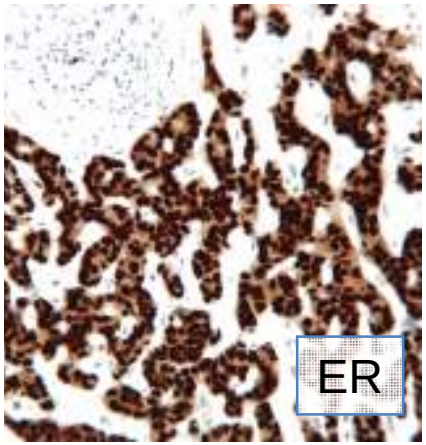
Metastatic adenocarcinoma:

colorectal

lung

pancreas

breast

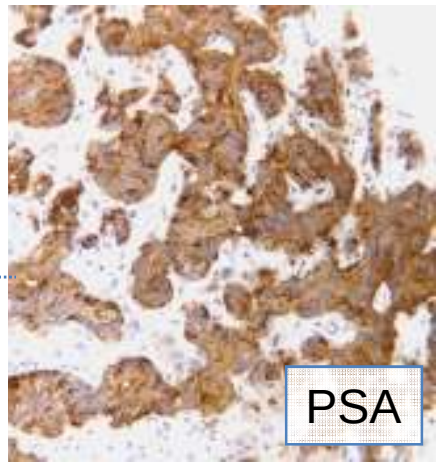


stomach

gall bladder/bile duct

prostate

gynae



Immunohistochemistry - differential diagnosis of adenocarcinoma

Included in RCPath Liver Datasets and Tissue Pathways documents

% positivity for each marker									
Primary site	PSA	TTF 1	GCDP P15	CDX2	CK20	CK7	ER	Meso-thelin	
Breast	0	0	49	0	0	87	79	4	
Colon	0	0	6	86	76	3	1	7	
Lung	0	88	3	1	1	92	6	36	
Ovary serous	0	0	4	0	0	93	81	90	
Ovary mucinous	7	0	14	14	14	57	50	36	
Pancreas	0	4	1	1	2	94	0	49	
Stomach	2	2	0	0	21	50	0	19	
Prostate	100	8	4	4	0	0	8	0	
HCC		0	0	0	9	15	12	0	
Cholangio-carcinoma		0	0	22	49	86	0	44	

Ref: *Dennis et al Clin Cancer Res 2005;11;3766-3772*
and *Frisman D. immunoquery.com*

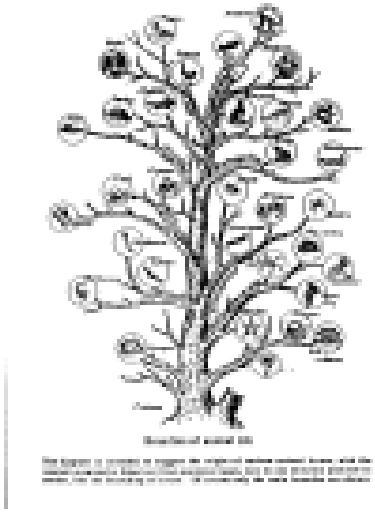
	CK7	CK20	ER	PR	TTF-1	PSA
Biliary	81	33	4	29	0	
Breast	83	7	63	43	0	0
Colon	16	88	2	20	0	0
Endometrium	85	5	31	100†	0	3
Kidney	9	2	3	8	0*	0*
Lung	85	13	5	21	85	0
Oesophagus	50	29	0	100†	0	0
Ovary	73	23	53	32	1	2
Pancreas	95	32	0	2	1	0
Prostate	11	14	10	0*	9	91
Salivary gland	100*	50*	25*	25*	0	
Stomach	49	37	0	5	1	3
Urothelium	74	72				0

NICE guidelines: Diagnosis and management of metastatic malignant disease of unknown primary origin

Classification of cholangiocarcinoma: site of origin

- Peripheral intrahepatic
- Hilar
- Extrahepatic ducts

Evolutionary tree – lumper or splitter



40% intrahepatic
7% hilar
53% extrahepatic

MacSween: Pathology of the liver:

15% intrahepatic
65% hilar
20% extrahepatic

Van Beers, HPB 2008;10;87-93

What is a cholangiocarcinoma?

- MacSween – Pathology of the liver:

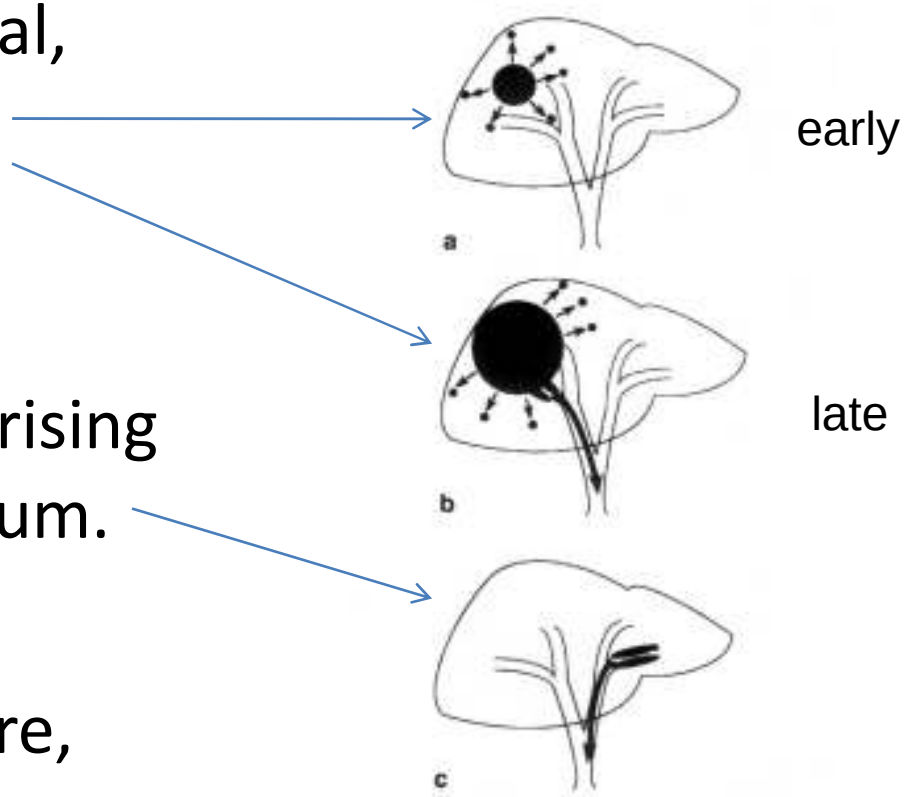
‘features are very similar among tumours from any site, close resemblance to ductal adenocarcinoma of pancreas’

- WHO – classification of tumours of the Digestive System:

‘grossly classifiable into 3 types – mass forming, periductal infiltrating and intraductal papillary’

Liver Cancer Study Group of Japan (1997)
WHO: intrahepatic cholangiocarcinoma (2000)

- Mass forming – peripheral, large, sclerotic centre, cellular expansile margin
- Periductal infiltrating – arising from large ducts near hilum.
- Intraductal papillary – rare, good prognosis



early

late

Does this apply in UK?

2. Liver tumour resections, Leeds

Jun 05-Jan 09:

107 Hepatocellular carcinoma

40 CholangioCa → Rare – limited numbers for prognostic factors

7 Hepatoblastoma

Most information in literature is from Japan
– different epidemiology
- ? Can be translated to West

Many more resections for metastatic colorectal cancer

Characteristics of 40 cholangiocarcinomas resected in Leeds June 2005-Jan 2009

	Periductal infiltrating	Intrahepatic mass forming	P value
Number	21	18	
Size (range) (mm)	30 (13-50)	87 (20-180)	<0.0002
Margins +ve	13 (8 duct margin)	6 (0 duct margin)	<0.003
Vascular invasion	15	12	0.39
Perineural infiltration	21	7	<0.00001
Nodes +ve	10	5	0.021

Plus 1 intraduct papillary adenocarcinoma

Proposal of progression model for ICC: Clinicopathological differences between hilar and peripheral types

Study of 87 tumours ***<50mm*** to investigate ***early*** patterns of spread.

	Periductal infiltrating	intrahepatic Mass forming	P value
number	38	49	
Size (mm)*	30 +/- 11.6	33 +/-10.9	0.16
Nodal metastases	16	3	0.01
Vascular invasion	25	25	0.24
Perineural invasion	29	14	<0.0001

Shinichi et al Am J Surg Pathol 2007:31:1059-1067.

Proposal of progression model for ICC: Clinicopathological differences between hilar and peripheral types

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Size (mm)*	30 +/- 11.6	33 +/-10.9	0.16
Nodal metastases	16	3	0.01
Vascular invasion	25	25	0.24
Perineural invasion	29	14	<0.0001
Extrahepatic recurrence	13	6	<0.028
Viral hepatitis	4/35	21/45	<0.002

Shinichi et al Am J Surg Pathol 2007:31:1059-1067.

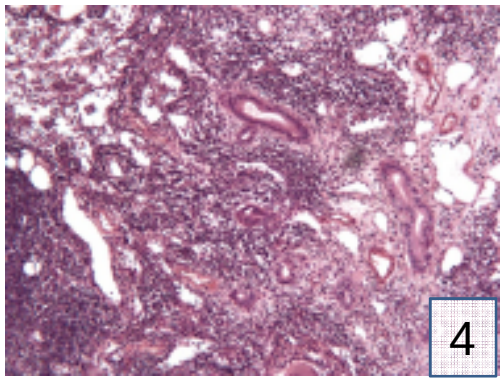
Hilar Cholangiocarcinoma

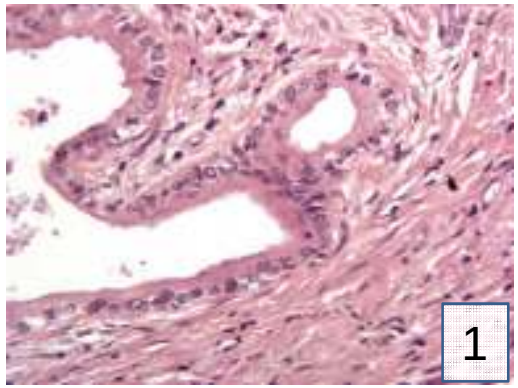
Hilar Cholangiocarcinoma – Pathological Features

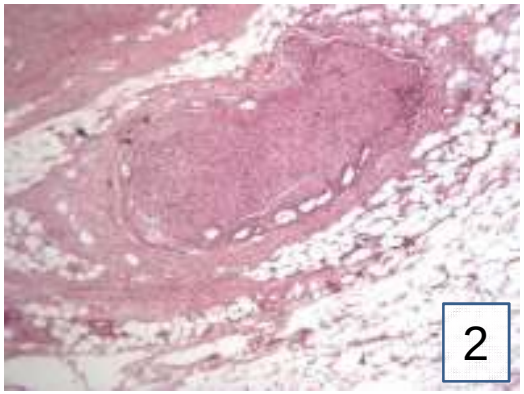
Desmoplastic / associated cholangitis / early lymphatic invasion
= can't detect its extent without histology

