LUDWIG INSTITUTE FOR CANCER RESEARCH

Imperial College London

Dysplasia in the Biliary Tract

BDIAP

2nd December 2016

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Biliary Dysplasia

- Background
- Classification of dysplastic lesions
- Gall bladder dysplasia

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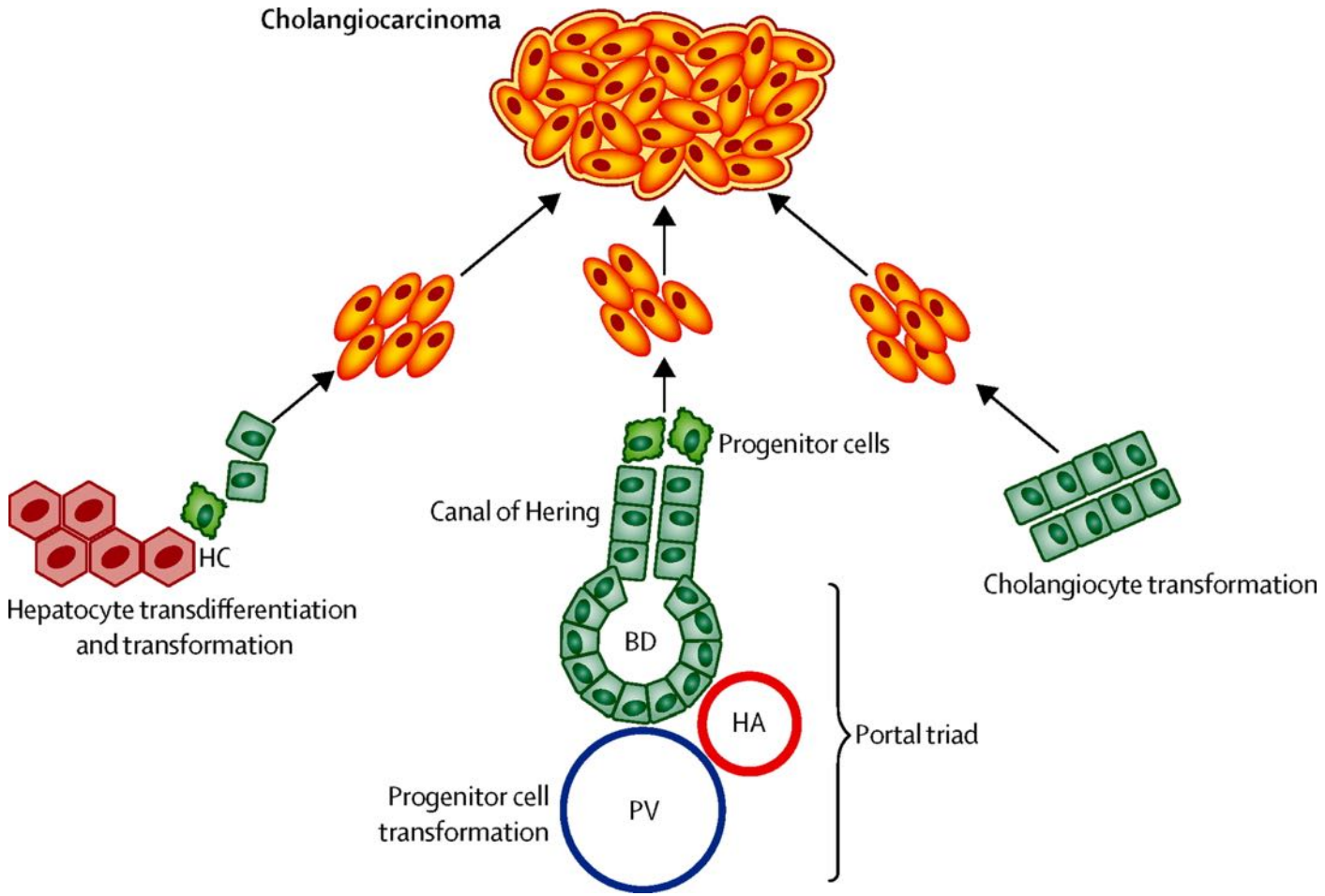
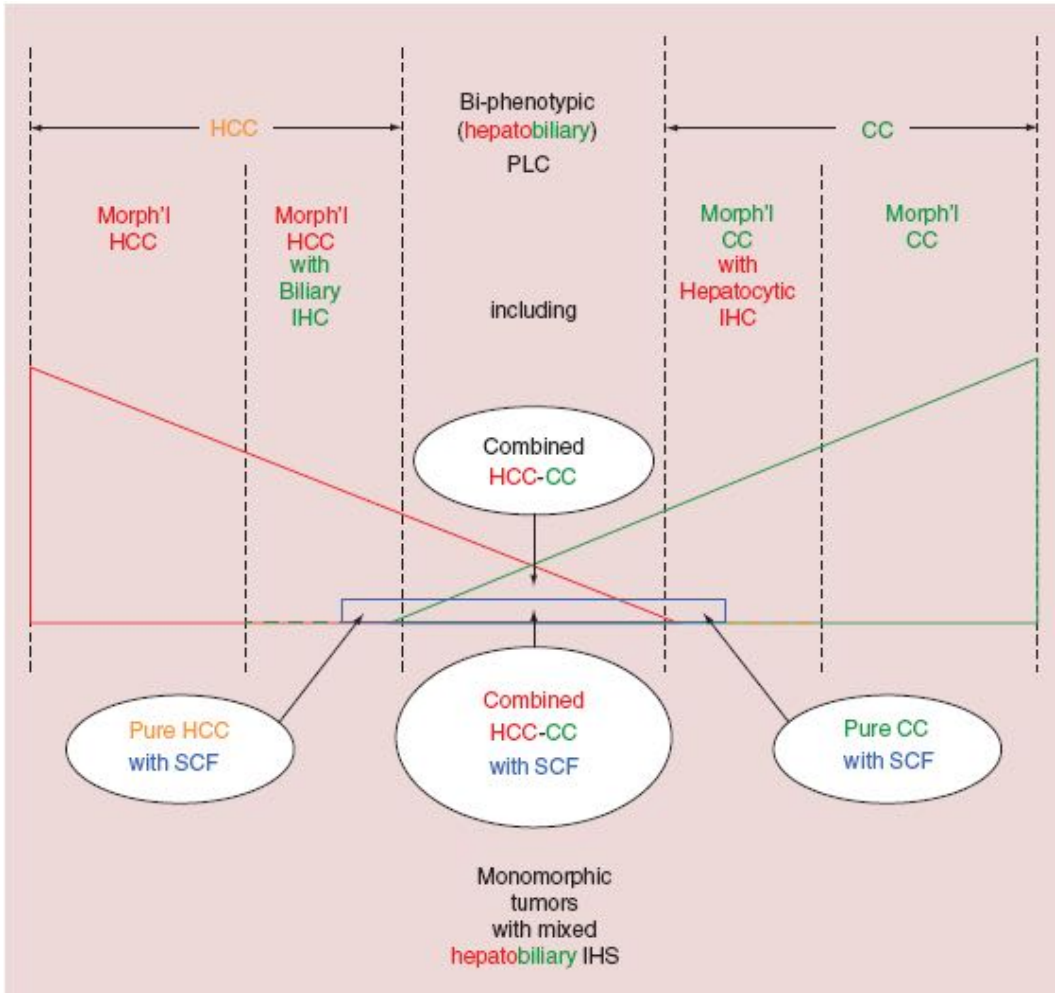


The Lancet 2014 383, 2168-2179DOI: (10.1016/S0140-6736(13)61903-0)



Hepat Oncol 2015;2:255-73.

Epidemiology of cholangiocarcinoma

- The incidence of intrahepatic cholangiocarcinoma is increasing in many western countries.
- Age-adjusted rates of cholangiocarcinoma are reported to be highest in Hispanic and Asian populations.
- Slight male predominance with the exception of the female Hispanic population.
- Unusual in children.
- Ampullary and intrahepatic – commonest in Asia.
- Gall bladder – South America.

Lancet 2014; 383: 2168–7

Risk factors for biliary neoplasia

- **West**

Gall stones

Primary sclerosing cholangitis

Abnormal choledocho-pancreatic junction

Choledochal cyst

- **Asia**

Hepatolithiasis

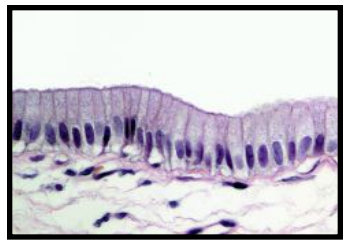
Flukes

Hepatitis B and C

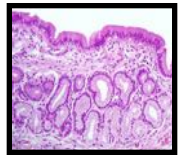
Metaplasia-Dysplasia-Carcinoma

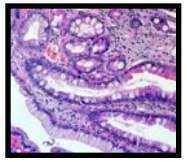
(Biliary intra-epithelial neoplasia)

Chronic Inflammation



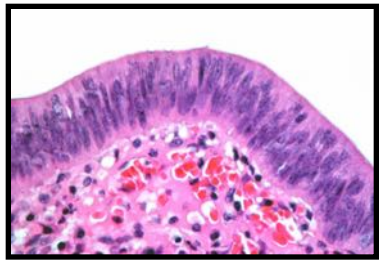
Pyloric metaplasia



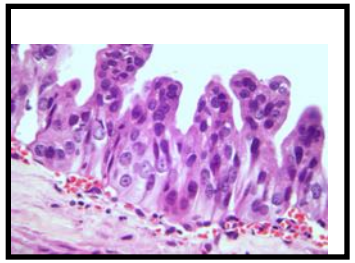


Intestinal metaplasia

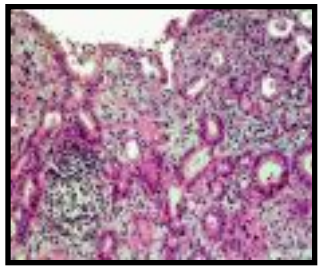
Low grade dysplasia



High grade dysplasia



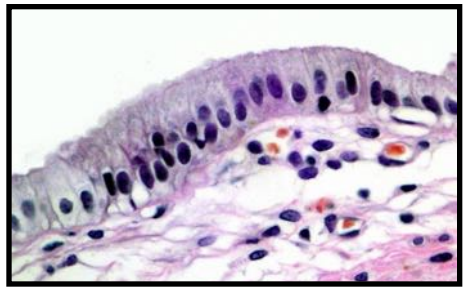
Invasive carcinoma



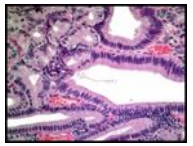
Mass lesion - Carcinoma

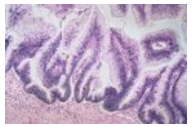
(Adenoma / Intraductal papillary neoplasm)

Normal mucosa



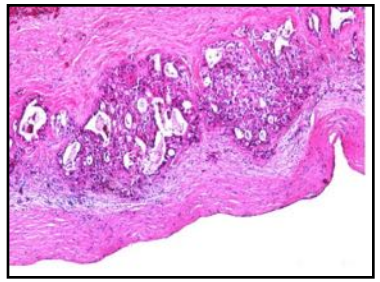
Adenoma





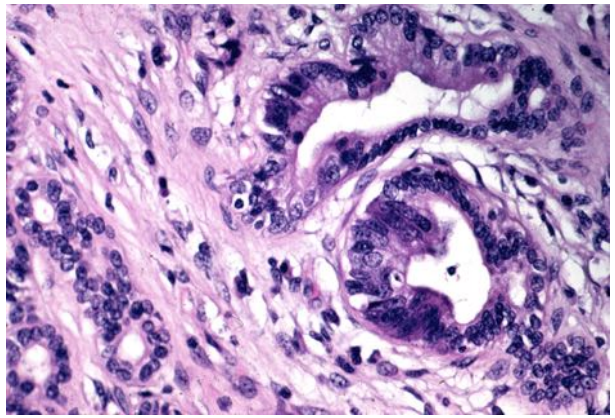
Intraductal papillary neoplasm

Invasive carcinoma



PSC and Cholangiocarcinoma

- In developed countries it is the greatest risk factor.
- 400 times as high as the risk in the general population.
- The annual risk of cholangiocarcinoma is 2%.



