National University Hospital

Biliary Diseases – an Overview

Dr Calvin Koh

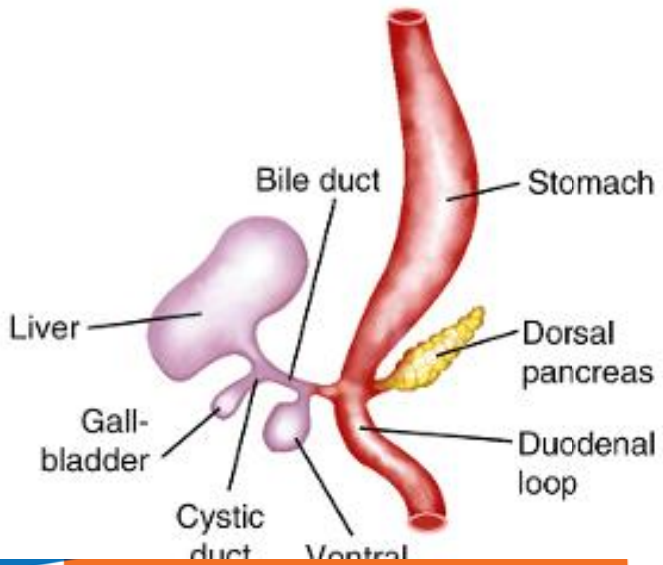
MBBS, FRCP, FASGE

Consultant, Division of Gastroenterology and Hepatology

Director, Endoscopy Centre

National University Hospital, Singapore

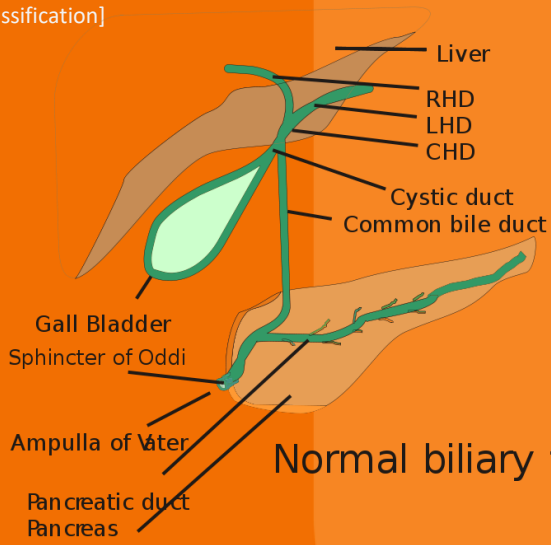
@DrCalvinKoh



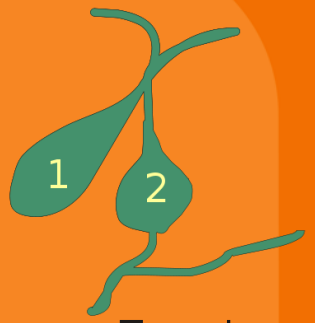
Scope

1. Development and Physiology
2. Gallstone Disease
3. Biliary Strictures and Malignancy

Development and Physiology



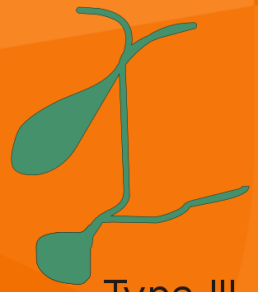
Normal biliary track



Type I



Type II



Type III



Type IV



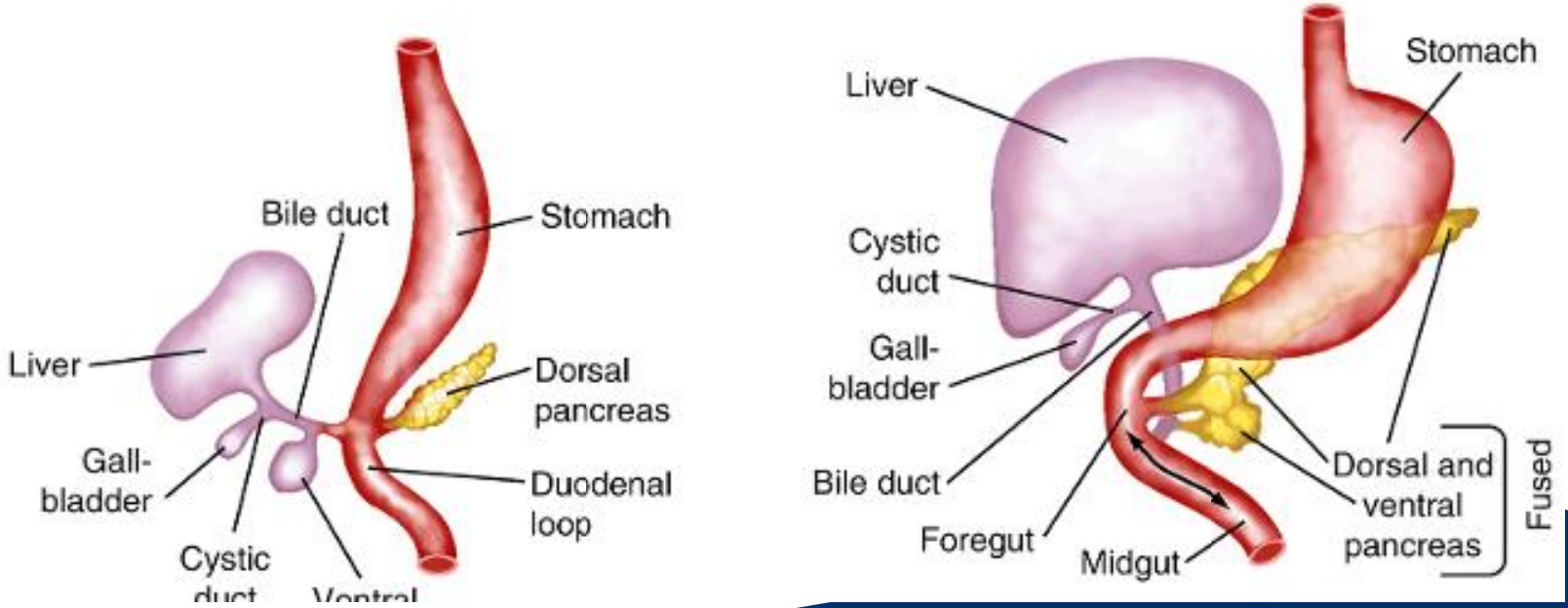
Type V

1= Gall bladder, 2= Cyst

[Insert data classification]

Embryology

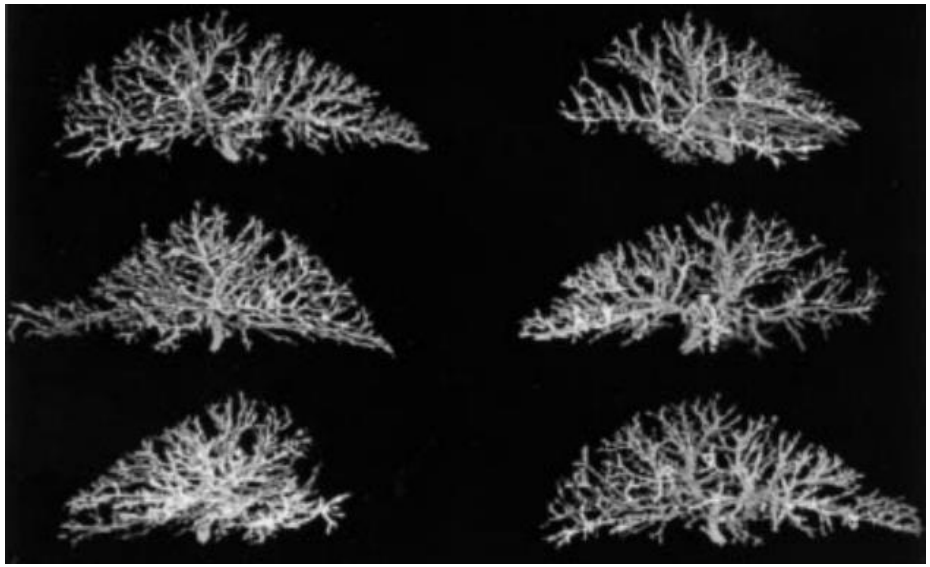
Hepatic diverticulum into a hepatic portion, which forms the liver parenchyma and the intrahepatic bile ducts; and a cystic portion, which forms the gallbladder, cystic duct, and the common bile duct. The primitive gallbladder is fully developed by 12 weeks gestation, and bile secretion begins at 16 weeks gestation.

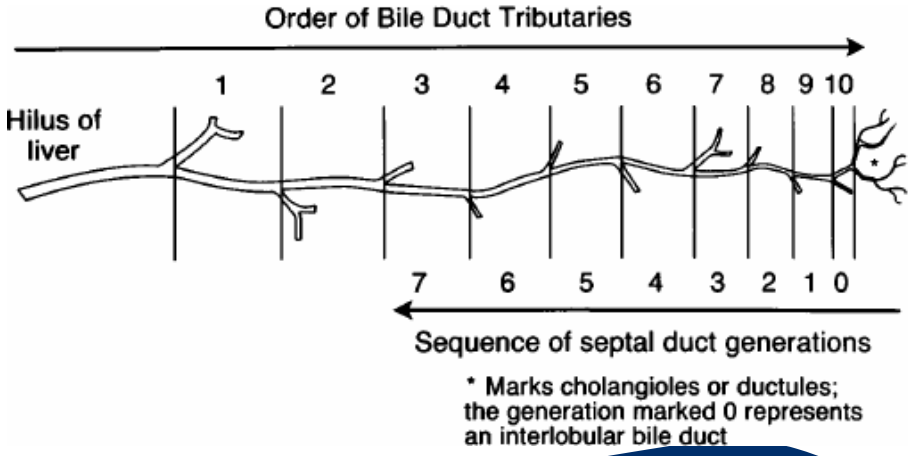


Bile Ducts

The liver has more than 2 km of bile ductules and ducts.

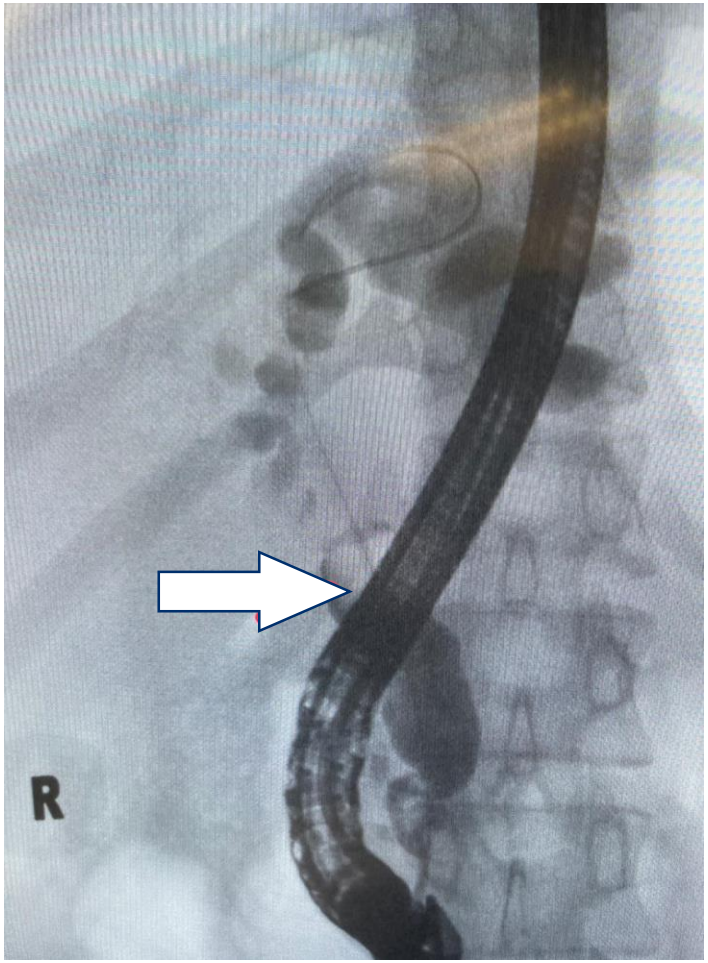
Mean internal surface of 398 cm^2 is magnified approximately 5.5-fold by the presence of microvilli and cilia at the apical surfaces of cholangiocytes that play an important role in the regulation of cholangiocyte functions.

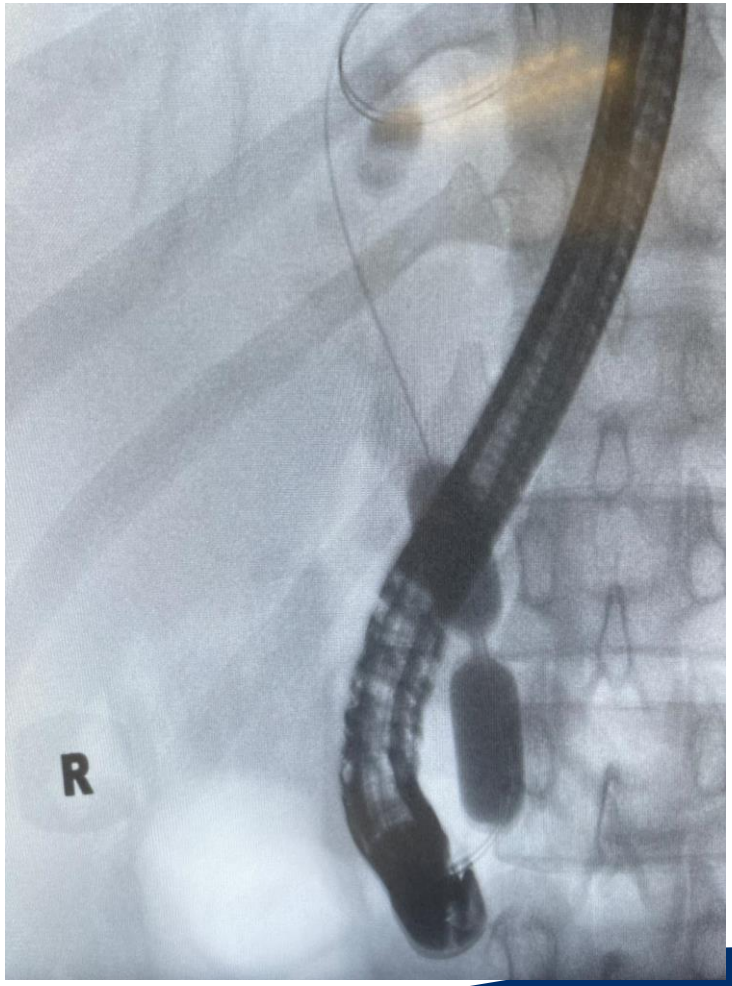




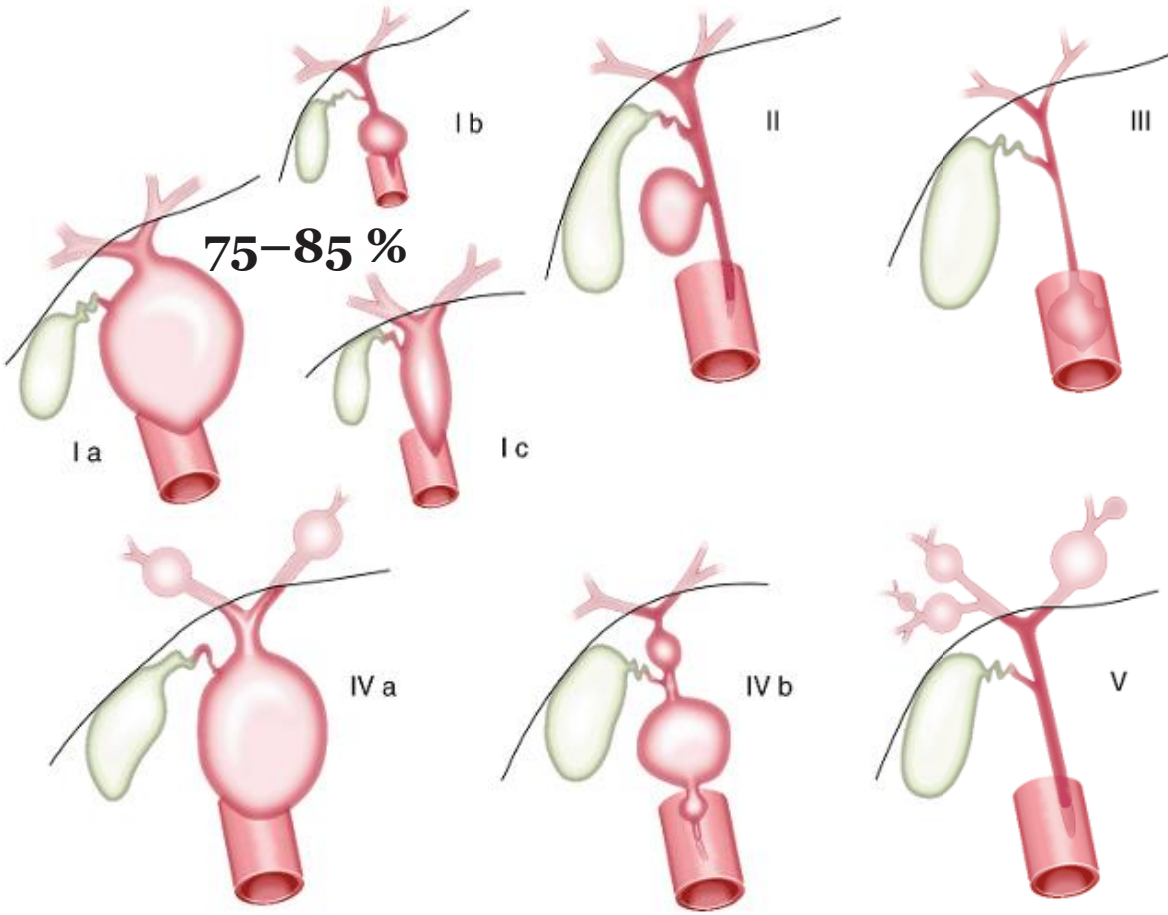
Ludwig J, Ritman EL, LaRusso NF, Sheedy PF, Zumpe G. Anatomy of the human biliary system studied by quantitative computer-aided three-dimensional imaging techniques. Hepatology. 1998 Apr;27(4):893-9.

20y F, abdominal pain, normal LFTs





Choledochal Cysts



Type Ia cysts are considered choledochal cysts in the narrow sense.

Type Ib and Ic represent segmental or diffuse fusiform dilation of the common bile duct, respectively.

Type II cysts are diverticula in the extrahepatic ducts

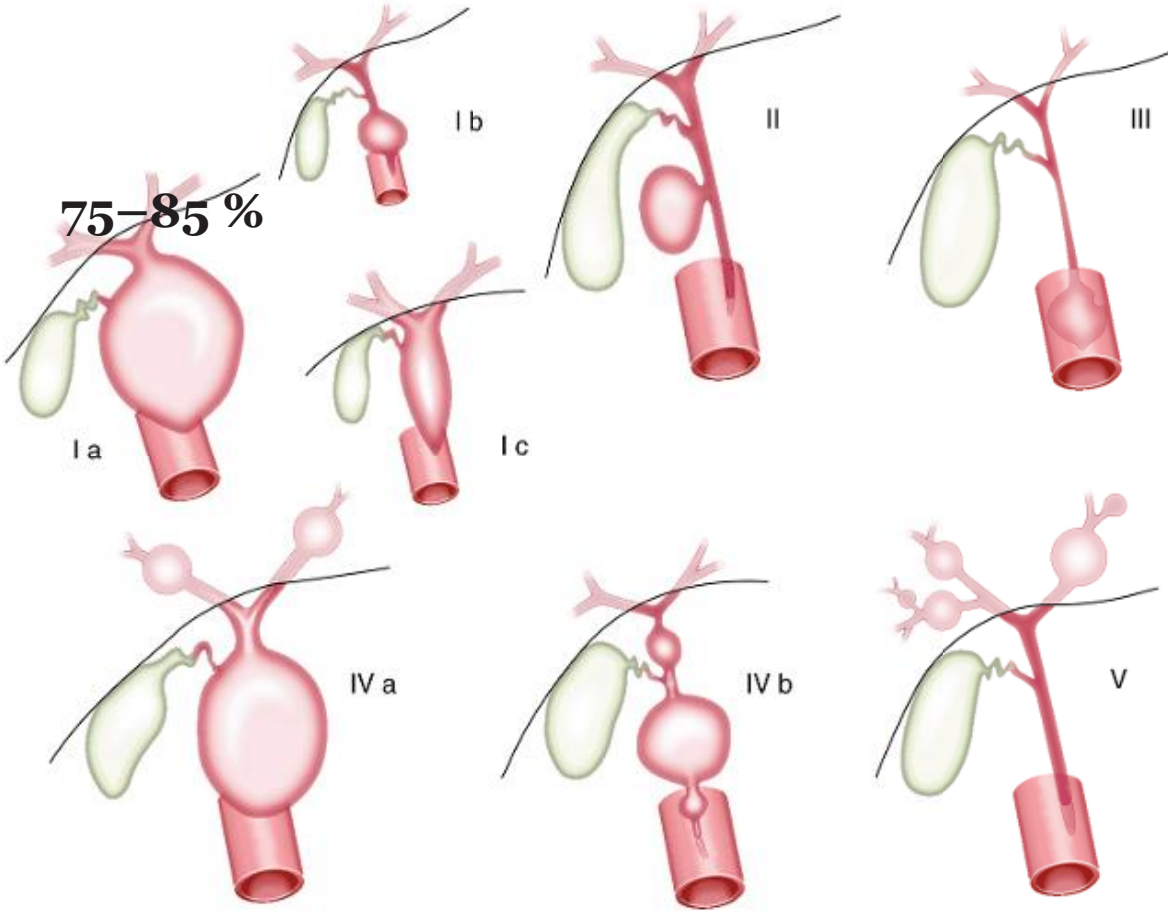
Type III cysts are choledochoceles

Type IVa cysts consist of multiple intra- and extrahepatic cysts, while type IVb are multiple cysts of the extrahepatic ducts only.