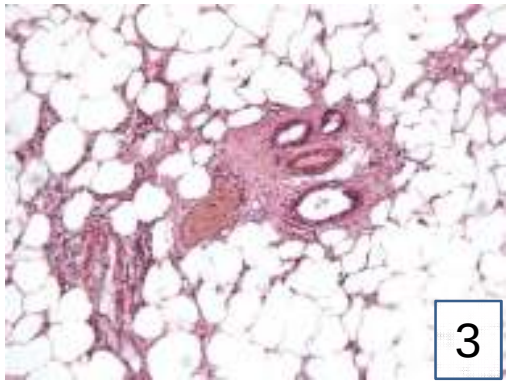
Characteristically:

1. Well differentiated
2. Perineural infiltration
3. Lymphatic invasion
4. Micrometastasis in nodes.

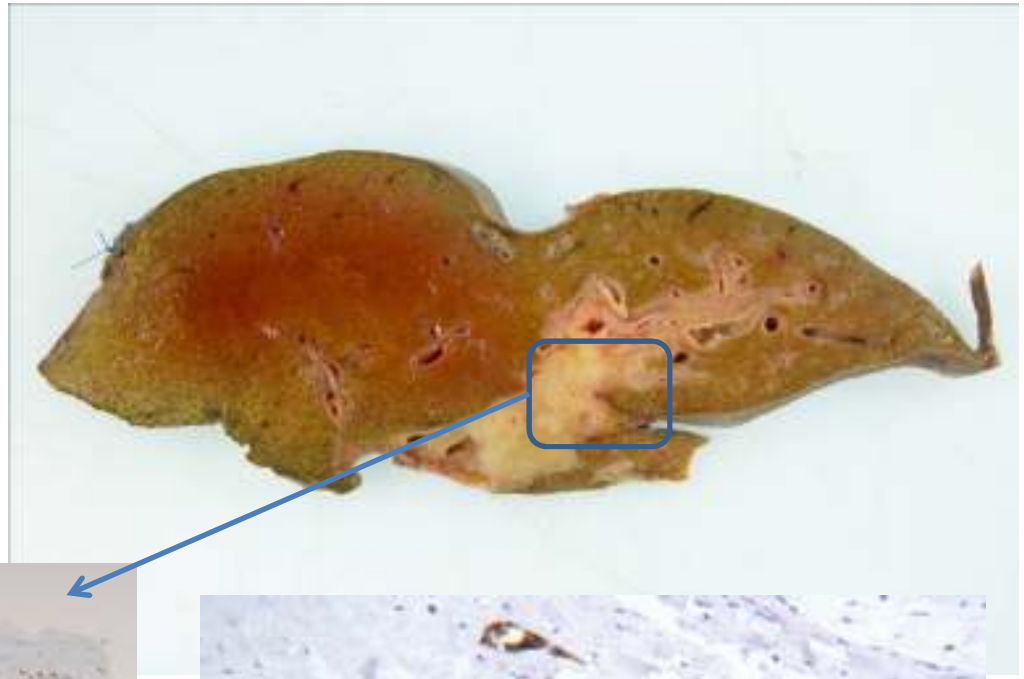




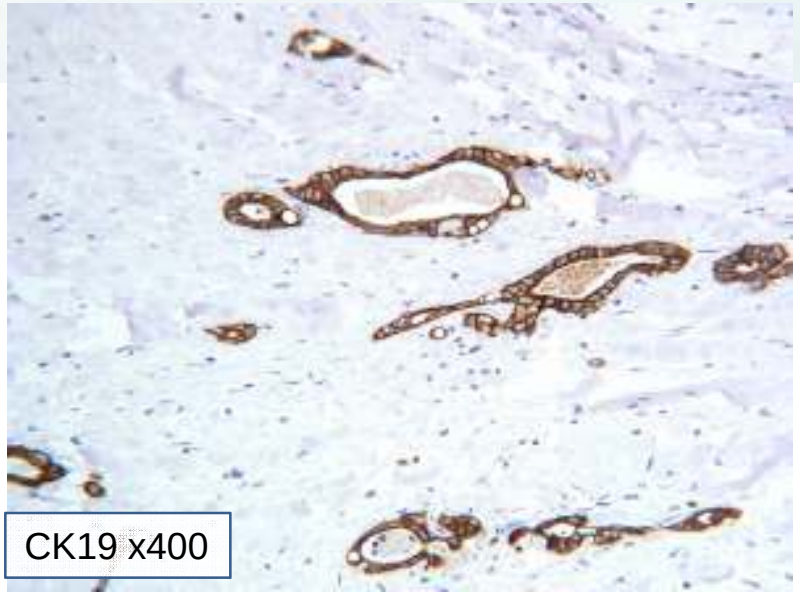




Hilar Cholangiocarcinoma - Klatskin tumour



CK19



CK19 x400

Cholangiocarcinoma, perihilar and extrahepatic ducts

Significant prognostic factors in 442 patients (75% perihilar), 1977-2005

Variable	univariate	Relative risk	multivariate
Differentiation	<0.0001	1.73	0.0002
Lymphatic invasion	<0.0001		
Venous invasion	<0.0001	1.38	0.0098
Perineural invasion	<0.0001	1.71	0.0067
pT stage	<0.0001	1.45	0.0038
Nodal metastasis	<0.0001	1.61	0.0005
Resection margins	<0.0001	1.51	0.0034

Igami T et al. Nagoya. Ann Surg 2009;249;296-302

Cholangiocarcinoma: frequency of R0 resection v survival

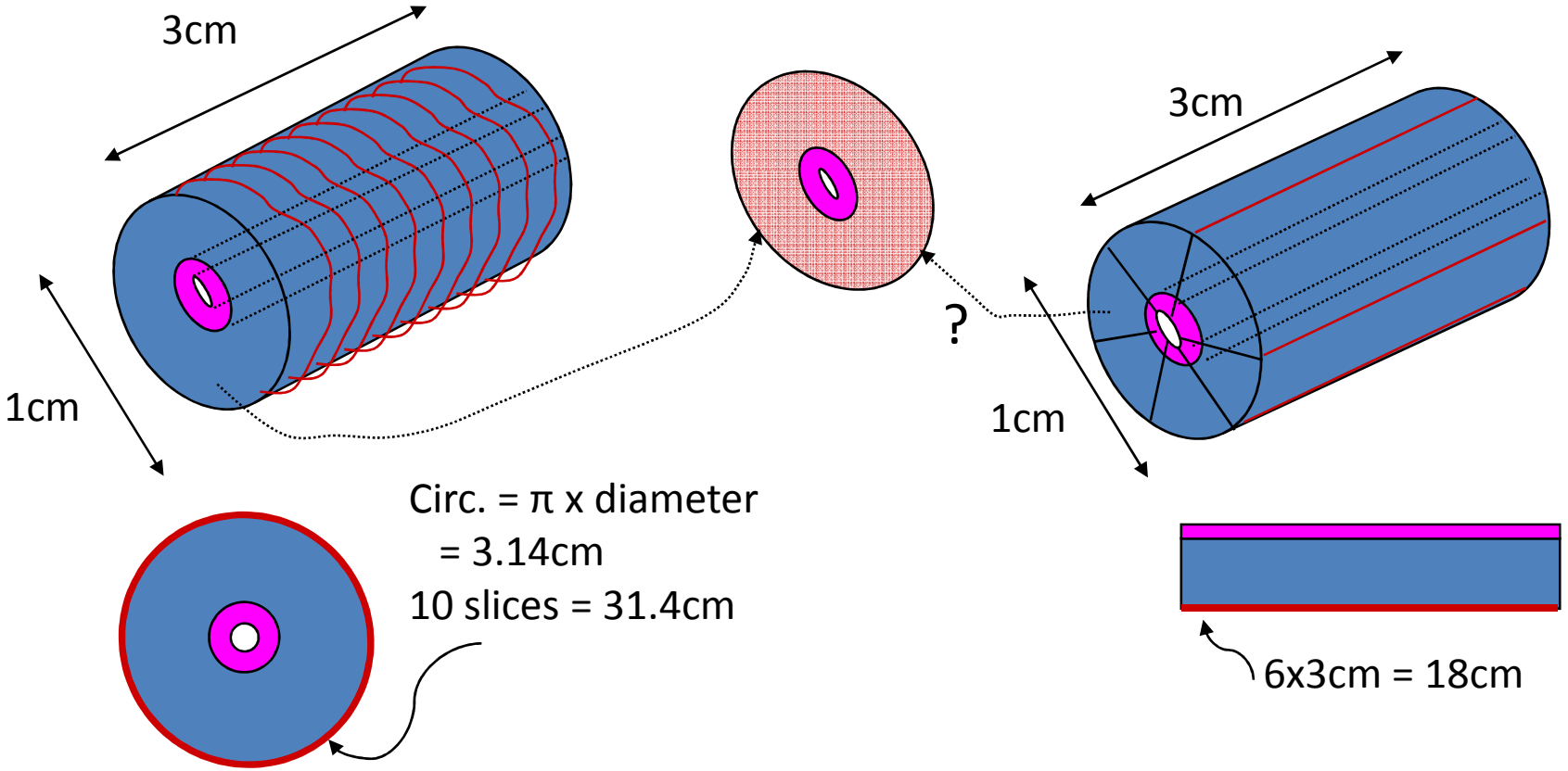
	Number of potentially curative resections	% R0 resections	5 year survival of R0 resection
Leeds	44	43%	45%
Nagoya	163	77%	30%
Sloan Kettering[1]	80	78%	29%
Tokyo[2]	65	48%	51%