PSC and Bile duct dysplasia

- bile duct dysplasia is still a relatively frequent finding, seen at least focally in 36% of benign end-stage PSC explants
- high frequencies of mucinous metaplasia , pyloric metaplasia, and pancreatic acinar metaplasia, which did not differ between cholangiocarcinoma and non-cholangiocarcinoma livers.
- livers with cholangiocarcinoma were more likely to harbor intestinal metaplasia, dysplasia and also contained greater numbers of dysplastic ducts than non- cholangiocarcinoma cases.

Am J Surg Pathol. 2010 Jan;34(1):27-34.

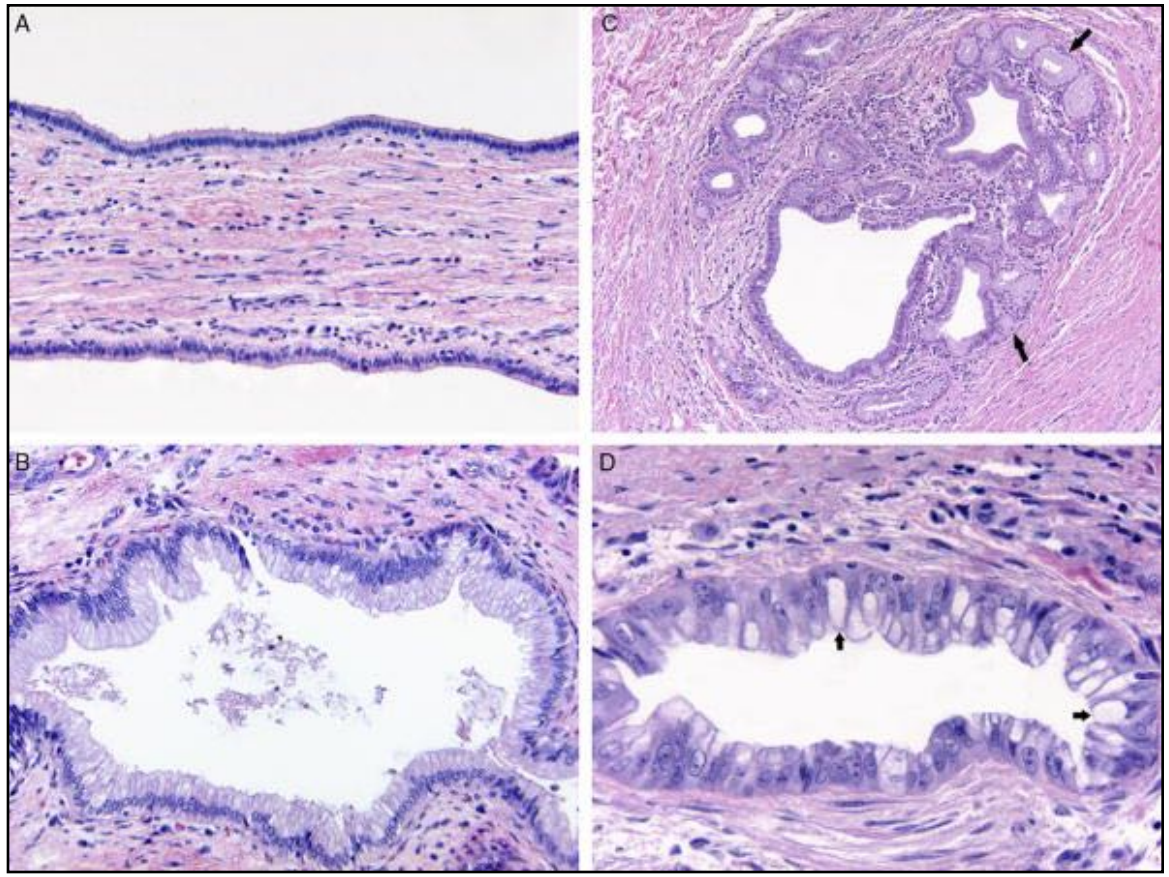
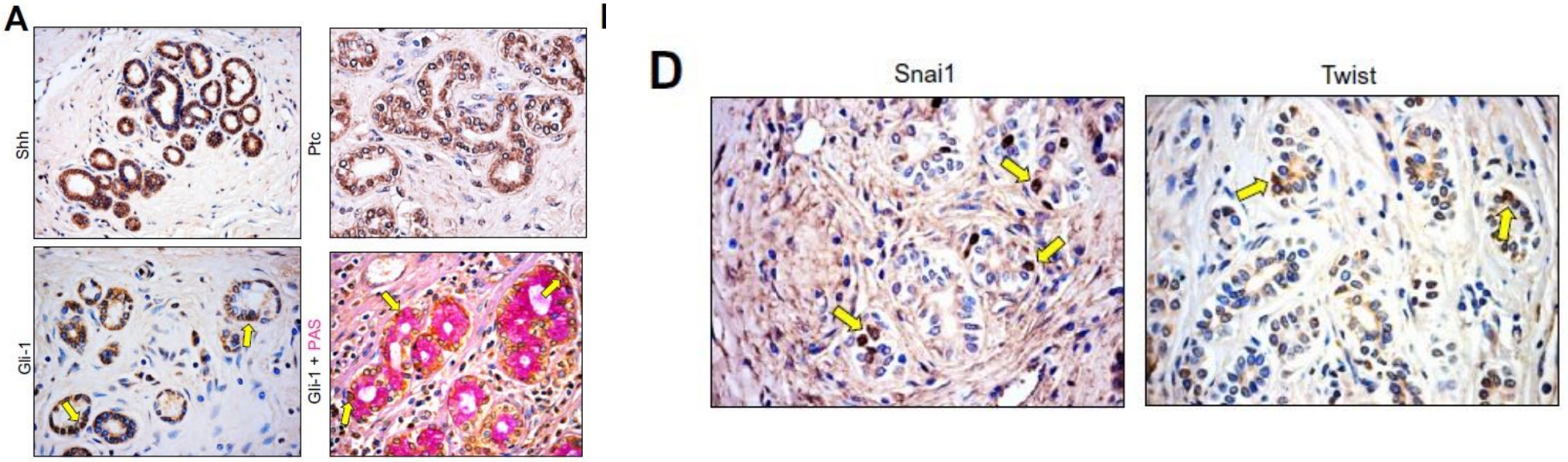


FIGURE 1. Bile duct metaplasia. A, Normal bile duct epithelium with cuboidal and low columnar cells. B, Mucinous metaplasia. C, Pyloric metaplasia (arrows). D, Intestinal metaplasia (in this case involving a dysplastic bile duct). Arrows mark examples of goblet cells.

American Journal of Surgical Pathology. 34(1):27-34, January 2010.

Role of peribiliary glands in PSC

Peribiliary glands expressed Hedgehog pathway and epithelial-to-mesenchymal transition traits in primary sclerosing cholangitis.



Journal of Hepatology 2015 vol. 63 1220–1228

Expression of cell cycle–related molecules in biliary premalignant lesions

p21, p53, cyclin D1, and Dpc4 to be involved in both pathways

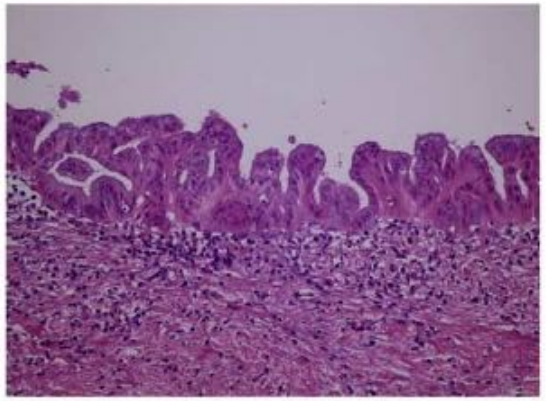
But for p53:

- expression was dramatically up-regulated at the invasive stage of biliary intraepithelial neoplasia
- expression was already up-regulated in LG intraductal papillary neoplasm and reached a plateau in HG intraductal papillary neoplasm

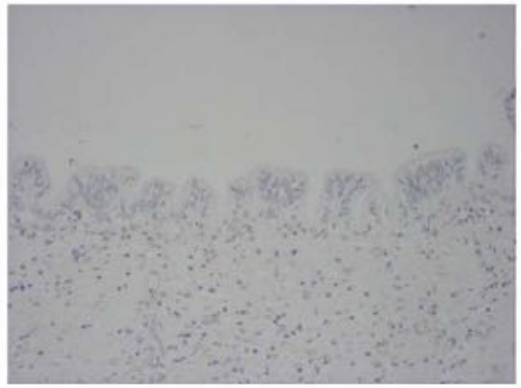
Human Pathology (2008) 39, 1153–1161

Biliary intra-epithelial neoplasia
Grade 2

HE

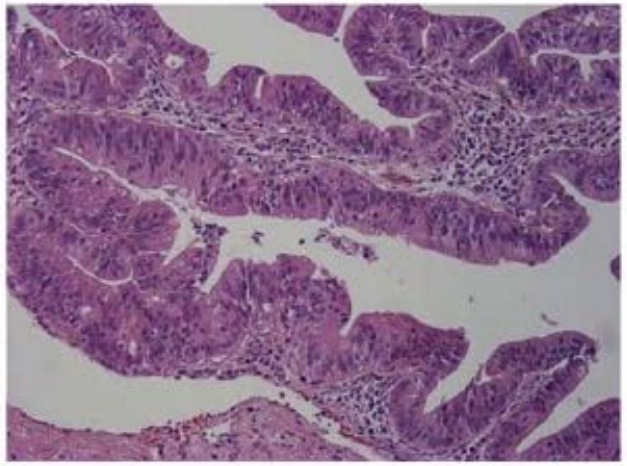


p53 (negative)

