Sclerosing diseases of the biliary tree

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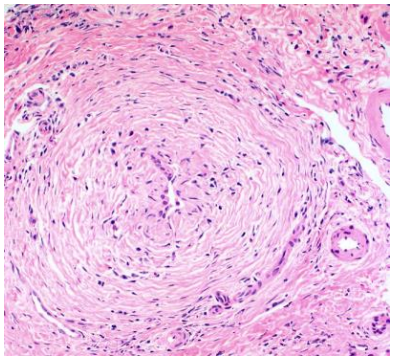
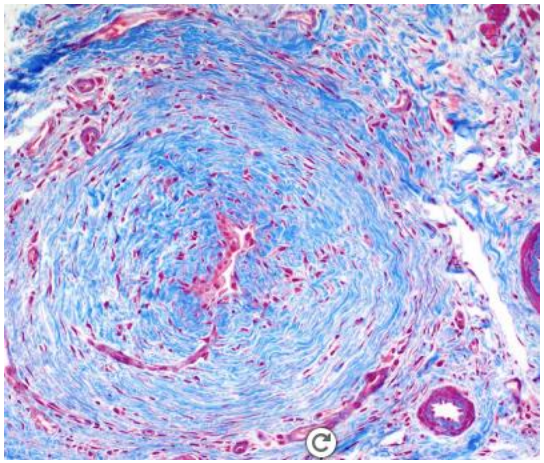




Bible Class 18.09.2024

Reiner Wiest M.D.

IBD-PSC: epidemiology, incidence, prevalence….?

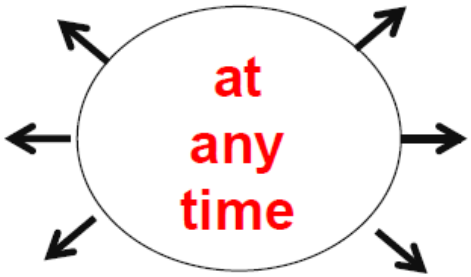
- Usually young (30-40 y) male (2:1)
- Incidence (northern europe): 1/100.000/year

IBD-patients

- UC: 2.4 – 7.5%
- MC: ~3.4 %
- develop PSC

↓

Minority PSC



PSC-patients

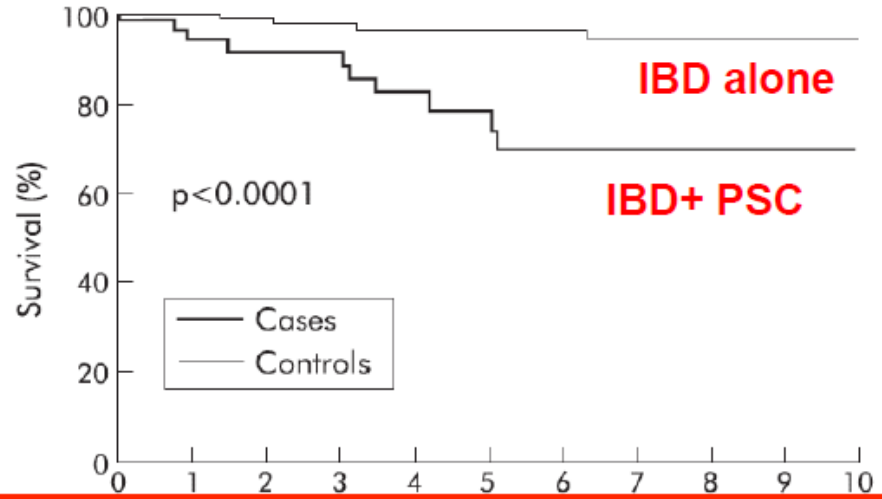
- 60-80% in IBD pts
- in UC: 48%-86%
- in MC: up to 13%

↓

Majority IBD

Prognosis of IBD in dependency on PSC

- Medical records Mayo Clinic 1987-1992
- IBD + PSC (n=71) vs. IBD alone (n=142)



HR 9.7
(95% 2.3 – 41)

Adjusted
Age, duration,
rectal sparing etc.

Prognosis in PSC:
65% survival at 10 years without OLT
median survival (or OLT) after diagnosis ~ 9 years

What can cause sclerosing of biliary tree ?

Sclerosing cholangitis of unknown origin

PSC: Primary sclerosing cholangitis

IgG4-SC: IgG4-related sclerosing cholangitis

Secondary sclerosing cholangitis

Infection: recurrent, chronic bacterial/parasitic/pyogenic cholangitis

Immunodeficiency: e.g. congenital, AIDS patients

Mechanical/toxic: stone, surgical, trauma, CTx, drug

Cholangiocarcinoma, diffuse metastasis

Ischemic: vascular trauma, arterial insuff., PNH

Pancreatobiliary disease: CF, CP, ABCB4-CP

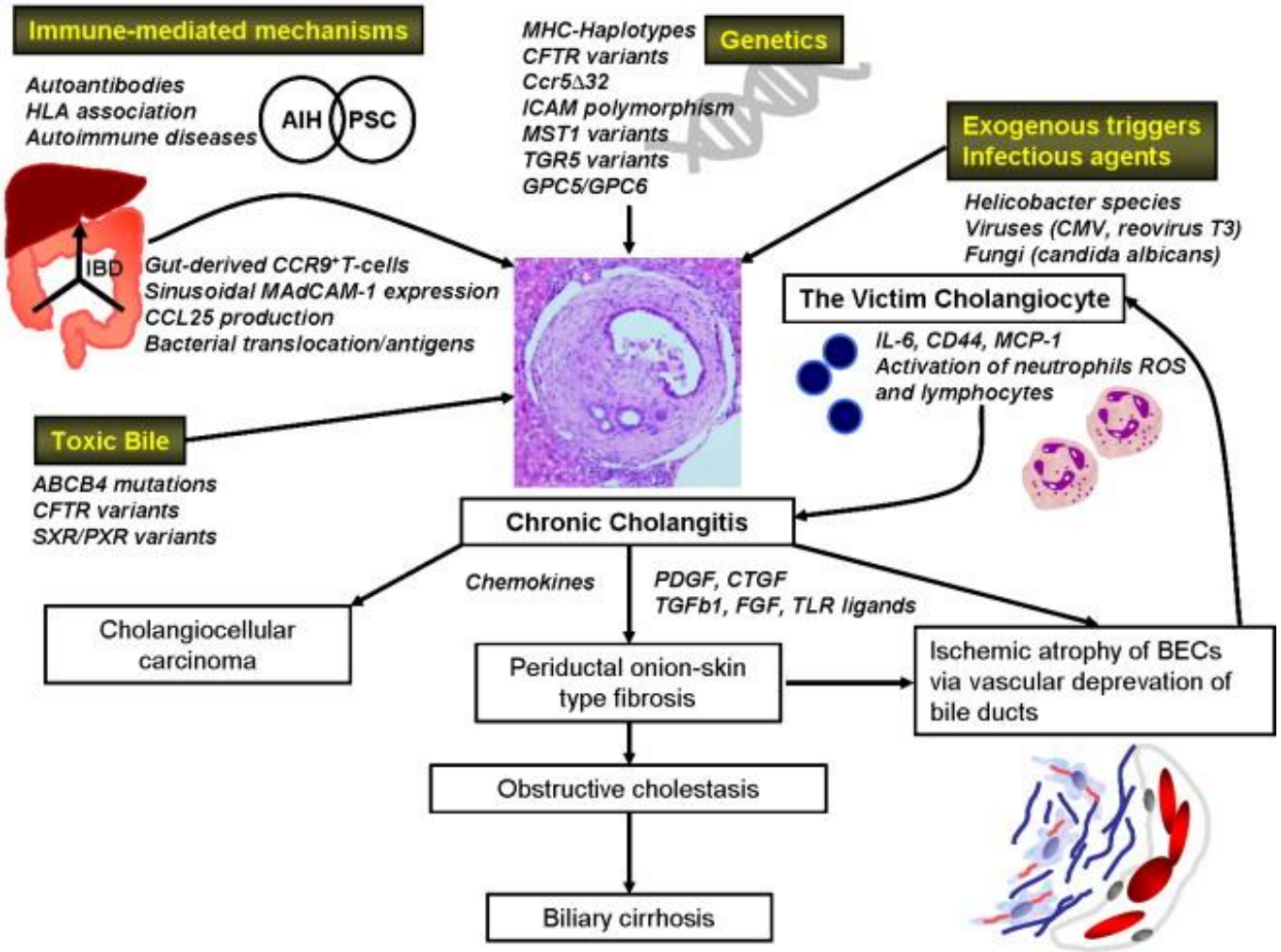
Systemic inflammatory disease: Sarcoidosis, GvHD, Eosinophilic

Others: Portal-hypertensive Biliopathy, Masto-, Histozytosis, Caroli,

.....mimicking: amyloidosis, allograft rejection, hodgkin`s disease.....

Pathogenesis of Primary Sclerosing Cholangitis ?

PSC



Most difficult questions in the bible class history !

PSC

Which genes are shared between UC and PSC?

IL2, CARD 9 and REL

Hanse et al. Hepatology 2011

Which cell-type is responsible for PSC development after colectomy ?

Memory α4β7-CCR9+CD8+T-cells primed by retinoic dependent iDC

Eksteen B et al. Gastroenterology 2009

PSC

Factors modulating risk for PSC ?

- **IBD, mostly UC**
- **2-4% (max 8%) of IBD patients, in their lifetime**
- **up to 88% of PSC-patients suffer IBD**

- **male predominance**
- **Sometimes family history of disease**
- **smoking protectes against PSC**

Symptoms in PSC ?
Prognosis in patient with and without symptoms ?

- often **asymptomatic** (about 50%)

- right upper quadrant pain, abdominal discomfort,

- fatigue, pruritus, fever/chills and weight loss (malnutrition, malabsorption of fat-soluble vitamins with deficiencies in vitamin A, D, E; osteoporisis)

- **If symptoms**: time till death or transplantation reduced

  9 years vs. 12-18 years

Lab tests of Primary Sclerosing Cholangitis ?

- **cholestatic (↑GGT, ↑ AP, bilirubin)**

+ high transaminases (2-3x normal value) in a majority of patients

Other lab tests?