Type V cysts consist of single or multiple cystic dilations of the intrahepatic ducts "Caroli Disease"

Complications include recurrent cholangitis, stone formation, stricture formation, pancreatitis, biliary cirrhosis, liver abscess, and cyst rupture.
Risk of Malignancy including in the remnant biliary tree

Choledochal Cysts



Type I – cyst excision and biliary reconstruction (choledochojejunostomy or hepaticojejunostomy)

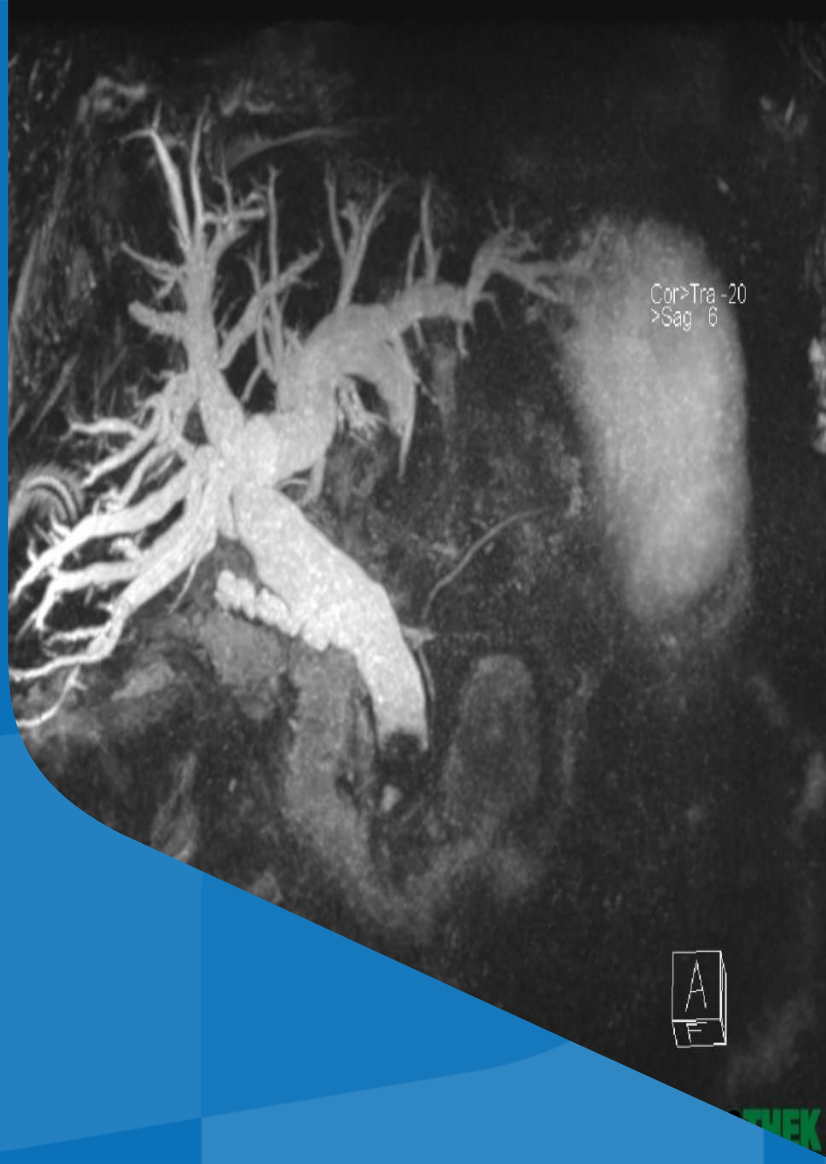
Type II – cyst excision

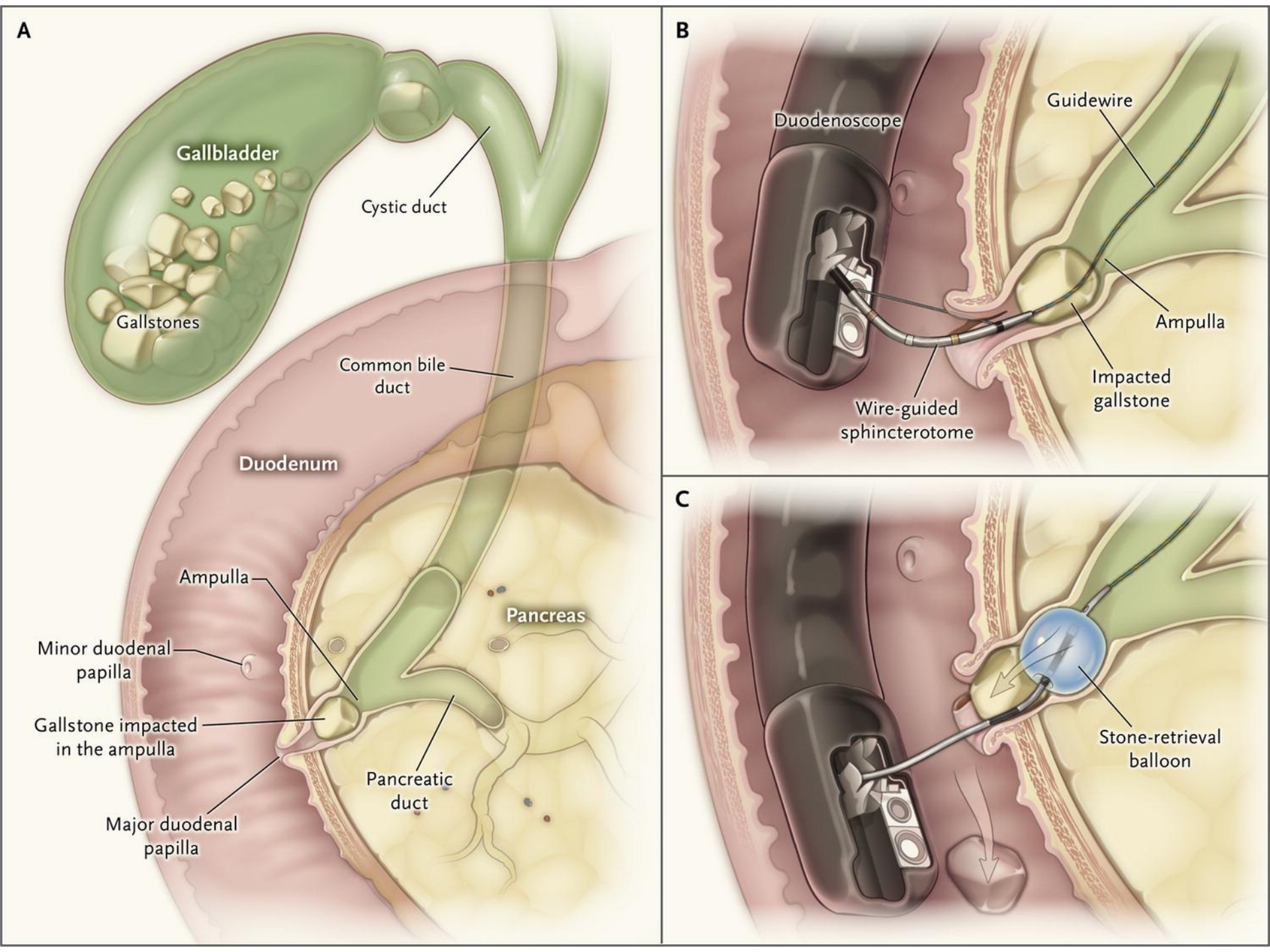
Type III cysts are choledochoceles (tx if required by biliary sphincterotomy or pancreaticoduodenectomy)

Type IVb – extrahepatic cyst excision

Type IV and V – depends on liver involvement ?resection/transplant

GALLSTONE DISEASE




A
Gallbladder
Cystic duct
Gallstones
Common bile duct
Duodenum
Ampulla
Pancreas
Minor duodenal papilla
Gallstone impacted in the ampulla
Pancreatic duct
Major duodenal papilla
B
Duodenoscope
Guidewire
Ampulla
Impacted gallstone
Wire-guided sphincterotome
C
Stone-retrieval balloon

Who gets an ERCP?



GUIDELINE





The role of endoscopy in the evaluation of suspected choledocholithiasis

This is one of a series of statements discussing the use of GI endoscopy in common clinical situations. The Standards of Practice Committee of the American Society for Gastrointestinal Endoscopy prepared this text. In preparing this guideline, a search of the medical literature was performed by using PubMed. Additional references were obtained from the bibliographies of the identified articles and from recommendations of expert consultants. When few or no data exist from well-designed prospective trials, emphasis is given to results of large series and reports from recognized experts. Guidelines for appropriate use of endoscopy are based on a critical review of the available data and expert consensus at the time that the guidelines are drafted. Further controlled clinical studies may be needed to clarify aspects of this guideline. This guideline may be revised as necessary to account for changes in technology, new data, or other aspects of clinical practice. The recommendations were based on reviewed studies and were graded on the strength of the supporting evidence (Table 1).[1]

This guideline is intended to be an educational device to provide information that may assist endoscopists in

from indiscriminant and/or invasive biliary evaluation should also be minimized. This guideline addresses the role of endoscopy in patients with suspected choledocholithiasis.

INITIAL EVALUATION

Choledocholithiasis is most commonly suspected in the scenarios of symptomatic cholelithiasis and acute biliary pancreatitis (ABP), with other presentations such as de novo bile duct stones in the postcholecystectomy patient occurring less often. The initial evaluation of suspected choledocholithiasis should include serum liver biochemical tests (eg, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, and total bilirubin) and a transabdominal ultrasound (US) of the right upper quadrant. Fractionation of bilirubin can be considered in clinical scenarios in which isolated indirect hyperbilirubinemia (eg, Gilbert syndrome) may be present.

Liver biochemical tests may have the most utility in excluding the presence of CBD stones; the negative predictive value of completely normal liver biochemical test

GASTROINTESTINAL ENDOSCOPY Volume 71, No. 1 : 2010: p1-9

Initial Evaluation of Suspected Choledocholithiasis

"Initial evaluation of suspected choledocholithiasis should include serum **liver biochemical tests** and a transabdominal **ultrasound** (US)

mean bilirubin level in series of patients with choledocholithiasis has been reported at 1.5 to 1.9 mg/dL, and only a minority (one third or less) of patients have a bilirubin level of 4 mg/dL or higher

Transabdominal ultrasound 22-55% sensitivity for CBD stone, but 77-87% sensitive for biliary dilatation, often seen in obstructive CBD stones with jaundice.



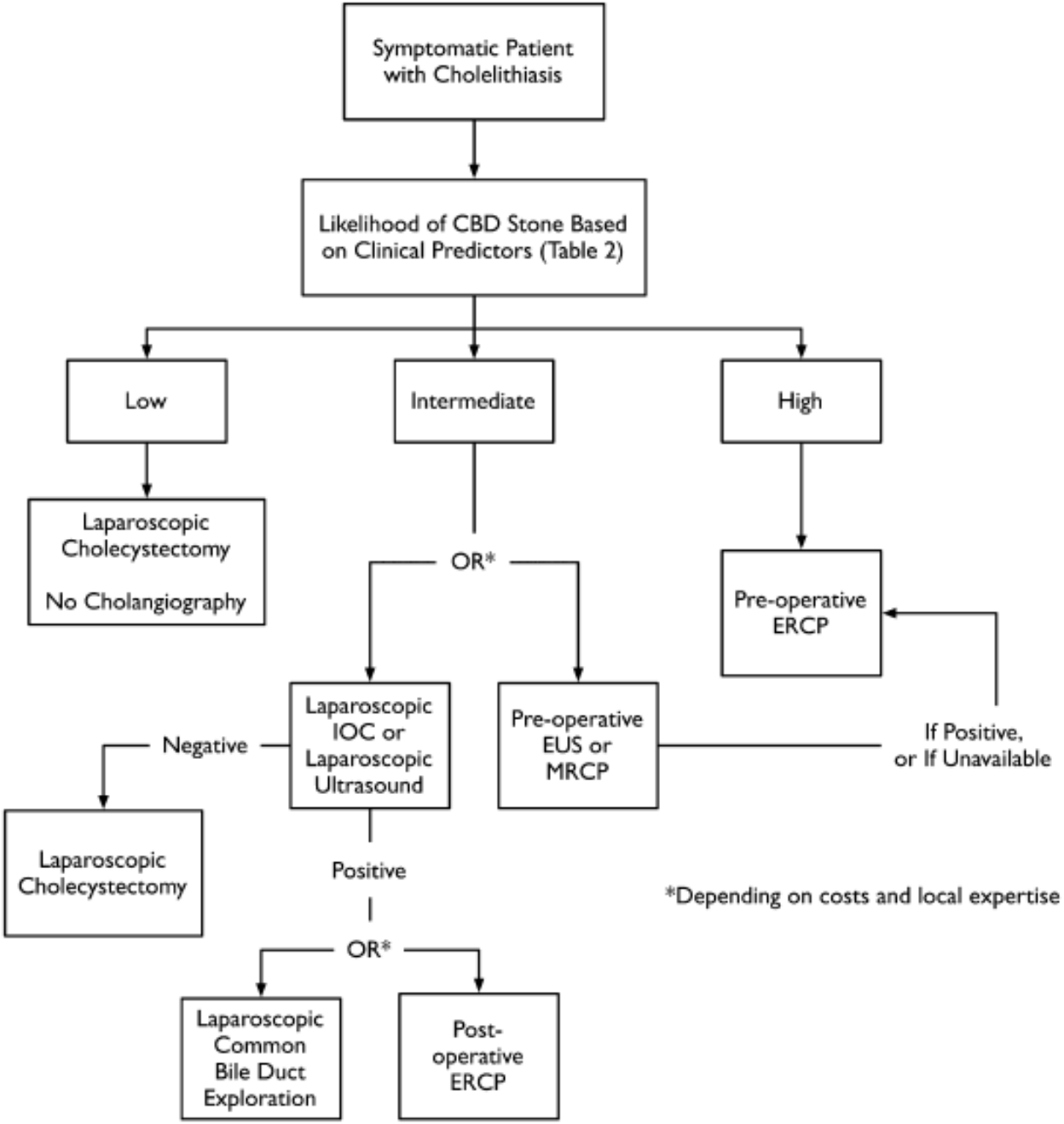
GASTROINTESTINAL ENDOSCOPY Volume 71, No. 1 : 2010: p1-9

Predictors of Choledocholithiasis

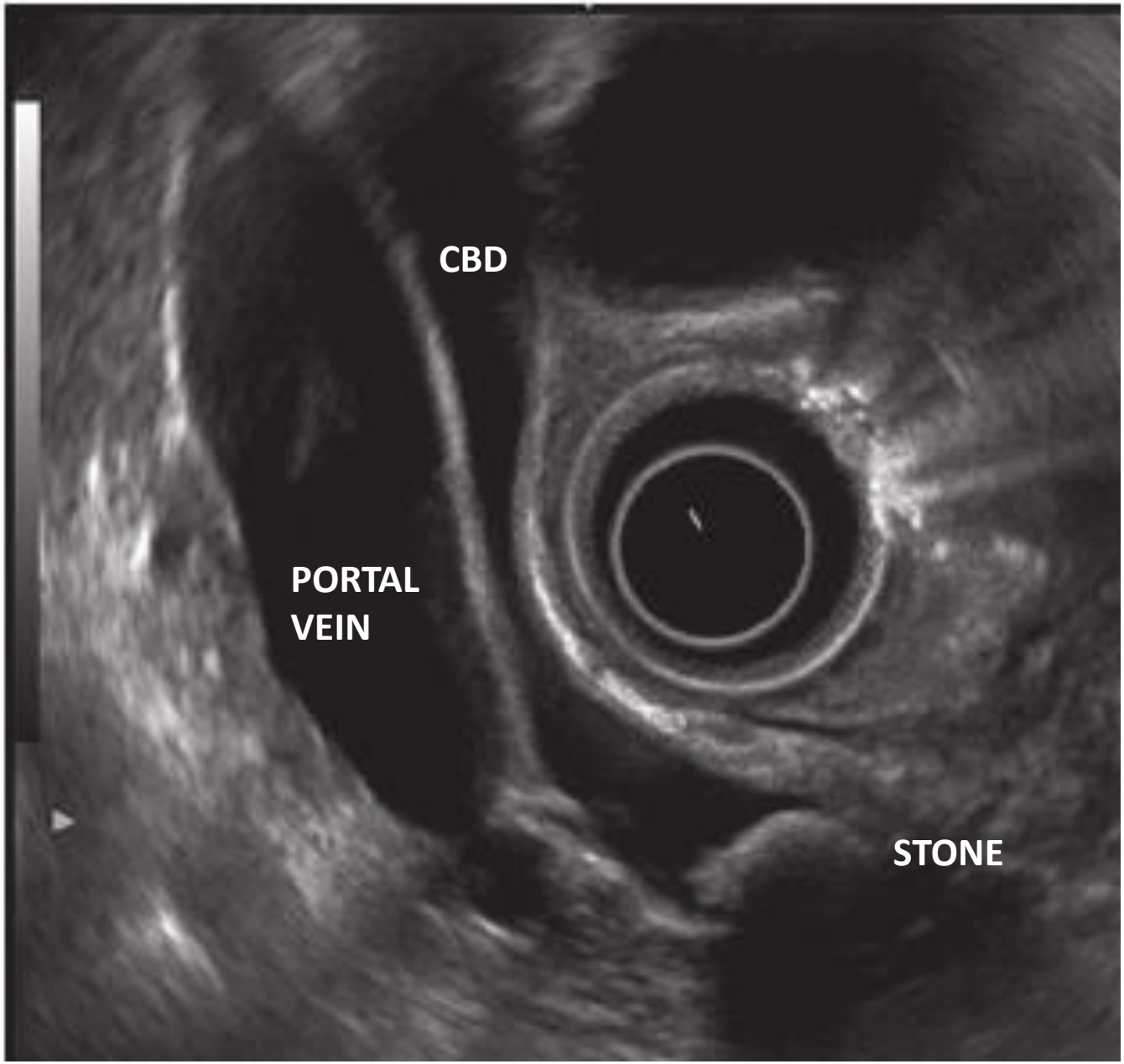
Very Strong	Strong	Moderate
CBD stone on transabdominal US	Dilated CBD on US (>6 mm with gallbladder in situ)	Age older than 55 y
Bilirubin >4 mg/dL (68 umol/L)	Blirubin 1.8-4 mg/dL (30 – 68 umol/L)	Abnormal liver biochemical test other than bilirubin
Clinical ascending cholangitis		Clinical Gallstone Pancreatitis

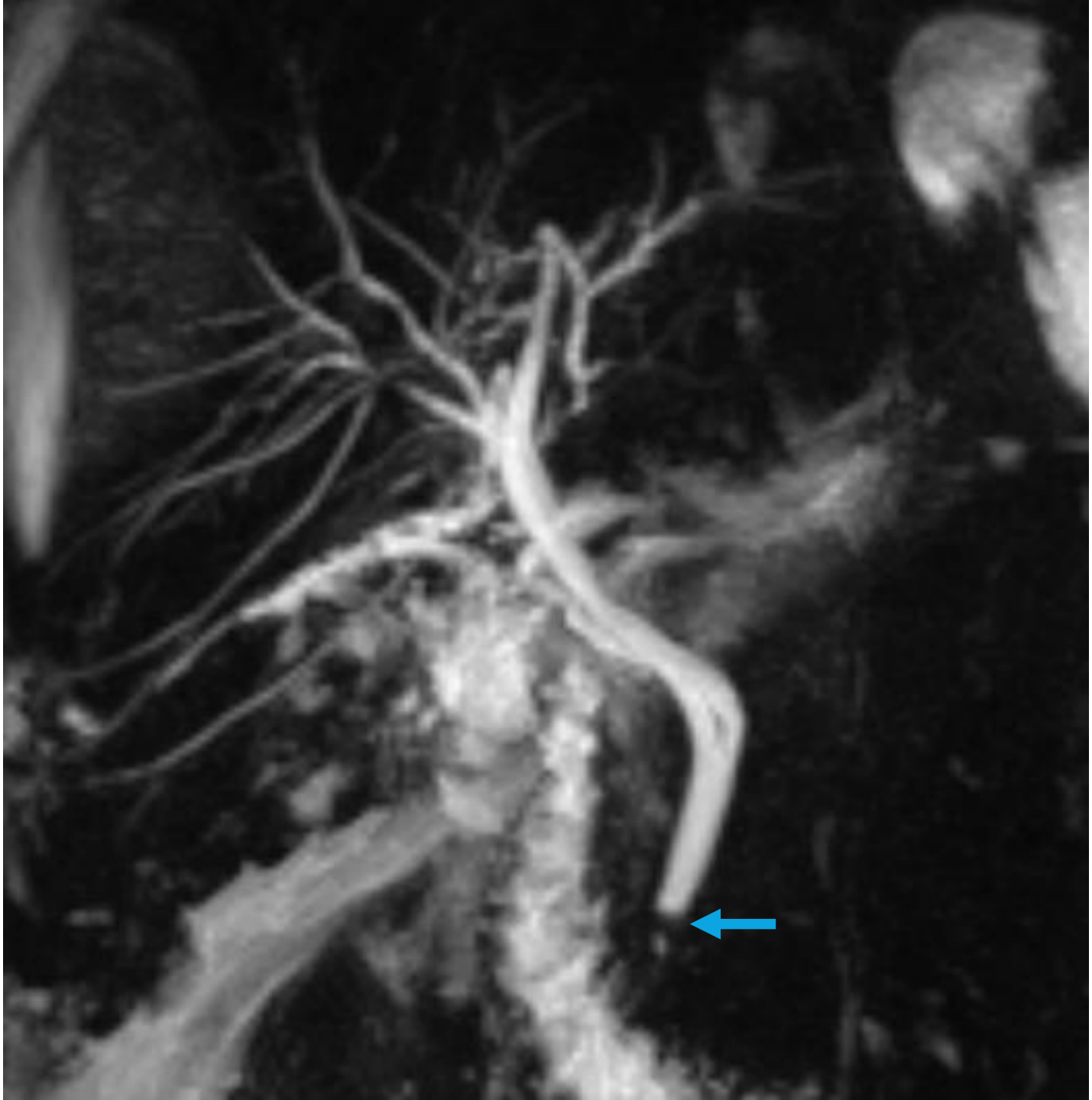
Presence of any very strong predictor	High
Presence of both strong predictors	High
No predictors present	Low
All other patients	Intermediate