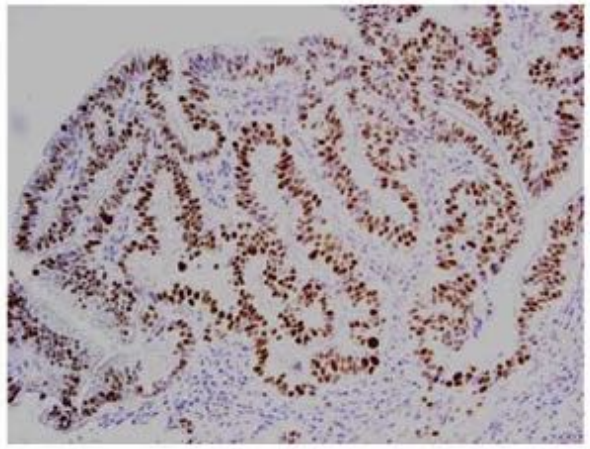


Intraductal papillary neoplasm
Grade 2

HE



p53 (positive)



Biliary Dysplasia

- Background
- Classification of dysplastic lesions
- Gall bladder dysplasia

Precursor lesions of cholangiocarcinoma

- **Similar lesions arise in the pancreas**

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

Path Int. 2010 Jun;60(6):419-29.

Proposal of a new disease concept "biliary diseases with pancreatic counterparts". Anatomical and pathological bases.

Histol Histopathol 2014 Jan;29(1):1-10.

Precursor lesions of cholangiocarcinoma

- Most invasive cancers arise from preexisting precursor lesions:

WHO Premalignant Lesions of the gall bladder and bile ducts (2010)

- Adenoma: tubular, papillary, tubulo-papillary
- Biliary intra-epithelial neoplasia (BilIN)
- Intraductal / intracystic papillary neoplasm (IPN)
- Mucinous cystic neoplasm

WHO Classification 2010

- Biliary papilloma
- Biliary papillomatosis
- Papillary cholangiocarcinoma
- Mucin-producing bile duct neoplasm
- Biliary cystadenoma/adenocarcinoma (without ovarian-like stroma)

→ Intraductal papillary neoplasm of the bile duct (IPNB)

- Biliary cystadenoma/adenocarcinoma with **ovarian-like stroma**

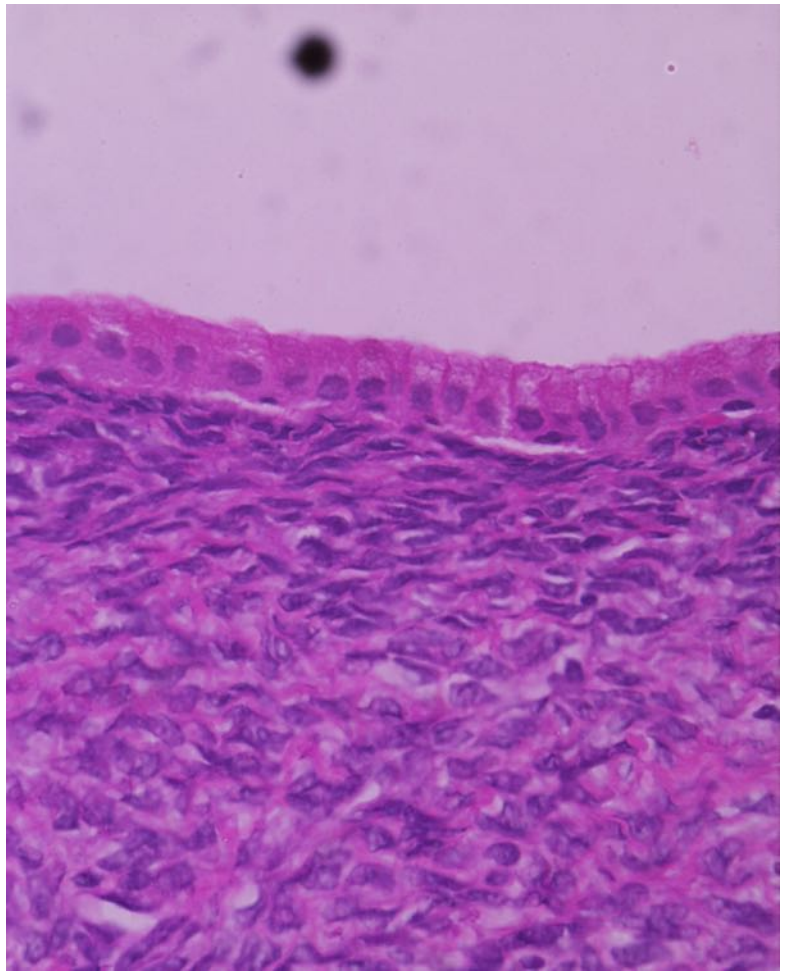
→ Mucinous cystic neoplasm (MCN) of the liver

Mucinous cystic neoplasm (MCN)

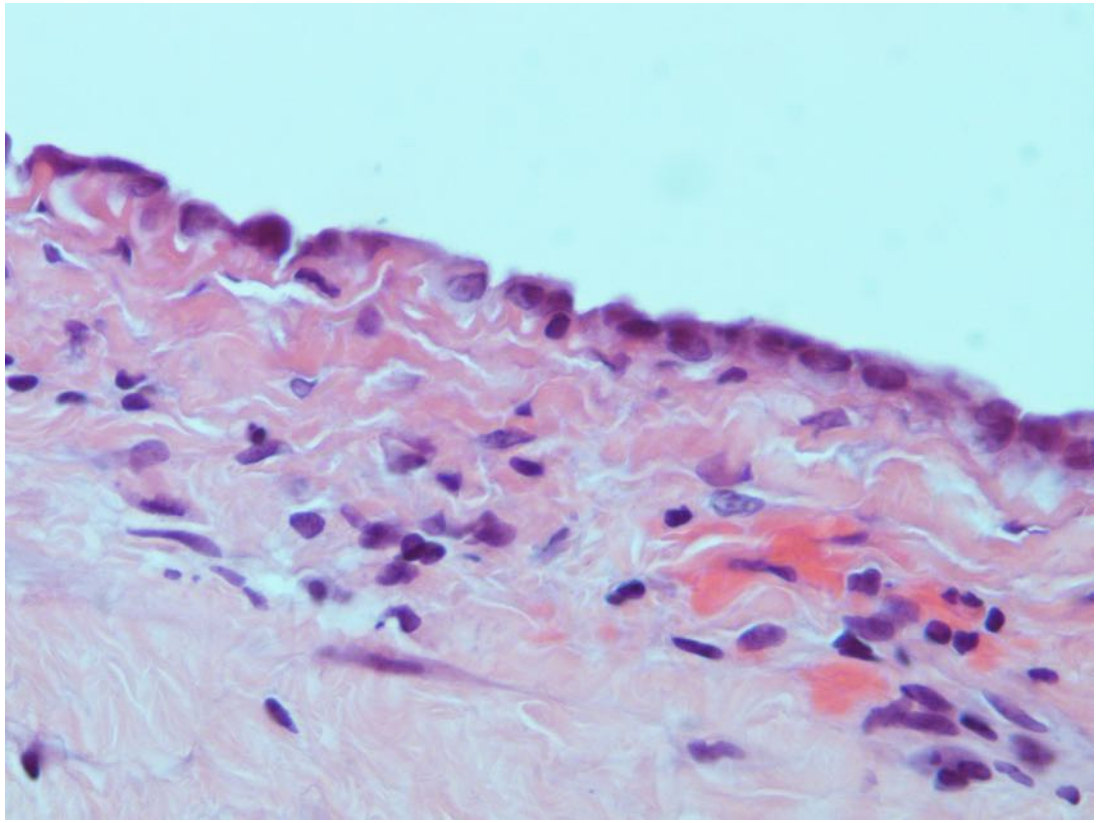
- Perimenopausal females
- Usually involves intrahepatic bile ducts
- Lined by columnar, biliary epithelium
- Ovarian-like stroma in the wall.
- Not connected to the biliary tract
- Low risk of malignant change

Modern Pathology (2011) 24, 1079–1089

Mucinous cystic neoplasm



Simple Biliary Cyst



Precursor lesions: Macroscopic Pathology

- Biliary Intra-epithelial neoplasia:

  Usually cannot be seen

- Intraductal papillary neoplasms:

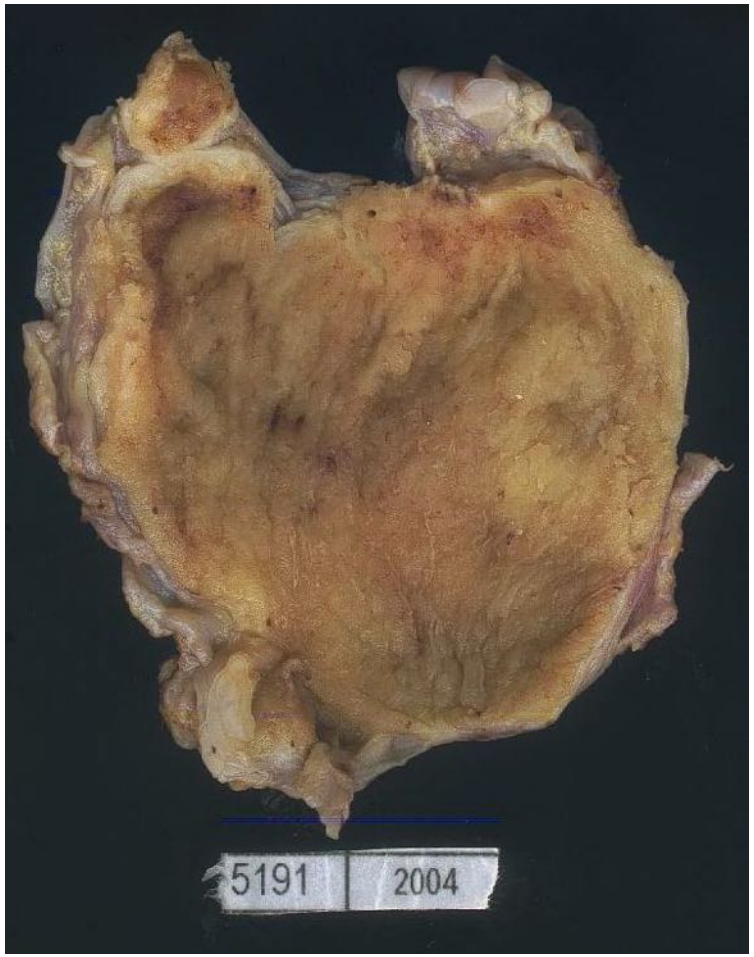
  Exophytic papillary lesion

  May be secondary cystic change

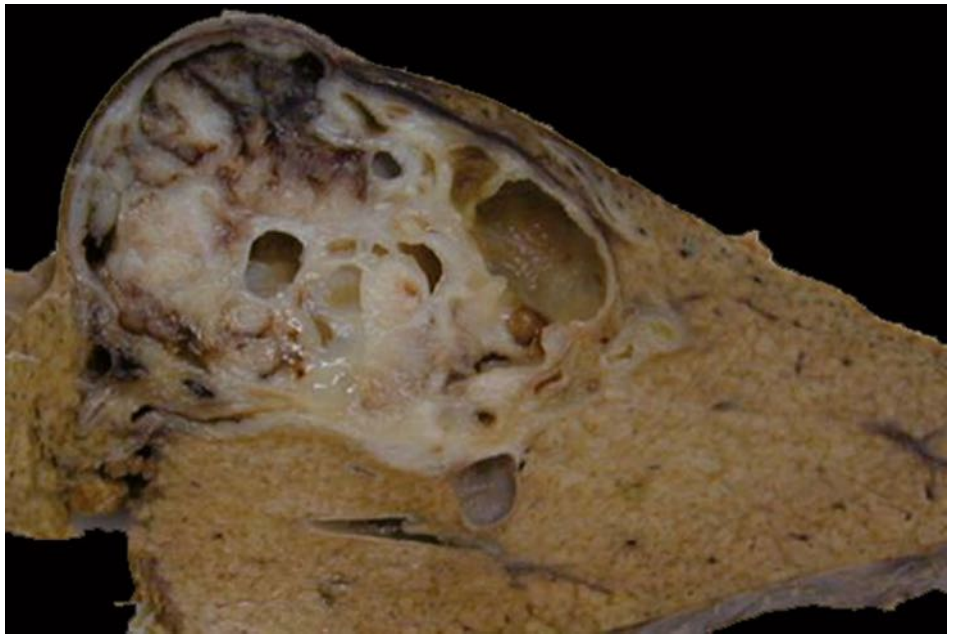
- Adenoma

  Exophytic

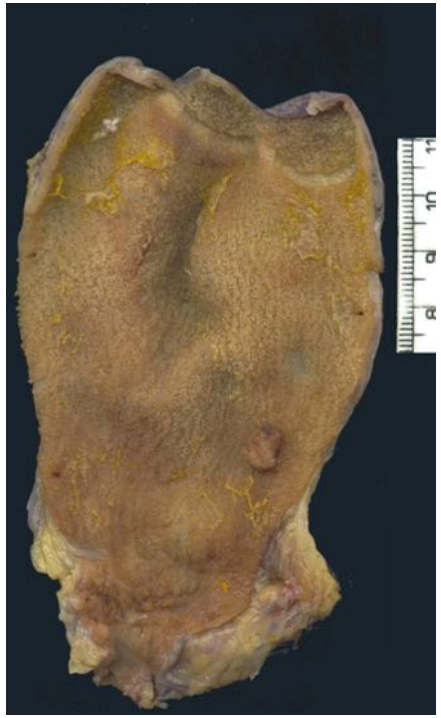
Biliary intra-epithelial neoplasia



Intraductal papillary neoplasm



Adenoma

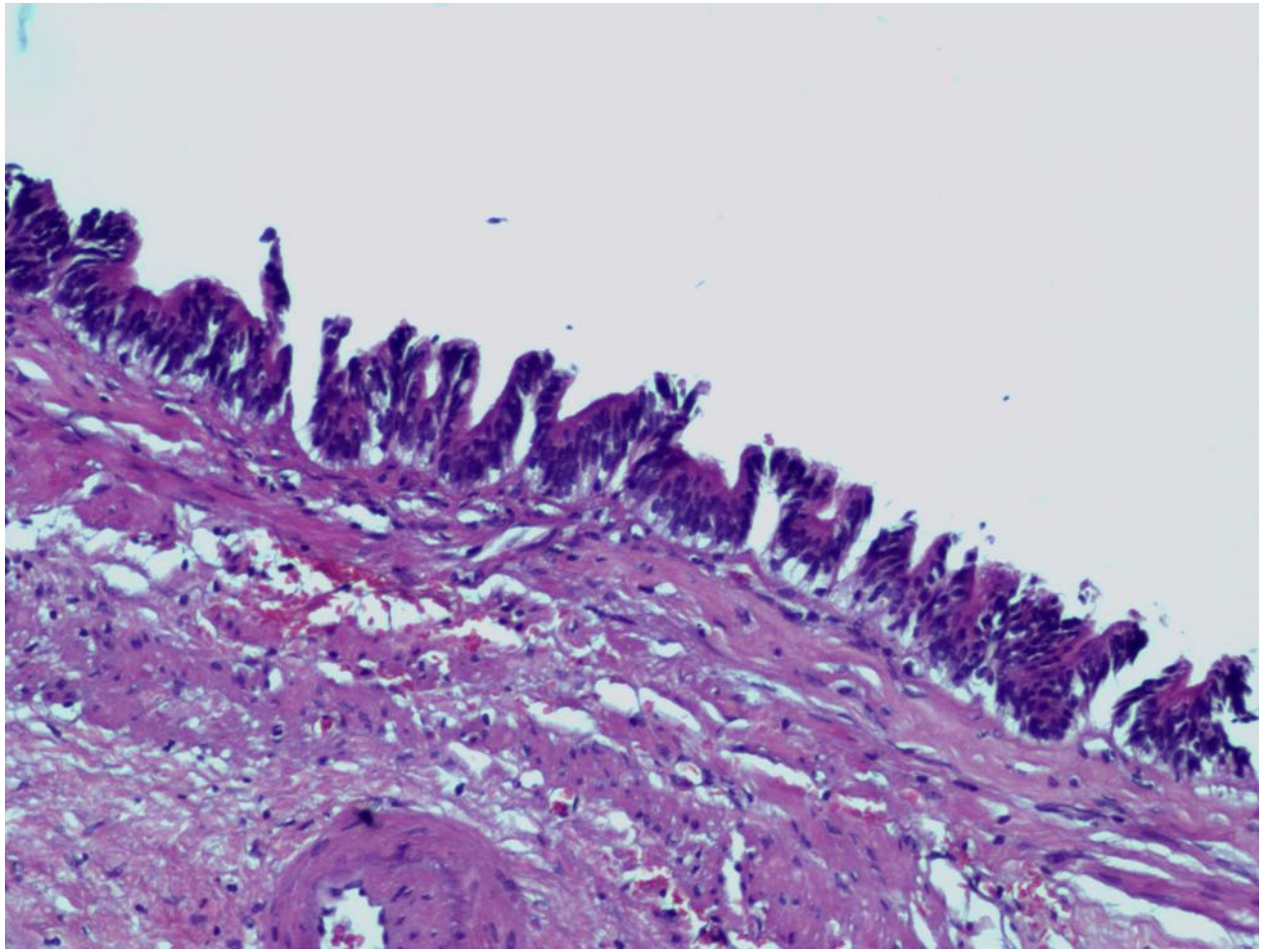


Biliary intra-epithelial neoplasia: Microscopic Pathology

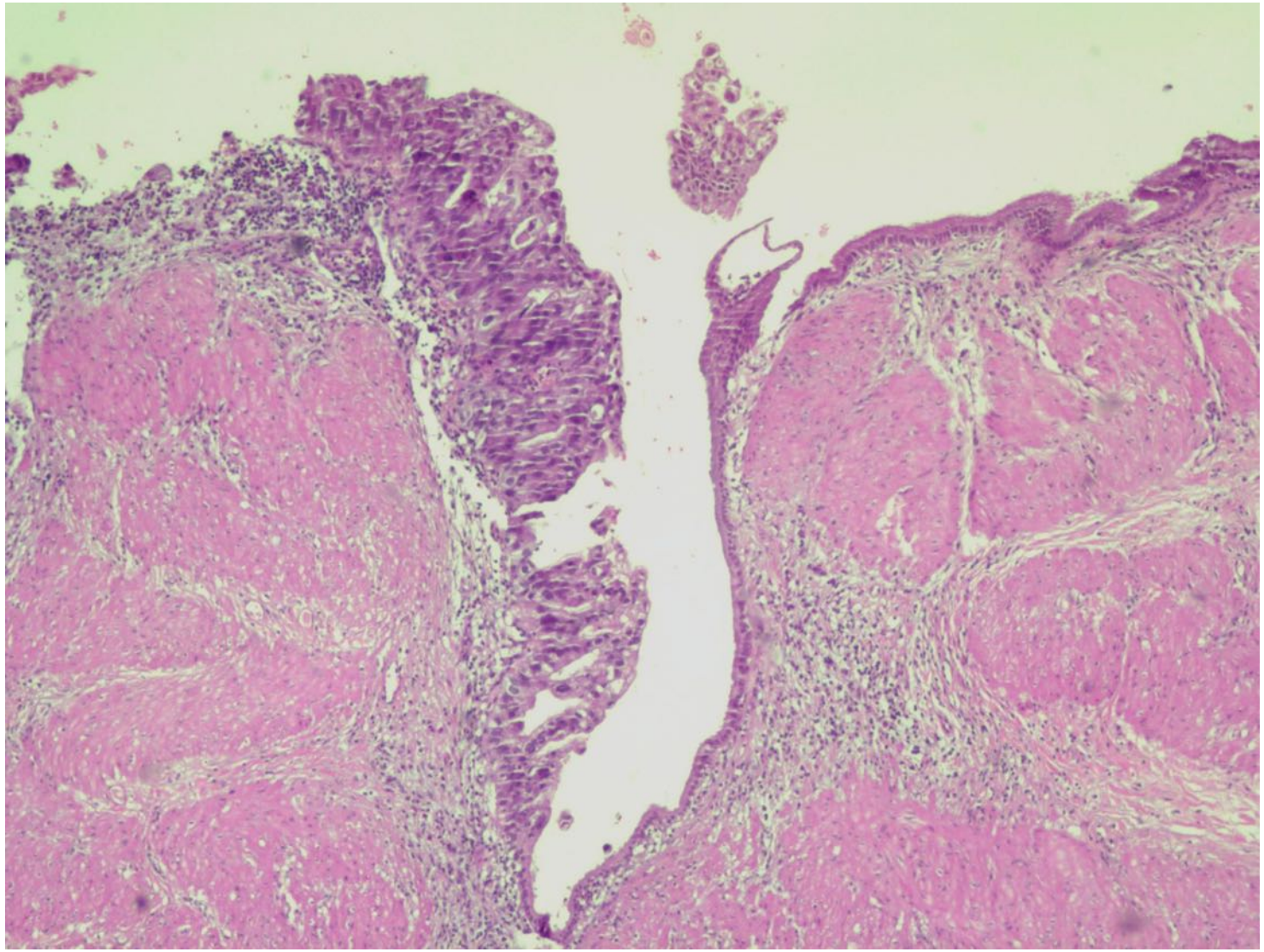
- Flat but may be micropapillary projections
- Classic and intestinal types (Histopathology 2011 Dec;59(6):1100-100.)
- Abrupt transition to dysplastic epithelium
- May be involvement of underlying peribiliary glands or Rokitansky-Aschoff sinuses.
- Grading: BilIN1-3 or high grade /low grade