-Serology : Antibodies

Antibody	Prevalence
Anti-neutrophil cytoplasmic antibody	50%–80%
Anti-nuclear antibody	7%–77%
Anti-smooth muscle antibody	13%–20%
Anti-endothelial cell antibody	35%
Anti-cardiolipin antibody	4%–66%
Thyroperoxidase	7%–16%
Thyroglobulin	4%
Rheumatoid factor	15%

9

Cave: all antibodies non-specific……

Diagnosis of Primary Sclerosing Cholangitis ?

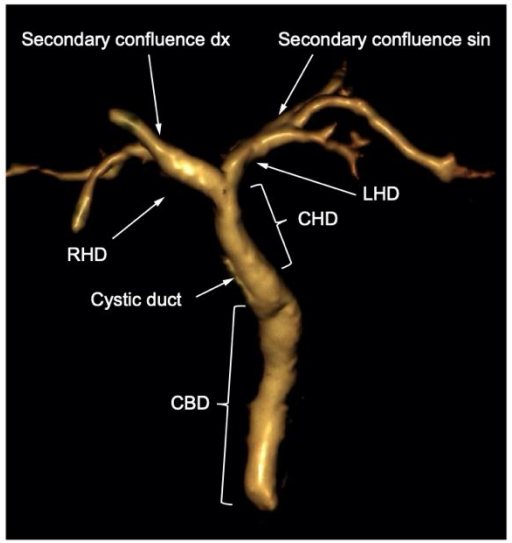
-Lab: CHOLESTASIS (not other wise explained…)

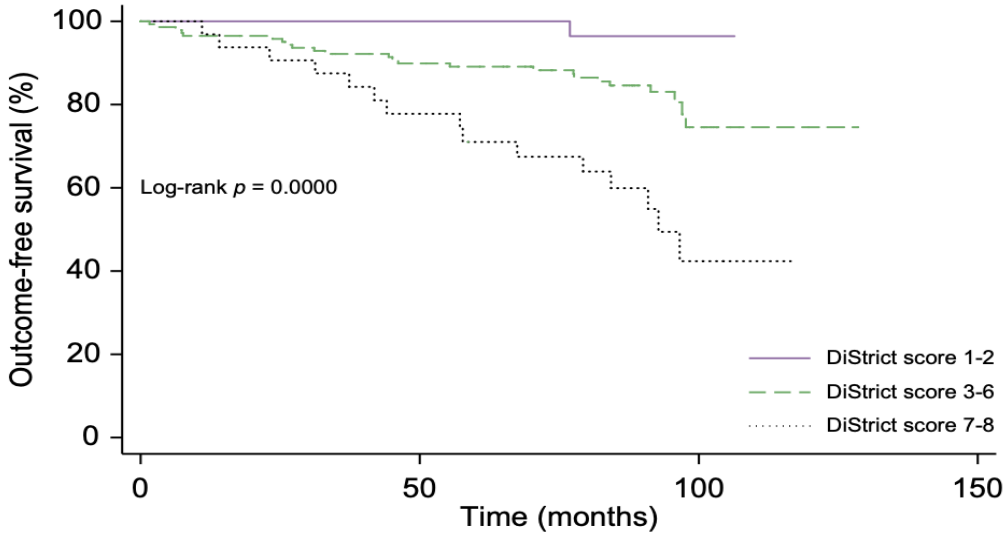
- **MRC (P) Method of choice**

- ERC(P)

} abnormal cholangiogram (strictures / dilatations)

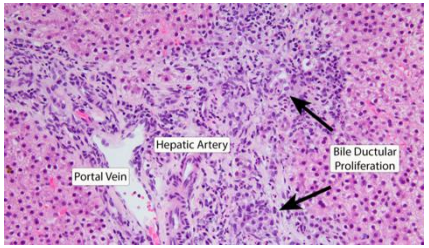
District-Score on MRCP in PSC for large-duct PSC





What is small duct PSC ?

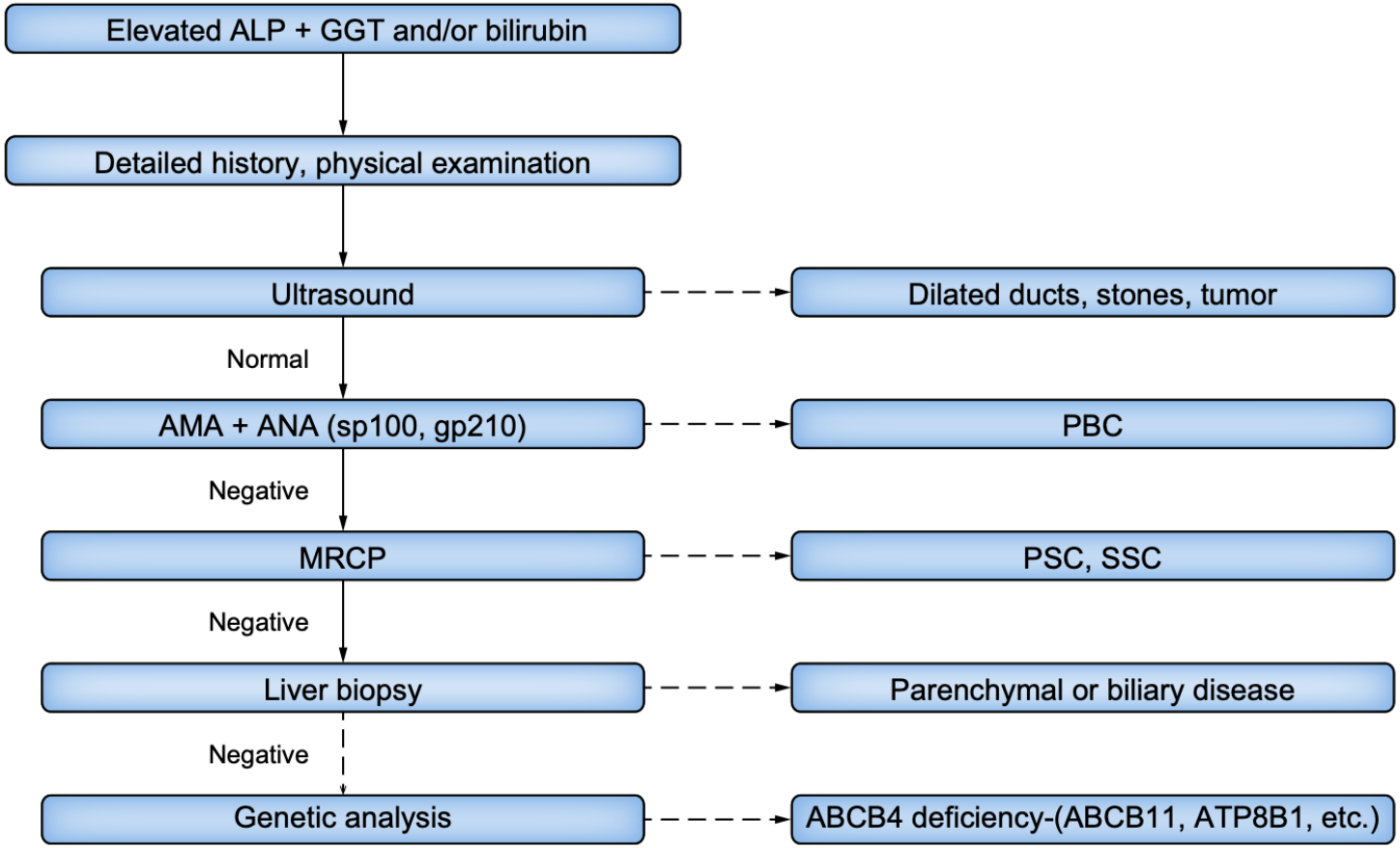
- Disease variant which is characterized
  by typical cholestatic and **histological features** of PSC
  but normal bile ducts on cholangiography
- Survival is longer
- Lower risk for CCA
- 20% develop large duct disases over 7-10 years



Normal cholangiogram but high suspicion → perform ?

→ Liver Biopsies (small duct PSC and/or Overlap-Syndrom with AIH)

Diagnostic algorythm in PSC



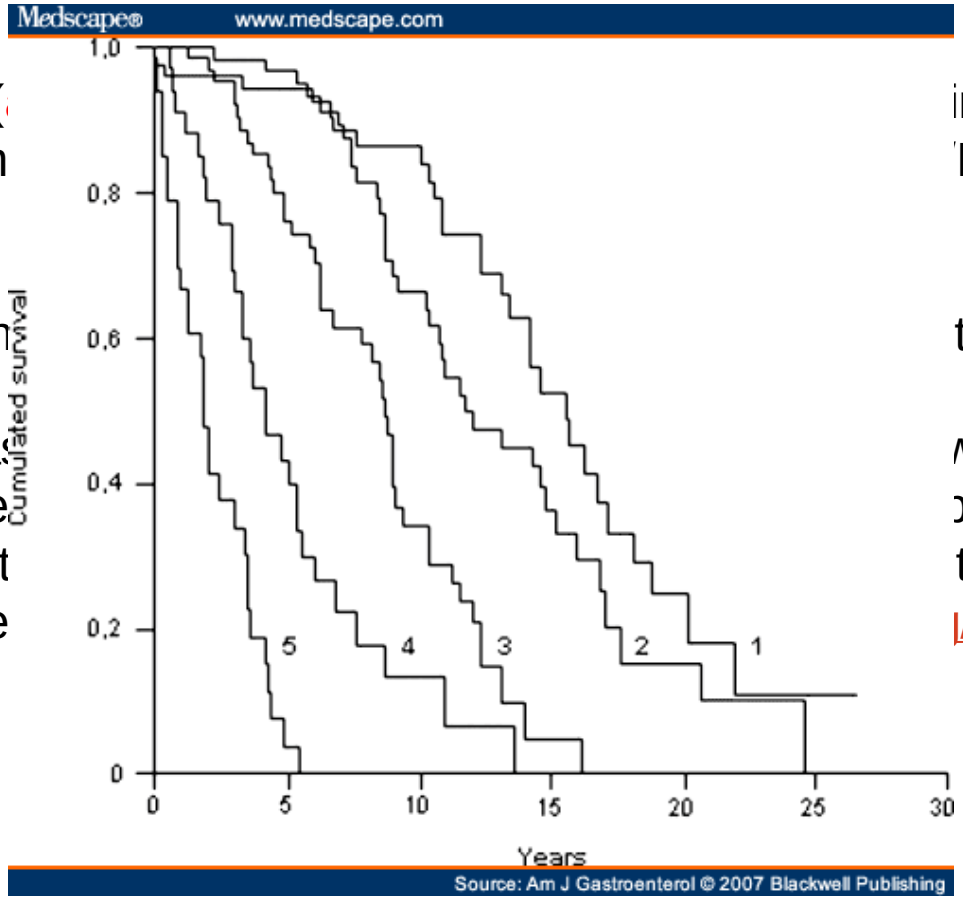
EASL guidelines J.Hepatol 2022

Mayo Risk Score for PSC?