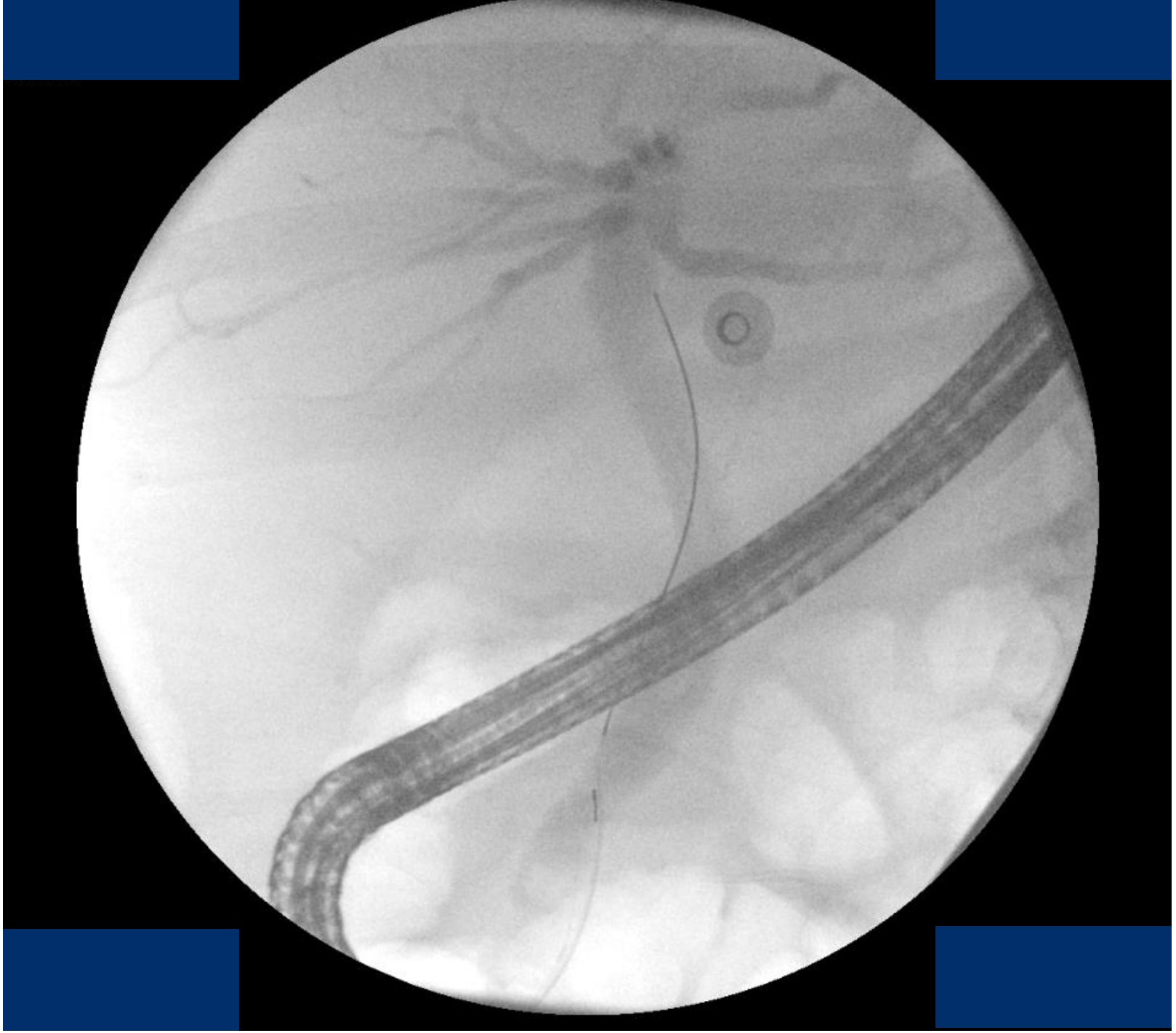
GASTROINTESTINAL ENDOSCOPY Volume 71, No. 1 : 2010: p1-9



GASTROINTESTINAL ENDOSCOPY Volume 71, No. 1 : 2010: p1-9


CBD
PORTAL
VEIN
STONE





Clinical Features to Consider

Presence of Gallbladder/gallstones in gallbladder

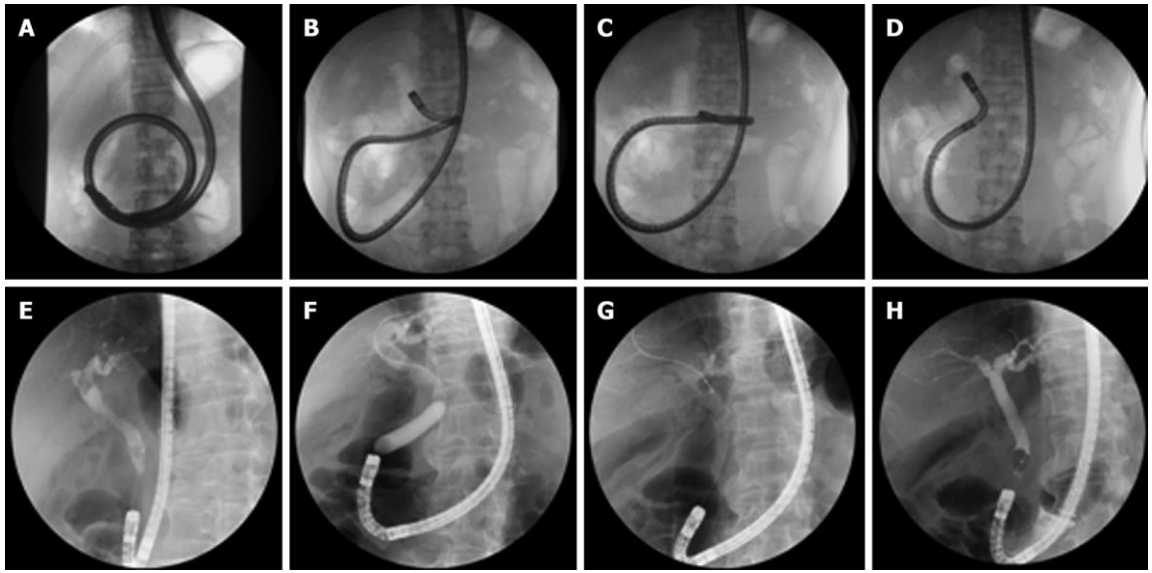
Size of CBD and previous imaging.

Contraindications to EUS/MRCP

- Multiple comorbids, non-compatible ICD/pacemaker, severe claustrophobia, inability to breath-hold etc.

Antiplatelets/Anticoagulation/NOACs

Previous gastric surgery / gastrectomy/bilroth.



Scope Yoga takes time!

The NEW ENGLAND JOURNAL of MEDICINE

CLINICAL THERAPEUTICS

John A. Jarcho, M.D., *Editor*

ERCP for Gallstone Pancreatitis

Evan L. Fogel, M.D., and Stuart Sherman, M.D.

This Journal feature begins with a case vignette that includes a therapeutic recommendation. A discussion of the clinical problem and the mechanism of benefit of this form of therapy follows. Major clinical studies, the clinical use of this therapy, and potential adverse effects are reviewed. Relevant formal guidelines, if they exist, are presented. The article ends with the authors' clinical recommendations.

"The role and timing of ERCP in patients with acute biliary pancreatitis has long been controversial.

"The timing of ERCP, inclusion criteria, methods of diagnosing biliary pancreatitis, and assessment of severity differ among studies. Perhaps as a result of these factors, results are conflicting, with some studies suggesting a benefit for selected patients undergoing ERCP and others showing no benefit and perhaps a worse outcome, regardless of the severity of disease

Fogel, N Engl J Med 2014;370:150-7.

Data for Early ERCP vs Conservative in Acute Biliary Pancreatitis

Table S4. Results of selected trials comparing early ERCP vs. conservative management in acute biliary pancreatitis

Trial	No. of patients		Morbidity		Mortality	
	ERCP	conservative	ERCP	conservative	ERCP	conservative
Neoptolemos (ref. 3)						
Mild	34	34	4 (12%)	4 (12%)	0	0
Severe	25	28	6 (24%)*	17 (61%)	1 (4%)	5 (18%)
Total	59	62	10 (17%)*	21 (34%)	1 (2%)	5 (8%)
Fan (ref. 4)						
Mild	34	35	6 (18%)	6 (17%)	0	0
Severe	30	28	4 (13%)*	15 (54%)	1 (3%)*	5 (18%)
Total	64	63	10 (16%)*	21 (33%)	1 (2%)	5 (8%)
Nowak (ref. 5)						
Mild	137	75	13 (9%)*	19 (25%)	1 (1%)*	4 (5%)
Severe	41	27	17 (41%)*	20 (74%)	3 (7%)*	9 (33%)
Total	178	102	30 (17%)*	39 (38%)	4 (2%)*	13 (13%)
Fölsch (ref. 6)[a]	126	112	58 (46%)	57 (51%)	14 (11%)	7 (6%)
Oria (ref. 7)						
Mild	34	31	2 (6%)	4 (13%)	0	0
Severe	17	21	10 (71%)	8 (38%)	3 (18%)	1 (5%)
Total	51	52	12 (24%)	12 (23%)	3 (6%)	1 (2%)
Zhou (ref. 8)						
Mild	13	18	0	0	0	0
Severe	7	7	1 (14%)*	5 (71%)	0	0
Total	20	25	1 (5%)*	5 (25%)	0	0
Chen (ref. 9)[b]	21	32	1 (5%)	6 (19%)	0	2
Tang (ref. 10)[b]	30	30	1 (3%)	3 (10%)	0	2

a: data not provided according to predicted severity of pancreatitis; b: all patients were predicted severe pancreatitis; *p<0.05.

Fogel, N Engl J Med 2014;370:150-7.

Table S5. Meta-analyses and Systematic Reviews of Early ERCP vs conservative therapy in acute biliary pancreatitis: complications

Review	Predicted Severity of Pancreatitis		Benefit of early ERCP intervention?	
	mild	severe	mild	Severe
Sharma (ref. 11)	*ERCP 25% vs conservative 38.2%, RRR 34.6%, p<0.001		*yes	
Ayub (ref. 12)	OR 4.64 (0.22, 98.12)[+]; P=0.32	OR 0.27 (0.14, 0.53); P=0.00011	no	yes
Moretti (ref. 13)	RD 1.8% (-5.6%, 9.3%); P=0.6	RD 38.5% (-53%, -23.9%); P<0.0001	no	yes
Petrov (ref. 14)	RR 0.86 (0.62, 1.19); p=0.36	RR 0.82 (0.32, 2.10); p=0.68	no	no
Uy (ref. 15)	RR 0.88 (0.62, 1.24); p=0.47	RR 1.12 (0.79, 1.60); p=0.52	no	no
Tse (ref. 16)	Local Atlanta[@]: RR 0.99 (0.52, 1.90) Authors[^]: RR 1.23 (0.62, 2.45) Systemic Atlanta: RR 0.95 (0.18, 5.02) Authors: RR 0.84 (0.42, 1.67)	 RR 0.70 (0.36, 1.39) RR 0.56 (0.27, 1.18) RR 0.52 (0.16, 1.71) RR 0.61 (0.33, 1.13)	 no no no no	 no no no no

Fogel, N Engl J Med 2014;370:150-7.

Table S6. Meta-analyses and Systematic Reviews of Early ERCP vs conservative therapy in acute biliary pancreatitis: mortality

Review	Predicted Severity of Pancreatitis		Benefit of early ERCP intervention?	
	mild	severe	mild	severe
Sharma (ref. 11)	*ERCP 5.2% vs conservative 9.1%, RRR 42.9%, p<0.05		*yes	
Ayub (ref. 12)	OR 0.75 (0.35, 1.62)[+]; P=0.47	OR 0.62 (0.27, 1.41); P=0.25	no	no
Moretti (ref. 13)	RD 0	RD 4.3% (-16, 7.5); P<0.24	no	no
Petrov (ref. 14)	RR 1.90 (0.25, 14.55); p=0.53	RR 1.28 (0.20, 8.06); p=0.80	no	no
Uy (ref. 15)	RR 4.53 (0.22, 92.88); p=0.33	RR 2.70 (0.80, 9.17); p=0.11	no	no
Tse (ref. 16)	RR 4.53 (0.22, 92.88); p=0.33	RR 0.64 (0.26, 2.32; p=0.65	no	no

Fogel, N Engl J Med 2014;370:150-7.

LEARNING POINT

1. **In patients with biliary pancreatitis, ERCP can be delayed unless there is evidence of clinical decompensation or acute cholangitis.**
2. **In patients with stable or improving disease in the presence of choledocholithiasis, ERCP can be deferred.**

Table 1. Indications and Contraindications for ERCP in Patients with Acute Biliary Pancreatitis.

Indications

Suspected bile-duct stones as the cause of pancreatitis established clinically, and one of the following:

- Cholangitis (fever, jaundice, sepsis)
- Persistent biliary obstruction (conjugated bilirubin level >5 mg/dl [86 μmol per liter])
- Clinical deterioration (worsening pain, increasing white-cell count, worsening vital signs)
- Stone detected in the common bile duct on imaging

Contraindications

Absolute

- Unstable medical condition precluding safe administration of moderate sedation or general anesthesia
- Decision by competent patient not to provide consent for the procedure
- Endoscopist with inadequate training in ERCP

Relative (may be overcome)

- Anatomical condition (gastroduodenal disease or surgical alteration) that would impede endoscopic access to the major papilla; may be overcome in the case of a long Roux limb, for example, with the use of modified equipment and accessories
- Clinically significant or uncorrectable coagulopathy; may be overcome, since a biliary stent can be placed without need for sphincterotomy

Fogel, N Engl J Med 2014;370:150-7.

When to assess for CBD stones before cholecystectomy?
Key Points:

"Current practice guidelines endorsed by gastroenterological and surgical societies recommend stratifying patients to high likelihood, intermediate likelihood, or low likelihood categories for choledocholithiasis.

High
- >50% chance
  - Straight to ERCP

Intermediate
- 10-50%
  - MRCP/EUS both ~95% sensitivity

Low
- <10%
  - Straight to lap cholecystectomy

Direct Cholecystectomy with Intro-Op Cholangiogram is an option

"Local resources and technical expertise in endoscopic and surgical management should dictate the optimal management strategy in patients with an intermediate risk for choledocholithiasis

Yang D, Yachimski P, AGA Institute Series: Focus on Enhancing High- Value Care When does assessment for bile duct stones need to be performed prior to cholecystectomy for calculus gallbladder disease?, Clinical Gastroenterology and Hepatology (2017), doi: 10.1016/ j.cgh.2017.06.045

Pregnancy and CBD Stone?

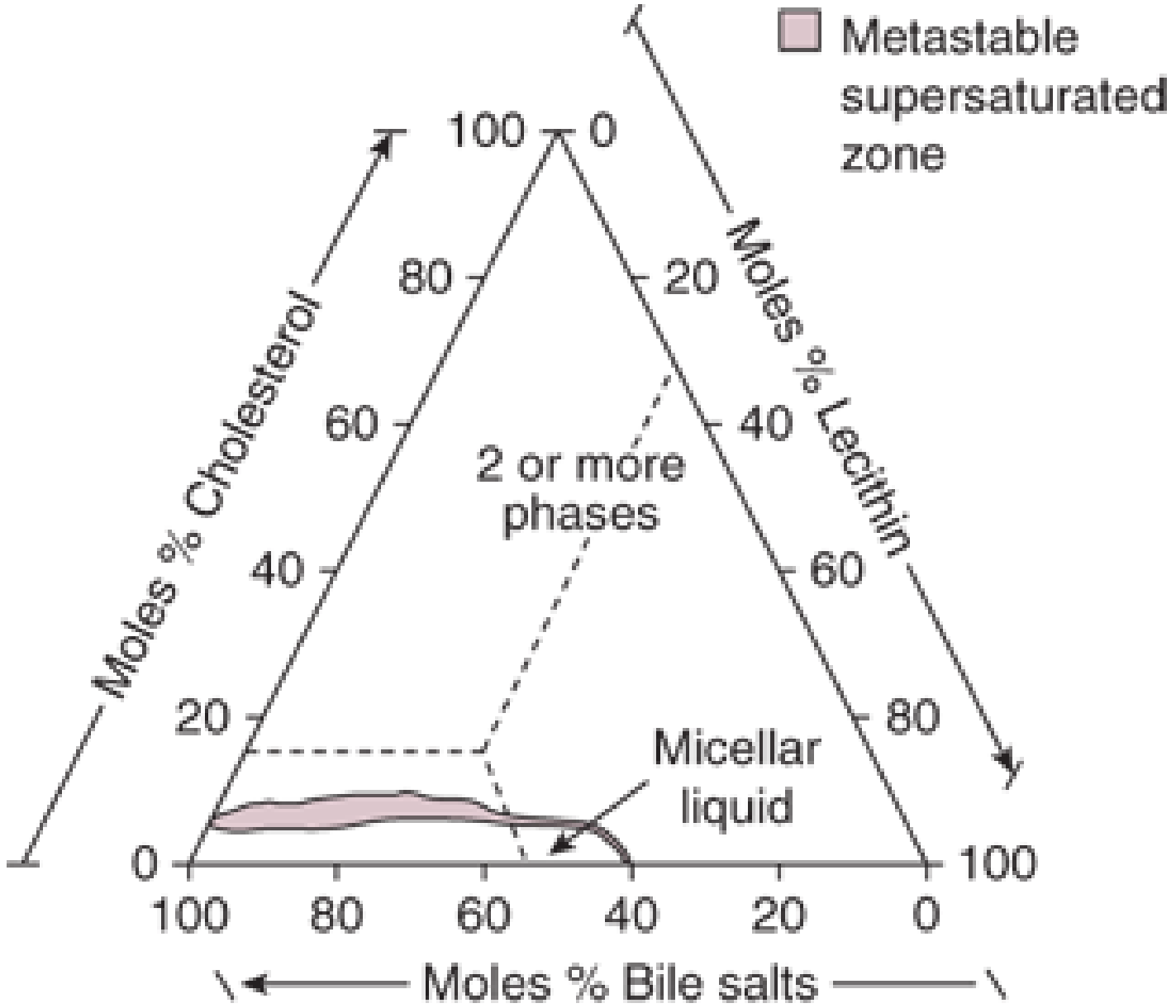
The best time for operative intervention is in the **second trimester of pregnancy**

a) when the risk profile to the fetus is best – 1st trimester teratogenicity, 3rd trimester preterm labour

b) limited technical problems associated with the enlarging uterus.

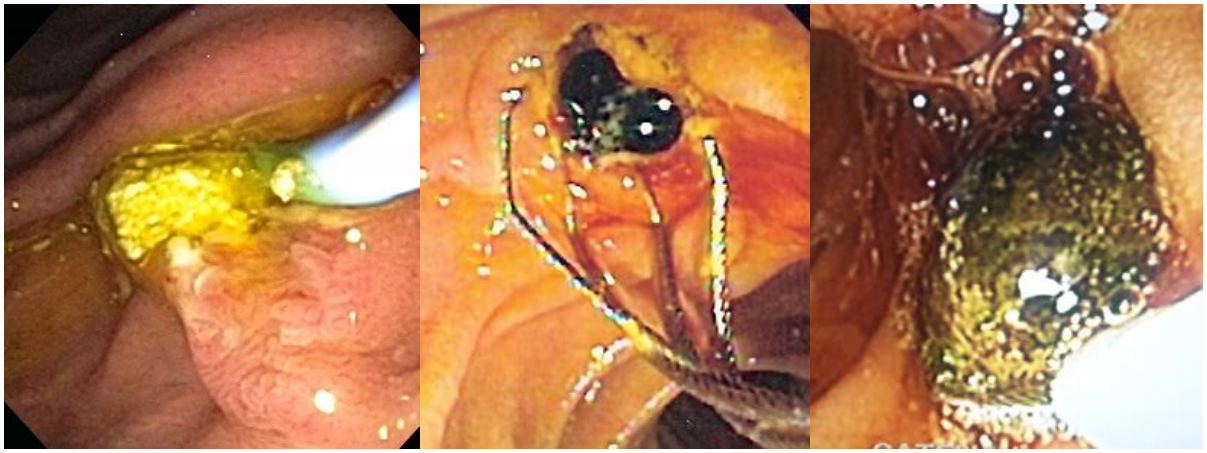


The patient would have a high risk of recurrence of her gallstone pancreatitis in the third trimester if cholecystectomy is deferred.