1. Jarnagin WR *et al*. Ann Surg 2001:234:507-17
2. Kosuge T et al. Ann Surg 1999:230:663-674

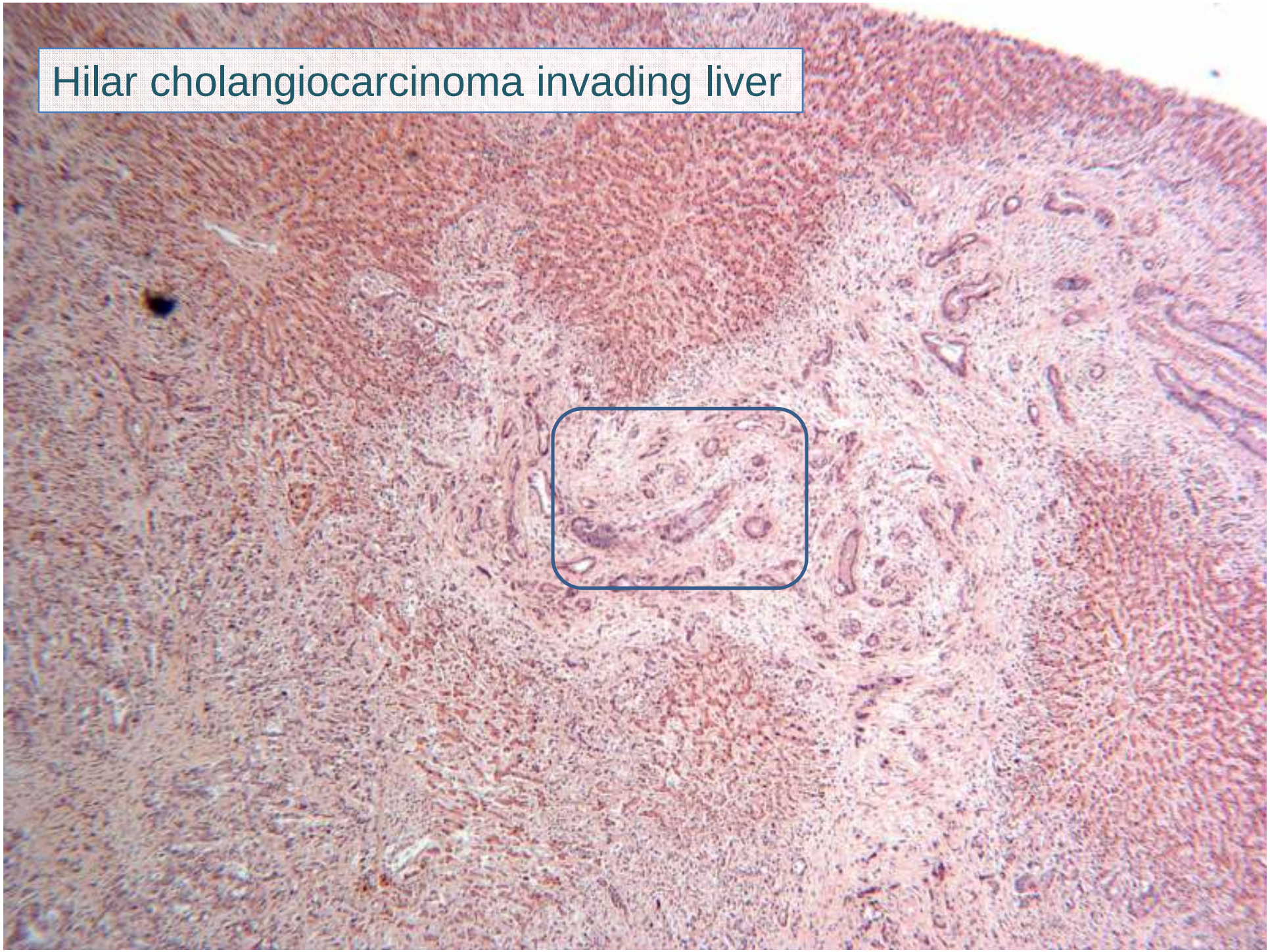
Circumferential margin: transverse or longitudinal sections?

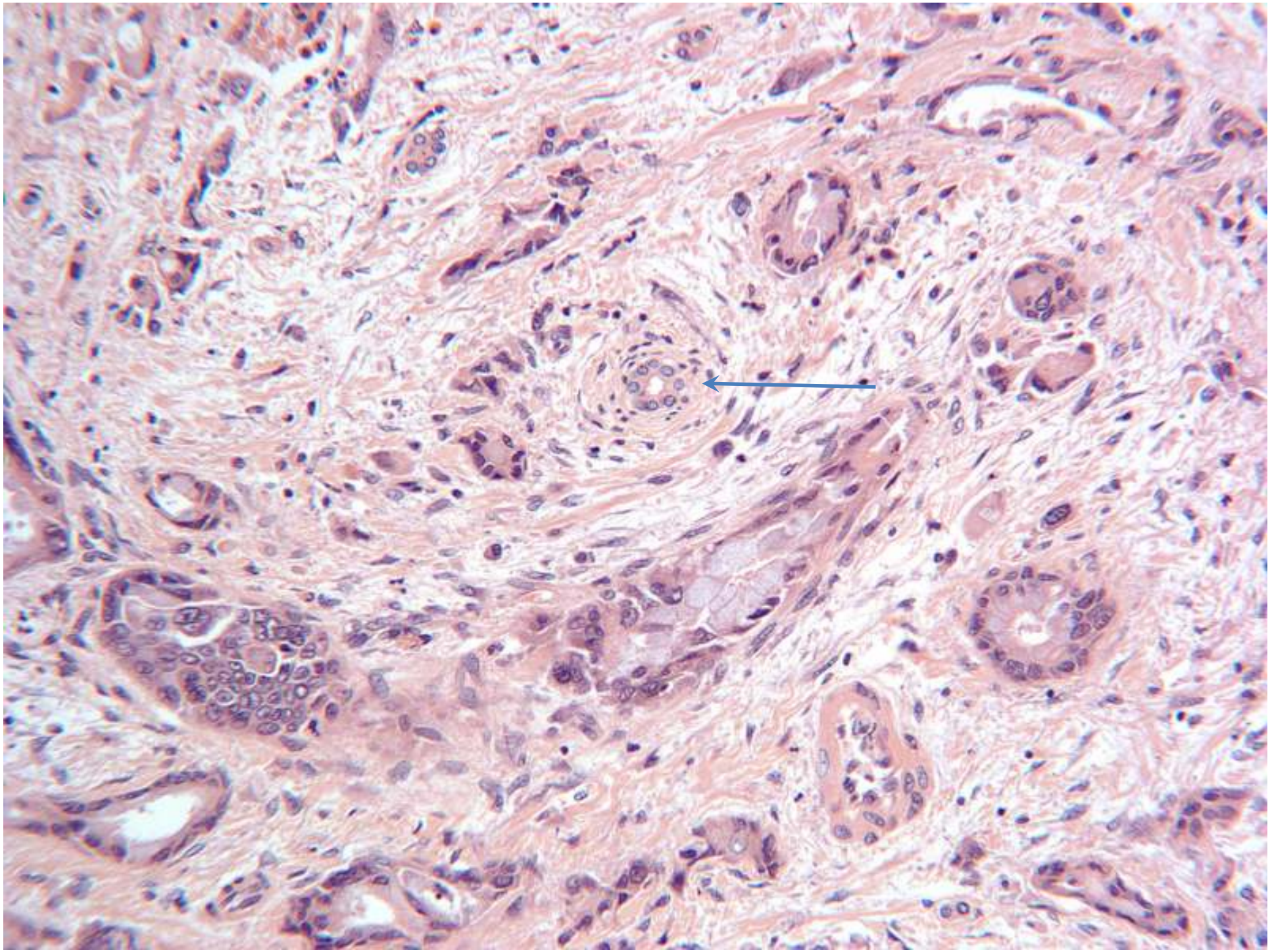
Serial transverse sections give better sampling of circumferential margin

Longitudinal sections give extent of tumour infiltration along duct wall*



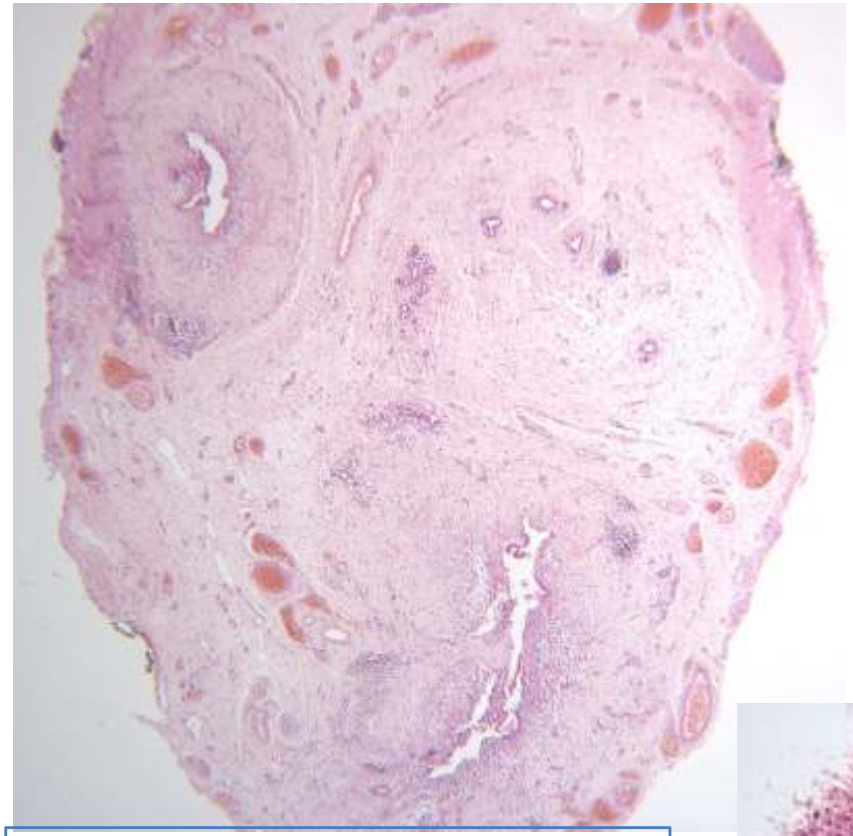
** Sakamoto E et al. Ann Surg 1998;227;405-11*


Hilar cholangiocarcinoma invading liver

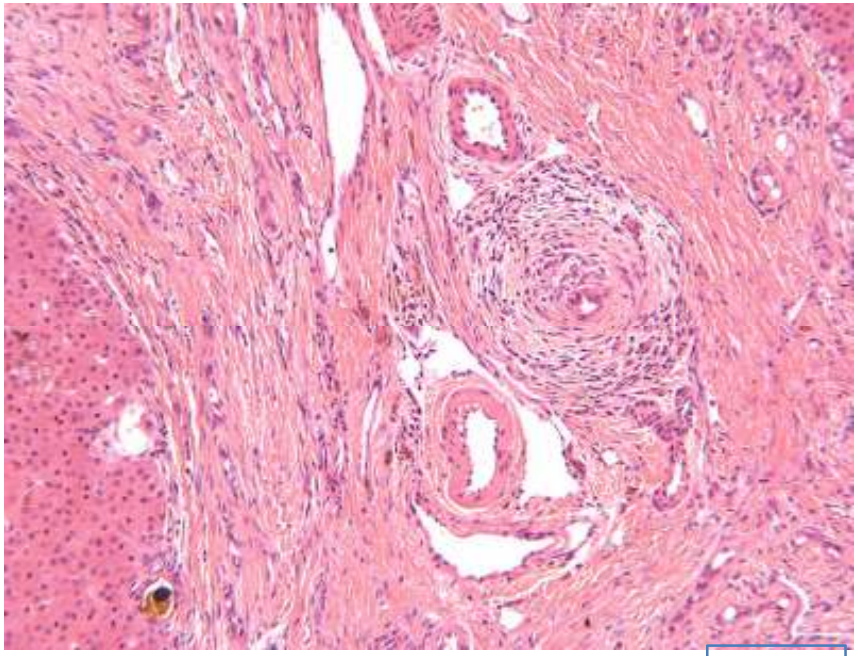


Perihilar cholangiocarcinoma

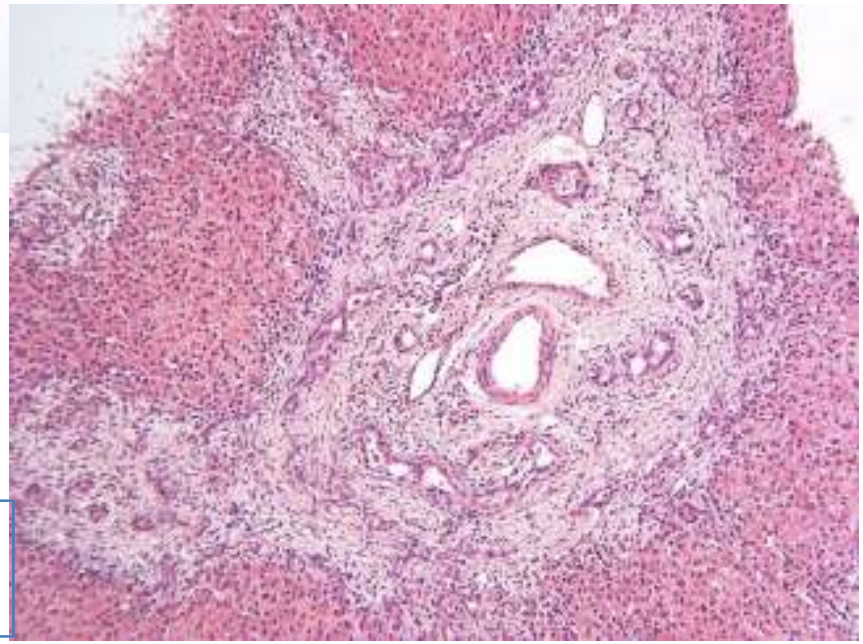
- Desmoplastic,
- Well differentiated tubular
  and poorly differentiated infiltrative
- Infiltrates liver along portal tracts
- No tumour mass – acquires infiltrative pattern early in development
- Cells spread out – go to nerves, nodes and resection margins