R= (0.0295 * (in mg/dL)) -
(0.8389 * (serum L) + (1.2426 *

Poin t.

Each unit increas with a 2.5-fold
increase in the oward slope
over time in st t shows an
acce l/)



Kim et al. Mayo Proc 2000

Most common complications of PSC ?

- **Cholangiocarcinoma = most common cause of death**
  (0.6-1.5%/year and up to 20% life-time risk in PSC
  up to 50% diagnosis in 1st year after PSC-diagnosis)

- **Biliary (secondary) Cirrhosis**
  → portal hypertension/ liver failure
  → hepatocellular carcinoma
  (about 2% per year)

- **Colorectal Carcinoma**
  5-10 fold increase

Mortality accounted for by
CCA ca. 32 %
CRC ca. 8 %

Liver failure ca. 15 %
LTx-comoplications 9 %

Bergquist A et al. JHep 2022
Weissmueller TJ et al. Gastroenterology 2017

Main phenotypic prognostic factors in PSC ?

Good prognostic factors:

- Younger age at diagnosis
- Female sex
- Small duct disease
- Crohn's disease (as opposed to ulcerative colitis)
- Normal or mildly elevated ALP (with or without UDCA)

Poor prognostic factors:

- Extensive intra- and/or extra-hepatic biliary involvement
- Liver synthetic dysfunction or portal hypertension
- Severe parenchymal fibrosis or cirrhosis
- Jaundice

Dyson JK et al. Lancet 2018

Which PSC patient is at high risk for complications ?

“Low risk” of events:

- Small duct PSC and no evidence of cirrhosis

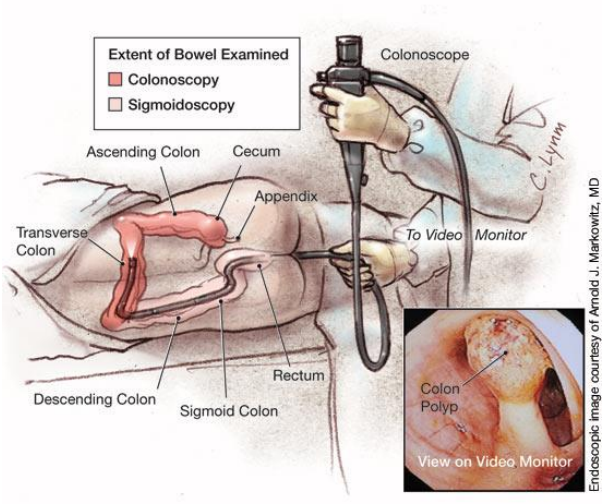
OR

- Classical PSC and (all to be present): asymptomatic with normal bilirubin, albumin, platelets, and PT, ALP <1.5 ULN, LSM (VCTE) <6.5 kPa (or ELF test <7.7), limited biliary changes on MRI/MRCP.

“Significant risk” of events if any present:

- Symptomatic, ALP >1.5 ULN, abnormal bilirubin, albumin, platelets or PT, LSM (VCTE) >9.9 kPa (or ELF test >10.6), extensive biliary changes (especially intra-hepatic biliary dilatation) on MRI/MRCP.

Colon and PSC:
When colonoscopy in PSC ?



- **Every PSC** patient at least once,
  at ED even asymptomatic patients
- **Plus Biopsy** even if macroscopically intact
  (4 quadrant in each colon segment+Ileum)
- **Every (3-)5 year** after PSC diagnosis, if first colposcopy is bland or when symptoms develop to seek IBD
- **IBD: annual** surveillance colonoscopy with chromoendoscopy
  (also after LTx)

Characteristic features of IBD in PSC ?

- **High prevalence pancolitis**
- **Predominant inflammation right side**
- **Rectal sparing**
- **Mild course**
- **Back-Wash-Ileitis**

Impact of PSC on Colorectal Cancer Risk in IBD ?

Cumulative risk (dysplasia and/or CRC): after 20 years

with PSC vs. Without PSC: 7% vs. 1.3%, p<0.01

OR 5.1 (95% CI 3.58 -6.41)

Soetikno et al. GIE 2002

IBD and CRC (with vs. without PSC):

- 19 vs. 29 years of age , p<0.05
- younger at onset of IBD

Predilection on prox. Colon (76% right-sided)

Brackmann S et al. Scand J Gastro 2008

Shetty Am J Gastroenterol 1999

When to advocate procto-colectomy in PSC ?

- **Any high grade dysplasia or colonic cancer**
- **High grade inflammation despite optimal pharmacological therapy**
- **Low-grade dysplasia at multiple sites or multiple occasions (follow-up)**
- **low threshold after LTx and persistent high inflammatory activity**

<u>Typ of surgery:</u>

- **preferred complete/total proctocolectomy iwith**
- **Ileal Pouch-Anal-Anastomosis (IPAA) = pouch created from the ileum**

IBD and colonoscopy after LTx for PSC

- **1/3 experiences exacerbation of IBD after liver transplantation**
- **Low threshold for repeat colonoscopy in order to**

  exclude drug-effects (MMF-associated colitis)

  Infectious etiologies (C Diff or Cryptosporidiosis colitis…)

- **Selected cases = individual decisions – tricky to handle**

  recurrent PSC after liver transplantation and severe colitis

  trial: swith Tacrolimus to Cyclosporin

- **If running well: do not forget annual colonoscopy after LTx**

  (even higher risk of malignancy after transplantation/ immunosupp.)

IBD and course of disease for PSC ?

- **PSC can occur before and after onset of IBD or even after LTx**
- **Presence of UC (IBD) with active inflammation: progression of PSC**
- **Favourable outcome in PSC-IBD patients undergoing colectomy**
- **Higher inflammatory activity in colon/UC after LTx = increases risk of PSC recurrence**
- **Anti-TNF-/Vedolizumab treatment is safe post-LTx**
- **IBD-treatment else follows the same recommendations and guidelines as without PSC**

De Vries AB et al. WJG 2015
Weismueller TJ et al. Gastroenterology 2017
Nordenvall C et al. APT 2018

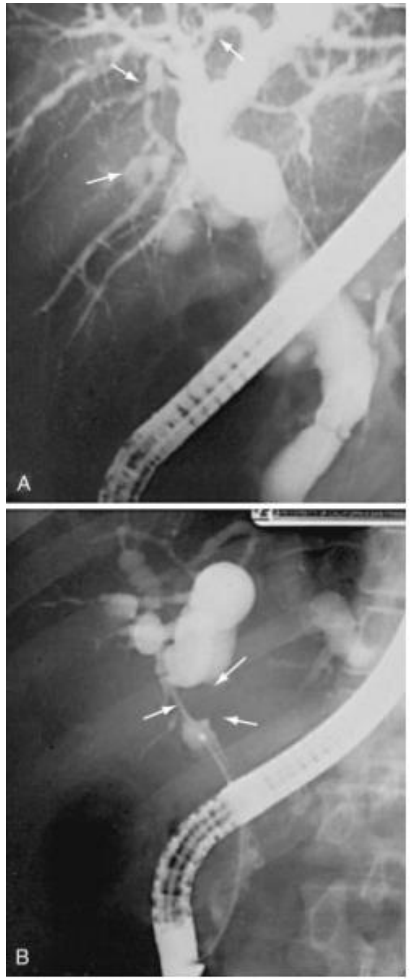
When to go for ERCP ?

- **Established PSC**:
  i) therapeutic indication or ii) risk of CCA

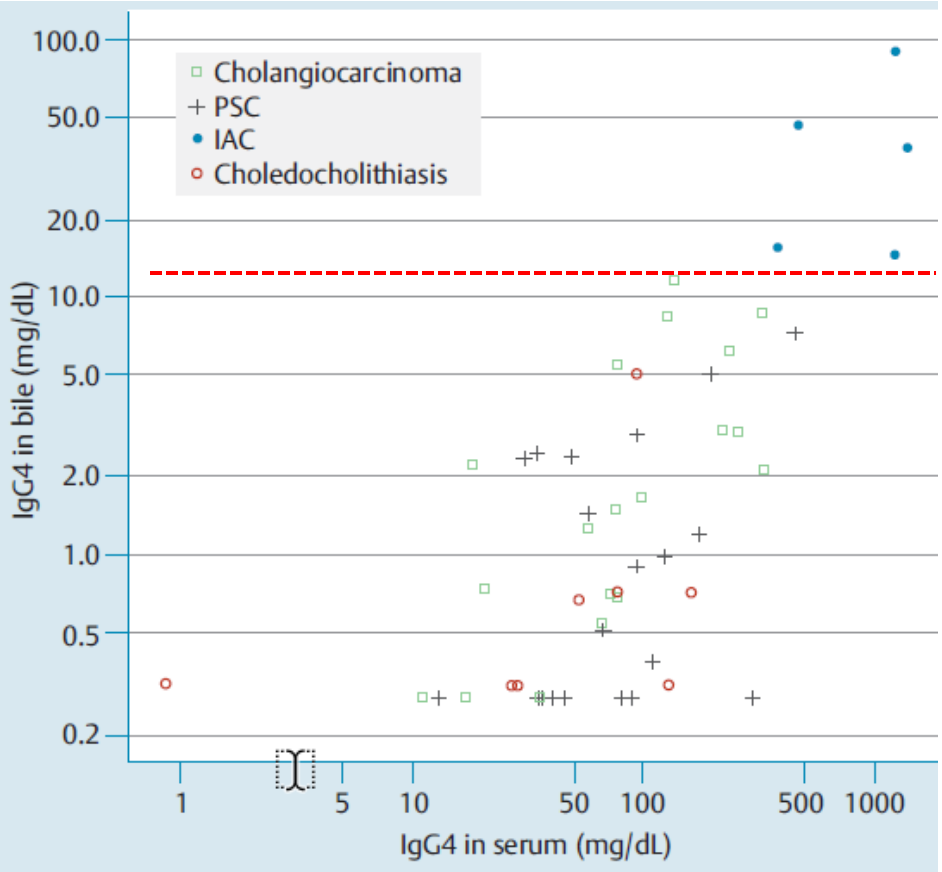
  -clinically relevant or worsening symptoms
  jaundice, cholangitis, pruritus, weight loss
  -rapid increase of AP and/or bilirubin
  -new or progression of known dominant stricture (MR)

- **persistent PSC suscpicion** despite normal high-quality MR/MRCP and normal liver biopsy

In advanced stage/cirrhosis: benefit maybe limited



Besides Cholangiogramm, what to do in ERCP to assess/test for IgG4-Cholangiopathy ?