Source: Brunicardi FC, Brandt ML, Andersen DK, Billiar TR, Dunn DL, Hunter JG, Matthews JB, Pollock RE: *Schwartz's Principles of Surgery: ABSITE and Board Review, 9th Edition:* http://www.accesssurgery.com
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Stones



Type	Cholesterol	Black Pigment	Brown Pigment
Location	Gallbladder, Ducts	Gallbladder, Ducts	Ducts
Major Constituents	Cholesterol	Bilirubin pigment polymer	Calcium Bilirubinate
Cholesterol %	>70%	<30%	30-70%
Consistency	Crystalline with nucleus	Hard	Soft, friable
% Radio opaque	15%	60%	0%
Associations		Hemolysis, Alcohol, Crohn's, Cirrhrosis	Infection

Diagnosis : Charcot's triad

RUQ pain, fever, jaundice.

High specificity (95.9%)

But low sensitivity (26.4%)

Also present in 11.9% of acute cholecystitis

Kiriyama et al. J Hepatobiliary Pancreat Sci (2012)

Tokyo Guidelines (TG18/13) criteria (updated 2018)

J Hepatobiliary Pancreat Sci (2018) 25:31–40
DOI: 10.1002/jhbp.509

GUIDELINE

Tokyo Guidelines 2018: initial management of acute biliary infection and flowchart for acute cholangitis

Fumihiko Miura · Kohji Okamoto · Tadahiro Takada · Steven M. Strasberg · Horacio J. Asbun · Henry A. Pitt · Harumi Gomi · Joseph S. Solomkin · David Schlossberg · Ho-Seong Han · Myung-Hwan Kim · Tsann-Long Hwang · Miin-Fu Chen · Wayne Shih-Wei Huang · Seiki Kiriyama · Takao Itoi · O. James Garden · Kui-Hin Liau · Akihiko Horiguchi · Keng-Hao Liu · Cheng-Hsi Su · Dirk J. Gouma · Giulio Belli · Christos Dervenis · Palepu Jagannath · Angus C. W. Chan · Wan Yee Lau · Itaru Endo · Kenji Suzuki · Yoo-Seok Yoon · Eduardo de Santibañes · Mariano Eduardo Giménez · Eduard Jonas · Harjit Singh · Goro Honda · Koji Asai · Yasuhisa Mori · Keita Wada · Ryota Higuchi · Manabu Watanabe · Toshiki Rikiyama · Naohiro Sata · Nobuyasu Kano · Akiko Umezawa · Shuntaro Mukai · Hiromi Tokumura · Jiro Hata · Kazuto Kozaka · Yukio Iwashita · Taizo Hibi · Masamichi Yokoe · Taizo Kimura · Seigo Kitano · Masafumi Inomata · Koichi Hirata · Yoshinobu Sumiyama · Kazuo Inui · Masakazu Yamamoto

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The author's affiliations are listed in the Appendix.

Correspondence to: Tadahiro Takada, Department of Surgery, Teikyo University School of Medicine, 2-11-1 Kaga, Itabashi-ku, Tokyo 173-8605, Japan
e-mail: t-takada@jshbps.jp

DOI: 10.1002/jhbp.509

Abstract The initial management of patients with suspected acute biliary infection starts with the measurement of vital signs to assess whether or not the situation is urgent. If the case is judged to be urgent, initial medical treatment should be started immediately including respiratory/circulatory management if required, without waiting for a definitive diagnosis. The patient's medical history is then taken; an abdominal examination is performed; blood tests, urinalysis, and diagnostic imaging are carried out; and a diagnosis is made using the diagnostic criteria for cholangitis/cholecystitis. Once the diagnosis has been confirmed, initial medical treatment should be started immediately, severity should be assessed according to the severity grading criteria for acute cholangitis/cholecystitis, and the patient's general status should be

Sensitivity 91.8%

Specificity 77.7%

Positive rate in acute cholecystitis : 5.9%

More accurate and reliable than Charcot's triad

Miura et al, J Hepatobiliary Pancreat Sci (2018) 25:31–40

TG18/TG13 Diagnostic Criteria for Acute Cholangitis

A. Systemic inflammation

A-1. Fever and/or shaking chills

A-2. Laboratory data: evidence of inflammatory response (white cell count, CRP etc)

B. Cholestasis

B-1. Jaundice (> 2mg/dL or 34 umol/L)

B-2. Laboratory data: abnormal liver function tests (ALT AST GGT ALP more than 1.5x upper limit of normal)

C. Imaging

C-1. Biliary dilatation

C-2. Evidence of the etiology on imaging (stricture, stone,stent, etc)

Suspected Diagnosis

A + B

A + C

Definite Diagnosis

A + B + C

Kiriyama et al. J Hepatobiliary Pancreat Sci (2012)
Miura et al, J Hepatobiliary Pancreat Sci (2018) 25:31–40

Severity assesment : TG18/13

Table 3 TG18/TG13 severity assessment criteria for acute cholangitis

Grade III (severe) acute cholangitis

"Grade III" acute cholangitis is defined as acute cholangitis that is associated with the onset of dysfunction at least in any one of the following organs/systems:

1. Cardiovascular dysfunction: hypotension requiring dopamine ≥5 μg/kg per min, or any dose of norepinephrine
2. Neurological dysfunction: disturbance of consciousness
3. Respiratory dysfunction: PaO_2/FiO_2 ratio <300
4. Renal dysfunction: oliguria, serum creatinine >2.0 mg/dl
5. Hepatic dysfunction: PT-INR >1.5
6. Hematological dysfunction: platelet count <100,000/mm^3

Grade II (moderate) acute cholangitis

"Grade II" acute cholangitis is associated with any two of the following conditions:

1. Abnormal WBC count (>12,000/mm^3, <4,000/mm^3)
2. High fever (≥39°C)
3. Age (≥75 years)
4. Hyperbilirubinemia (total bilirubin ≥5 mg/dl) 85umol/L
5. Hypoalbuminemia (<STD × 0.7)

Grade I (mild) acute cholangitis

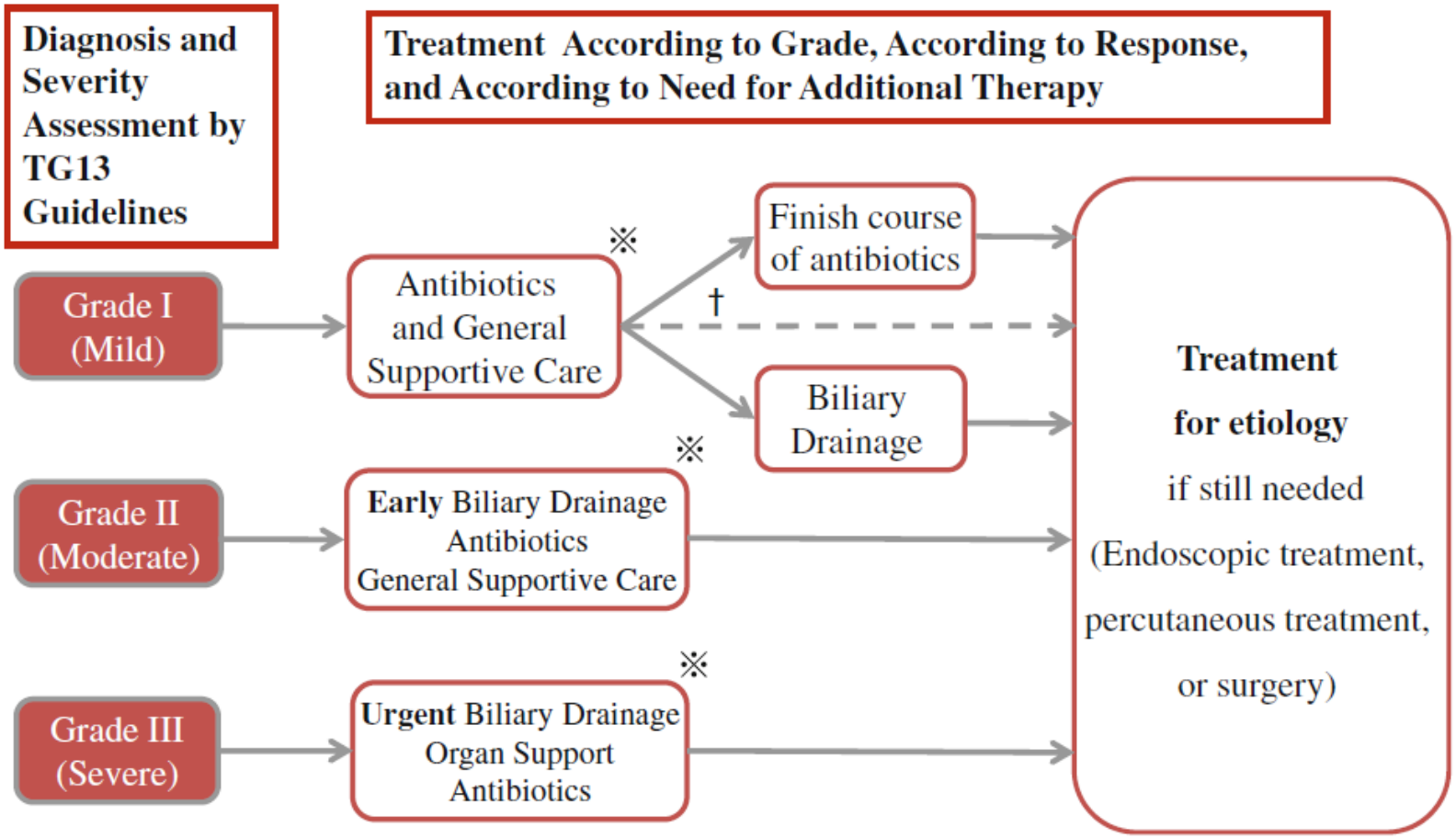
"Grade I" acute cholangitis does not meet the criteria of "Grade III (severe)" or "Grade II (moderate)" acute cholangitis at initial diagnosis

Cited from Kiriyama et al. [4]

STD lower limit of normal value

Kiriyama et al. J Hepatobiliary Pancreat Sci (2012)
Miura et al, J Hepatobiliary Pancreat Sci (2018) 25:31–40

Flowchart



※ Performance of a blood culture should be taken into consideration before initiation of administration of antibiotics. A bile culture should be performed during biliary drainage.

† Principle of treatment for acute cholangitis consists of antimicrobial administration and biliary drainage including treatment for etiology. For patient with choledocholithiasis, treatment for etiology might be performed simultaneously, if possible, with biliary drainage.

Kiriyama et al. J Hepatobiliary Pancreat Sci (2012)
Miura et al, J Hepatobiliary Pancreat Sci (2018) 25:31–40

Key Points

LFTs and US as initial evaluation

Those in intermediate risk get an MRCP /EUS

Tell the operator if post surgical anatomy (bilroth) – alters the difficulty of the procedure

In acute biliary pancreatitis, early ERCP would be indicated

a) severe cholangitis

b) persistent rising bilirubin

Pregnancy 2nd trimester is the golden window for intervention

Brown Stones = related to infections

Biliary Stricture and Malignancy



Indeterminate Biliary Stricture

"Biliary strictures in patients in whom cross sectional imaging is unrevealing (ie, without associated mass lesion) and without pathologic confirmation" - Bret Petersen *ERCP,* 2e edit Baron T et al, Elsevier 2013

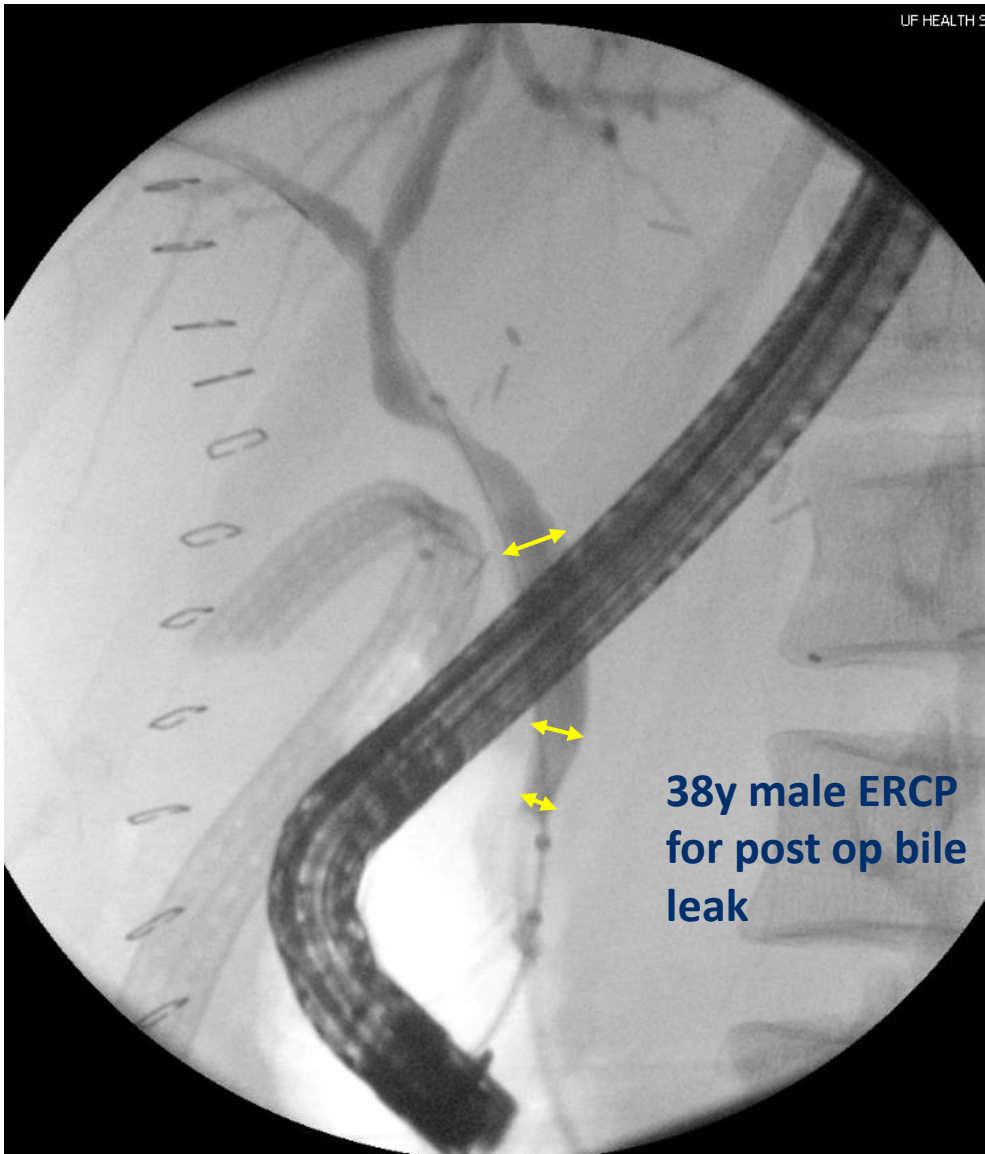
"basic work-up, including transabdominal imaging and ERCP with routine cytologic brushing, are non-diagnostic" – Victor DW *World J Gastroenterol* 2012; 18(43)

What is the CBD normal caliber?

Varies depending on the level

Generally 5-8mm

Increases with age, cholecystectomy



Not Assessed ≠Indeterminate

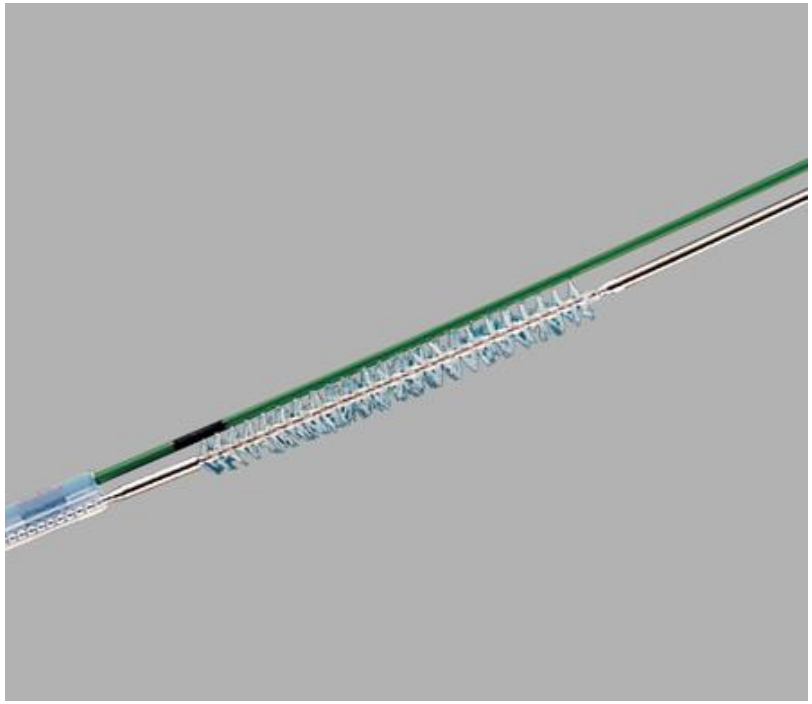


"Indeterminate" suggests some *attempt* has been made to determine the nature of the stricture.

basic work-up, including transabdominal imaging and ERCP with routine cytologic brushing, are non-diagnostic

Imaging, **NOT** cytopathology

Yield ~30-40%



A significant proportion of biliary strictures, both benign and malignant will fall into this category

Victor DW, Sherman S, Karakan T, Khashab MA. Current endoscopic approach to indeterminate biliary strictures. *World J Gastroenterol* 2012; 18(43): 6197-6205
Biliary Brush Image Cytomaxx II, Cook Medical

Case 1

62 y.o. female with a PMH significant for rheumatoid arthritis (has prev been on remicaide) who presents for an evaluation for jaundice, weight loss, and RUQ pain.

In the ED, pt was found to have a tbili of 11.7, dbili of 7.0, AST of 147, and ALT of 67. Pt has an Alk Phos of 2811 and lipase <3.

CT abd/pelvis was ordered which showed "diffuse intra and extrahepatic biliary ductal dilatation with the appearance of an intraductal soft tissue mass extending from the mid to distal common bile duct to the level of the ampulla. Further eval with ERCP and/or MRCP is recommended. Splenomegaly".





Question

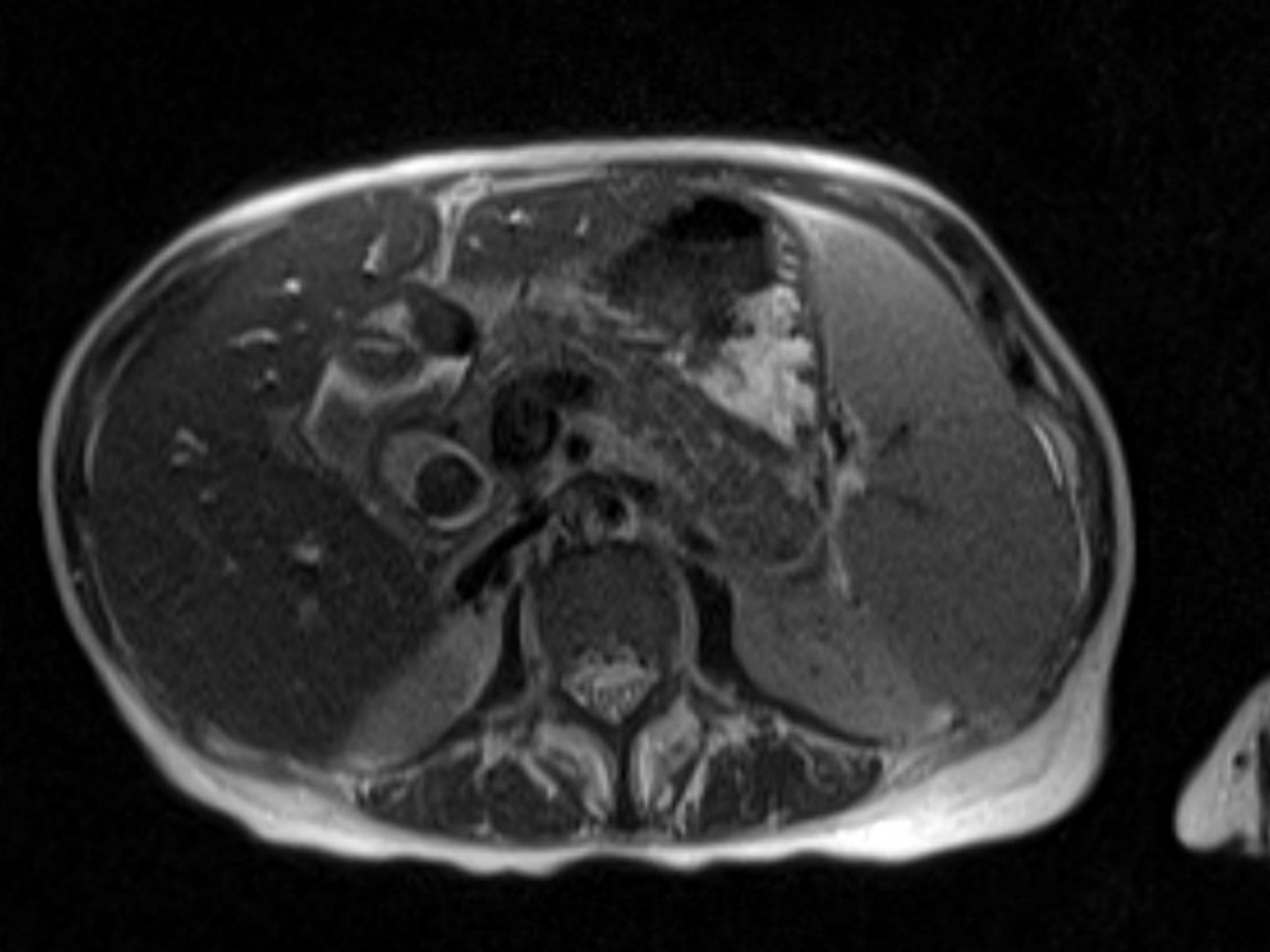
Is this an indeterminate biliary stricture?