(Best Pract Res Clin Gastroenterol. 2013 Apr;27(2):285-97)

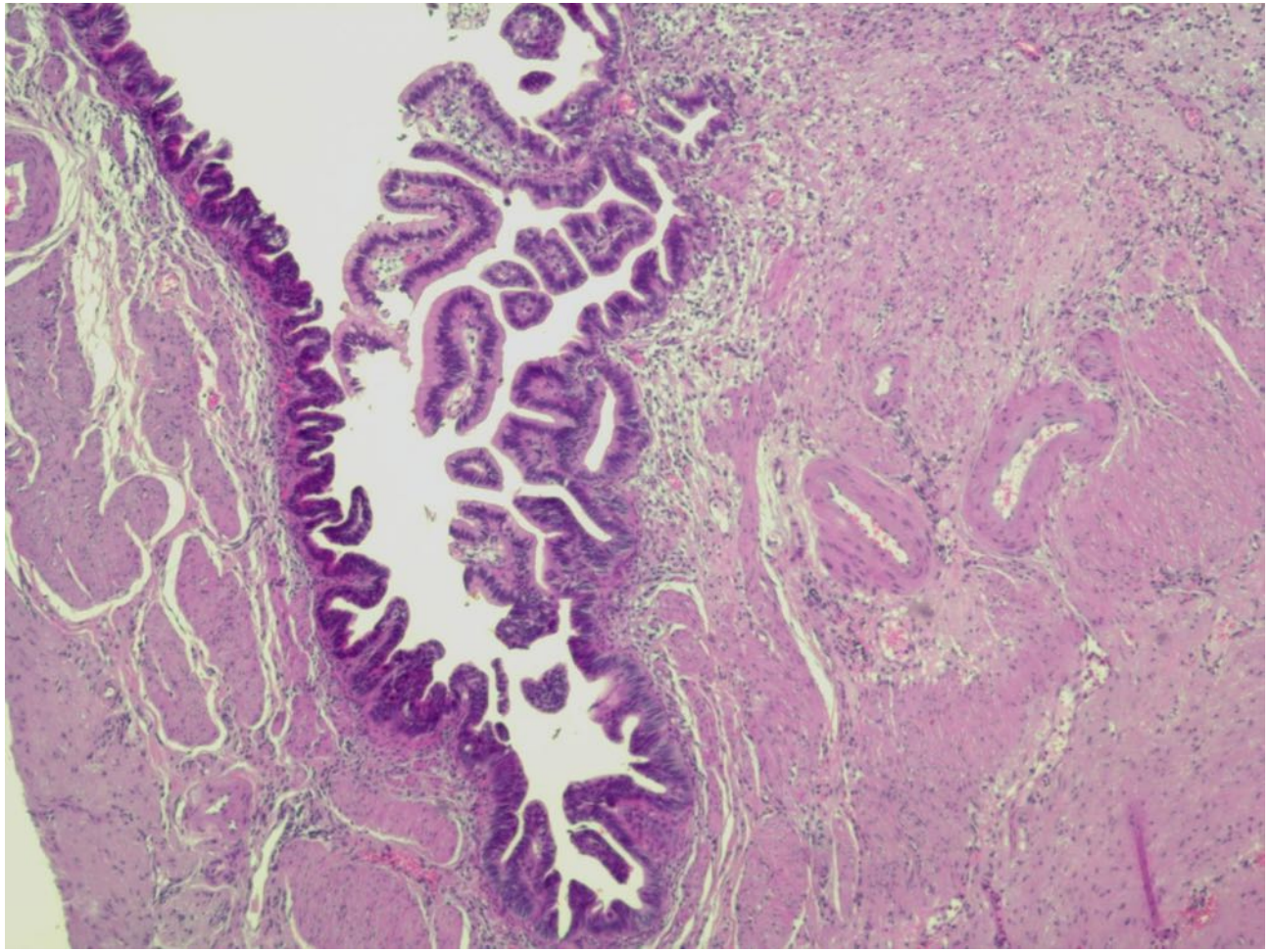
BillN with micropapillary projections



BillN with abrupt change



BillN involving Rokitansky-Aschoff sinus



Grading of BilIn

Table 1 Histological features of BilIN

Histology	BilIN-1	BilIN-2	BilIN-3
Cellular/nuclear atypia	+	+	++
Nuclear pseudostratification	+	+	+
Protruding of the nuclei (up to the ductal apical surface)	−	+	+
Loss of cellular/nuclear polarity	−	+	++

BilIN biliary intraepithelial neoplasia

−, likely absent; +, present; ++, prominent

J Gastroenterol (2014) 49:64–72
(Modern Pathology (2007) 20, 701–709)

BilIN 1-3

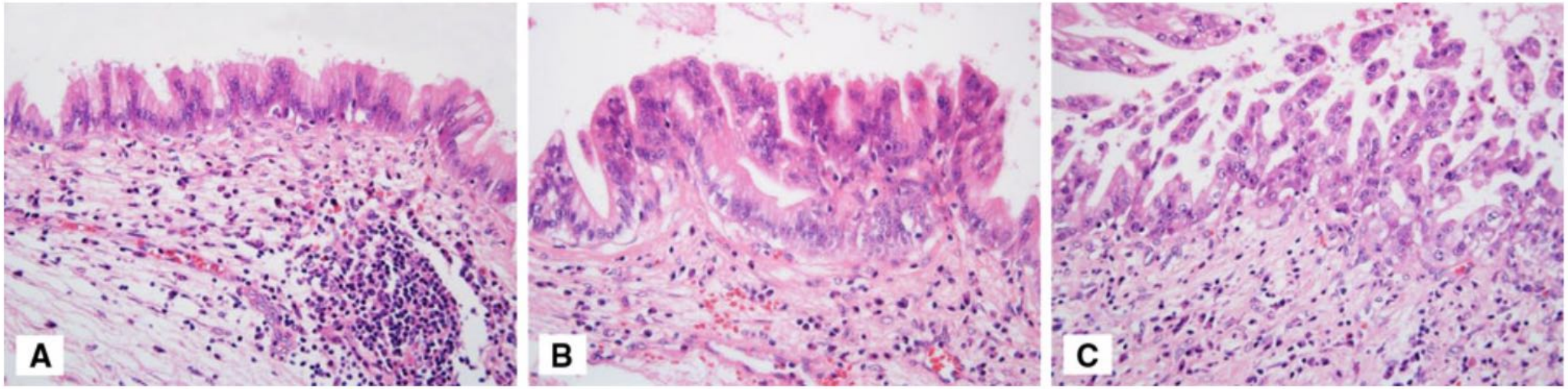


Fig. 1 Biliary intraepithelial neoplasia (BilIN). **a** BilIN-1, **b** BilIN-2, **c** BilIN-3. H&E. ×400

J Gastroenterol (2014) 49:64–72

Biliary intra-epithelial neoplasia: Microscopic Pathology

Table 1 Kappa values of interobserver agreement on the diagnosis of reactive and dysplastic biliary epithelial lesions occurring in primary sclerosing cholangitis, choledochal cyst and hepatolithiasis

	N	*Reactive*	*BilIN-1*	*BilIN-2*	*BilIN-3*	*Total*
United States	5	0.43	0.40	0.19	0.43	0.47
Europe	6	0.40	0.41	0.12	0.43	0.44
Asia	5	0.44	0.40	0.16	0.45	0.46
Total	16	0.42	0.40	0.16	0.44	0.45

N, number of participants.

0.00: poor agreement;
0.00–0.20: slight agreement;
0.21–0.40: fair agreement;
0.41–0.60: moderate agreement;
0.61–0.80: substantial agreement;
and 0.81–1.00: almost perfect agreement.