Portal plate,
extrahepatic biliary atresia



PSC



Ductal plate,
biliary embryogenesis

Bil IN – pre-malignant biliary epithelium, examples from patients with chronic biliary disease

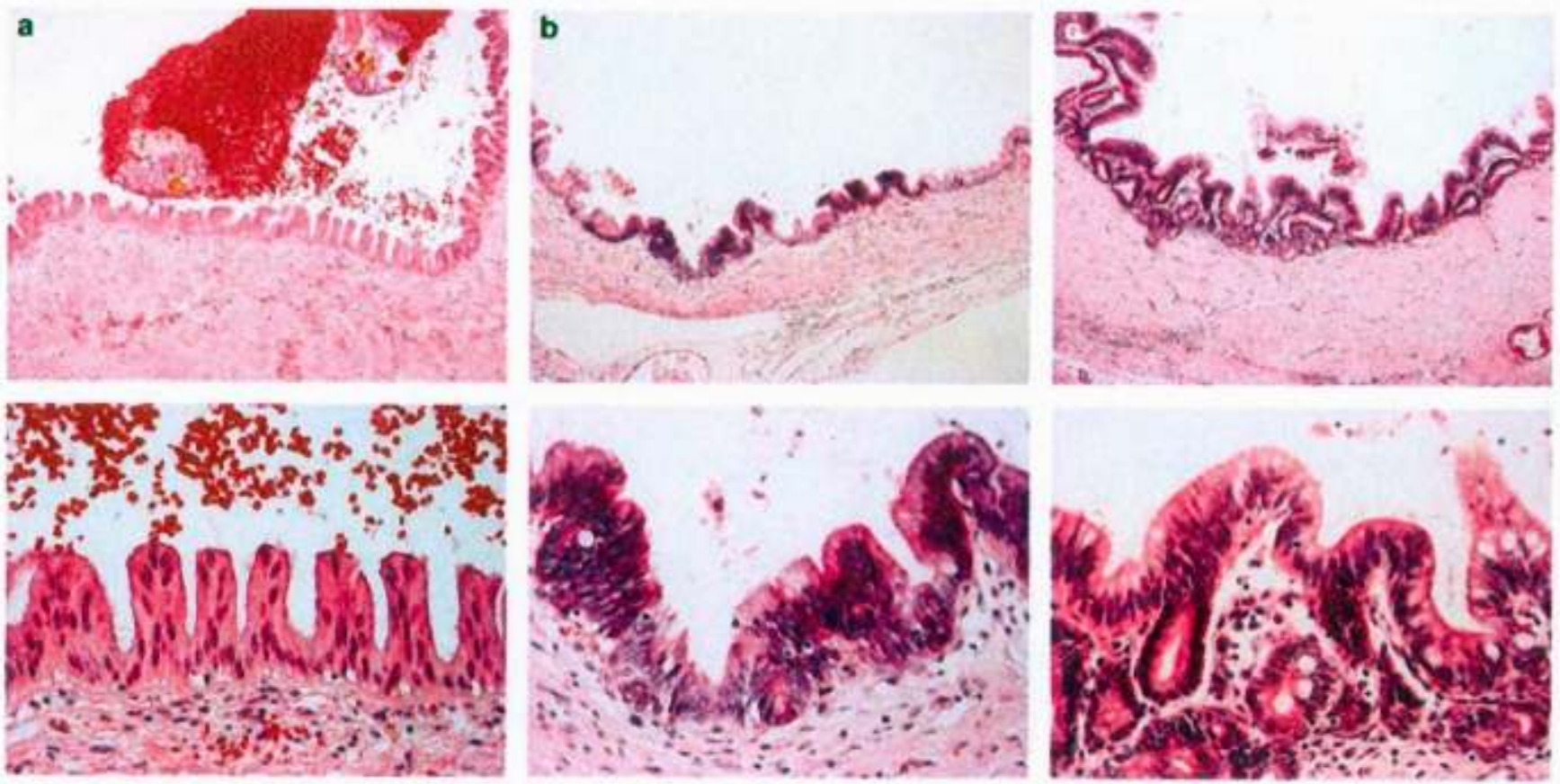


Figure 3 Histological pictures of biliary lesions diagnosed as BilIN-2 by more than nine participants (hematoxylin and eosin; upper, × 100; lower, × 400).

Pre-cancerous bile duct pathology in end-stage primary sclerosing cholangitis, with and without cholangiocarcinoma

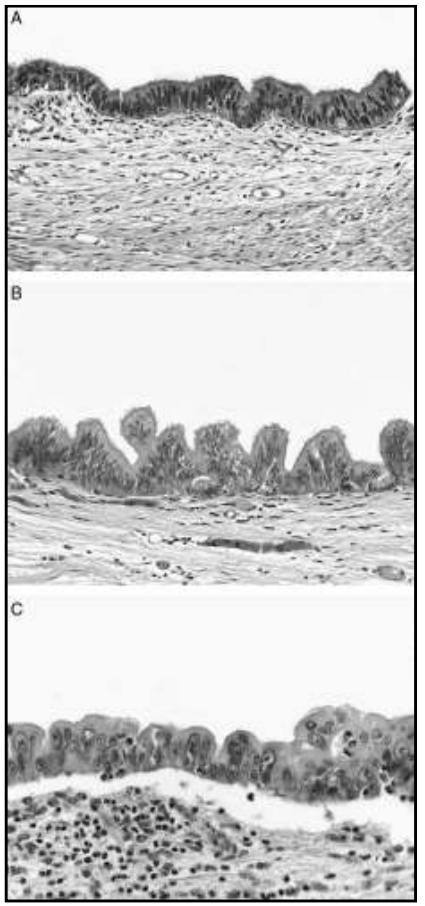
100 liver explants for PSC –

28 prior Rx for CholangioCa

2/72 had incidental CholangioCa

10 more blocks from large ducts

	Overall (100)	cholangioCa (30)	No cholangioCa (70)
Dysplasia (any)	50%	25 (83%)*	25 (36%)
Intestinal metaplasia	26%	13 (43%)	13 (19%)

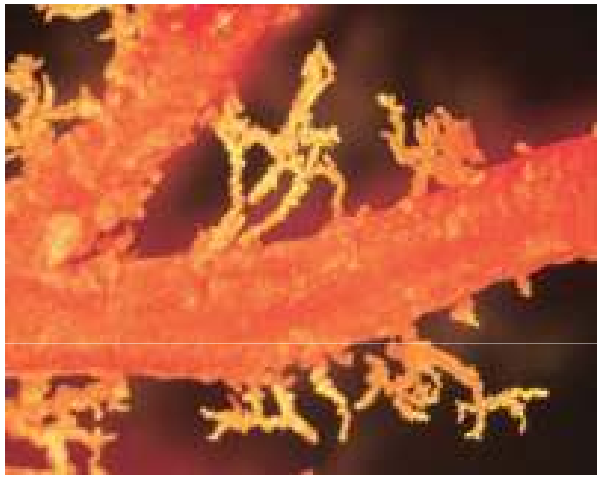


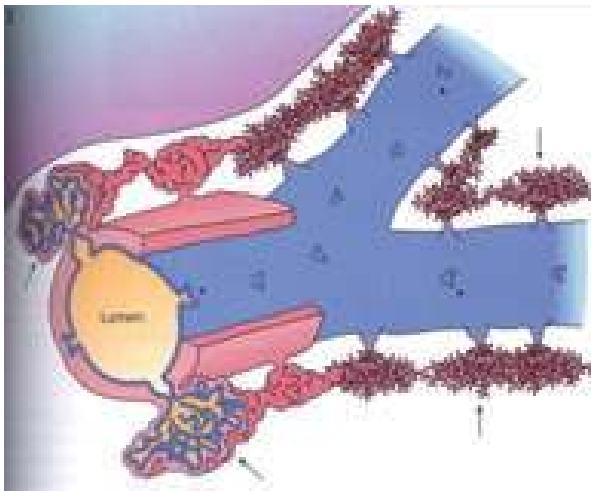
* Dysplasia more extensive and more high grade

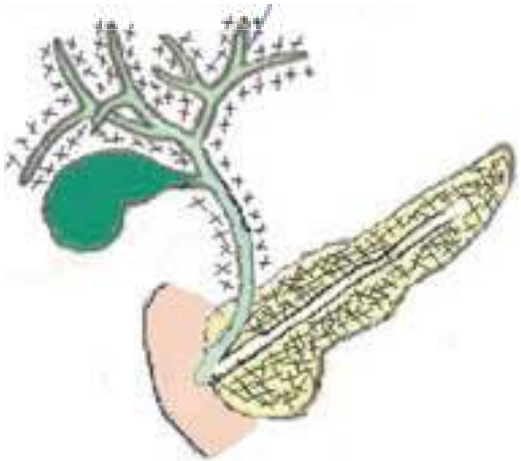
10% pancreatic metaplasia

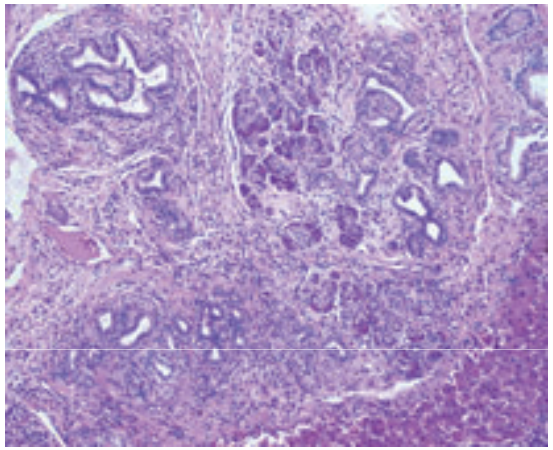
Lewis JT *et al* Am J Surg Pathol 2010;34;27-34

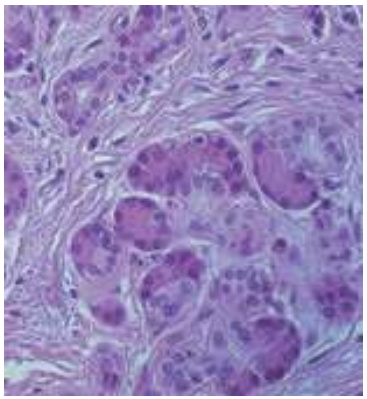
A novel approach to biliary tract pathology based on similarities to pancreatic counterparts: is the biliary tact an incomplete pancreas?