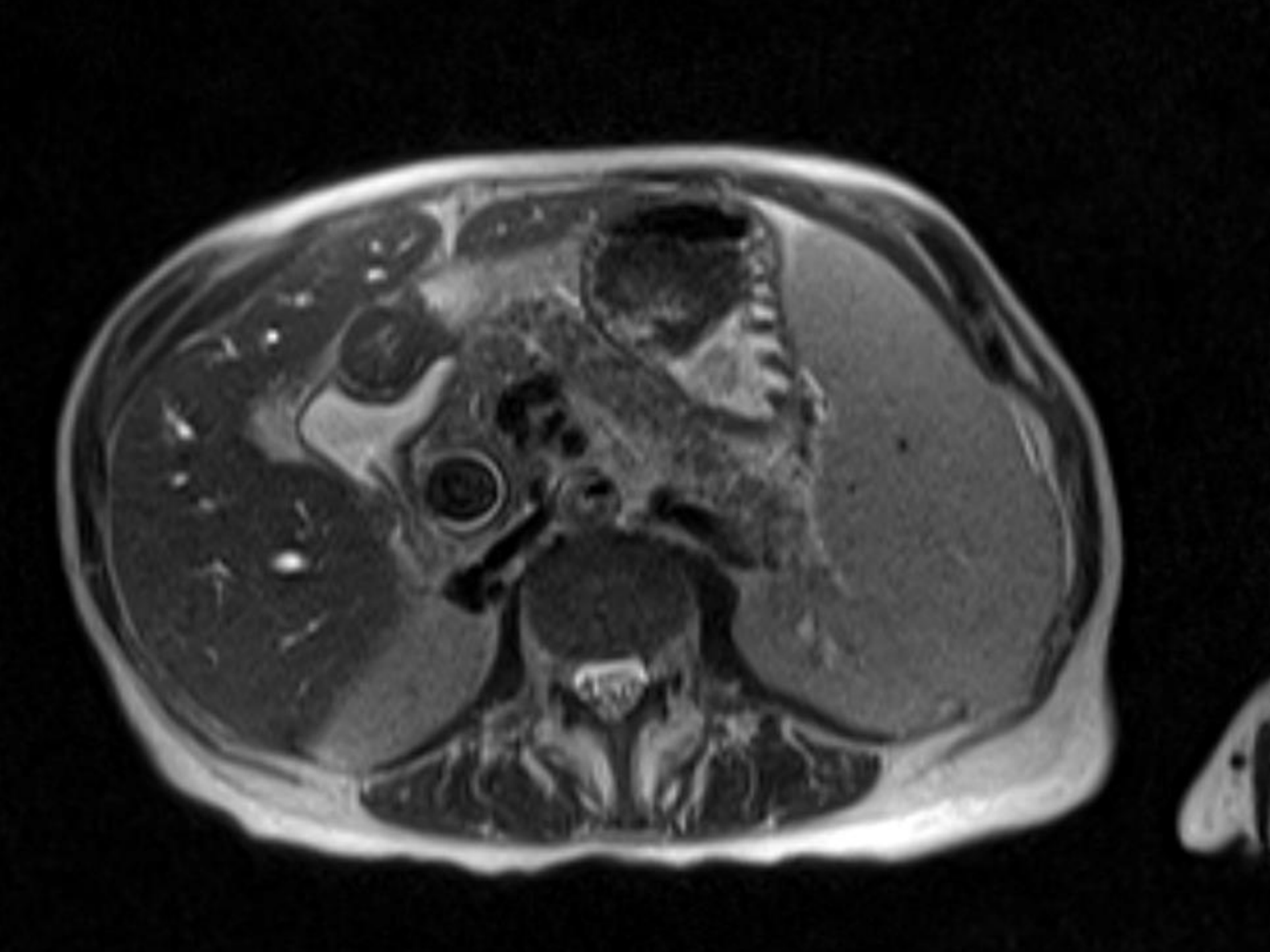
NO.

Key in this case is a detailed history.

On further questioning, patient had a cholecystectomy 8 years before for stone disease and had 2 “basket trawls” for stone removal, once around the time of the cholecystectomy and once 6 tears ago.

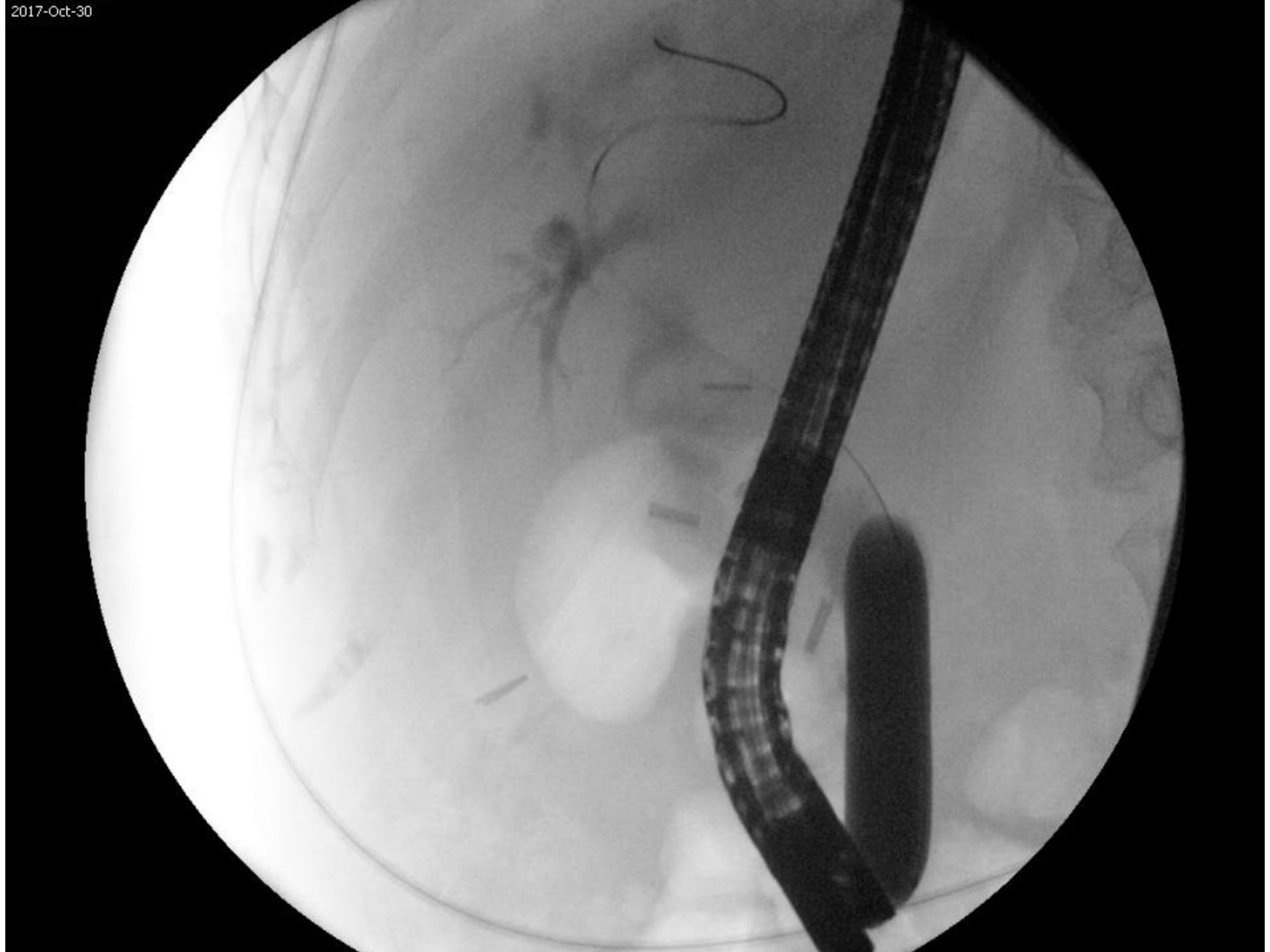
Doesn’t qualify as indeterminate stricture - inadequate biliary imaging, no further biliary evaluation.






2017-Oct-30


2017-Oct-30


2017-Oct-30

Initial Evaluation - Differentials

Malignant

Primary Cancer

- Pancreatic
- Biliary
- Hepatocellular
- Ampullary

Metastases

- Hilar lymph nodes
- Intrahepatic (to liver parenchyma)

Benign

Inflammatory

- Gallstone disease, Mirrizzi syndrome
- PSC
- Chronic Pancreatitis
- IgG4

Ischemic

- Post OLT liver transplantation
- Floxirudine chemotherapy

Traumatic

- Post op/anastamotic

Mechanical/extrinsic

- Pancreatic Pseudocyst

Initial Evaluation - Differentials

Malignant

Primary Cancer

- Pancreatic
- Biliary
- Hepatocellular
- Ampullary

Metastases

- Hilar lymph nodes
- Intrahepatic (to liver parenchyma)

Usually obvious

Benign

Inflammatory

- Gallstone disease, Mirrizzi syndrome
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Ischemic

- Post OLT liver transplantation
- Floxirudine chemotherapy

Traumatic

- Post op/anastamotic

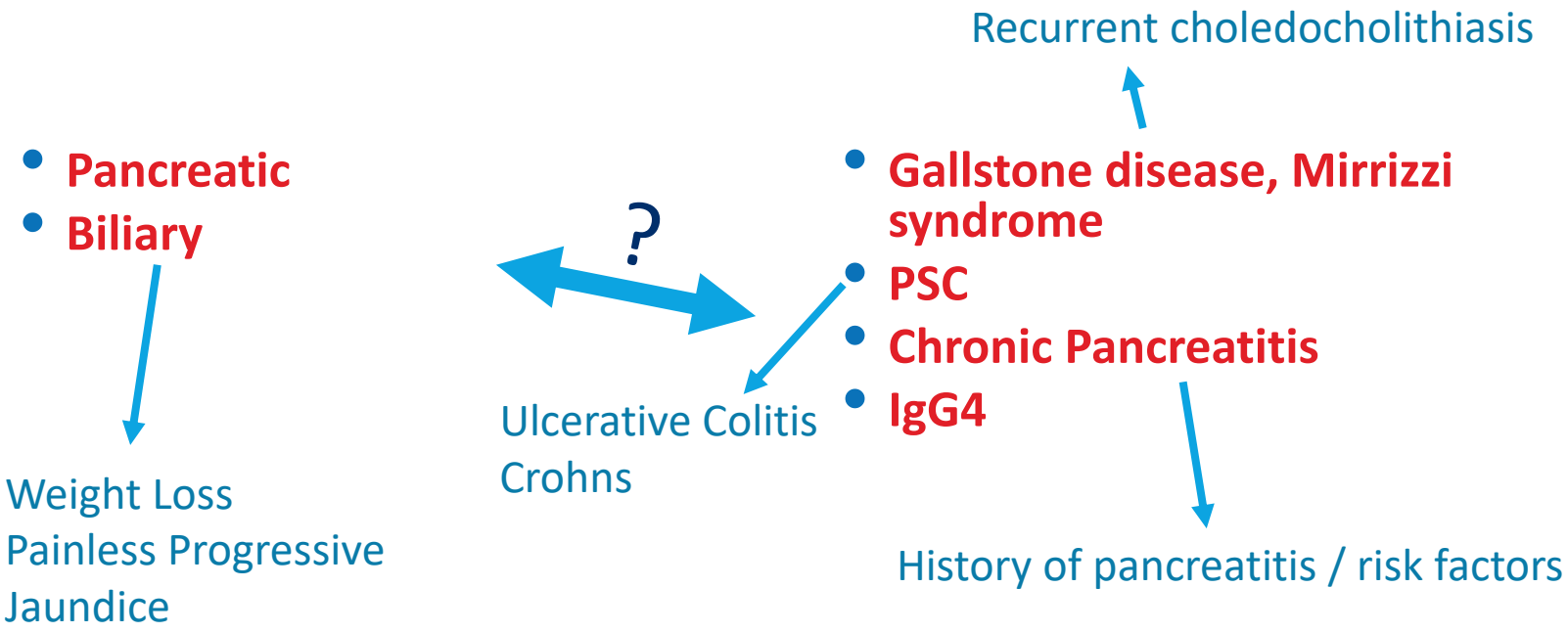
Mechanical/extrinsic

- Pancreatic Pseudocyst

Usually obvious

More commonly encountered clinical conditions

Initial Evaluation - Differentials



History and further evaluation guided by consideration of these differentials, as illustrated by the Case 1

IgG_4 disease

Besides autoimmune pancreatitis can cause:

Distal biliary strictures that mimic chronic pancreatitis or pancreatic cancer

Proximal biliary strictures mimicking sclerosing cholangitis

Generally responds to steroid therapy (HISORt)

(H) Histology suggestive of autoimmine pancreatitis

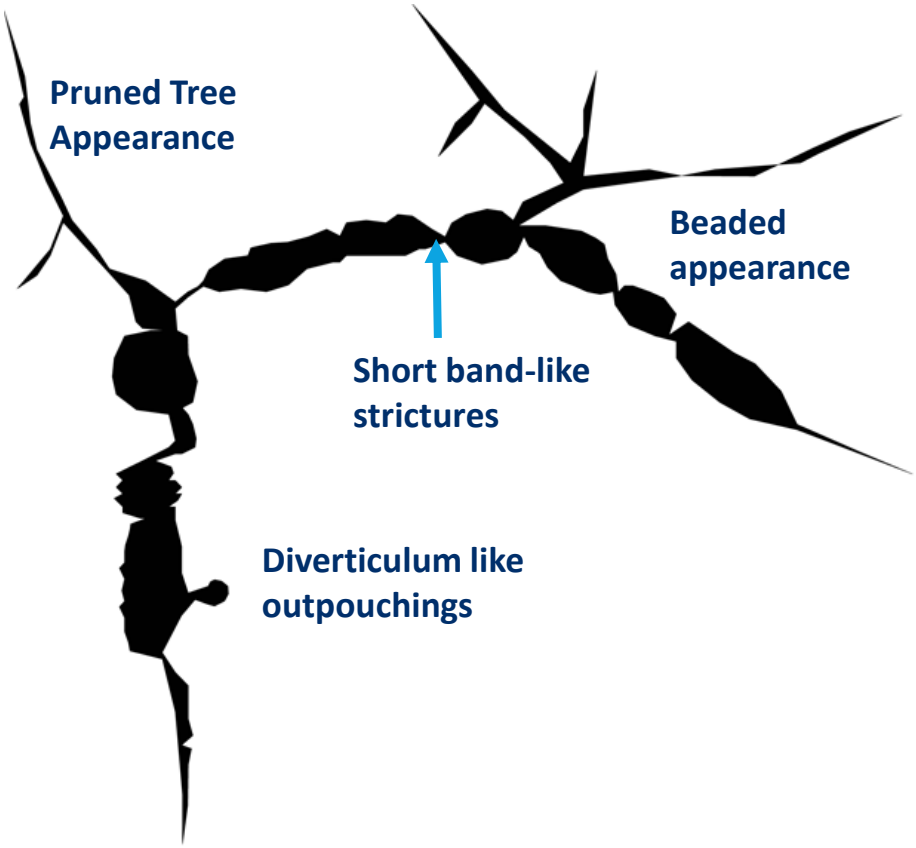
(I) Pancreatic **imaging** suggestive of autoimmine pancreatitis

(S) Serology (IgG4 ≥2 times the upper limit of normal)

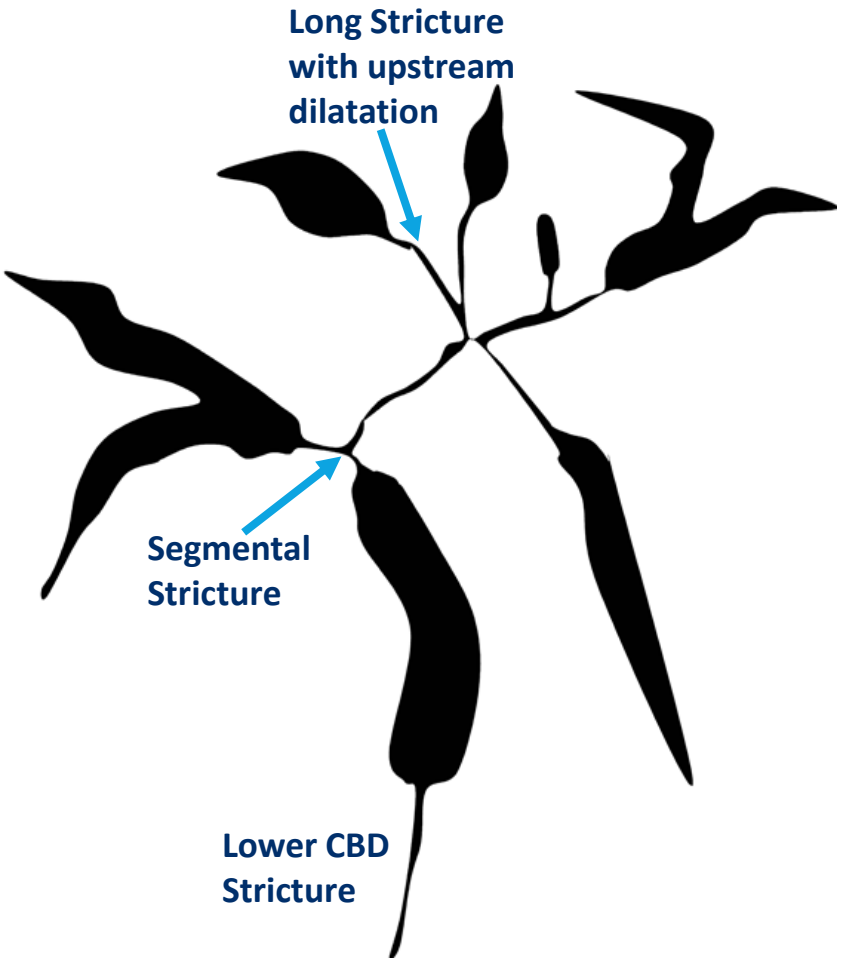
(O) Other organ involvement

Biliary strictures, parotid/lacrimal gland involvement, mediastinal lymphadenopathy, retroperitoneal fibrosis

(Rt) Response to steroid treatment - Resolution/marked improvement of pancreatic and extrapancreatic manifestations



Primary Sclerosing Cholangitis



IgG4 Cholagiopathy



Pruned-Tree Appearance
AKA
attenuation of intraparenchymal arborization

Diagram from Nakazawa et al, World J Gastroenterol 2013 19(43):7661-7670

Evaluation - Labs

Bilirubin levels don't always correlate with obstruction esp segmental obstruction.

Bilirubin classically peaks at 20mg/dL, levels above suggest some degree of hepatocellular injury which may be superimposed on obstruction.