IgG4-level in bile

PSC serum IgG4
can be elevated
but not
in bile (n=23/6)
AUC 0.99 (?)

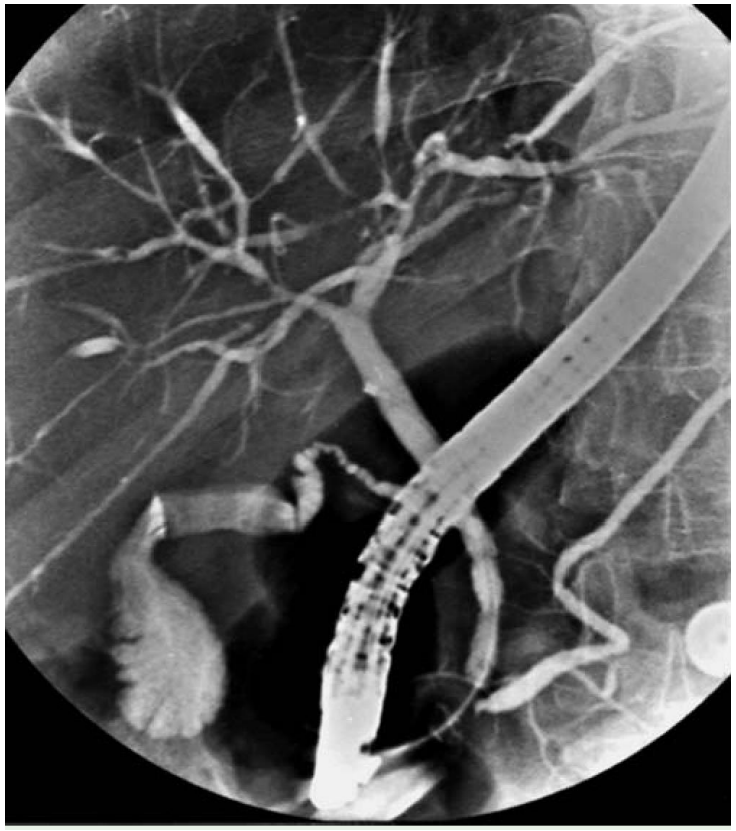
Biopsy papilla vateri

> 50%
IgG4 + in IAC/P

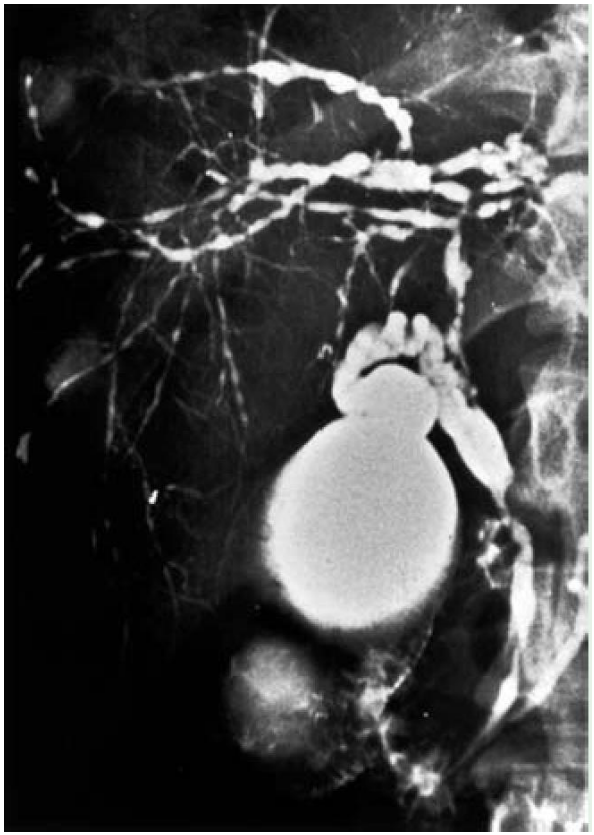
Vosskuhl, Lankisch et al. Endoscopy 2012

ERCP-findings: Amsterdam-classification

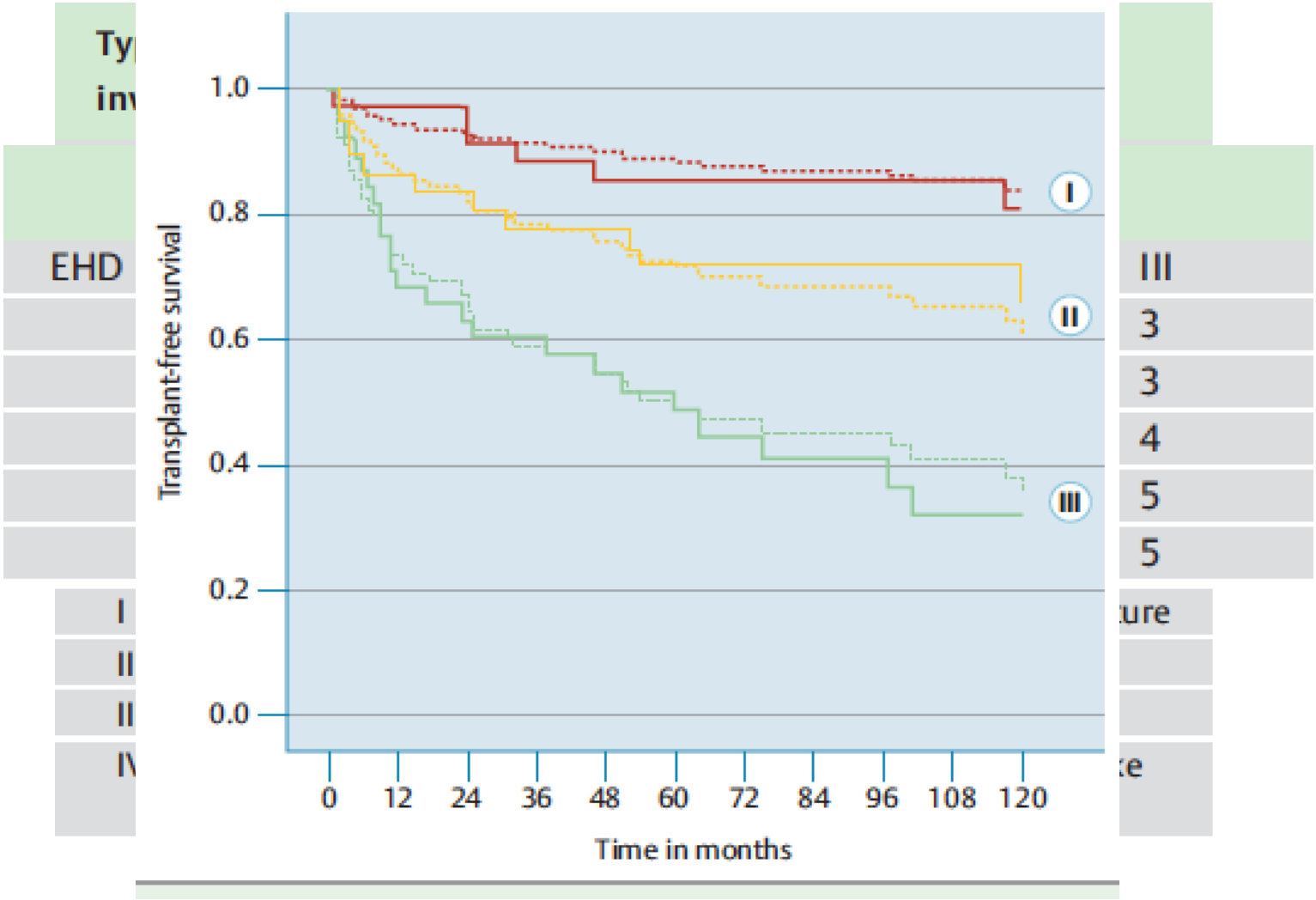
Full occlusion cholangiogramm mandatory:
Type I (intra- and extrahepatic)



Type II intra-
Type III extrahepatic



ERCP-findings: Amsterdam-classification



Relevant and high-grade stricture ? - definition, frequency, risks

Definition: relevant stricture: = high-grade on imaging in CBD or hepatic main ducts with signs or symptoms of obstructive cholestasis and/or bacterial cholangitis

High-grade stricture: >75% reduction of duct diameter

Frequency: 45% to 58% of PSC patients during follow up

Risks: CCA (about 5% in dominant stricture), cholangitis

ERCP: management of high-grade stricture ?

- Always use peri-interventional **antibiotics!**
- **Sphincterotomy** not routinely - only small if at all

  done when difficult access and/or therapeutic interventions
- Before any endoscopic therapy: **brush cytology** and/or **biopsy**

- **Dilatation** preferred method because majority of studies only dilated
- significant improvement in LTx-free survival only shown for dilatation

  scheme: repeat 1-4 weeks, CBD up to 8 mm, DHR/L 6 mm till success
- **Stenting**: increased risk of AE (cholangitis, pancreatitis, perforation)=

  only in selected cases and only short-term (1-2 weeks)
- ERC in PSC per se higher complication risk than other indications: > 6%

What you should know about portal hypertension (PH) in PSC ?