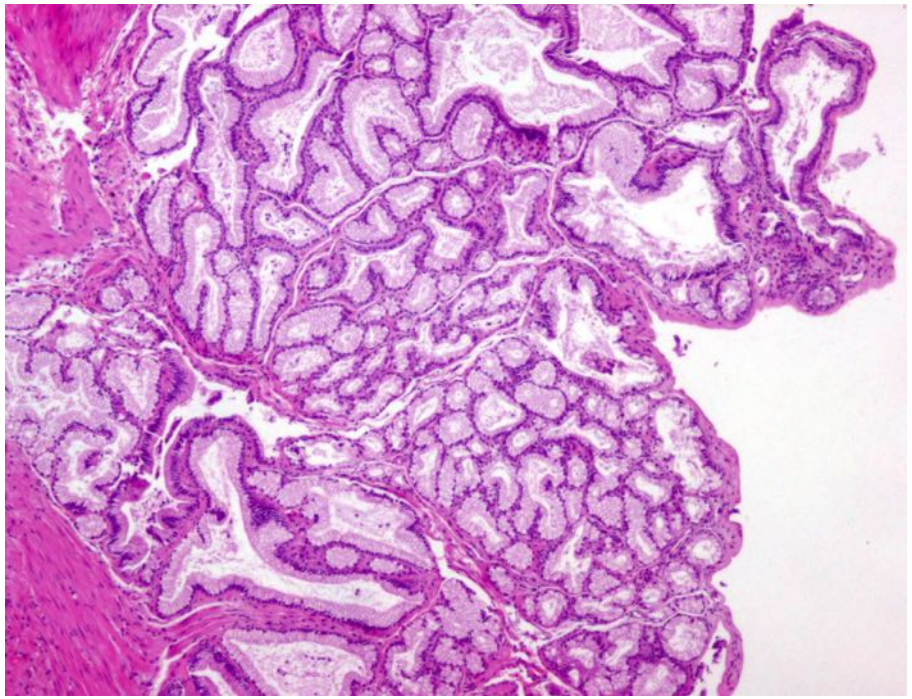
Modern Pathology (2007) 20, 701–709

Differential diagnosis of BilIN

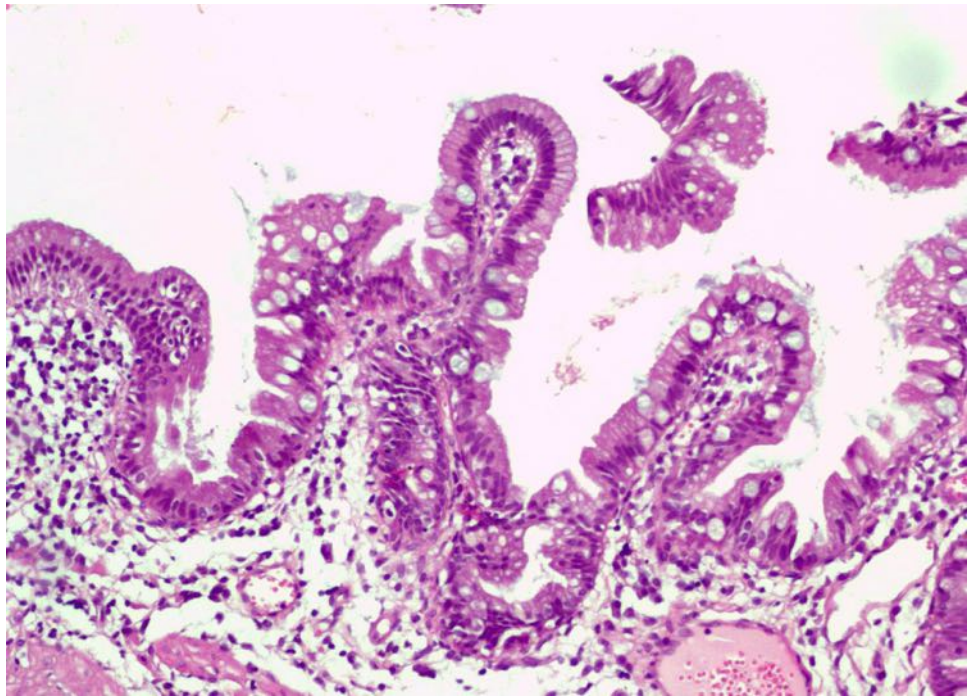
- Metaplasia
- Reactive changes
- (Pagetoid spread)

Differential diagnosis of BilIN Metaplasia

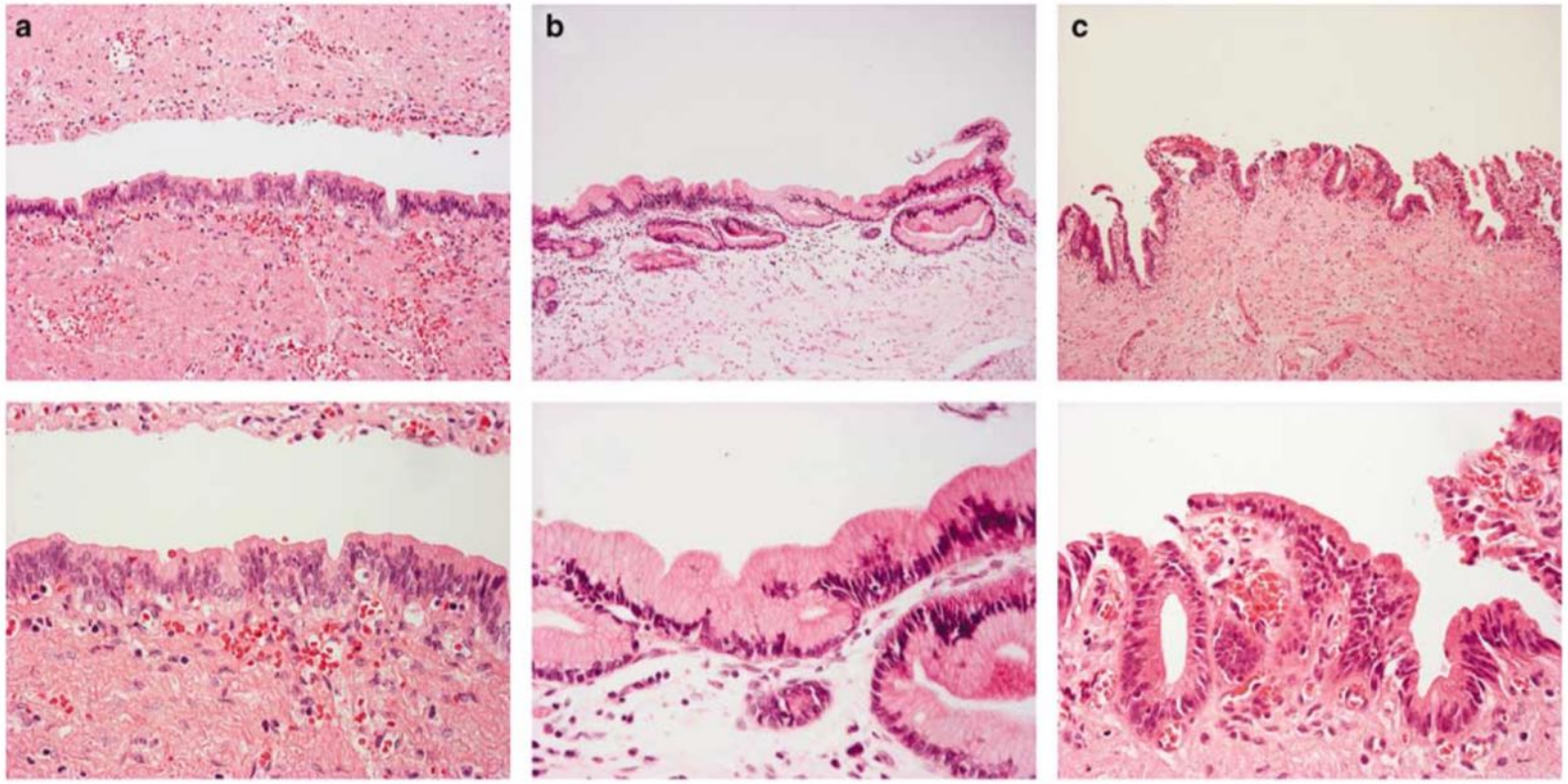
Pyloric metaplasia



Intestinal metaplasia



Differential diagnosis of BilIN: Reactive changes



Modern Pathology (2007) 20, 701–709

Differential diagnosis of BilIN: Reactive changes

Table 1. Morphologic Features To Distinguish Dysplasia From Reactive Atypia in Gallbladder

	Dysplasia	Reactive Atypia
Acute inflammation and/or ulceration	−	+
Intraepithelial neutrophils	−	+
Abrupt transition between normal and atypical epithelium	+	−
Fine nuclear chromatin	+	−
Prominent nucleoli	−/+	+
Surface maturation	−/+	+
Loss of polarity	+	−
History of instrumentation	−	+

Abbreviations: +, present; −, absent; +/−, can be present or absent.

Arch Pathol Lab Med. 2010;134:1621–1627

Intraductal Papillary Neoplasm: Microscopic Pathology

- Intraductal papillary neoplasm biliary equivalent of pancreatic intraductal papillary mucinous neoplasm

But:

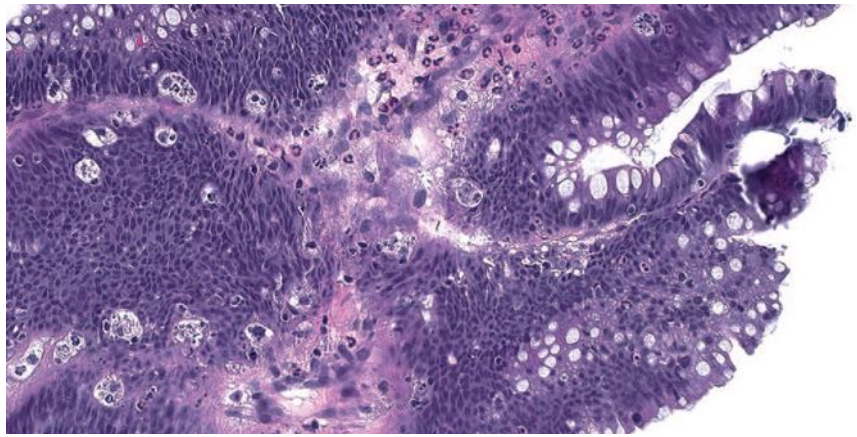
intracystic as well as intraductal: i.e. intraluminal

most are not mucinous

- high grade/ low grade
- may be secondary cystic change

Intraductal Papillary Neoplasm: Microscopic Pathology

- Half are associated with invasive cancer at the time of diagnosis
- 4 histological subtypes: intestinal, pancreaticobiliary, gastric, oncocytic

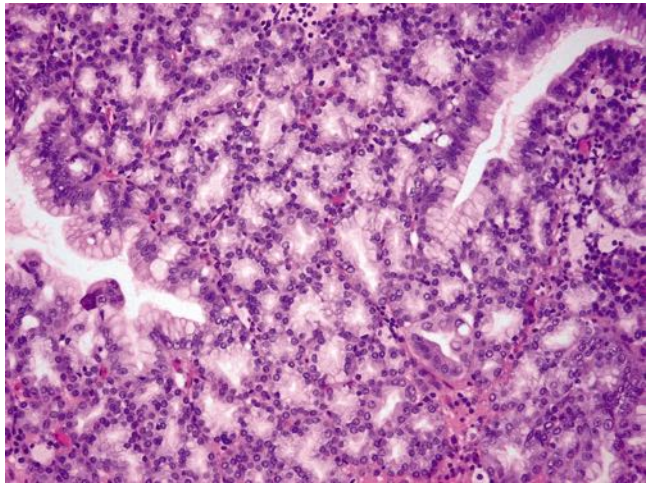


Intestinal type

Adenomas: Microscopic Pathology

May be classified according to:

- Architecture: tubular, papillary, tubulo-papillary
- Cell type: pyloric-gland like, intestinal, foveolar and biliary



Pyloric tubular adenoma

Intracystic papillary tubular neoplasms of the gall bladder

Intracholecystic papillary-tubular neoplasms (ICPN) of the gallbladder (neoplastic polyps, adenomas, and papillary neoplasms that are ≥1.0 cm): clinicopathologic and immunohistochemical analysis of 123 cases.

"They show variable cellular lineages, a spectrum of dysplasia, and a mixture of papillary or tubular growth patterns, often with significant overlap, warranting their classification under 1 unified parallel category, intracholecystic papillary-tubular neoplasm."