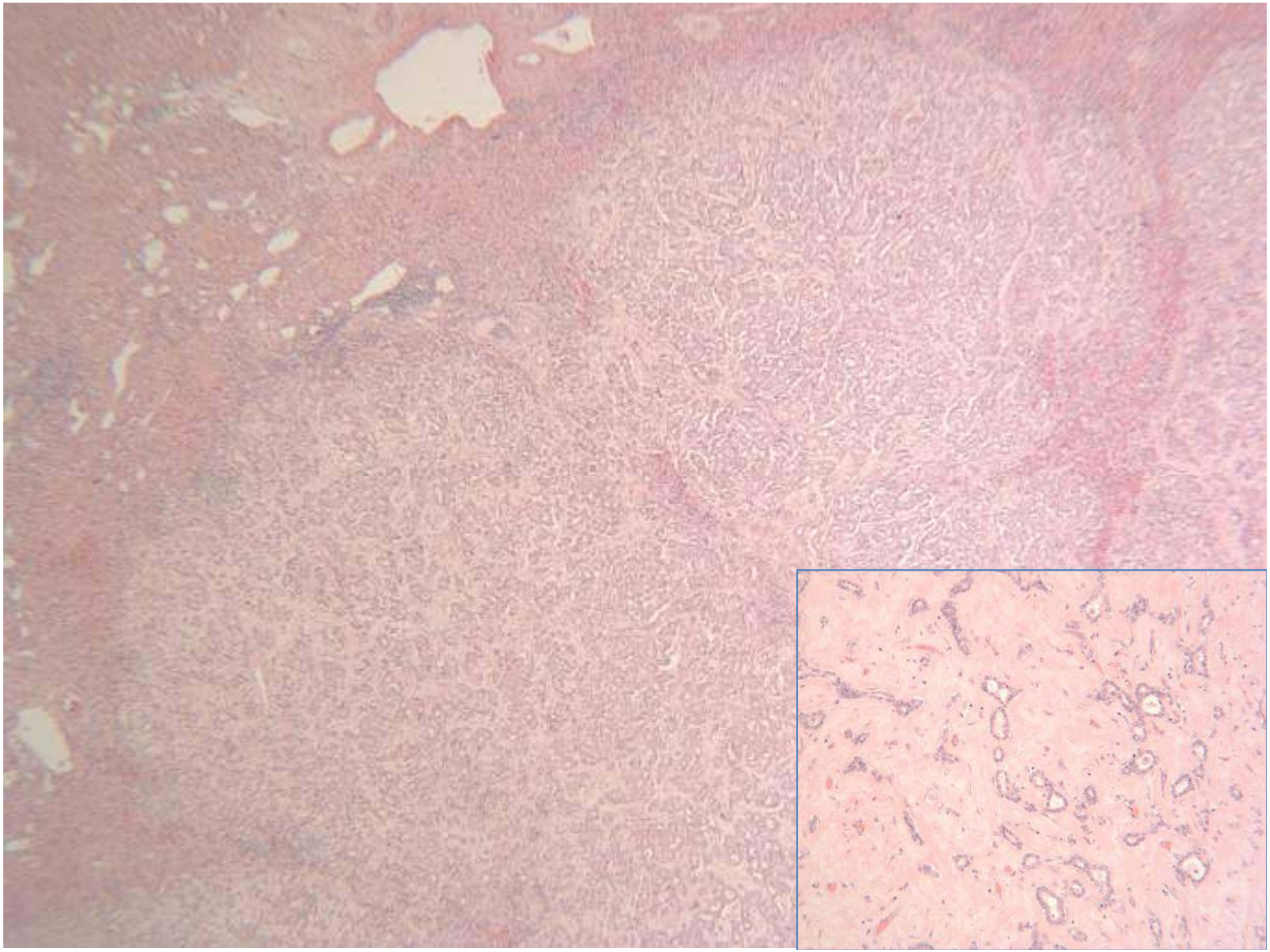
Nakanuma Y. Pathology International 2010;60;419-429

A novel approach to biliary tract pathology based on similarities to pancreatic counterparts: is the biliary tact an incomplete pancreas?

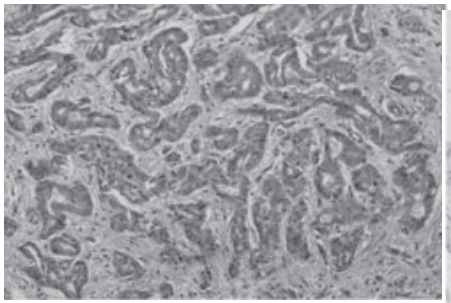
Biliary tree	pancreas
IgG4 related sclerosing cholangitis	Lymphoplasmacytic sclerosing pancreatitis
Primary sclerosingcholangitis	Idiopathic duct-centric chronic pancreatitis
Conventional cholangiocarcinoma	Invasive duct carcinoma
Bil IN 1-3	Pan IN 1-3
Intraductal papillary neoplasm - IPNB	IPMN-P
Biliary cystic tumour with bile duct communication (cystic IPN)	IPMN-P with cystic change
Mucinous cystadenoma with ovarian-like stroma	Mucinous cystadenoma with ovarian-like stroma

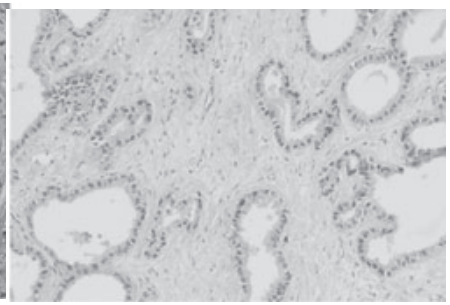
Nakanuma Y. Pathology International 2010;60;419-429

Intrahepatic, mass-forming cholangiocarcinoma



Pathology of peripheral intrahepatic cholangiocarcinoma with reference to tumorigenesis





	Ductular CC (8)	Ductal CC (9)	Combined (7)
edge	Replacing, incorporates tracts	compressive	Ductular at edge, Ductal in centre
Central sclerosis	yes	yes	yes
CK7 and CK19+ve, HepPar1 -ve	yes	yes	yes
NCAM +ve	11/15	0/16	N/A
Advanced chronic liver disease	62%	22%	29%

Nakanuma Y *et al.* Hepatology Resarch 2008;38;325-334

Pathology of peripheral intrahepatic cholangiocarcinoma with reference to tumorigenesis

Relation to other tumours:

1. Cholangiolocellular carcinoma (Steiner, 1959)
2. Sclerosing hepatic carcinoma (Omata, 1981)
3. Combined HCC-CC
4. Hepatic stem cell malignancies in adults (Theise, 2003)

WHO 2010: 'combined HCC-CC with stem cell features'

Nakanuma Y *et al.* Hepatology Resarch 2008;38;325-334

Pathology of peripheral intrahepatic cholangiocarcinoma with reference to tumorigenesis

Relation to other tumours:

1. Cholangiolocellular carcinoma (Steiner, 1959)

–small cords and ductules

included combined HCC-CC

no consensus on diagnostic criteria

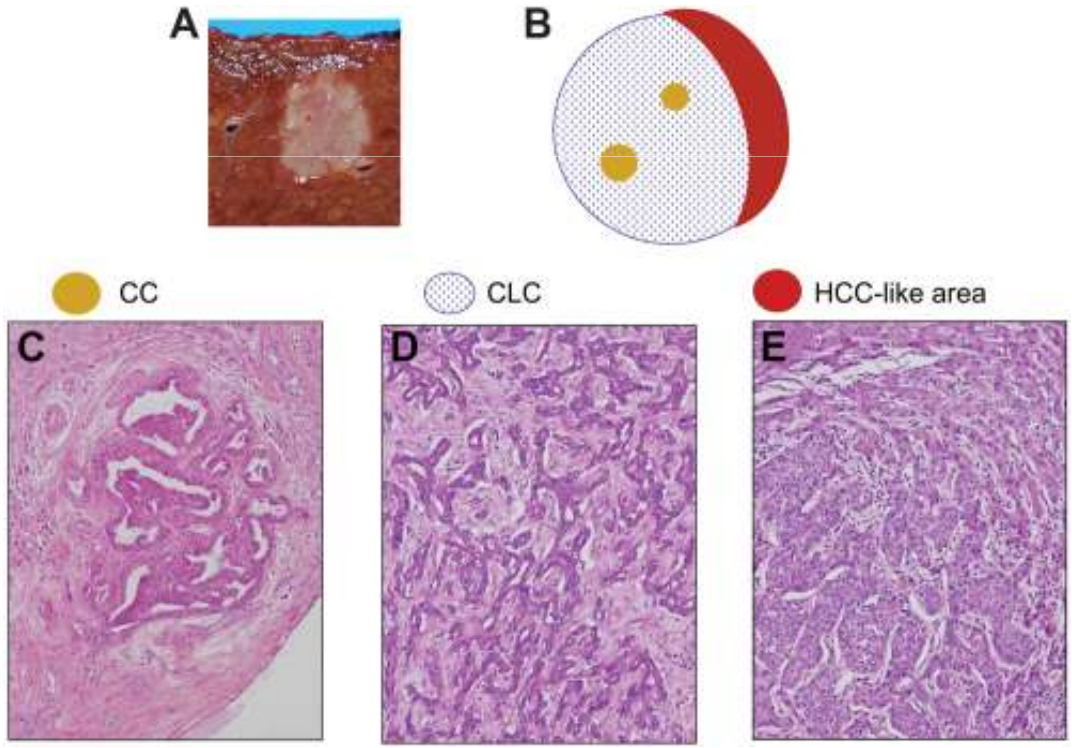
often multifocal

low association with chronic liver disease

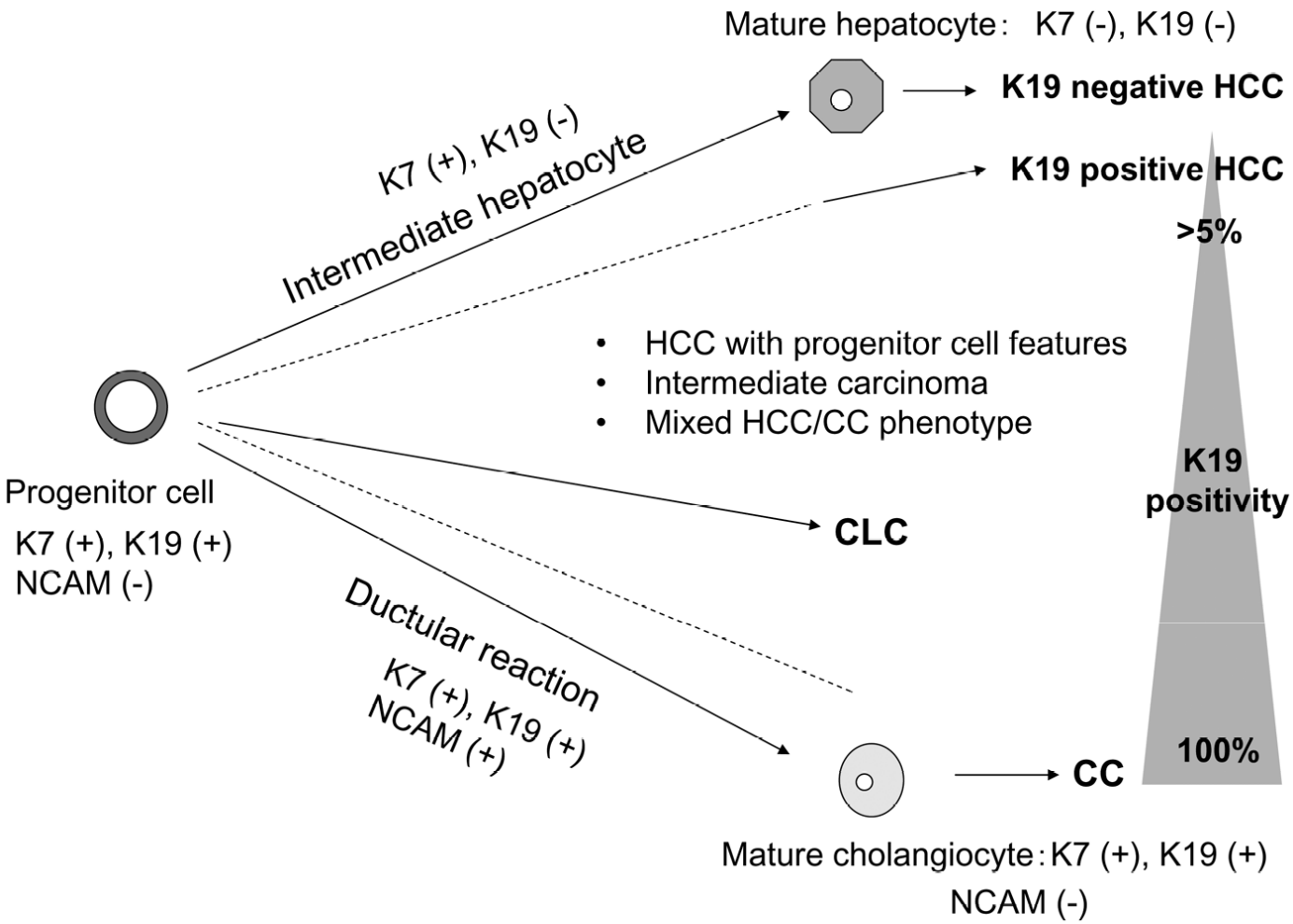
Nakanuma Y *et al.* Hepatology Resarch 2008;38;325-334

Clinicopathological study on cholangiolocellular carcinoma suggesting hepatic progenitor cell origin.

30 cases from Belgium and Japan, all with background chronic liver disease
>90% area cholangiolocellular
= small monotonous glands, abundant hyalinized stroma, lymphocytic infiltration



Komuta M, ...Roskams T. Hepatology 2008;47;1544-1556



'When a HPC develops into cancer this can give rise to tumours with a whole spectrum of phenotypes with varying hepatocellular and cholangiocellular differentiation characteristics'

Komuta M, ...Roskams T. Hepatology 2008;47;1544-1556

Pathology of peripheral intrahepatic cholangiocarcinoma with reference to tumorigenesis

Relation to other tumours:

2. Sclerosing hepatic carcinoma (Omata, 1981)

intense fibrosis with embedded tubules

includes hepatocellular, ductal and mixed

69% hypercalcaemia

Omata M et al. Liver 1981;1;33-49

Pathology of peripheral intrahepatic cholangiocarcinoma with reference to tumorigenesis

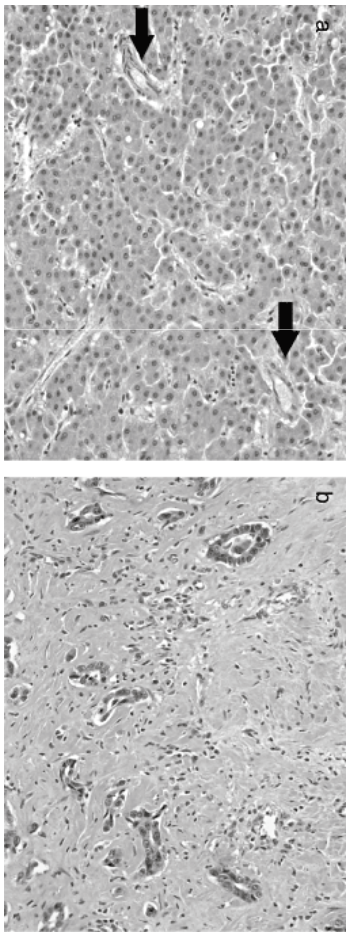
Pathology of combined hepatocellular-cholangiocarcinoma

Relation to other tumours:

3. Combined HCC-CC
Very rare (<1%) – see HCC (makes bile)
and CC (makes mucin)

Or by immuno – HepPar1+ve, pCEA/CD10 canalicular
plus – mucin/muc protein by immuno
- not just CK7 , CK19

both components intimately mixed



Yeh MM J Gastroenterol Hepatol 2010:25:1485-1492

Pathology of peripheral intrahepatic cholangiocarcinoma with reference to tumorigenesis

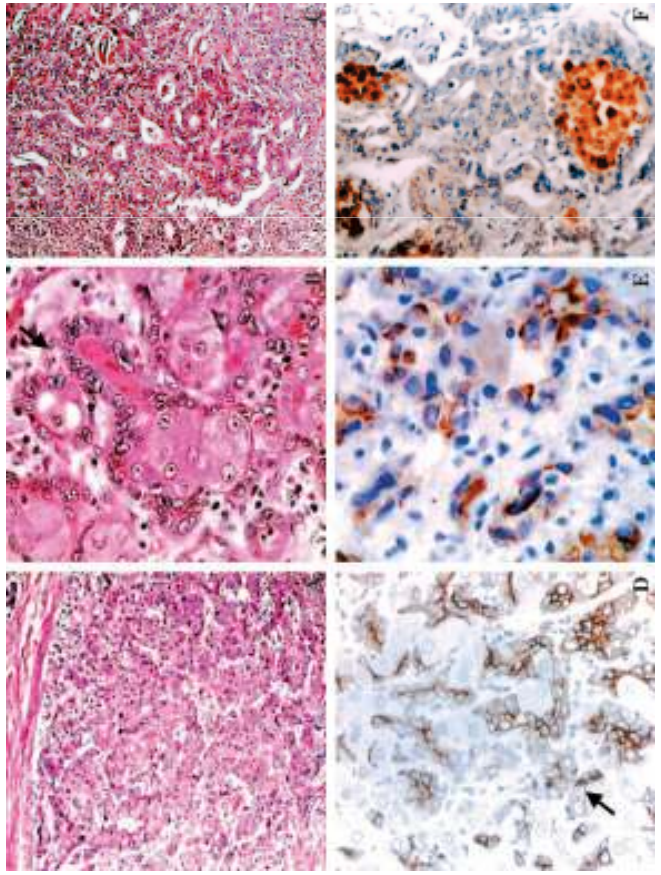
Relation to other tumours:

4. Hepatic stem cell malignancies in adults (Theise, 2003)

   Four small tumours

   contained undifferentiated cells with hepatic progenitor cells morphology and immunohistochemistry