Check INR – malabsorption of Vit K deficiency in chronic obstruction

Ca19-9 >1000 seen in cancer **OR** florid cholangitis, >100 suspicious (**if** no cholangitis or pancreatitis)

Evaluation – Imaging Overview

Non-invasive

- US
- CT
- MRCP → Best non-invasive test to evaluate biliary stricture
  Also provides a roadmap for invasive imaging to direct tissue sampling
  80% sensitivity and 87% specificity for PSC (Berstad, CGH2006)

Invasive

- EUS/FNA
- ERCP
- PTC

Both diagnostic and therapeutic – can sample and stent
Run the risk of cholangitis – introduce contrast into an obstructed system

Cholangiography: Benign vs Malignant Strictures

Malignant strictures tend to

- Progress over time
- Have abrupt shelf-like borders
- Be longer (length >10-14mm)
- Have intraductal polypoid/nodular areas

Cholangiography alone has 66% sensitivity for malignant and 51% specificity for benign strictures

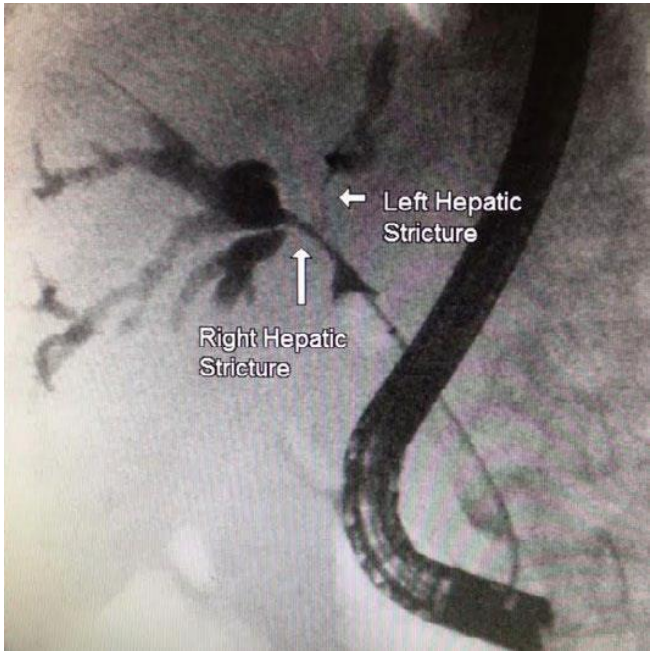




Image from Boston Scientific
http://www.bostonscientific.com/content/dam/bostonscientific/endo/portfolio-group/SpyGlass%20DS/Providing-a-Definitive-Diagnosis-of-Cholangiocarcinoma-SpyGlass-DS-System-Case-Study-By-Dr-%20Khosravi.pdf

Comparing Imaging Modalities

Table 6. Diagnostic accuracy of CT, MRI and ultrasound for assessment of ductal extent of the tumour

Source	Ductal extent correct/total patients (accuracy, %)
CT	
Akamatsu et al 2010 [12]	21/22 (95)
Kim et al 2010 [6]	16/20 (80)
Chen et al 2009 [18]	72/75 (96)
Watadani et al 2008 [19]	12/13 (92)
Endo et al 2007 [20]	13/15 (87)
Lee et al 2006 [22]	46/55 (84)
Unno et al 2007 [23]	17/24 (71)
Cho et al 2007 [5]	9/14 (64)
Summary estimates (95% CI)	86 (77–92)
MRI	
Masselli et al 2008 [9]	12/15 (80)
Kim et al 2010 [6]	15/20 (75)
Cho et al 2007 [5]	10/14 (71)
Ultrasound	
Looser et al 1992 [7]	13/22 (59)
Hann et al 1997 [8]	32/39 (82)

CI, confidance interval.

Study numbers are not large

CT and MR reasonably helpful

Later CT scans tend to report better results – better tech

Ruys AT et al, Brit J Radiol 2012 85:1255-1262

ERCP technique

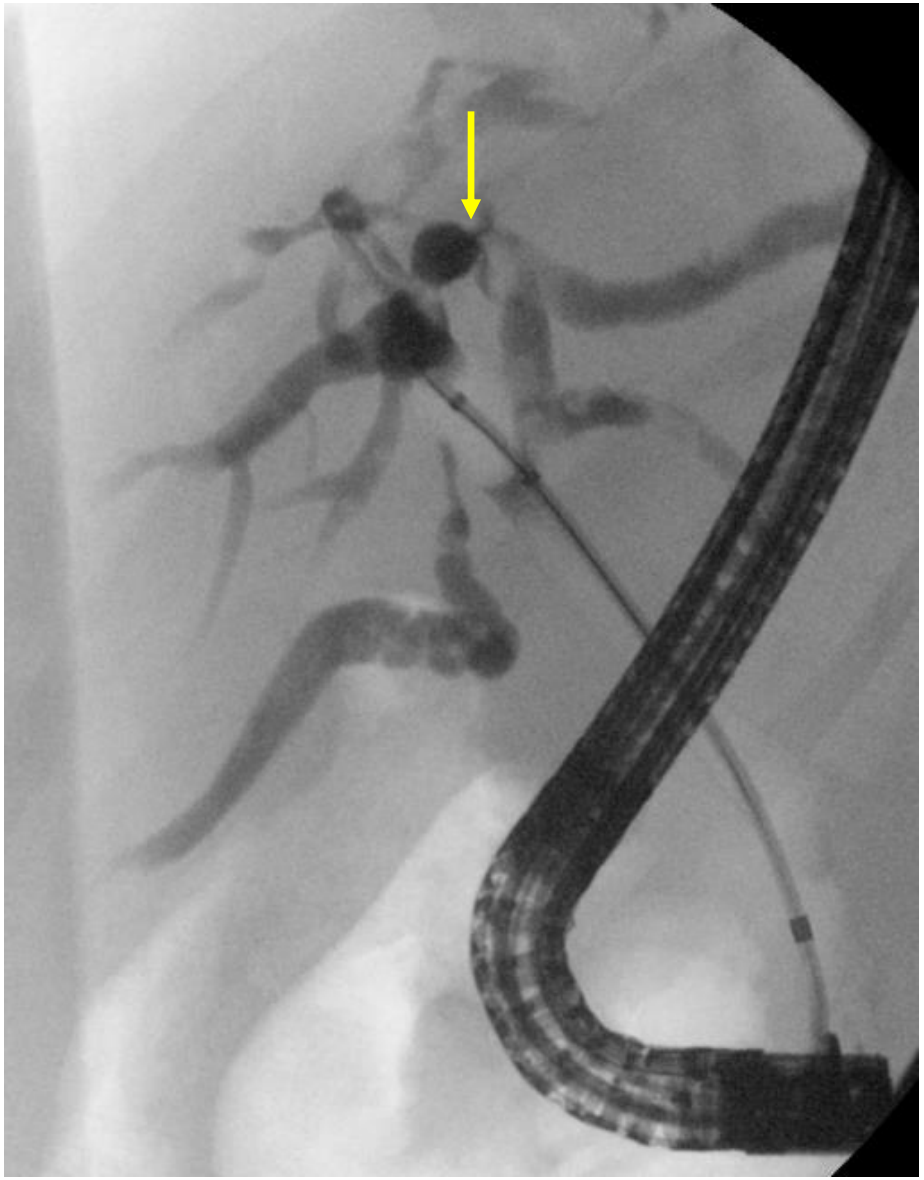
Cross sectional imaging (CT or MRCP to plan)

Pre-procedural antibiotics – reduce cholangitis

Minimize contrast injection – reduce cholangitis

Magnified images to sharpen detail.

Some lesions, particularly intrahepatic still required PTC for access.



Evaluation: Tissue Acquisition

Brush Cytology

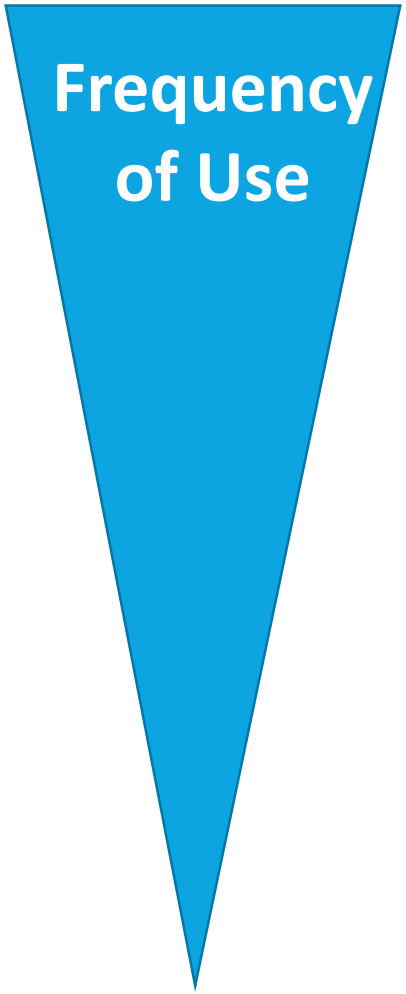
Forceps Biopsy

Cholangioscopy and targeted biopsies

EUS/FNA

FISH

Confocal Endomicroscopy



Brush Cytology

Most common method of sampling

Pooled data with sensitivity of 42%, specificity of 98%.

Data suggests higher yield with:

- More passes (>5)
- Longer brush
- Repeat brushing
- ?Brush with negative pressure



Fogel, Gastrointest Endosc 006;63:71-7
Bellis Gastrointest Endosc 2003; 58:176-82
Abbasi, *Asian Pac J Cancer Prev,* 17 (10), 4563-4566

Dominant Stricture in PSC

1560-fold increased risk of cholangiocarcinoma

ERCP-guided tissue acquisition with poor yield - Sensitivity 18-40%

- Submucosal as opposed to radial tumor growth
- Desmoplastic reaction
- Inadequate access of endoscopic devices
- Sampling under indirect visualization

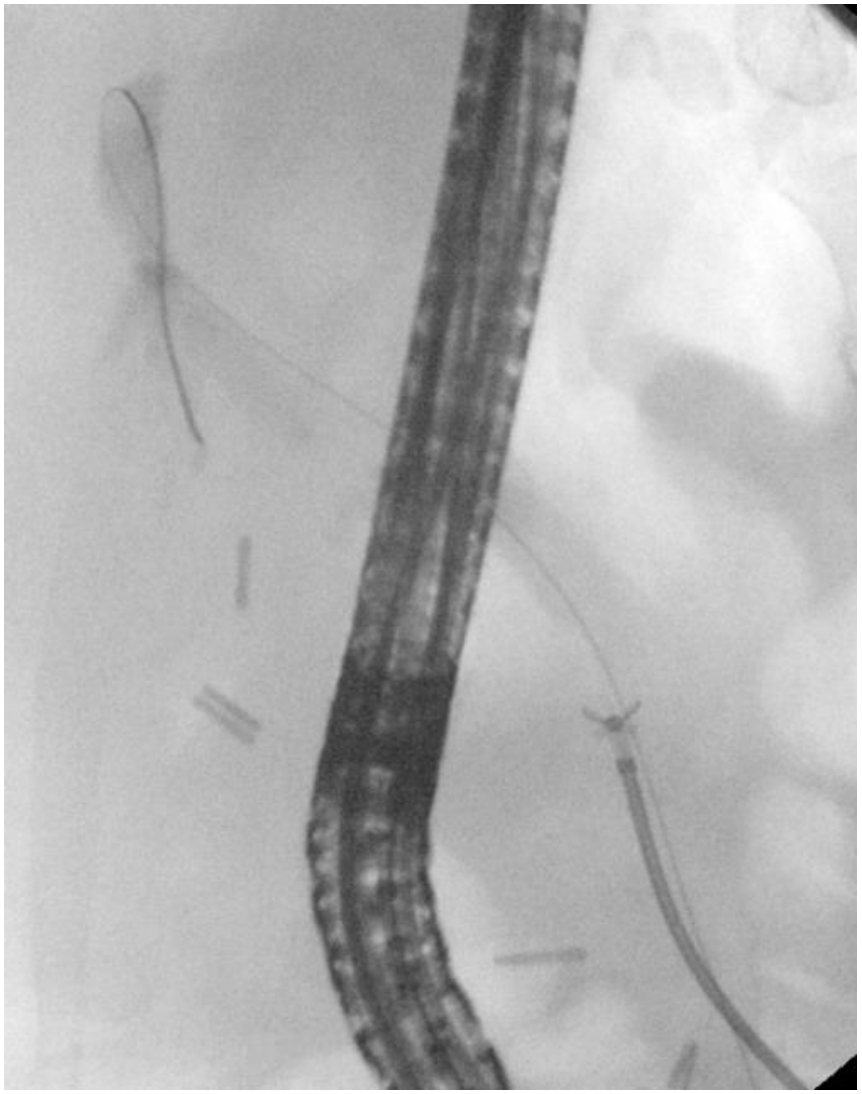
Chapman R et al. Diagnosis and management of primary sclerosing cholangitis. *Hepatology* 2010; **51**: 660-678
Coté GA, et al. Biliary stricture and negative cytology: what next? Clin Gastroenterol Hepatol 2011; 9: 739-743

Intraductal Forceps Biopsy

Provide pathology (not cytology) – allow for evaluation of tissue architecture.

Improved yield for detection of malignancy.

Meta-analysis of 500 patients over 5 studies shows: cumulative sensitivity of 56%, specificity of 97% and PPV of 97%

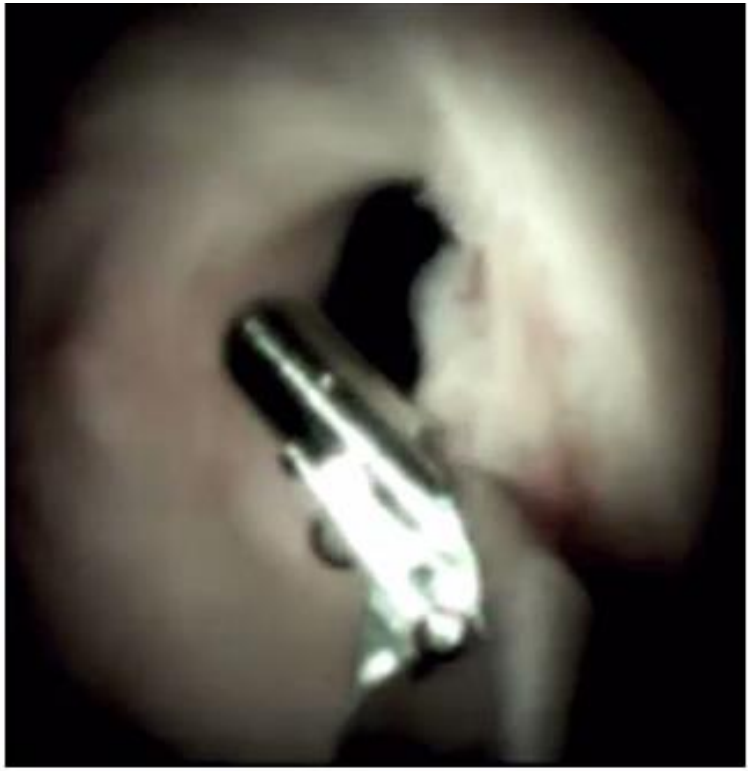


Cholangioscopy with Targeted Bx

Allows precise targeting – an enhancement over fluoroscopy guided biopsy (2D imaging).

Review of 10 studies and 456 patients for malignant biliary stricture

- Sensitivity of 60.1%
- Specificity of 98.0%



Navaneethan Gastrointest Endosc 2015;82:608-14

EUS/FNA and Intraductal US

EUS/FNA

Allows diagnosis by FNA – but might be technically challenging

Allows LN sampling – stage disease

FNA of primary tumor may seed and upstage tumor – contraindicated if consideration for transplantation.

Intraductal US

Fragile miniprobe inserted via duodenoscope and gives radial EUS pictures of the bile duct – assess depth of invasion.

Imaging only – no cyto/path.

FISH



FISH (Fluorescent in-situ hybridization)

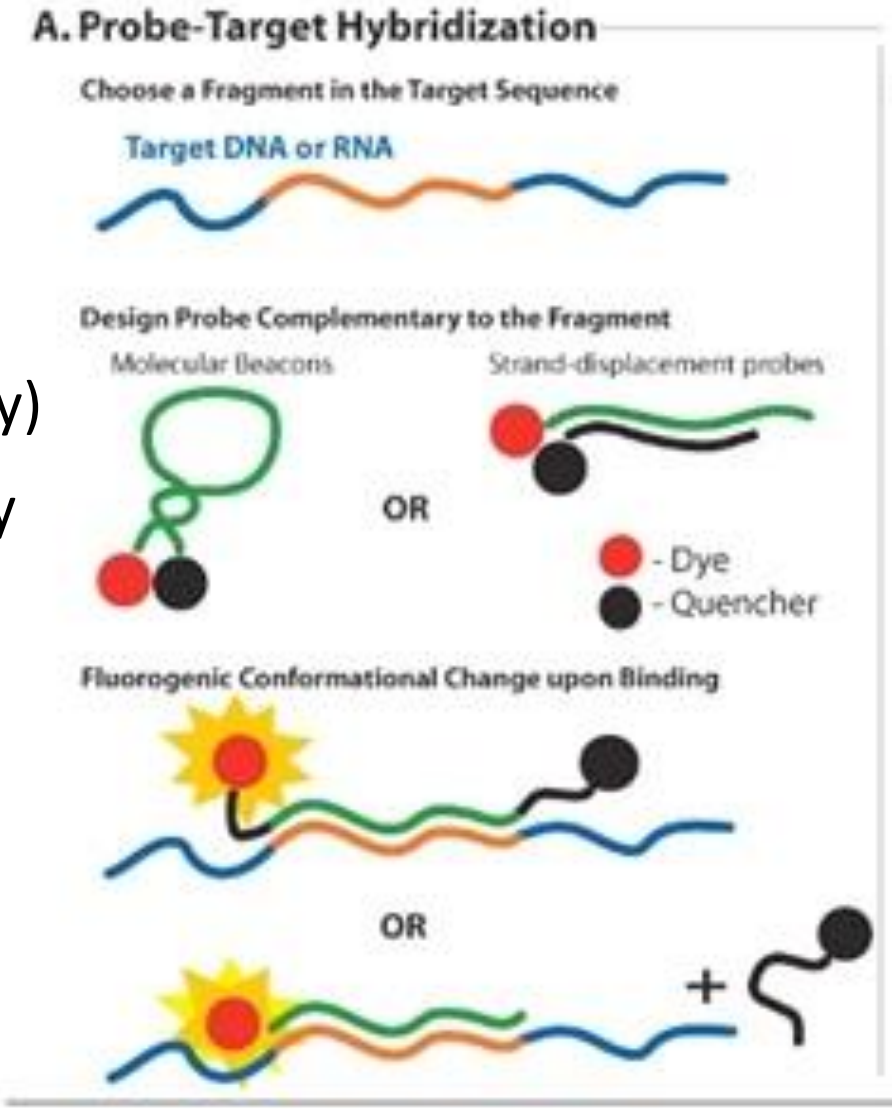
Adjunct tool used to evaluate cytology

Looks basically for extra chromosomal copies (polysomny)

Increases yield of brush cytology

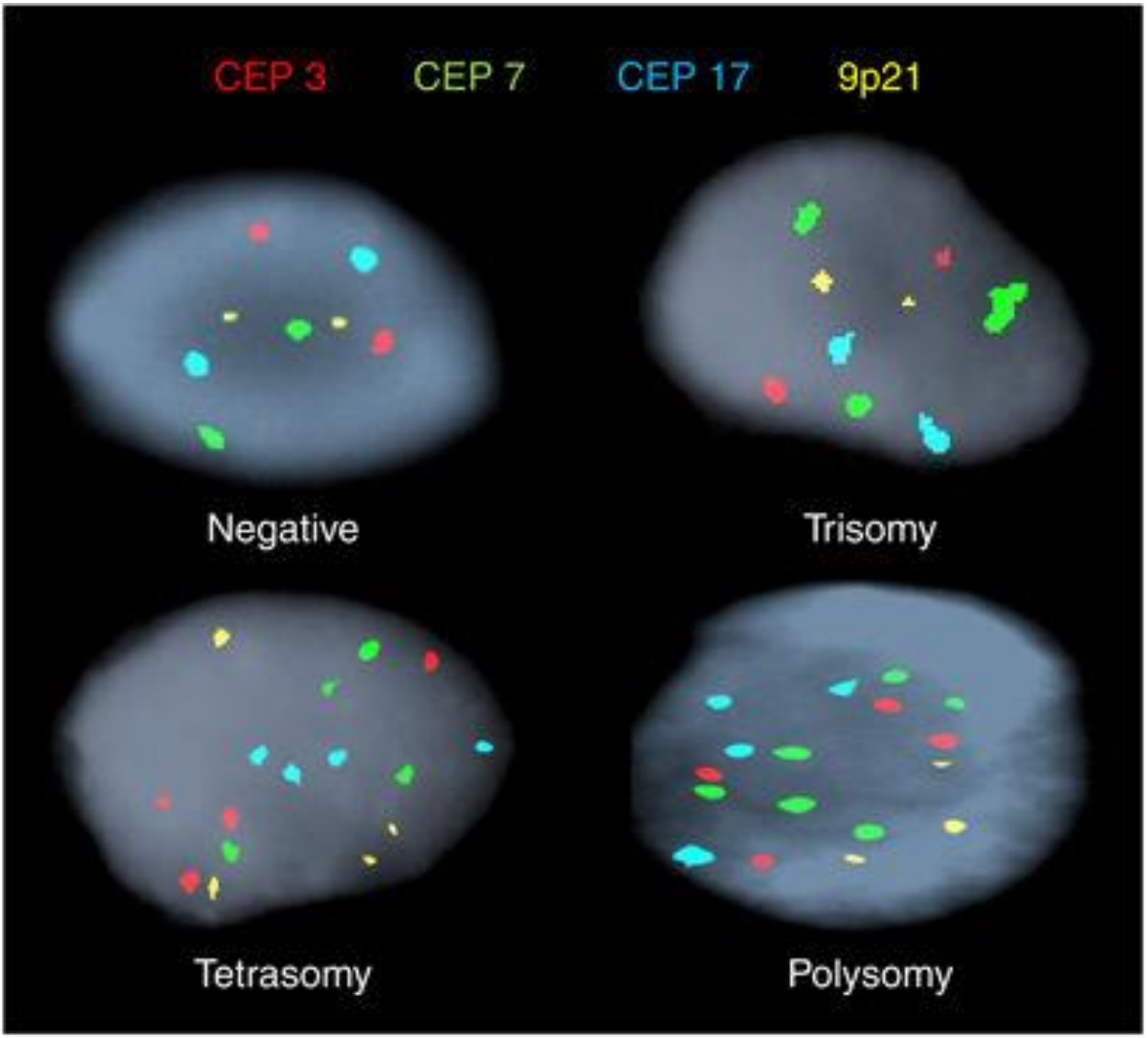
Kipp et al in a series of 66 patients showed sensitivities of:

- Cytology 15%
- Cytology + FISH 34%



Kipp BR et al, Am J Gastroenterol 2004; 99:1675-1681

FISH (Fluorescent in-situ hybridization)