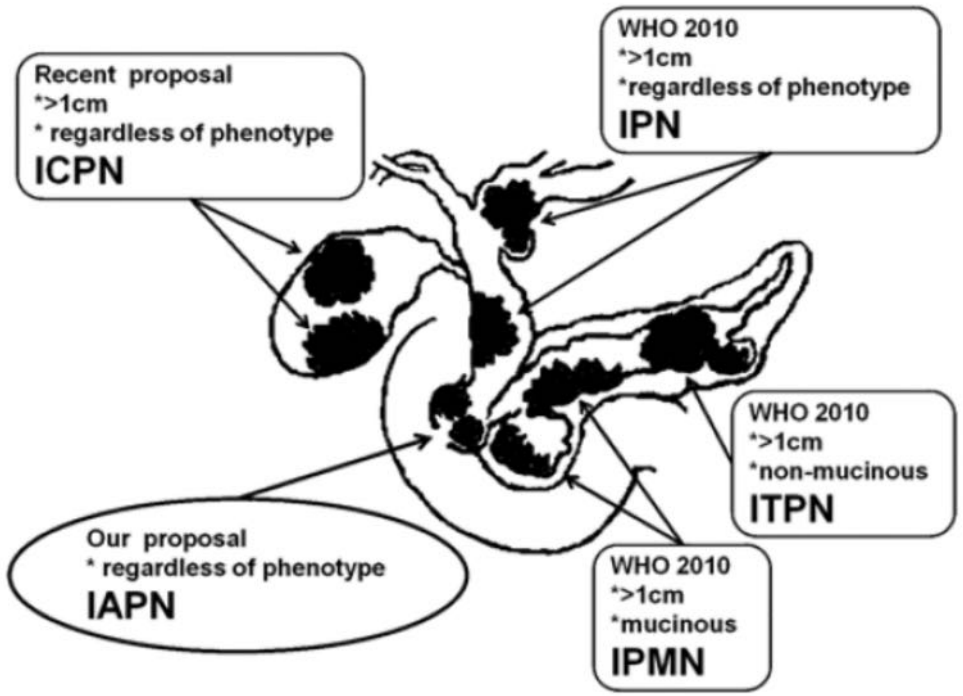
Am J Surg Pathol. 2012 Sep;36(9):1279-301.

Intracystic papillary-tubular neoplasms of the gall bladder

TABLE 1. Definition of ICPN

A GB neoplasm that is:
Intramucosal
Preinvasive neoplastic (dysplastic)
Mass forming; exophytic (papillary or polypoid)
≥ 1.0 cm
Compact
Distinct from the neighboring mucosa

Am J Surg Pathol. 2012 Sep;36(9):1279-301.



IPMN = intraductal papillary mucinous neoplasm
ITPN = intraductal tubulopapillary neoplasm
IPN = intraductal papillary neoplasm
IAPN = intra-ampullary papillary tubular neoplasm
ICPN = intracholecystic papillary-tubular neoplasm

Am J Surg Pathol. 2012 Sep;36(9):1279-301.

What needs to be included in the report:

- Size
- Dysplasia (extent of high grade)
- Architecture (extent of papillary architecture)
- (Cell type)
- Carcinoma / not
- Margin

Immunohistochemistry for dysplasia

Immunohistochemistry: for histological subtypes

CK7:	marker for biliary differentiation
MUC1:	marker for pancreatico-biliary tumour differentiation
CDX2:	marker for intestinal differentiation
MUC2:	marker for intestinal differentiation
MUC5AC:	marker for gastric foveolar differentiation
MUC6:	marker for pyloric differentiation

Immunohistochemistry: for disease progression

- With increased dysplasia and the development of invasive carcinoma:
  - increased expression of p53
  - increased expression of Ki-67
  - loss of membranous expression of Beta-catenin
  - loss of membranous expression of E-cadherin
  - loss of CD10 expression

CD15 in biliary dysplasia

- Expressed in 70.0%, cholangiocarcinoma-associated dysplasia dysplasia and in 100% of dysplasia in intraductal biopsies
- Expressed in 9% of benign bile duct
- CD15 is a sensitive and specific marker for intraepithelial (and invasive neoplasias) of the bile

Histopathology DOI: 10.1111/his.13041

Biliary Dysplasia

- Background
- Classification of dysplastic lesions
- Gall bladder dysplasia

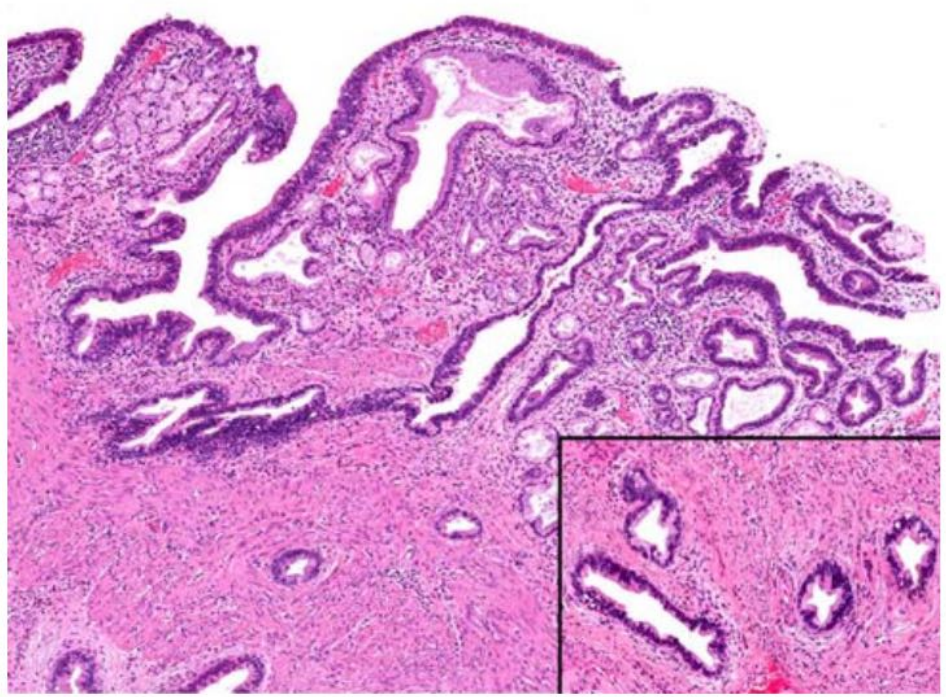
Incidental non-benign gallbladder histopathology after cholecystectomy in an United Kingdom population: Need for routine histological analysis?

4027 patients:

“Dysplasia, ranging from low to multifocal high-grade was demonstrated in 55 (1.37%). “

World J Gastrointest Surg. 2016 Oct 27;8(10):685-692.

Rokitansky-Aschoff Sinuses Mimicking Adenocarcinoma of the Gallbladder



Am J Surg Pathol 2013;37:1269–1274

The Royal College of Pathologists

Pathology: the science behind the cure

Tissue pathways for gastrointestinal and pancreatobiliary pathology

January 2016

GALL BLADDER: RECOMMENDATIONS

Open along the serosal surface.

Sample cystic duct margin. Take lymph node (if present). Sample gall bladder body and any focal lesions.

If high grade dysplasia or malignancy is found, examine the entire gall bladder histologically. If low grade dysplasia is found, examine additional blocks.

“Submitting the entire gallbladder in cases of dysplasia is not justified”.

When dysplasia is identified in a gallbladder, many experts recommend submission of the entire gallbladder for histologic examination.

We reviewed 16,611 gallbladder resections:

- 9 HGD
- 16 LGD
- 81 atypia

None of the HGD or LGD dysplasia were identified on gross examination, but all were identified as atypical on the initial slide submitted and correctly graded with the submission of 4 additional slides.

Am J Clin Pathol. 2012 Sep;138(3):374-6.

“Submitting the entire gallbladder in cases of dysplasia is not justified.”

89% HGD, 38% LGD, and 1% of 81 atypia cases were subsequently entirely submitted without identification of any new lesion.

We conclude that for cases of dysplasia and atypia review of the gross specimen and submission of up to 4 additional sections identify all significant lesions, and submission of the entire gallbladder is not justified.

Am J Clin Pathol. 2012 Sep;138(3):374-6.

“Submitting the entire gallbladder in cases of dysplasia is not justified.”: Letter 1

- Cholecystectomy is considered adequate therapy for Tis or T1 invasive cancers
- In more straightforward cases, we would recommend that consultants add a comment such as **“This final diagnosis relies on a thorough gross examination of the gallbladder and takes into account that no mucosal or muscular abnormalities were noted on gross examination.”**

Am J Clin Pathol. 2013 ;139(6):830.

Gallbladder Cancer: expert consensus statement

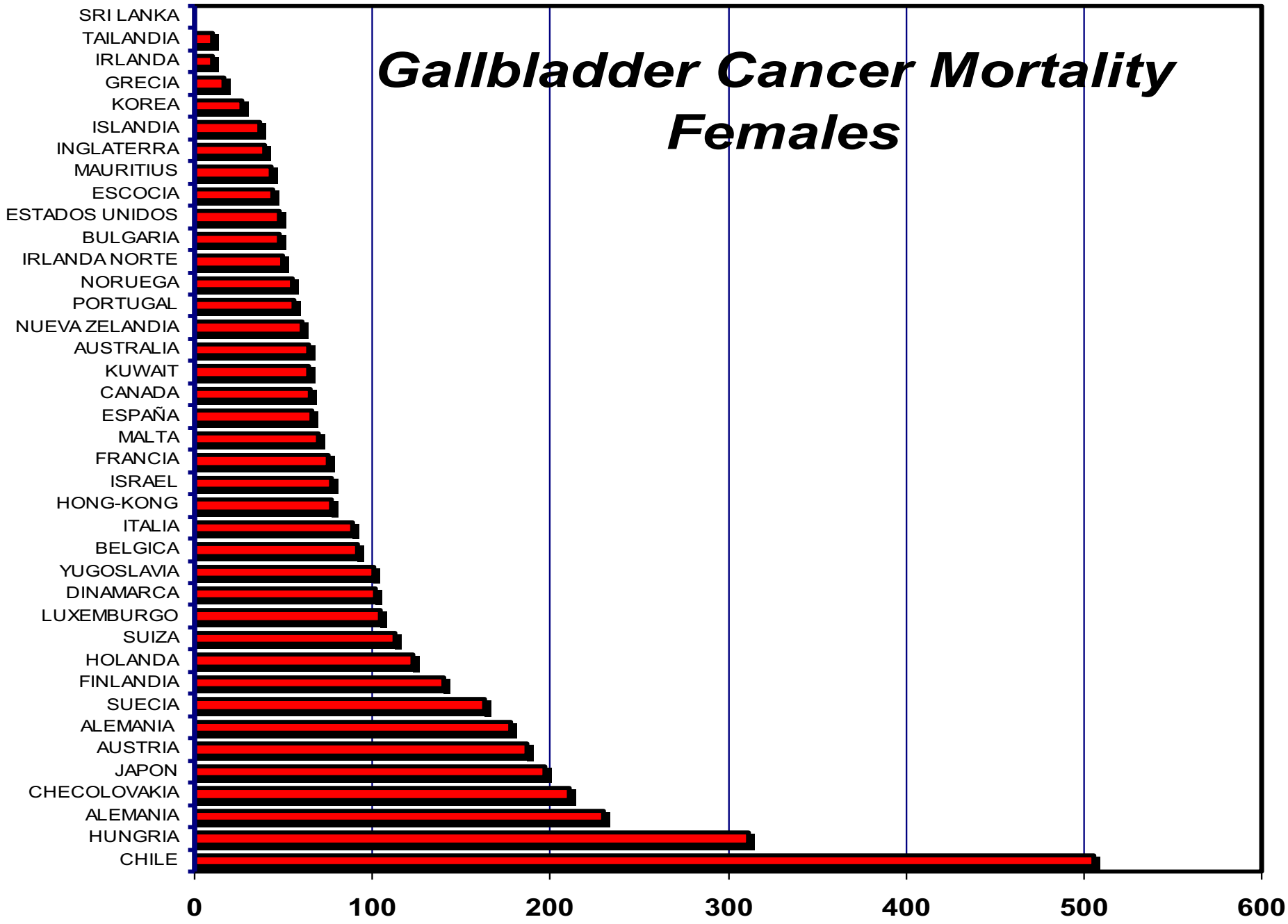
"Patients with T1b, T2 or T3 disease that is incidentally identified in a cholecystectomy specimen should undergo re-resection unless this is contraindicated by advanced disease or poor performance status."