   merged with mature HCC and CC components

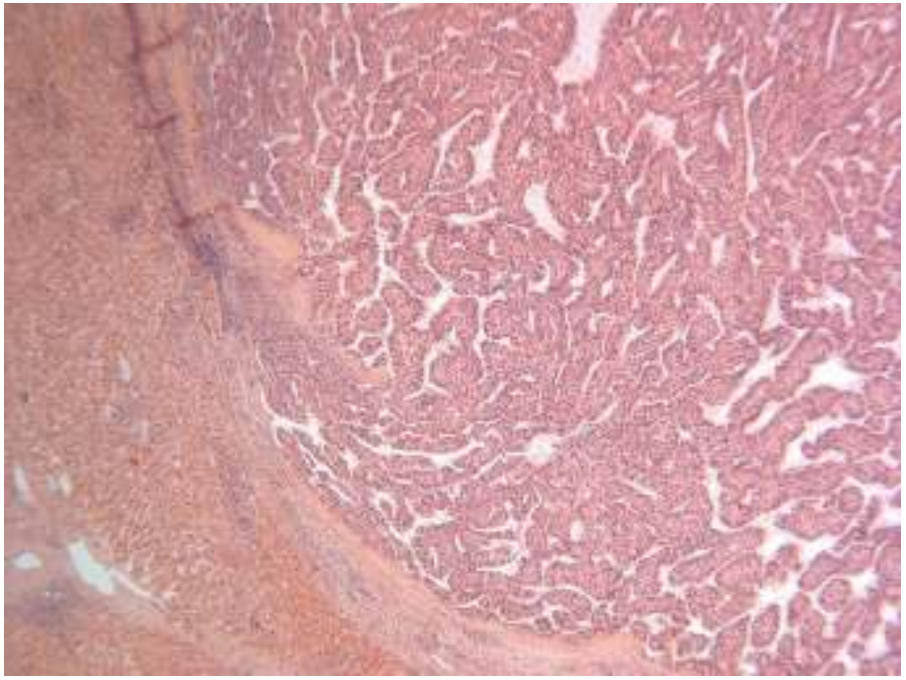


Mr FS 69M

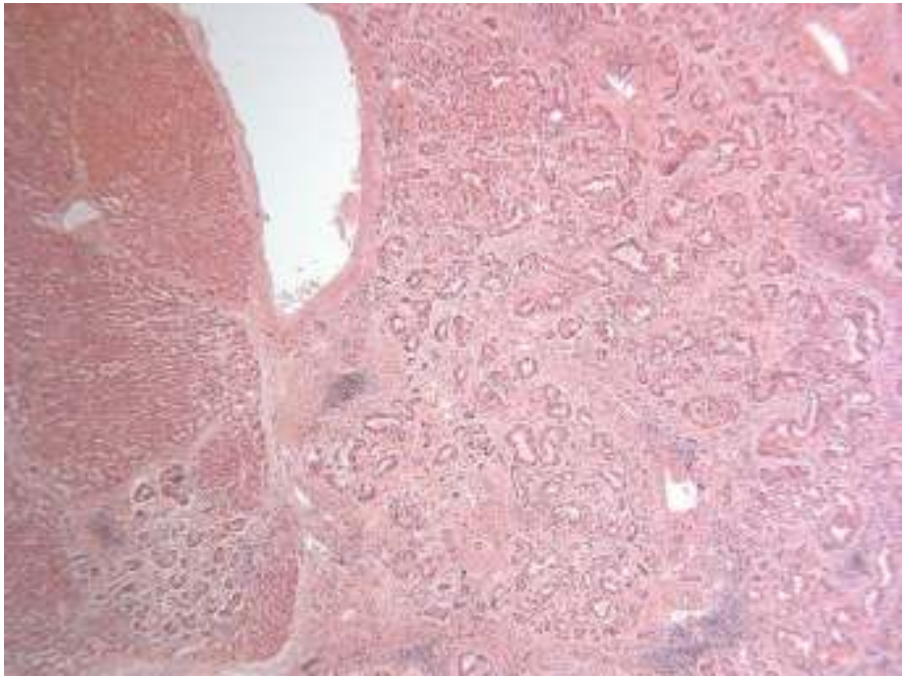
treated haemochromatosis,

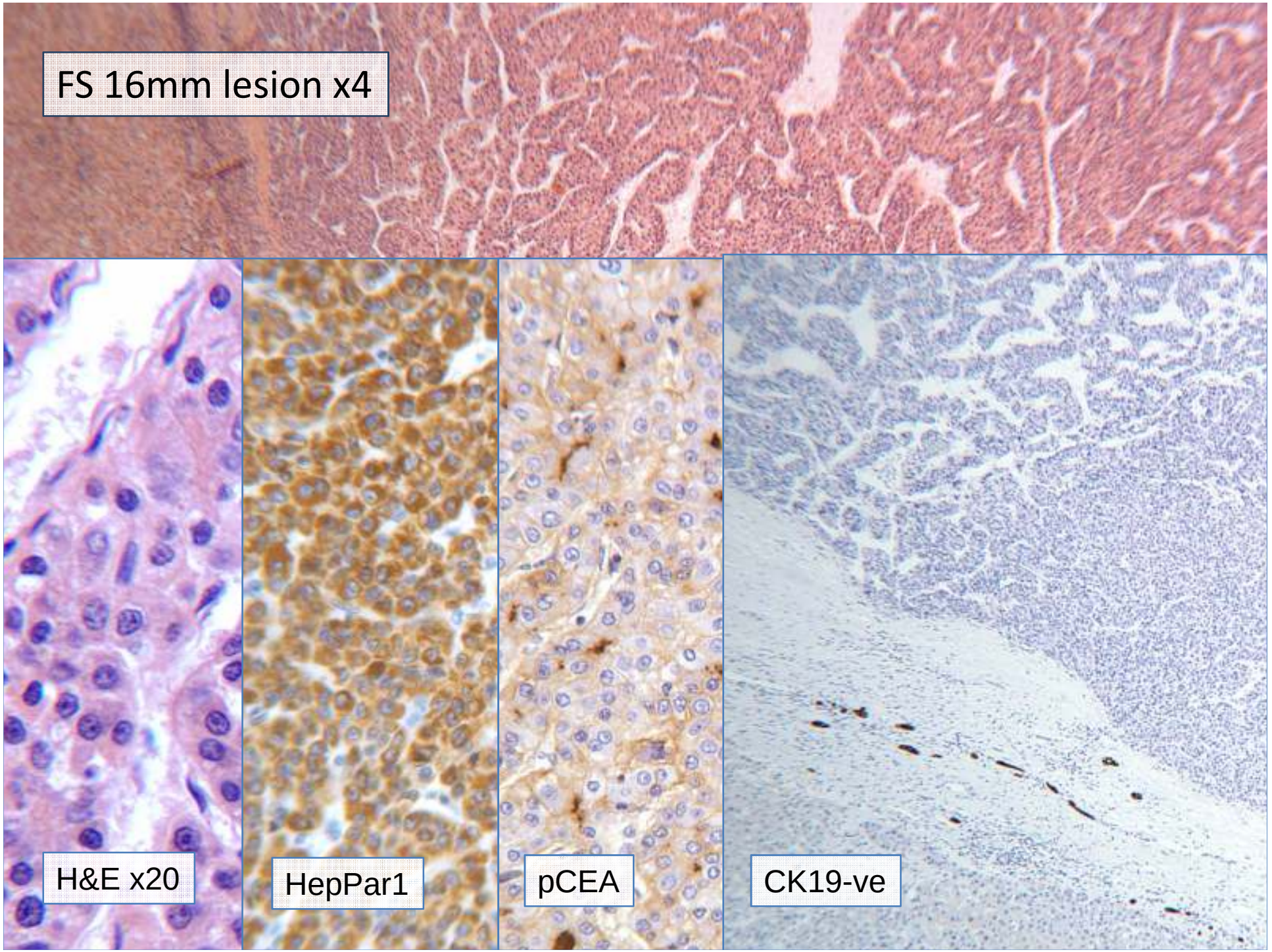
- Several early lesions on surveillance,
- Three lesions resected: 16mm 5mm 5mm