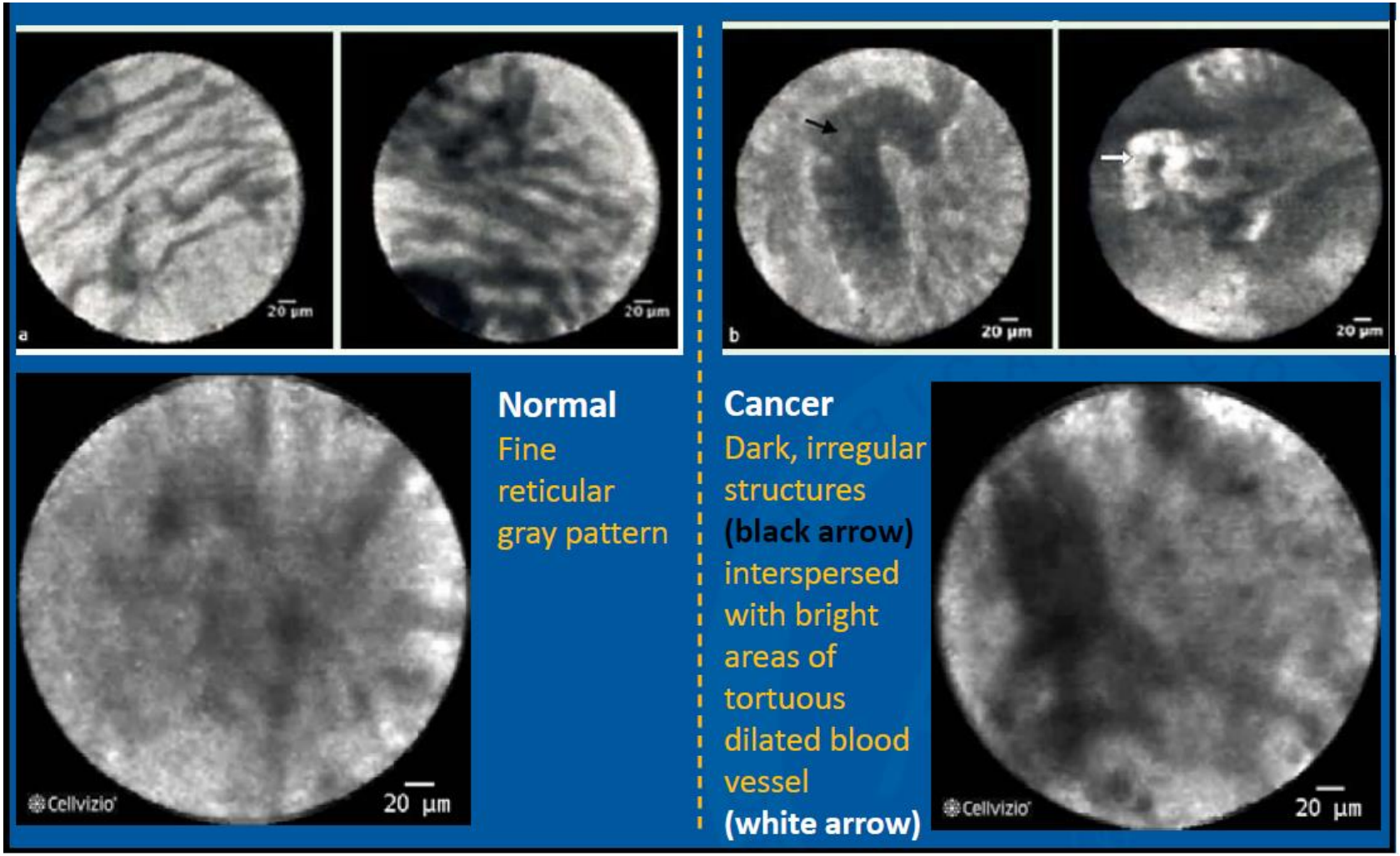


Centromere Enumeration Probe (CEP)
Chromosome 3 (red)
Chromosomes 7 (green)
Chromosomes 17 (aqua)

Locus specific probe
9p21 (gold)

Am J Gastroenterol 2015; 110:299–309

Confocal Endomicroscopy



Wallace M et al, Endoscopy 2011; 43:882-891

Combination

ORIGINAL ARTICLE: Clinical Endoscopy

Diagnostic accuracy of conventional and cholangioscopy-guided sampling of indeterminate biliary lesions at the time of ERCP: a prospective, long-term follow-up study

Peter V. Draganov, MD,[1] Shailendra Chauhan, MD,[1] Mihir S. Wagh, MD,[1] Anand R. Gupte, MD,[1] Tong Lin, BS,[2] Wei Hou, PhD,[3] Chris E. Forsmark, MD[1]

Gainesville, Florida, USA

Background: The diagnostic accuracy of cholangioscopy-guided sampling has not been rigorously evaluated.

Objective: To prospectively evaluate the accuracy of cholangioscopy-guided mini-forceps sampling and compare it with standard cytology brushings and forceps biopsies for the tissue diagnosis of indeterminate biliary lesions.

Design: Prospective, long-term follow-up, paired design cohort study.

Setting: Tertiary center.

Patients: Patients undergoing cholangioscopy for the evaluation of indeterminate biliary lesions.

Interventions: Each patient underwent triple sampling with cholangioscopy-guided mini-forceps, cytology brushing, and standard forceps.

Main Outcome Measurements: Diagnostic accuracy of each sampling method compared with the patient final status (cancer vs no cancer).

Results: A total of 26 patients (17 cancer positive/9 cancer negative) were enrolled. The mean follow-up in the patients with no cancer was 21.78 (SD ±6.78) months. The procedure was technically successful in all cases (100%). Sample quality was adequate in 25 of 26 (96.2%) of the cytology brushings, in 26 of 26 (100%) of the standard forceps biopsies, and in 25 of 26 (96.2%) of the mini-forceps biopsies. The sensitivity, accuracy, and negative predictive values were 5.9%, 38.5%, and 36% for standard cytology brushings; 29.4%, 53.8%, and 42.8% for standard forceps biopsies; and 76.5%, 84.6%, and 69.2% for mini-forceps biopsies, respectively. When comparing the 3 methods of sampling, mini-forceps biopsy provided significantly better sensitivity and overall accuracy compared with standard cytology brushing ($P < .0001$) and standard forceps biopsy ($P = .0215$).

Limitations: Potential for selection bias.

Conclusions: Cholangioscopy-guided biopsies of indeterminate biliary lesions have significantly higher accuracy compared with ERCP-guided cytology brushings and standard forceps biopsies, but negative findings on mini-forceps biopsy cannot rule out malignancy with a high degree of certainty. (Clinical trial registration number: NCT01227382.) (Gastrointest Endosc 2012;75:347-53.)

Cholangioscopy-guided biopsy has better results

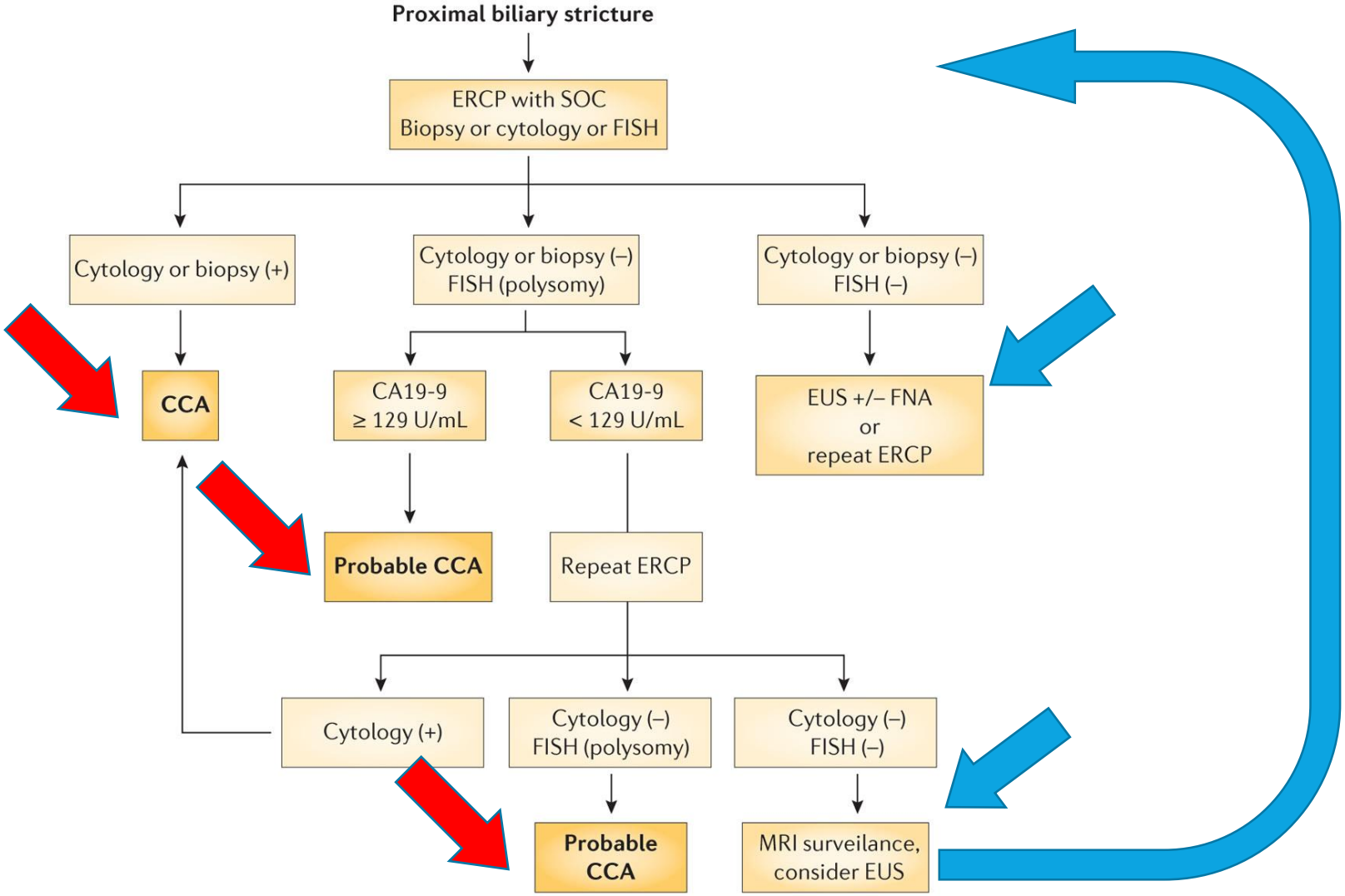
TABLE 4. Performance characteristics of the 3 sampling methods

	Sensitivity, %	Specificity, %	Negative predictive value, %	Accuracy, %	*P* value
Cytology brush	5.8	100	36	38.5	.0001
Standard forceps biopsy	29.4	100	42.8	53.9	.0215
Mini-forceps biopsy	76.5	100	69.2	84.6	N/A

N/A, Not available.

REPEAT and RE-EVALUATE

Figure 4 Algorithm for the evaluation of a proximal biliary stricture or distal stricture with a non-diagnostic EUS

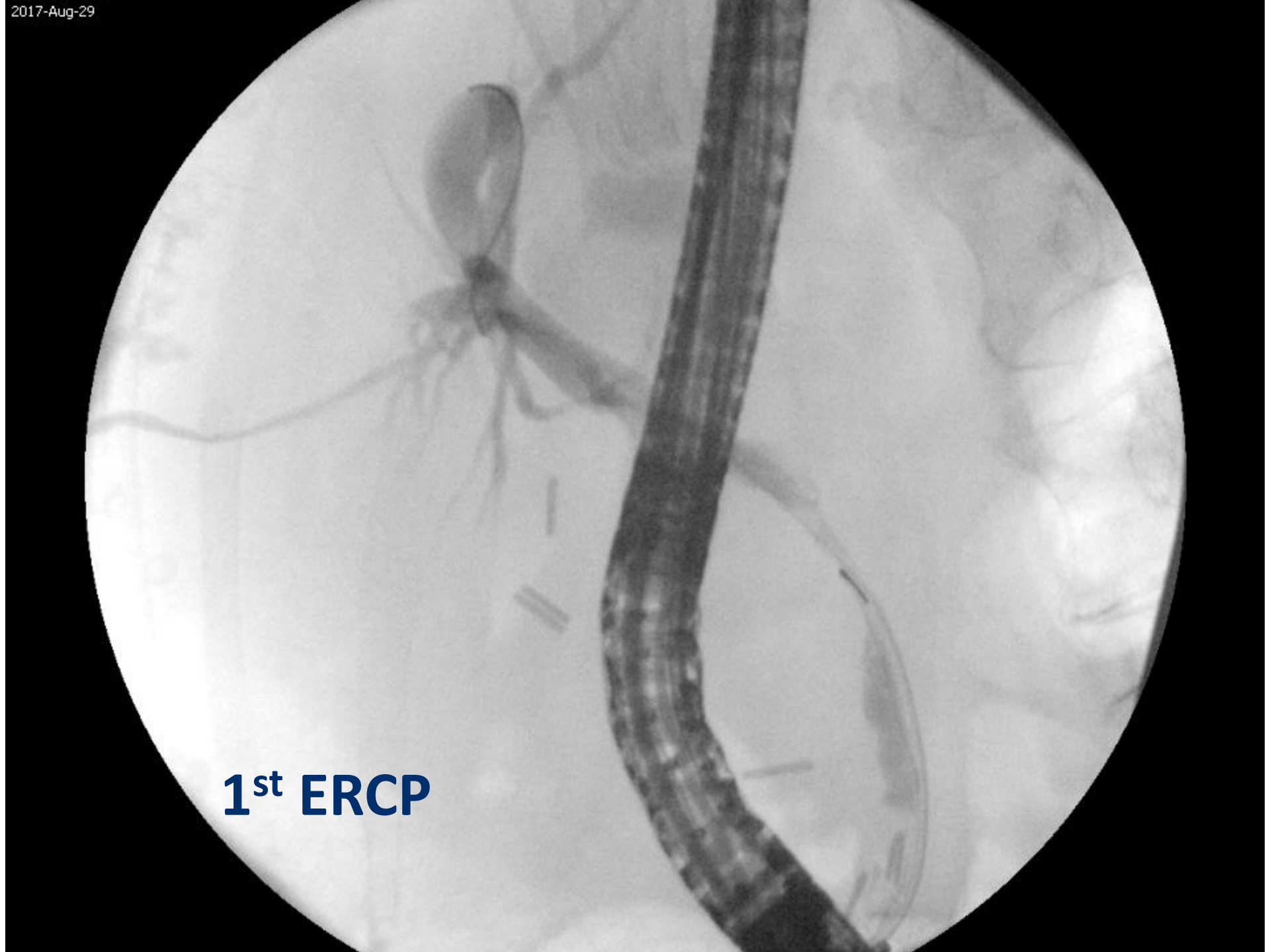


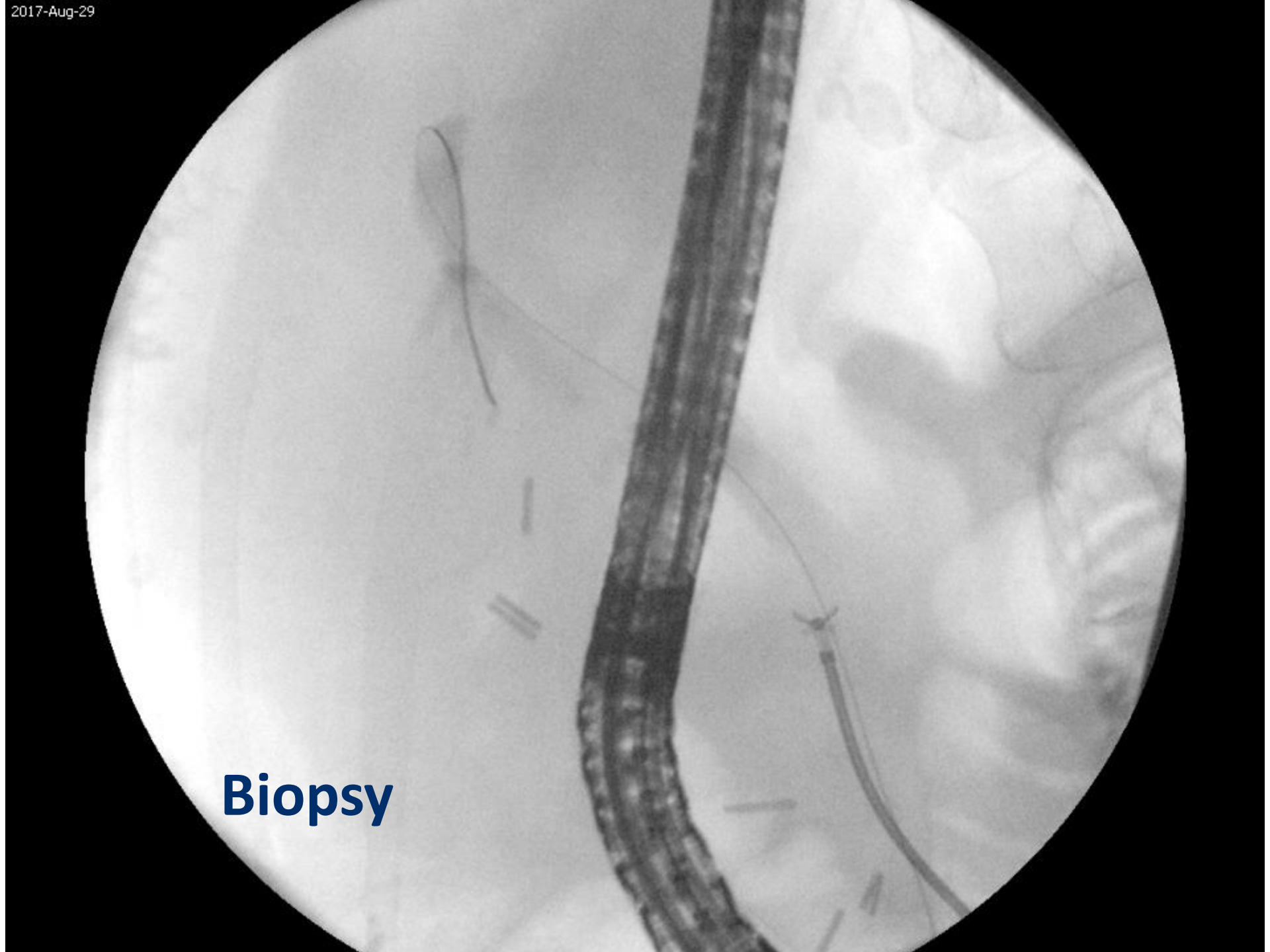
Bowlus, C. L. *et al.* (2015) Evaluation of indeterminate biliary strictures
Nat. Rev. Gastroenterol. Hepatol. doi:10.1038/nrgastro.2015.182
Nature Reviews | Gastroenterology & Hepatology

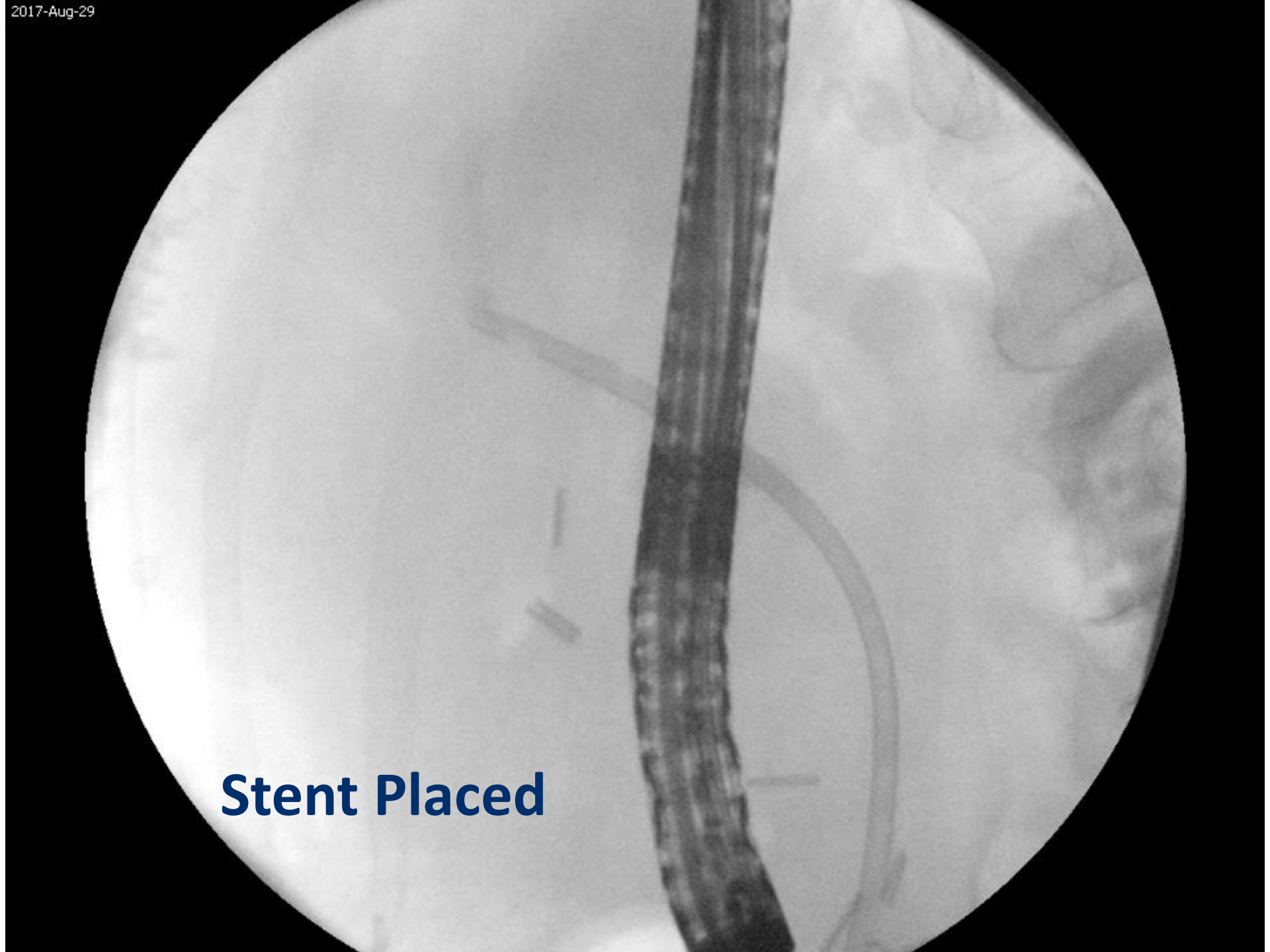
Case 2

75y female presented with biliary stricture originally planned for Whipple procedure 8/28/17 – intraoperatively pancreas appeared normal with evidence of annular pancreas.