- **Recommendations do follow Baveno VII and EASL guidelines**
- **Clinical significant PH can occur in absence of cirrhosis:**

  e.g. due to pre-sinusoidal PH and hence

  HVPG can underestimate full degree of PH
- **GEV maybe present in PSC patients with HVPG < 10 mmHg**

- **Nodular regenerative Hyperplasia (NRH) and/or portal venopathy**
- **Causing portal hypertension in 3-5% of cases**

Singh S et al. Clin Gastro Hepatol 2013; Abraham SC et al. Am J Surg Pathol 2006

What about osteoporosis in PSC ?

237 PSC patients (74% with IBD)

Osteoporosis in 15% = 24-fold increased risk vs. matched control

Osteopenia up to 40% of PSC-patients

Risk factors for presence/development of osteoporosis in PSC ?

- ✓ **Older age (> 54)**
- ✓ **Low BMI (< 24 kg/m2)**
- ✓ **Active IBD/inflammation and/or IBD > 19 y**

Prevalence:

all three vs. None

75% vs. 3%

1% loss in bone mass/year

Bone densitometry

In cirrhosis and/or cholestasis every 2 years

At first diagnosis of PSC any patient should undergo DEXA-testing

Angulo P et al. Gastro 2011, Younossi Z et al. AJG 2000

PSC and CCA: epidemiology, risk, prognosis

- Life-time risk up to 15-20% (=400-fold increased)
- 10-year cumulative risk: 6-9% (incidence-rate ca. 0.5%/year)
- Up to 50% discovered at initial diagnosis of PSC (or < 1 year FU)
- Prognosis dismal: ≤ 2 years median overall survival

- **Risk factors for CCA:**
  - ✓ Presence and duration of IBD (but not PSC)
  - ✓ UC with colorectal cancer/ dysplasia
  - ✓ Elevated serum bilirubin, variceal bleeding
  - ✓ NKG2D gene polymorphism

When to suspect CCA in PSC ?

- **Newly diagnosed PSC with high-grade stricture/s**
- **Known PSC with worsening of signs/symptoms and/or progressive strictures or**
- **New mass lesion on imaging**

Most common location of CCA in PSC ?

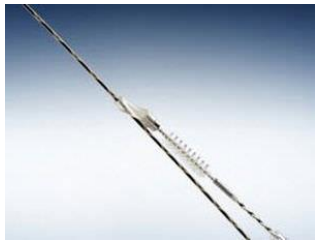
- **50% perihilar**
- **42% CBD**
- **8% intrahepatic**

Work-up when CCA is suspected in PSC ?

- **Experienced multi-disciplinary team is recommended**
- **Cross-sectional imaging = first diagnostic test**

  usually contrast-enhanced MRI (4-phase CT)
- **Potentially followed by ERCP when high-grade stricture is present**

Stricture – diagnostic work-up for CCA in PSC ?



Brush-cytology:

Sensitivity 43%; Specificty 97%, NPV 87%*

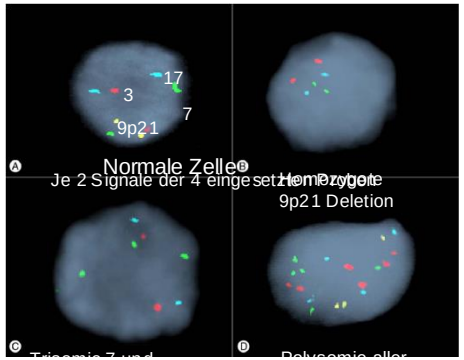
Chance of CCA in dominant stricture: ca. 5%

> 90% CBD or perihilar in location

Lack of dominant stricture does not rule out CCA-> always do Brushing!

FISH/chromosomal assessment:

- Polysomy prognostic as relevant as proven CCA
- Dominant stricture: polysomy: 88% specificity for CCA
- Persistent polysomy-> 69% develop CCA



Cholangioscopy with SpyBite-Biopsy

- Improves diagnostic yield
- Triple (Brush+Biopsy+FISH): increased sensitivity to 82% (NPV 87%)

Stricture – diagnostic work-up for CCA in PSC ?

Molecular profiling in cholangiocarcinoma: A practical guide to next-generation sequencing

Albrecht Stenzinger [a], Arndt Vogel [b], Ulrich Lehmann [c], Angela Lamarca [d,e], Paul Hofman [f], Luigi Terracciano [g,h], Nicola Normanno [i,*]

- NGS testing should be performed early, ideally at first diagnosis of CCA.
- Both DNA and RNA should be extracted from the same biopsy to allow for either RNA-seq or DNA-seq NGS.
- RNA-seq is recommended for detection of novel gene fusions and to provide information on gene expression and alternative splicing.
- Use an approved CDx NGS test to match identified genomic alterations to approved targeted treatments.

Cancer Treatment Reviews 2024

PSC and Gallbladder: Polyps and Cancer

- Risk for GB-cancer: 1 per 1000 patient-years

Annual ultrasound recommended

Any mass lesion > 8 (-10) mm or growth or

CEUS-positivity: cholecystectomy

Van Erp Liv International 2020; Eaton JE AJG 2012; Buckles AJG 2002

Routine Surveillance in PSC

Every 12 months (for all, every 6 months pts with significant risk):

-clinical evaluation (including quality of life)

-serum liver tests: ALP, AST, Platelets, PT

Every 12 months (even for patients at low risk)

-MRI/MRCP and/or US (attention gallbladder)

-colonoscopy

-Elastography and/or ELF test

*Liver imaging by US every 6 months in patients with cirrhosis. §Ductal imaging every 3 years in small duct PSC with stable liver tests. **Every 5 years in those without IBD at initial staging. AFP, alpha fetoprotein; ALP, serum alkaline phosphatase; DEXA, dual energy X-ray absorptiometry; EGD, esophagogastroduodenoscopy; ELF test, serum enhanced liver fibrosis test; IBD, inflammatory bowel disease; LSM, liver stiffness measurement; MRCP, magnetic resonance cholangiopancreaticography; PT, prothrombin time; US, ultrasound.

When clinically indicated or ALP/Bili increase or △LSM > 1.5kPa/y or ductal progression then what to do ?

- Suspected cholangiocarcinoma: serum CA 19.9 and MRCP/ MRI liver with contrast and ERCP with cytologic or histologic sampling
- Suspected features of auto-immune hepatitis or drug toxicity: serum IgG and autoantibodies of AIH, consider liver biopsy
- Suspected clinically relevant portal hypertension (Baveno VII criteria[114]): EGD, consider non-selective beta blockers

MRI: parenchymal changes, ductal changes, signs portal hypertension
Plus nowadays MR-elastography with good diagnostic accuracy

Medical Treatment of PSC ? UDCA – others ?

- still no evidence that UDCA is beneficial in improving symptoms or transplant-free survival but 15-20mg/kg/day can be given.

- **High-dosage: > 25 mg/kg: even poorer clinical outcome (CRC, cirrhosis, varices, need for liver transplantation or death)**

- UDCA is also not recommended as chemopreventive agent (CRC) but some data indicate a reduction in risk for CRC (Singh S et al. IBD 2013; 19: 1631-38 meta-analysis)

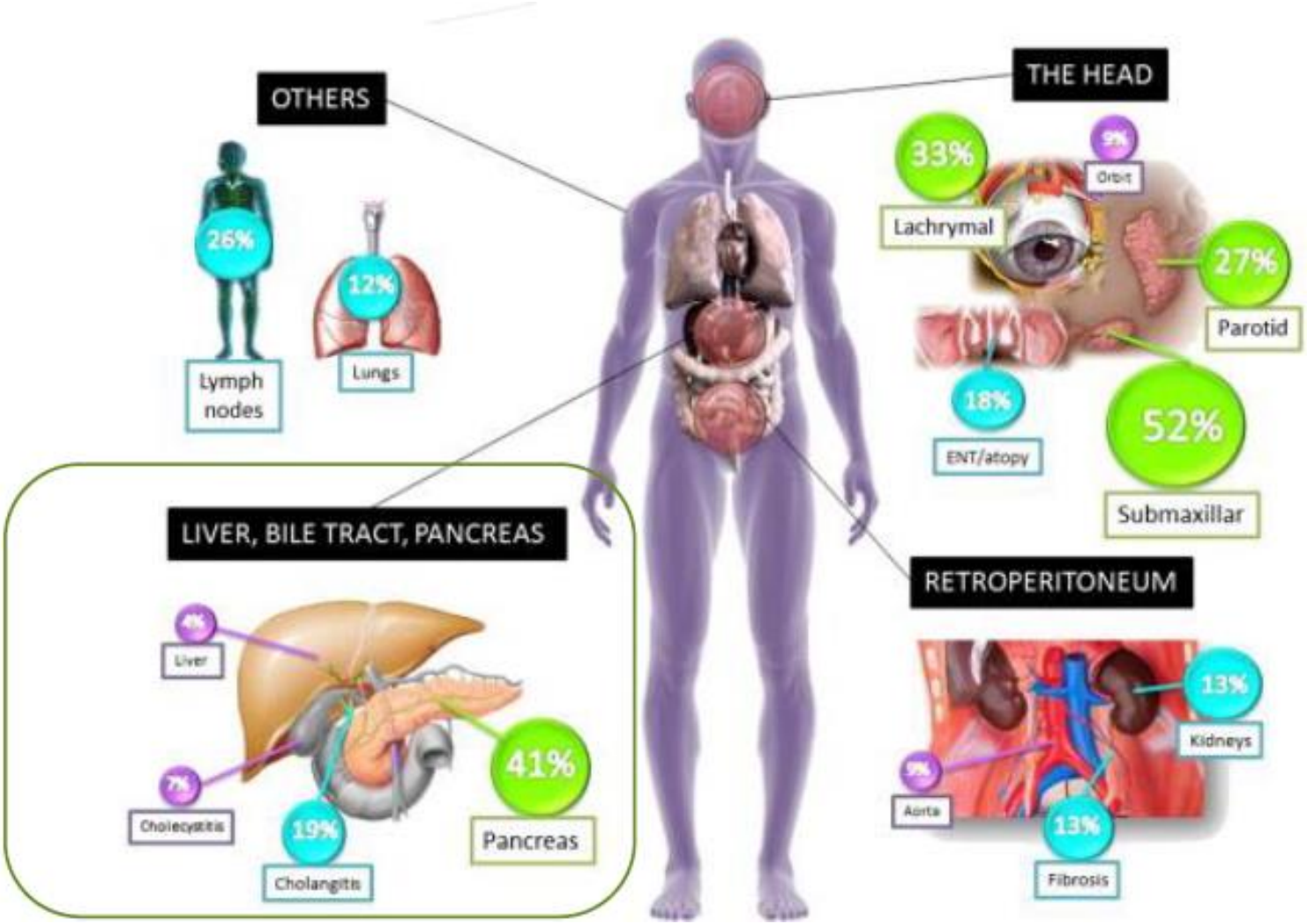
- Corticosteroids, Immunosuppresants for AIH (overlap-patients)

Liver Transplantation in PSC: when, how...