HPB 2015, 17, 681–690

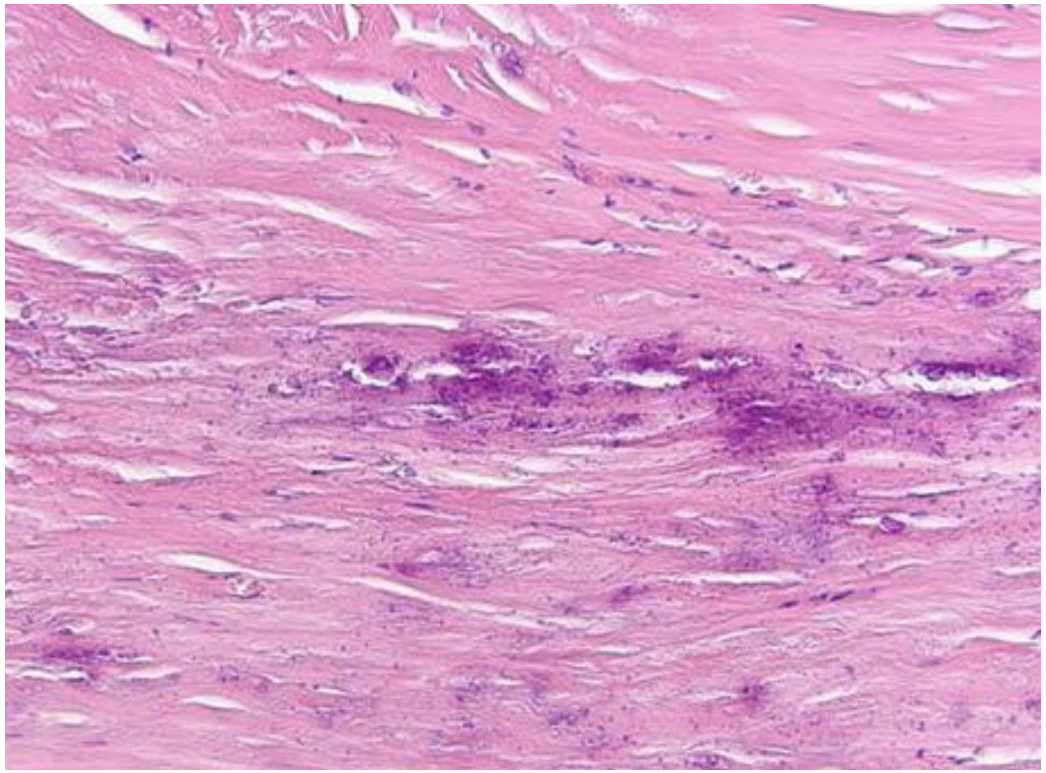
“Submitting the entire gallbladder in cases of dysplasia is not justified. “: Letter 2

- Pyloric metaplasia: no additional sections
- Intestinal metaplasia: 2 additional cassettes
- LGD: 2 additional cassettes
- HGD: 12 cassettes

Am J Clin Pathol 2013;140:278-28


Gallbladder Cancer Mortality
Females
SRI LANKA
TAILANDIA
IRLANDA
GRECIA
KOREA
ISLANDIA
INGLATERRA
MAURITIUS
ESCOCIA
ESTADOS UNIDOS
BULGARIA
IRLANDA NORTE
NORUEGA
PORTUGAL
NUEVA ZELANDIA
AUSTRALIA
KUWAIT
CANADA
ESPAÑA
MALTA
FRANCIA
ISRAEL
HONG-KONG
ITALIA
BELGICA
YUGOSLAVIA
DINAMARCA
LUXEMBURGO
SUIZA
HOLANDA
FINLANDIA
SUECIA
ALEMANIA
AUSTRIA
JAPON
CHECOLOVAKIA
ALEMANIA
HUNGRIA
CHILE
0
100
200
300
400
500
600

Hyalinizing Cholecystitis: (Porcelain Gall Bladder)



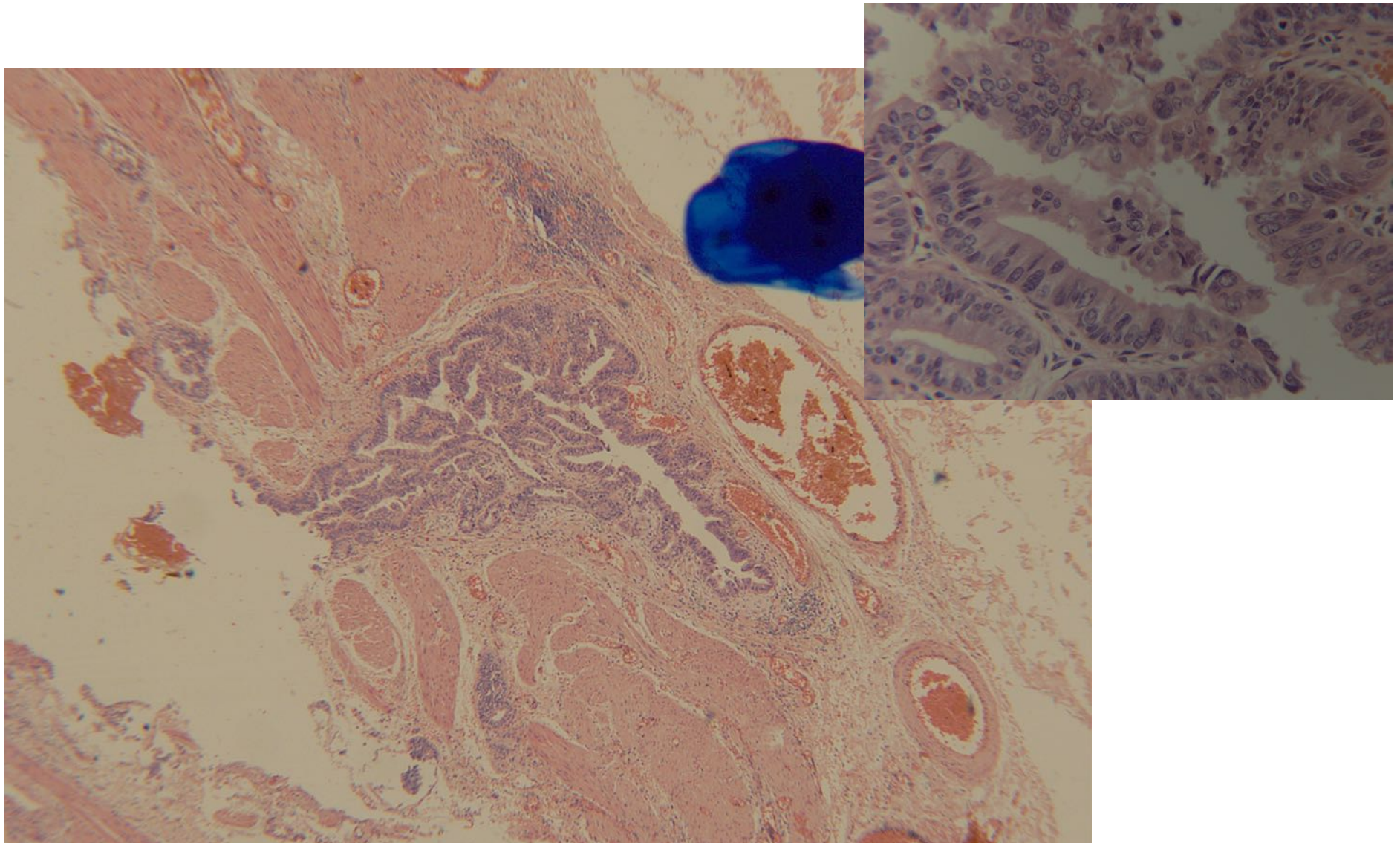
Am J Surg Pathol 2011;35:1104–1113

Hyalinizing Cholecystitis (Porcelain Gall Bladder)

- 2% of cholecystectomies
- carcinoma seen in 15% of these (OR = 4.6)
- only 42% of the invasive cases were associated with calcifications

Am J Surg Pathol 2011;35:1104–1113

Dysplasia at resection margins



Dysplasia at resection margins 1

- BilIN was detected in the margin in 53 % and was mainly low-grade.
- Patients with R1 resections had a significantly shorter overall survival than those with R0 resections irrespective of the presence of BilIN.
- This diagnosis does not require additional resection.

Virchows Arch. 2015 Feb;466(2):133-41.

Dysplasia at resection margins 2

- 5 patients with high-grade dysplasia at the cystic duct margin without evidence of gall bladder malignancy were identified.
- Radiologic imaging was abnormal in two patients of which one had an enlarged portacaval lymph node.
- All 5 patients underwent exploration and resection of either the cystic duct stump or the bile duct. One patient was found to have a node-positive adenocarcinoma of the cystic duct.
- Underlying cholangiocarcinoma should be considered, especially, if imaging reveals any abnormalities.

HPB 2011; 13: 865–868.

Biliary Dysplasia

- Background
- Classification of dysplastic lesions
- Gall bladder dysplasia