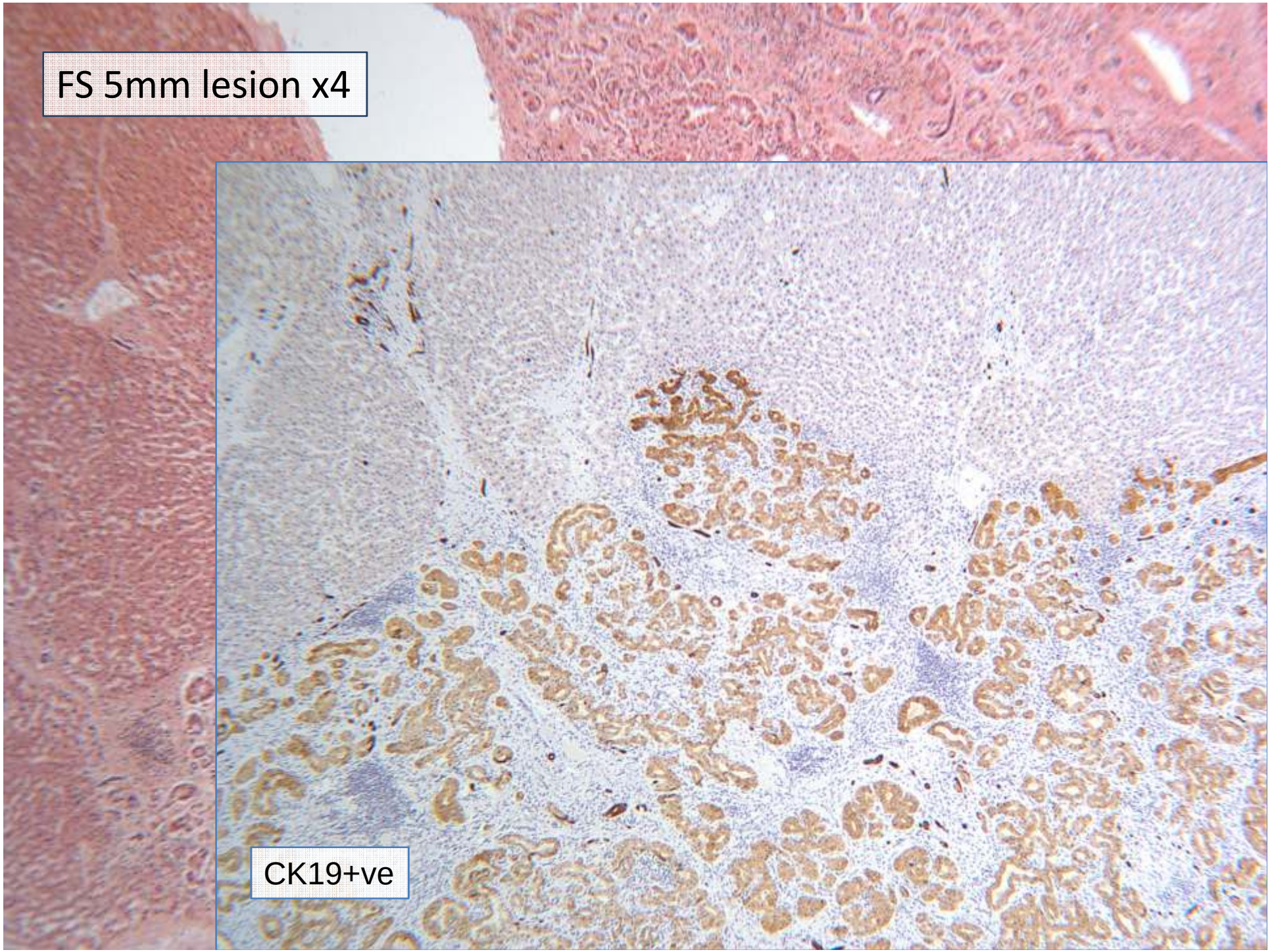
16mm lesion

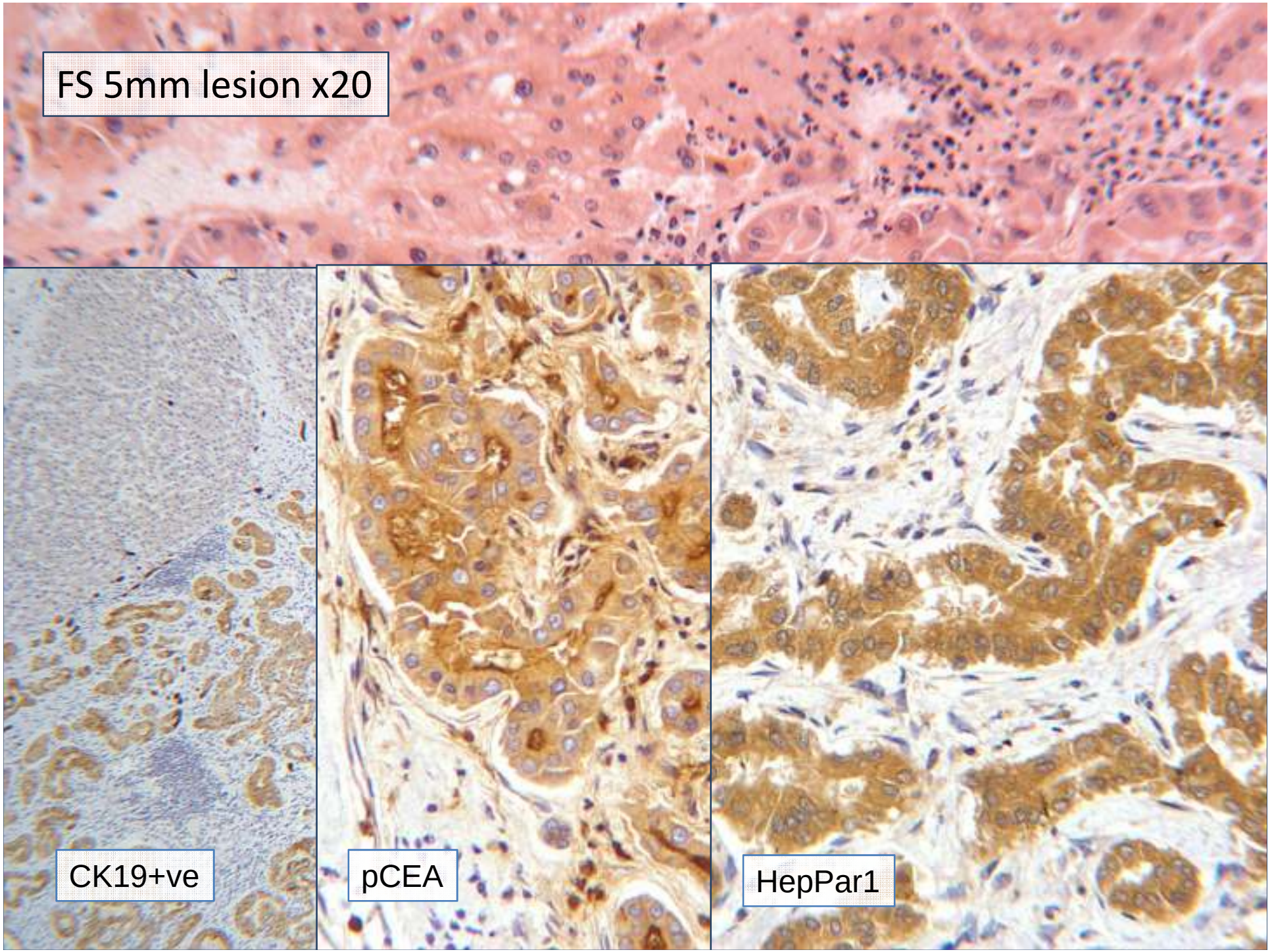


5mm lesion

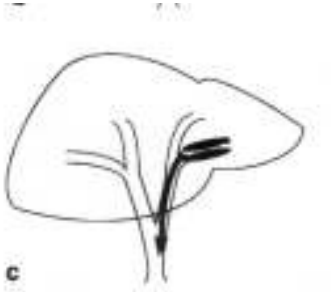


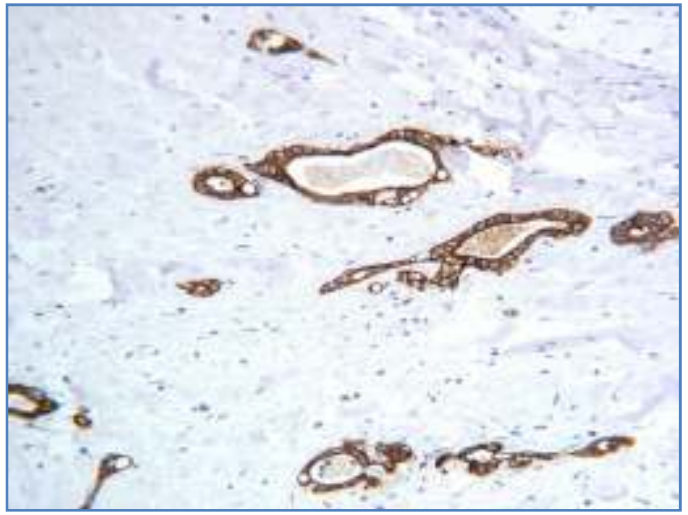

FS 16mm lesion x4
H&E x20
HepPar1
pCEA
CK19-ve


FS 5mm lesion x4
CK19+ve

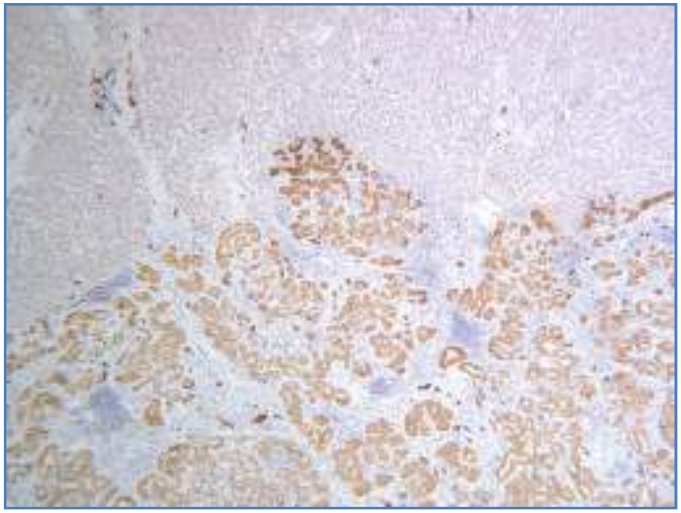

FS 5mm lesion x20
CK19+ve
pCEA
HepPar1

Periductal infiltrating:





peripheral mass forming



Intraductal papillary – IPN – may be cystic

Cholangiocarcinoma

Hilar cholangiocarcinoma – right or left duct or common duct

‘ Klatskin tumour’

Intrahepatic cholangiocarcinoma

= intrahepatic malignancy with biliary epithelial differentiation

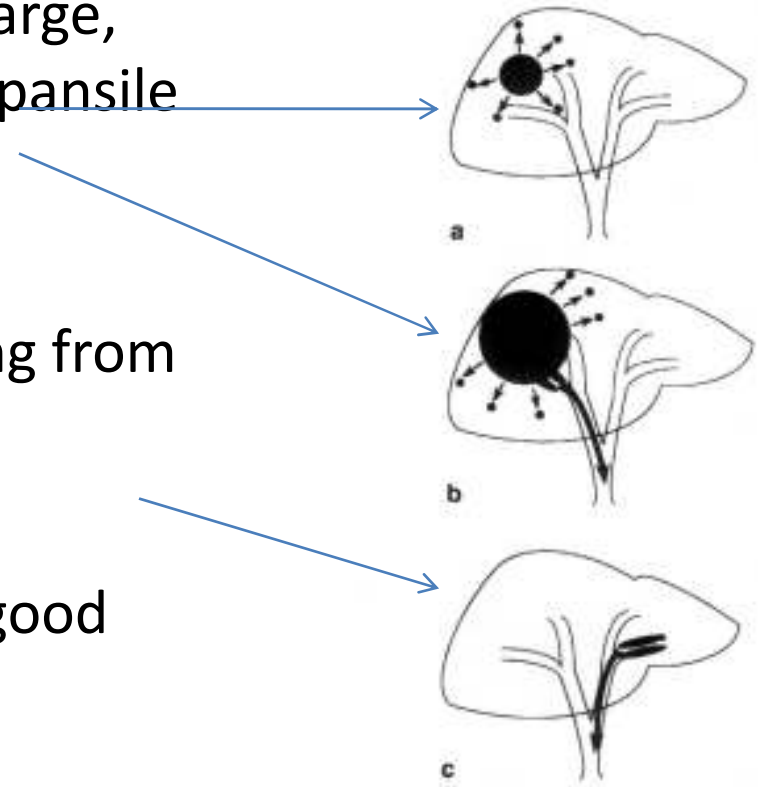
Distinguish – large ducts near hilum

- conventional cholangiocarcinoma with periductal infiltrating pattern
- intraductal papillary

small peripheral ducts/ductules

Liver Cancer Study Group of Japan (1997)
WHO: intrahepatic cholangiocarcinoma (2000)

- Mass forming – peripheral, large, sclerotic centre, cellular expansile margin
- Periductal infiltrating – arising from large ducts near hilum.
- Intraductal papillary – rare, good prognosis



early

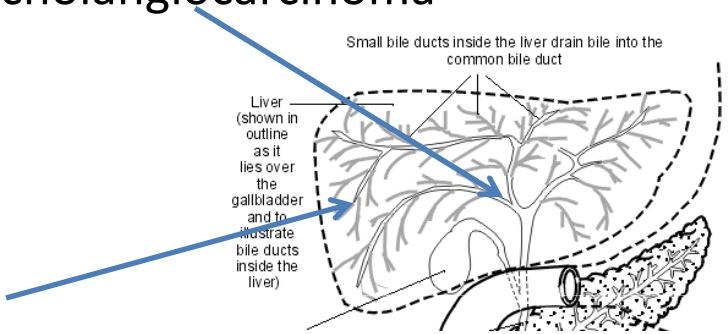
late

Intrahepatic Cholangiocarcinoma

Large bile ducts with peribiliary glands –

periductal infiltrating, characteristics of hilar cholangiocarcinoma

Associated with – PSC, choledochal cysts, parasites



Peripheral – mass forming - small ducts

features resembling ductular reaction

often mixed phenotype

progenitor cell – biliary and hepatocellular characteristics

Associated with – cirrhosis, especially hep B and C

Intraductal papillary – spreads along lumen, includes cystic tumours that lack mesenchymal stroma

Standards and Datasets for Reporting Cancers

Dataset for liver resection specimens (including gall bladder) and liver biopsies for primary and metastatic ~~Carcinoma~~ (2nd edition)

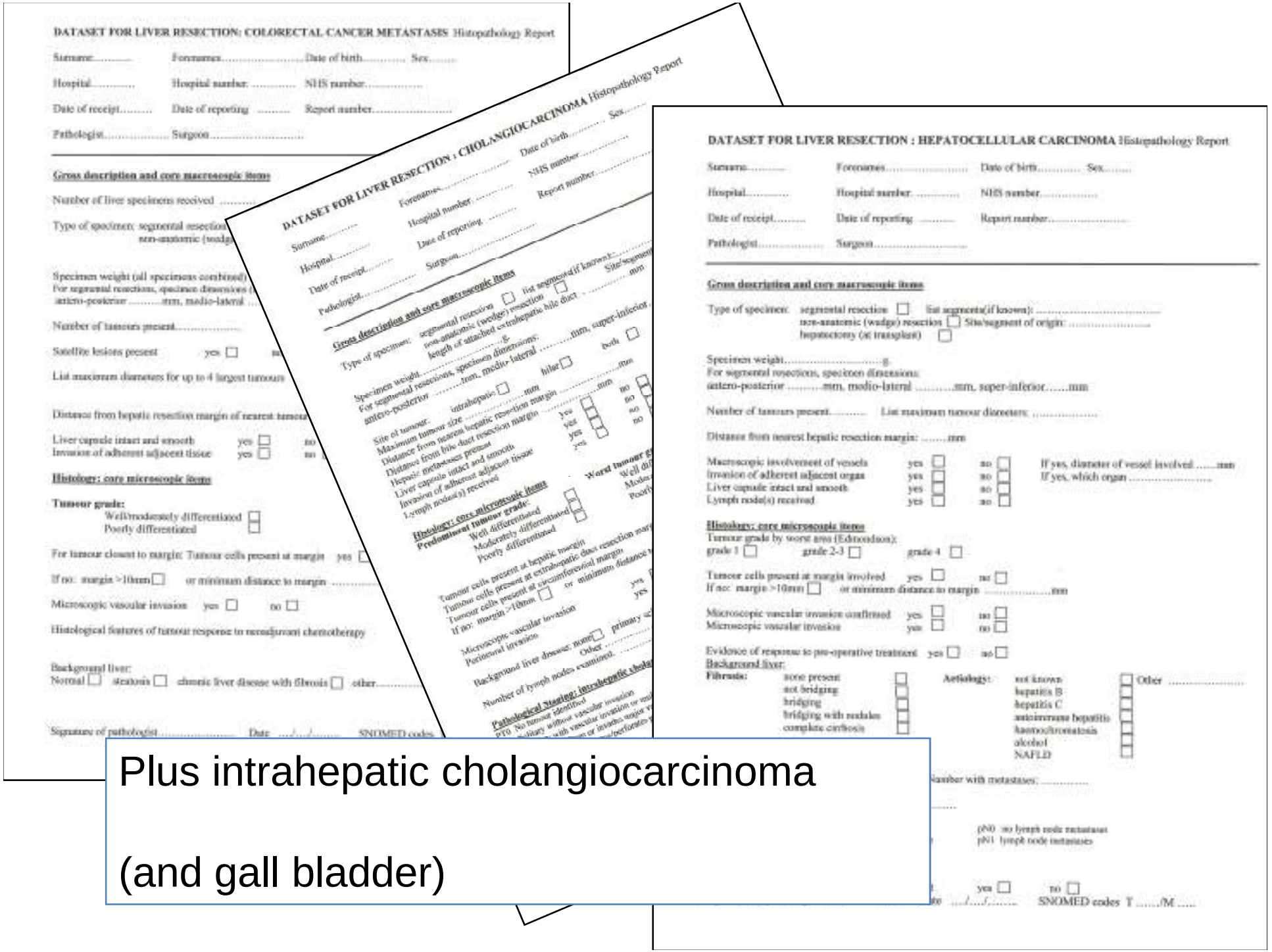
DRAFT: March 2010 31st October 2010

JIW, SGH, RDG

1st ed. 23 pages

2nd ed. 32 pages and counting

TNM 7 - recognises diversity in cholangiocarcinoma


DATASET FOR LIVER RESECTION: COLORECTAL CANCER METASTASES Histopathology Report
DATASET FOR LIVER RESECTION : CHOLANGIOCARCINOMA Histopathology Report
DATASET FOR LIVER RESECTION : HEPATOCELLULAR CARCINOMA Histopathology Report
Plus intrahepatic cholangiocarcinoma
(and gall bladder)