- One of the best indications per se: 5y survival > 80%
- Listed due to **complications of cirrhosis, portal hypertension**
- **Specific of PSC** (rarely): Recurrent/ refractory cholangitis, intractable pruritus often frail patients (sarcopenia, osteopenia etc.)

- **CCA:** perihilar and < 3 cm
- Mayo-Protocol: neoadjuvant radiation, radiation-sensitization chemotherapy, oral capecitabine, laparoscopy before LTx
- Re-PSC of graft: 20-25% in 5-10 years
- Higher risk of graft rejections in PSC than other indications

Frequencies and types of IgG4-related diseases



Brito-Zeron et al. Autoimmunity Reviews 2014

IgG 4 and its specific features are…

Half-life in serum	**21 days**
% of total IgG normally	**2-4%**
kDA size	**150 kDA**

IgG4-hepatobiliary disease – HISORT is…. ?

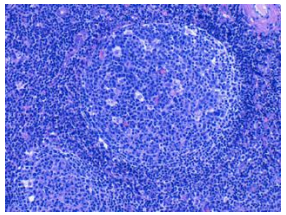
IgG4

(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

Adapted from: Chari ST, Takahashi N, Levy MJ, et al. A diagnostic strategy to distinguish autoimmune pancreatitis from pancreatic cancer. Clin Gastroenterol Hepatol 2009; 7:1097.

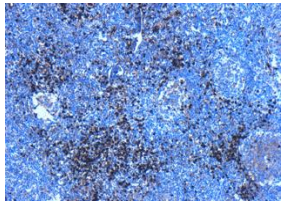
Microscopic characteristics in IgG4-hepatobiliary disease

IgG4



- lymphoplasmacytic infiltration
- storiform pattern of fibrosis
- obliterative phlebitis with a variable presence of eosinophils

- ✓ >10 IgG4+ plasma cells per HPF in a biopsy specimen
- ✓ >50 IgG4+ plasma cells per HPF in a resection specimen
- ✓ Plus an IgG4+:IgG+ plasma cell ratio of >40%



Brush cytology not sufficient

Biopsy to go for= cholangioscopy

Plus Biopsy of papilla: up to 52-72% positive in IgG4-RD

IgG4-hepatobiliary disease – epidemiology, risk factors

IgG4

- **Most frequent extra-pancreatic manifestation of IgG4-related diseases**
- **In AIP: ca. 10% IgG4-SC and 23% IgG4-Hepatopathy**
- **Rarely (1-8%) hepatic involvement without AIP**
- **Male (7:1!), > 60 year of age,**

- **Risk factors: chemicals/toxins (blue-collar-worker),**

  allergy/atopy/eosinophlia, other autoimmune disease (thyroid, coeliac..)

  Genetic pre-disposition (HLA-DRB1, IL1R1)

IgG4-serum levels- how useful ? Differentiate PSC

IgG4

- > 1.4g/l: 25-80% of IgG4-SC (but 20-30% normal levels)
- > 2.5 g/l: IgG4-SC vs. PSC: sensitivity 70-89%, specificity 95%
- 1.4-2.8 g/l: ratio IgG1:IgG4 > 0.24: sensitivity 86%, specificity 95%, NPV 90%
- > 5.6 g/l: specificity and PPV 100% (?) vs. PSC (+ CCA)

PSC per se:

- > 20% liver explants present with IgG4+cell infiltrate (but NOT diffusely)
- > 10% present with increased serum IgG4 (> 1.4 g/l)
- both conditions associate with worse prognosis/= seek CCC
- + associates with: reduced HLA-B*08, increased –B*07, DR-B1*15 frequency

Diagnosing IgG4-hepatobiliary disease

H – Histology
- Lymphoplasmacellular infiltrate
- Obliterative phlebitis
- Storiform fibrosis
- IgG4+ plasma cells:
  - Biopsy: >10/HPF
  - Resection: >50/HPF
  - IgG4+/IgG+ plasma cell ratio >0.4

I – Imaging

1. Non-invasive imaging: CT/MRCP+MRI
2. EUS, ERCP, cholangioscopy + histopathology

Suggestive of IRC:
- Bile duct wall thickening
  - Longitudinal, >2.5 mm, band-shaped
  - >0.8 mm in non-strictured areas
- Absence of short bile duct stenoses

S – Serology
- Serum IgG4
  - >4x ULN pathognomonic
  - 1-2x ULN: IgG4/IgG1 ratio >0.24 indicative of IRC
- Serum IgG2 high
- Future: single accurate diagnostic test?

O – Other organs
- History of organ resection, biopsy material
- Careful history and physical examination
- Imaging and histology upon indication
- Assess pancreatic involvement including exo- and endocrine function
- Future: role for whole body PET-CT?

Rt – Response to therapy

After 2-4 weeks of induction therapy
- Biochemical: ALP, gGT, bilirubin
- Serology: serum IgG4
- Imaging: improved biliary strictures
- Future: role for whole body PET-CT?

Presence of biliary strictures

A: Previous histology
compatible with IRC or type 1 AIP

B: Imaging + serology
1. Classical imaging findings of type 1 AIP
+
2. Elevated serum IgG4

C: Pathognomonic serology
Serum IgG4 >4 xULN

D: Miscellaneous
Two or more of the following:
- Serology: elevated serum IgG4
- Imaging: findings suggestive of type 1 AIP
- Other organ involvement
- Bile duct biopsy: IgG4⁺ plasma cells >10/HPF

Probable IRC:
Assess response to steroid therapy

Definitive IRC:
Start treatment:
- Remission induction with prednisone (0.5-0.6 mg/kg/day)
- After 2-4 weeks: consider immunomodulator for maintenance of remission and steroid sparing effect
- Refractory patients: reconsider diagnosis; consider rituximab

Follow up:
Imaging: improved biliary strictures
Biochemical: ALP, γGT, bilirubin ↓
Serology: IgG4

Every effort should be made to rule out biliary or pancreatic malignancy before starting corticosteroid therapy

Features contradictory of IRC diagnosis:
- Non-response to prednisone therapy (biochemical, serological, imaging)
- Pancreatic duct dilatation with pancreatic atrophy
- Atypical brush cytology (positive FISH)

Autoantigens described in IgG4-hepatobiliary disease ?