Referred for evaluation of biliary stricture.


2017-Aug-29
1st ERCP


2017-Aug-29
Biopsy


2017-Aug-29
Stent Placed

Results

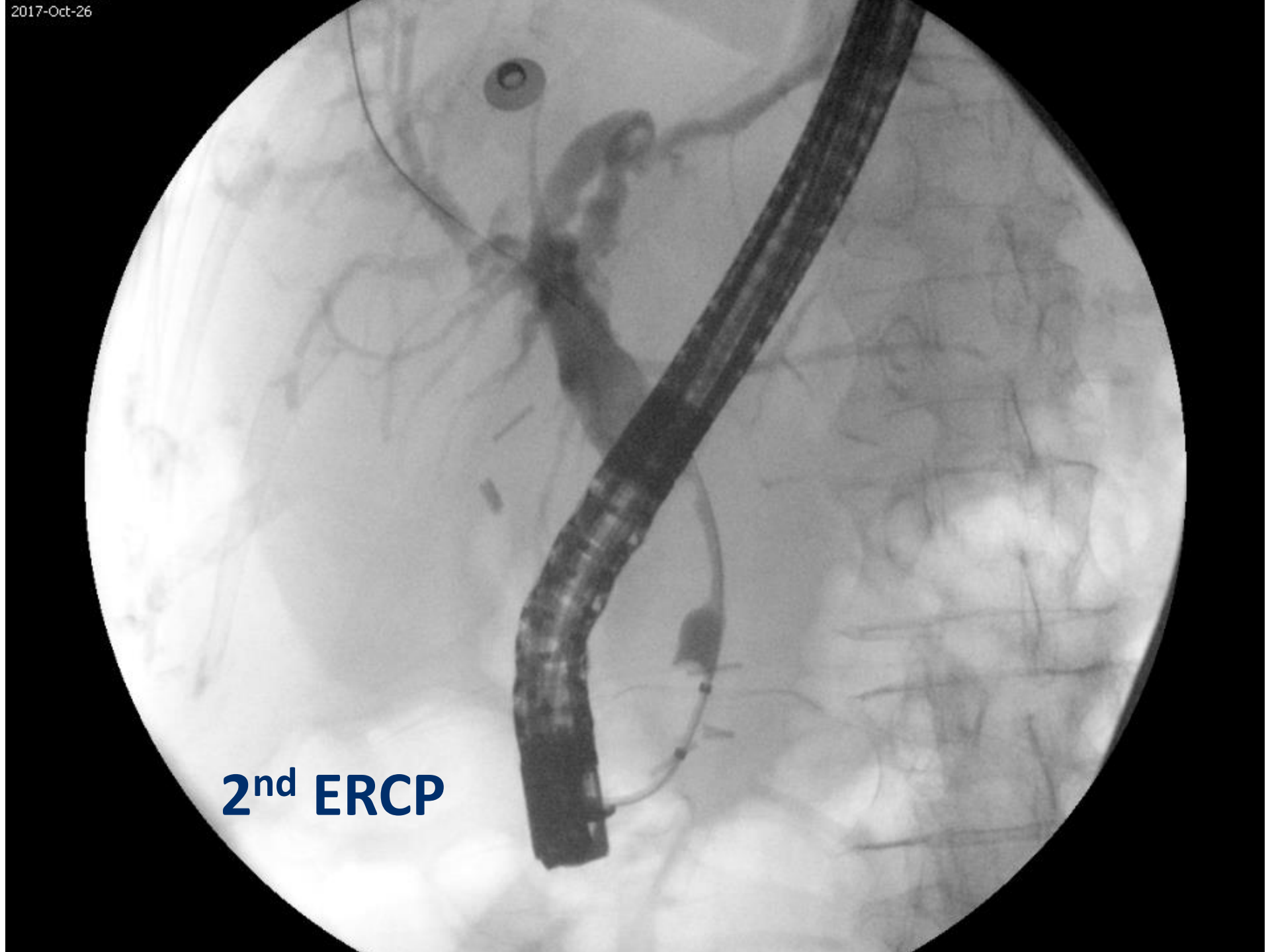
Common bile duct, biopsy:

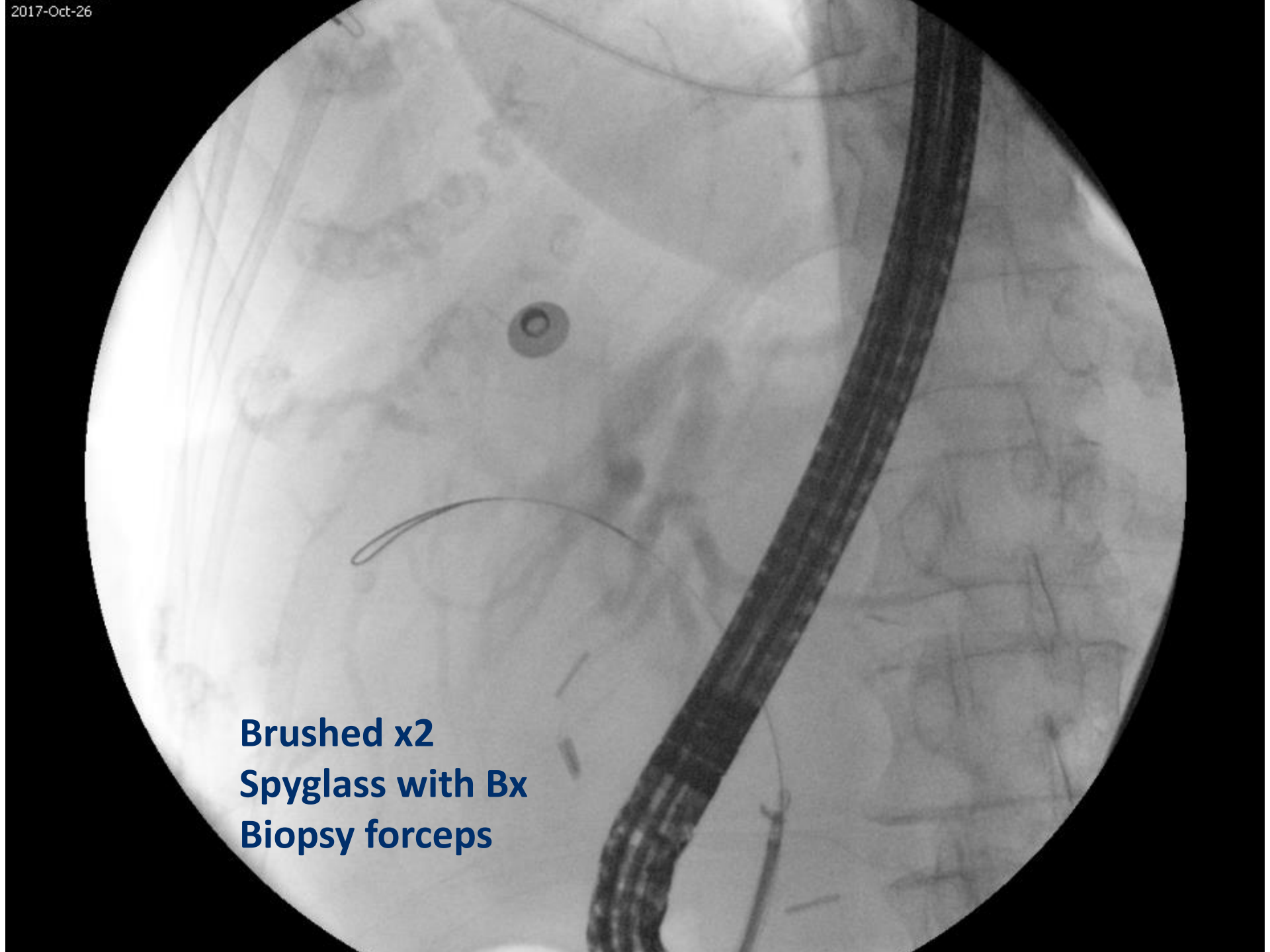
- Minute fragments of benign fibrous tissue and epithelium. Negative for high grade dysplasia and malignancy.

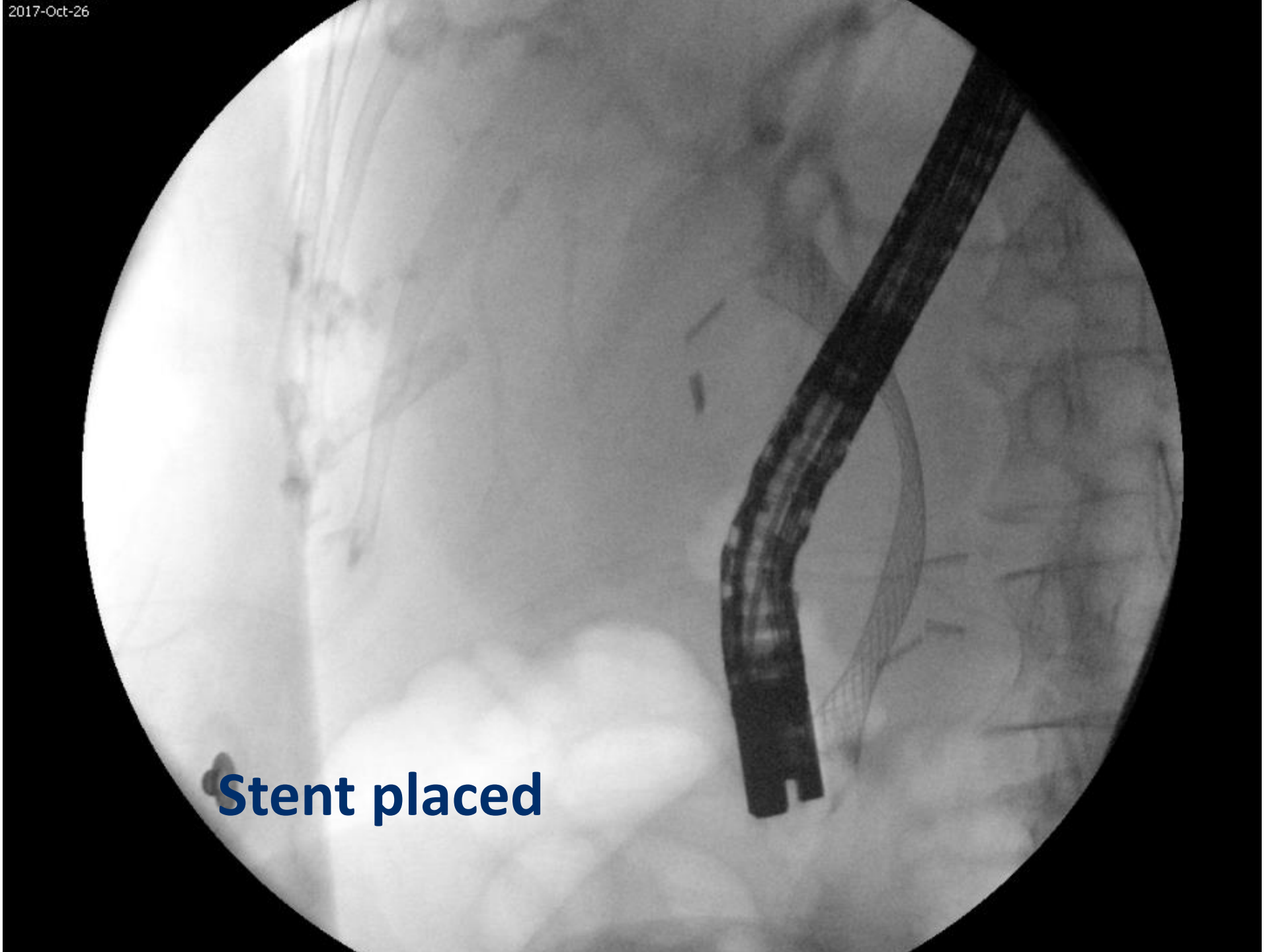
Cytology: Suspicious cells are present

- Markedly atypical ductal epithelial cells, suspicious for adenocarcinoma.

Patient returned with obstructive jaundice Bil 1.0 to 4.0mg/dL with ALP 151 to 357


2017-Oct-26
2nd ERCP


2017-Oct-26
Brushed x2
Spyglass with Bx
Biopsy forceps


2017-Oct-26
Stent placed

Cytology – Suspicious cells seen

- Comment “Markedly atypical ductal epithelial cells, suspicious for adenocarcinoma”

Pathology – adenocarcinoma

Notes on Primary Sclerosing Cholangitis

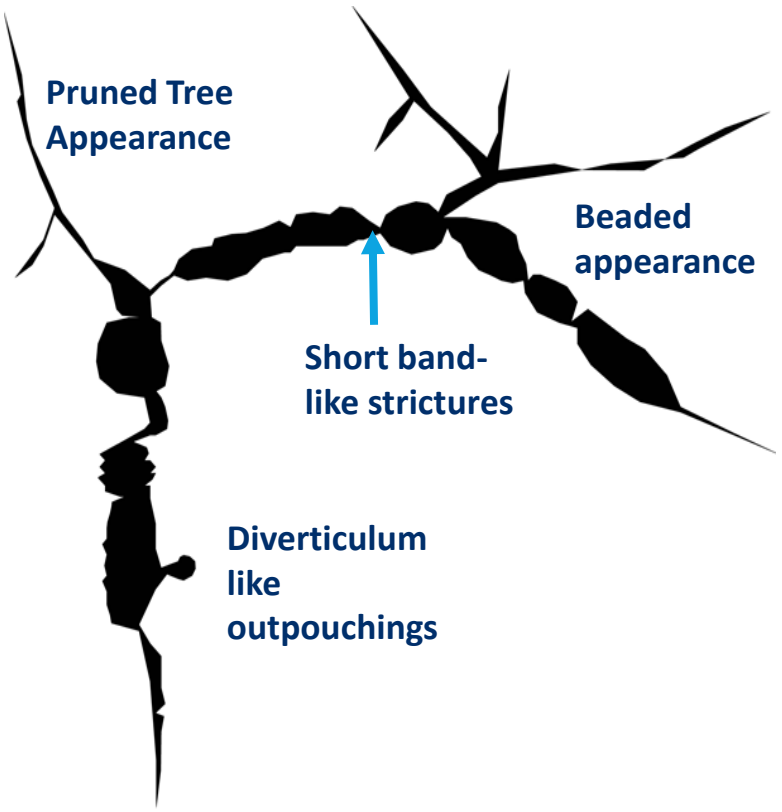
Large Duct
Coexists with IBD in 60-80%, typically pancolitis with ileal/rectal sparing
Non IBD PSC seems to be on the rise
HLA A∗01, B∗08, DRB1∗03 haplotype

Small Duct
Biochemical, histologic features without the cholangiographic findings
5-20% of all PSC

Some cases have overlap features with AIH (7.5% score probable AIH), and autoantibodies ANA, SMA may be present without other features of AIH

Labs
Chronic ALP elevation 3-4x ULN, others (transaminases, bilirubin) may be transient or fluctuating. Hyperglobinemia is frequent with IgM elevated in 50%, ANCA may be positive – observed in 65%.

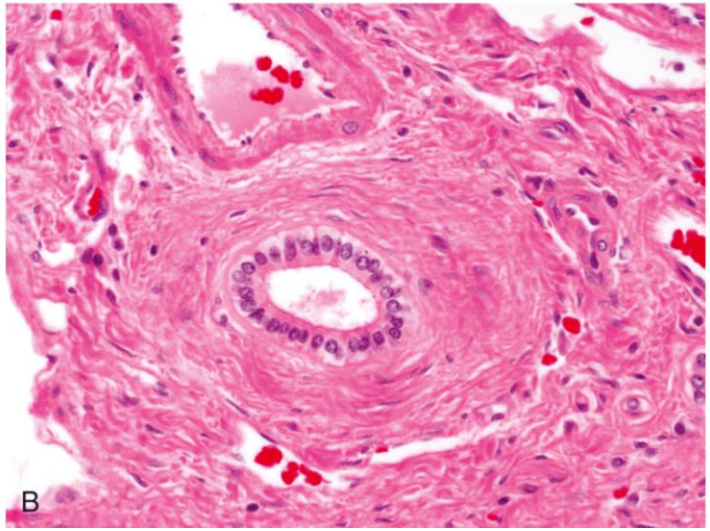
Imaging (MRCP/ERCP)
Multiple stricturing / Ectasia of the bile duct
Attenuation of intraparenchymal arborization "pruned tree"



Notes on Primary Sclerosing Cholangitis

Histology

Diffusely thickened, fibrotic duct wall. The fibrosis is accompanied by a mixed inflammatory infiltrate that may involve the epithelium and biliary glands



Characteristic bile duct lesion (although <50%) is a fibro-obliterative process that may lead to an “onion-skin” appearance of concentric fibrosis surrounding medium-sized bile ducts

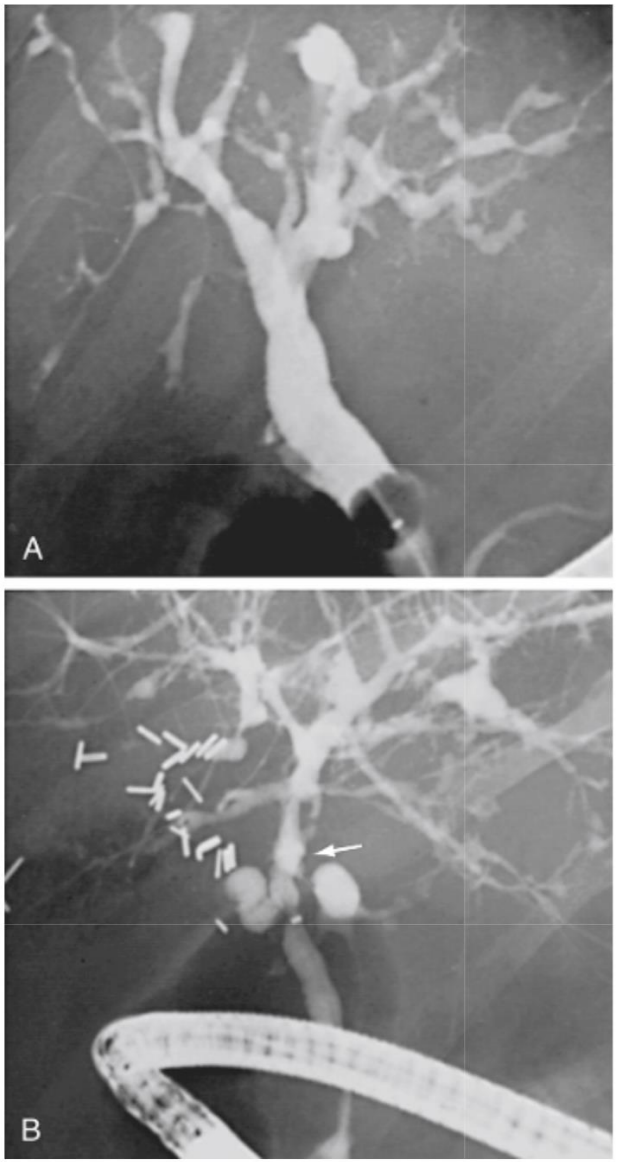
Notes on Primary Sclerosing Cholangitis

Complications
Cholestasis

Stricture management - Placement of a biliary stent after balloon dilation appears to increase the risk of complications compared with balloon dilation alone, although in some cases short term stent is required for mx

Cholangiocarcinoma – lifetime risk 5-20% highest in first year of diagnosis then 1.5-2% annual risk

Liver Transplant



SUMMARY

Diverse differentials, but always think of 3 malignancy, malignancy and malignancy.

Multiple evolving tools to help in the evaluation

- Imaging
- Endoscopy

The negative predictive value of the best investigations are not high – consider repeat evaluation especially if clinical suspicion is high

ERCP is often NOT the final solution

- The stent drains but doesn't "cure".
- Surgery, transplantation, steroids, chemotherapy etc.

Thank you.

NUHS
National University Health System

National University Hospital
Ng Teng Fong General Hospital
Alexandra Hospital
Jurong Community Hospital
National University Polyclinics
Jurong Medical Centre
National University Cancer Institute Singapore
National University Heart Centre Singapore
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