IgG4

- **Annexin A11**
- **Laminin 511-E8**
- **Galectin-3**
- **Prohibitin 1**

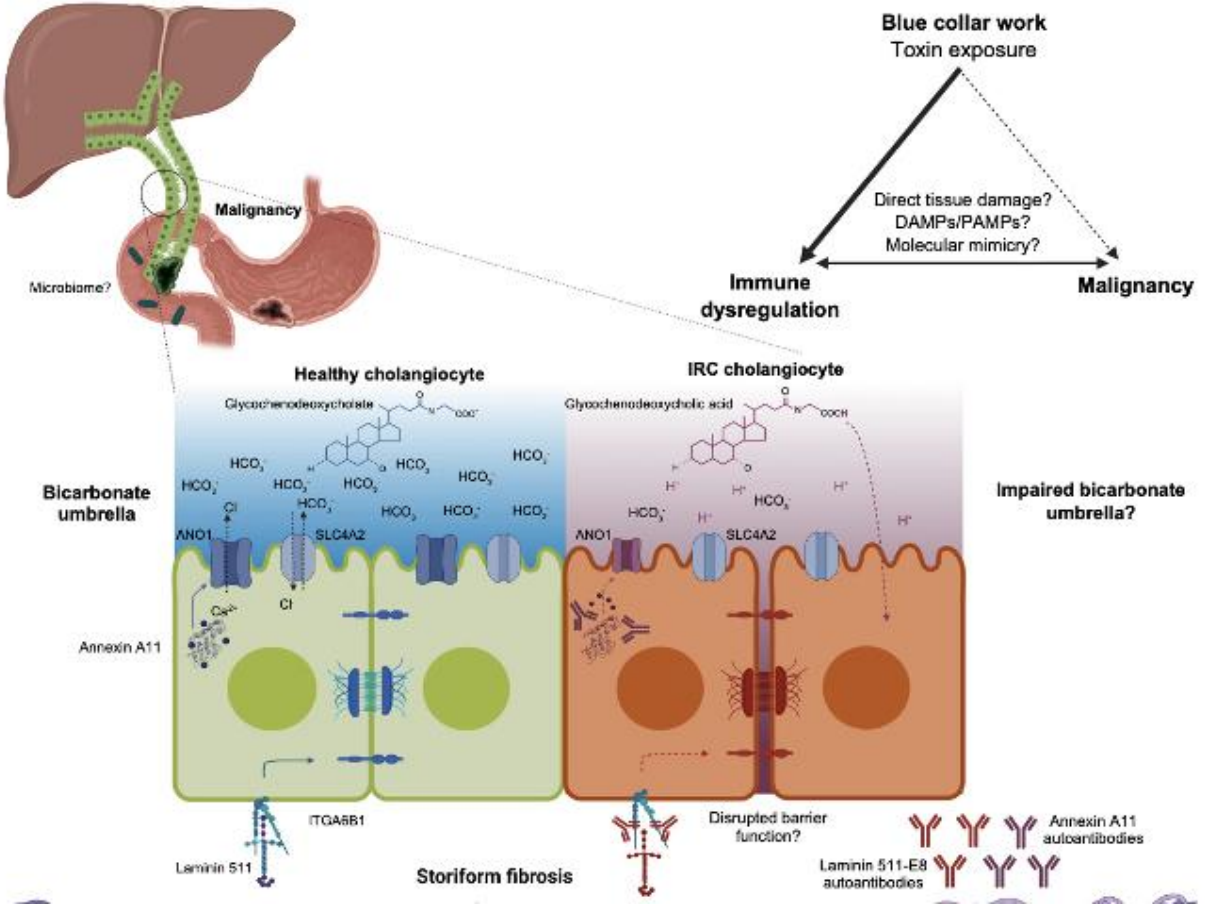
= mechanisms of molecular mimickry

Role of auto-antibodies against auto-antigens in IgG4-hepatobiliary disease

Autoantibodies
Against Annexin A11
Anti-Annexin A11
IgG1/IgG4

Mediate

Weakening of
HCO3-/bicarbonate
umbrella

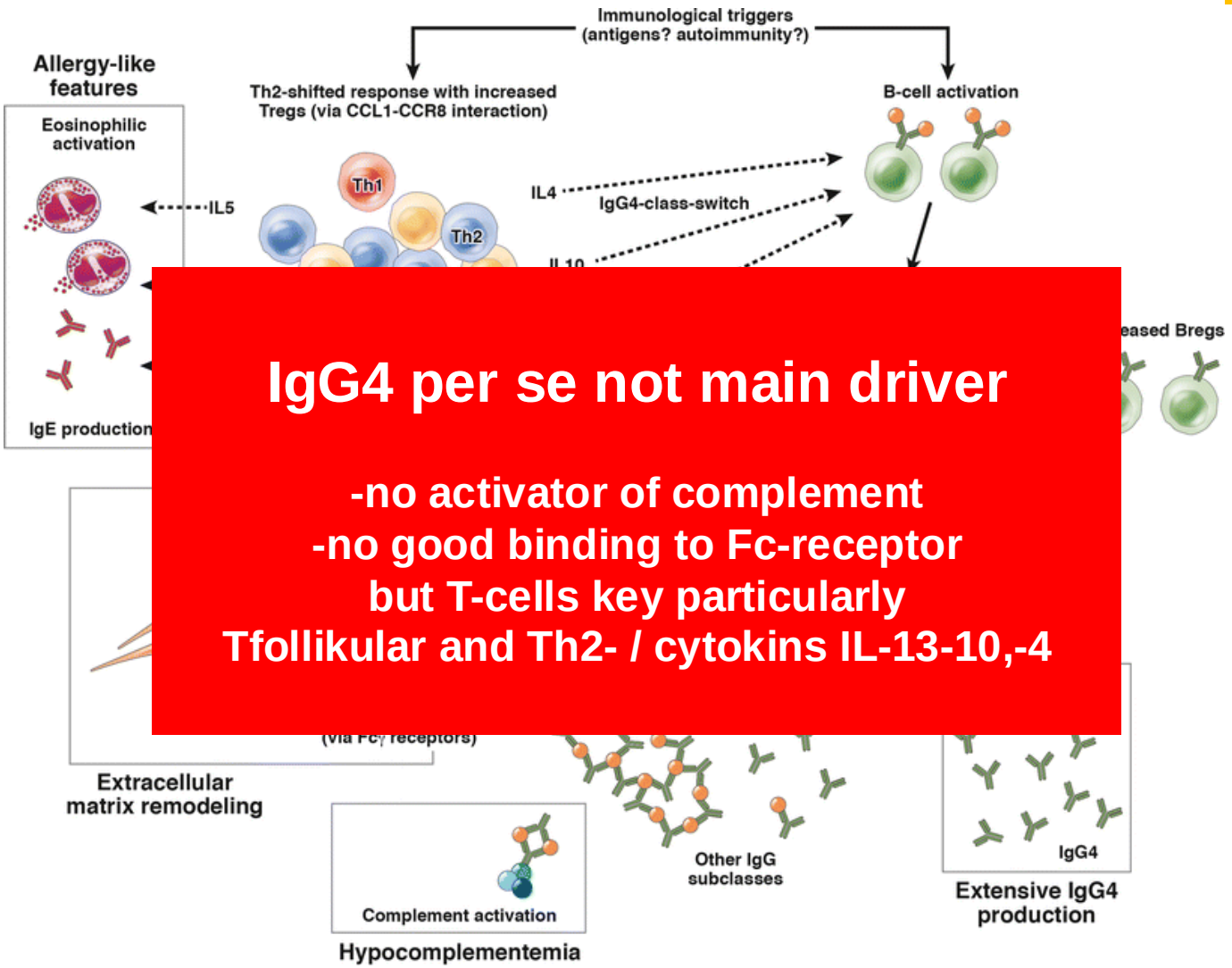


Laminin 511-E8 (ECM) protects cholangiocytes against T-Ly Induced barrier dysfunction (e.g. via IL4 and toxic BA)

Reich M et al. J.Hep 2021 Kersten et al. J.Hepatology 2023

Which immune cells are involved in pathophysiology of IgG4-hepatobiliary disease ?

IgG4

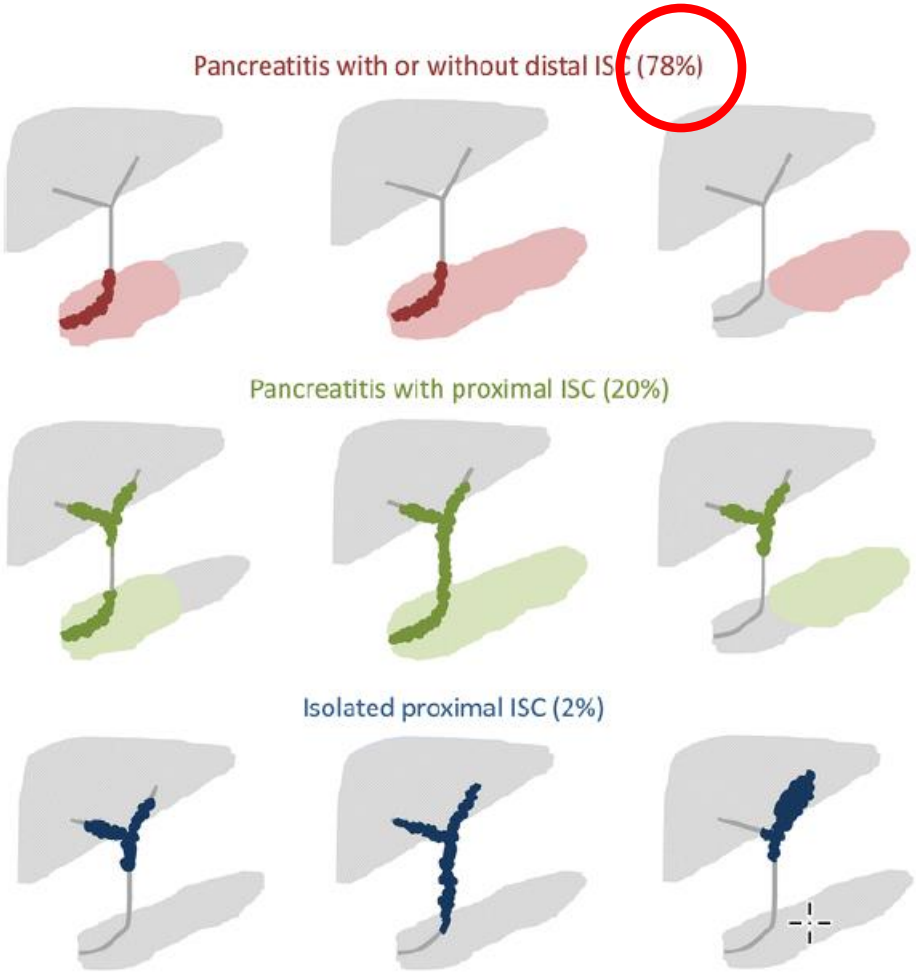


IgG4 per se not main driver

-no activator of complement
-no good binding to Fc-receptor
but T-cells key particularly
Tfollikular and Th2- / cytokins IL-13-10,-4

Kamisawa et al. Lancet 2015

Distribution and frequency of biliary tree involvement in IgG4-related disease ?



Close association
With AIP
Some studies > 90%

Zen et al. J Gastroenterol 2016
Briton-Zeron et al. Autoimmunity Review 2014

IgG4-sclerosing cholangitis: classification

IgG4

Distal CBD
Most frequent
Often with AIP

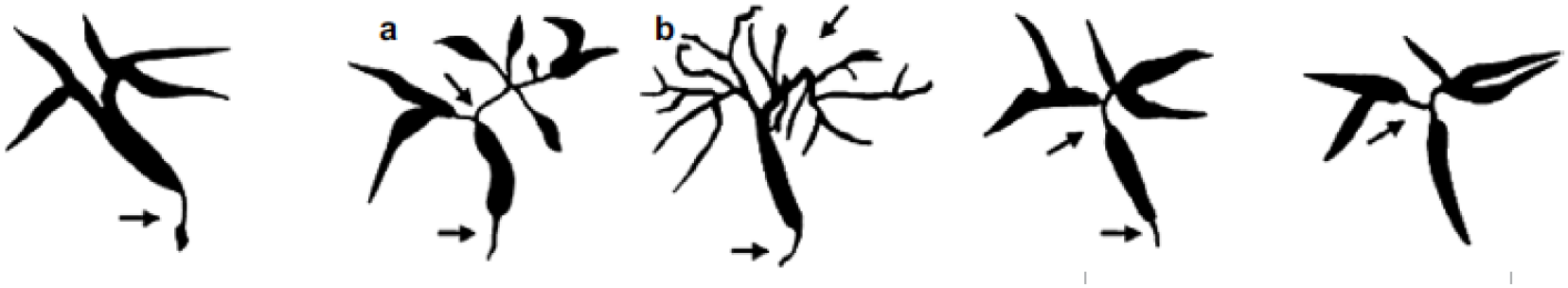
A: with
Pre-stenotic
dilatation

B: without
Pre-stenotic
dilatation

Hilar + CBD

Hilar alone

Type 1 | **Type 2** | **Type 3** | **Type 4**



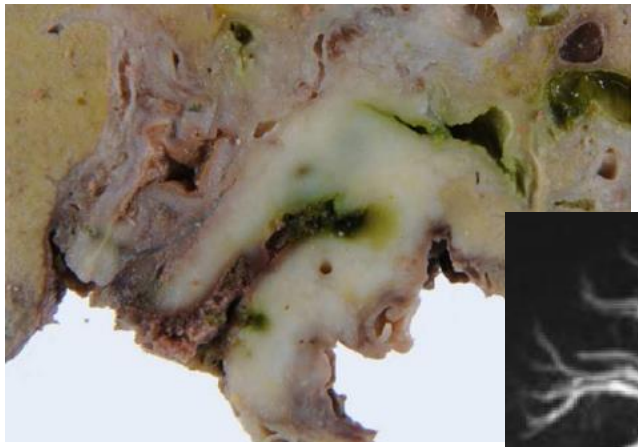
DD: pancreatic Ca,
Distal CCC, CP

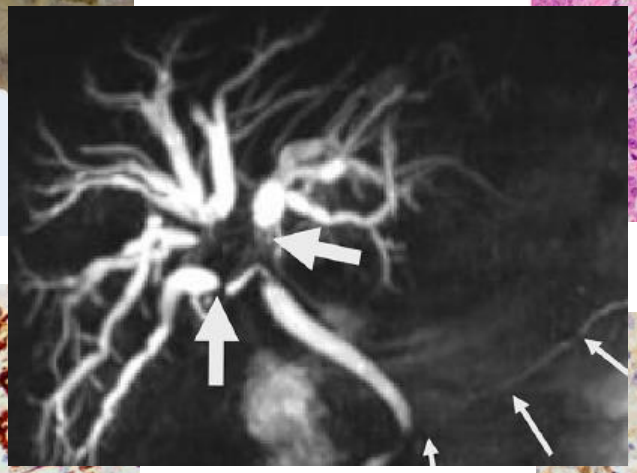
DD: PSC, SSC

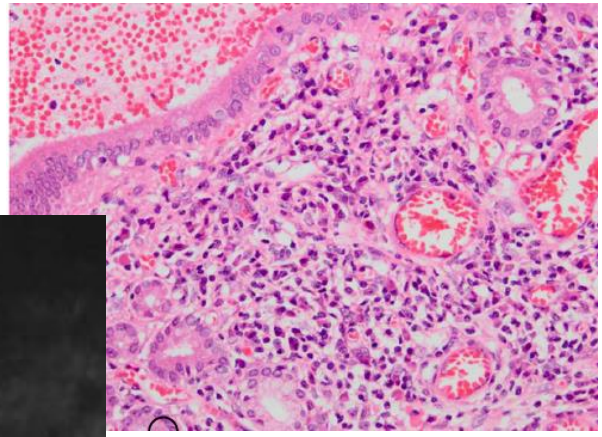
DD: Hilar CCA

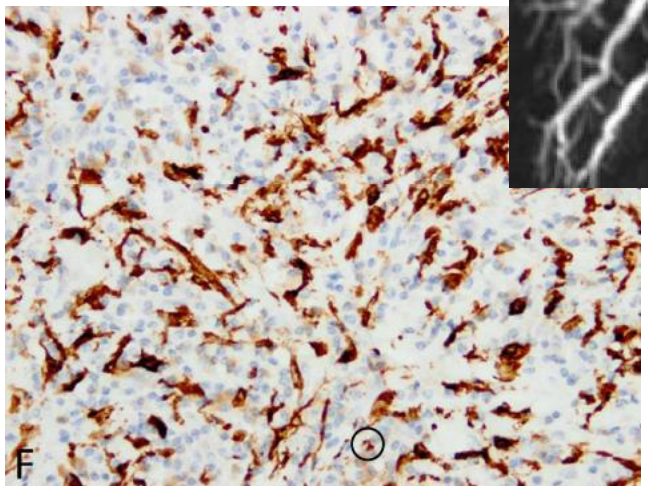
Okazaki et al. J.Hepatol 2014

Type 3 – IgG-SC mimicking central CCC/Klatskin IV

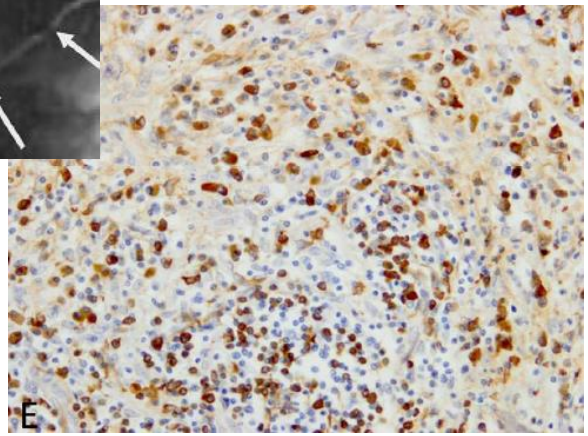








Zen et al.
J.Gastroenterol 2016



Typical ERCP-features in IgG4-sclerosing cholangitis ?

IgG4

Strictures in cholangiogramm:

- ✓ **Long + multifocal**
- ✓ **mild dilatations upstream**
- ✓ **thin diffusely narrowed pancreatic duct**

Malignancy must be excluded

Sensitivity 45% = forget it !

Diagnostic endoscopic optimized work-up ?

IgG4

Particularly isolated (biliary) IgG4-slerosing cholangitis difficult to diagnose

All you can do:

- **ERCP (plus cholangioscopy)**
- **Brush-cytology, biopsy**
- **Bile fluid**
- **EUS (plus FNA)**
- **Ampullary biopsy**
- **Liver biopsy**

Caveats/problems:

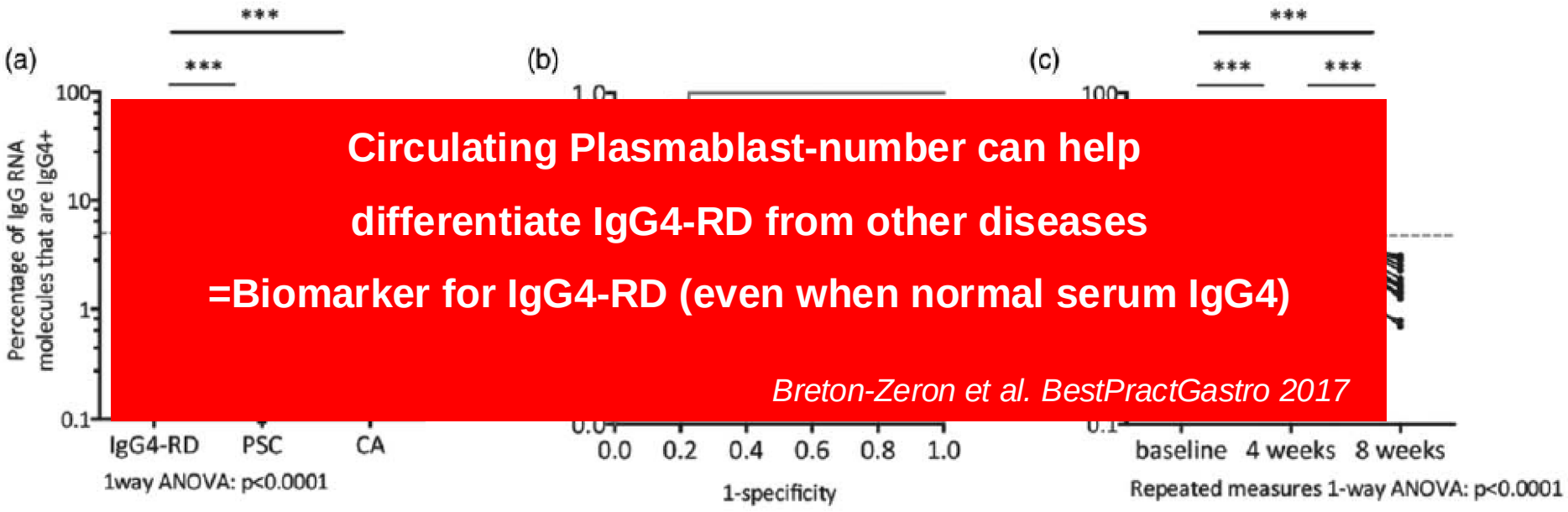
- ✓ **patchy disease**
- ✓ **insufficient tissue/cells**
- ✓ **reduced numbers IgG4-cells**

  E.g. in fibrotic stages
- ✓ **IgG4-cells in other diseases**

  e.g. malignancy, inflammation

How to differentiate PSC/CCA from IgG4-SC ?

NGS-> qPCR for expanded B-Cell-Clone and IgG4+-RNA



Circulating Plasmablast-number can help differentiate IgG4-RD from other diseases

=Biomarker for IgG4-RD (even when normal serum IgG4)

Breton-Zeron et al. BestPractGastro 2017

Sensitivity 94%, Specificity 99%

*: some sIG4 high,
only one false positive (cirrhotic)

Breuers et al. Curr Opin Gastroenterol 2017

Treatment for IgG4-sclerosing cholangitis ?

IgG4

Corticosteroid 0.6 (-1) mg/kg KG

(30-40mg/Tag) for 4 weeks

Tapering: 5mg/week, ending at week 12

- **Re-assess after 4-6 weeks**
- **Serum IgG4: only minority will normalize**
- **Complete resolution of strictures and liver tests = response**
- **Achieved in about 2/3 of IgG4-SC**

Recurrence/Refractory IgG4-sclerosing cholangitis Risk ? Treatment-Options ?

- **Ca. 50% will show some recurrence (majority < 6 months after EOT)**
  - **Risk-factors:** high IgG4, multi-organ-involvement, prior recurrence

    Typ 2-4 (hilar and intrahepatic disease manifestation)
    - **Immunmodulators: best evaluated azathioprine**
  - **Rescue: Rituximab (Anti-CD20-> killing expanded B-cell-clone)**

Maintenance treatment of IRC is suggested with steroid-sparing immunosuppressants for up to 3 years (*e.g.* azathioprine, 6-mercaptopurine, mycophenolate mofetil) and potentially beyond, starting during predniso(lo)ne tapering, to reduce the risk of IRC relapse. Rituximab can alternatively be considered when relapse has occurred **(LoE 5, weak recommendation, 100% consensus).**

Ghazale A Gastroenterol 2008; EASL CPG 2022 J.Hepatology

IgG4-SC differs from PSC in.....

- **Rare disease**
- **Usually multi-organ-disease**
- **Histology needed to confirm diagnosis**
- **More benign disease**

less malignant development (2-fold*), infrequent end-stage cirrhosis

- **Good response to steroids**

*: presumably only if chronically active disease

Secondary sclerosing cholangitis in critical ill patients sSC-CIP

- **All mechanical ventilation ICU (high—pressure)**

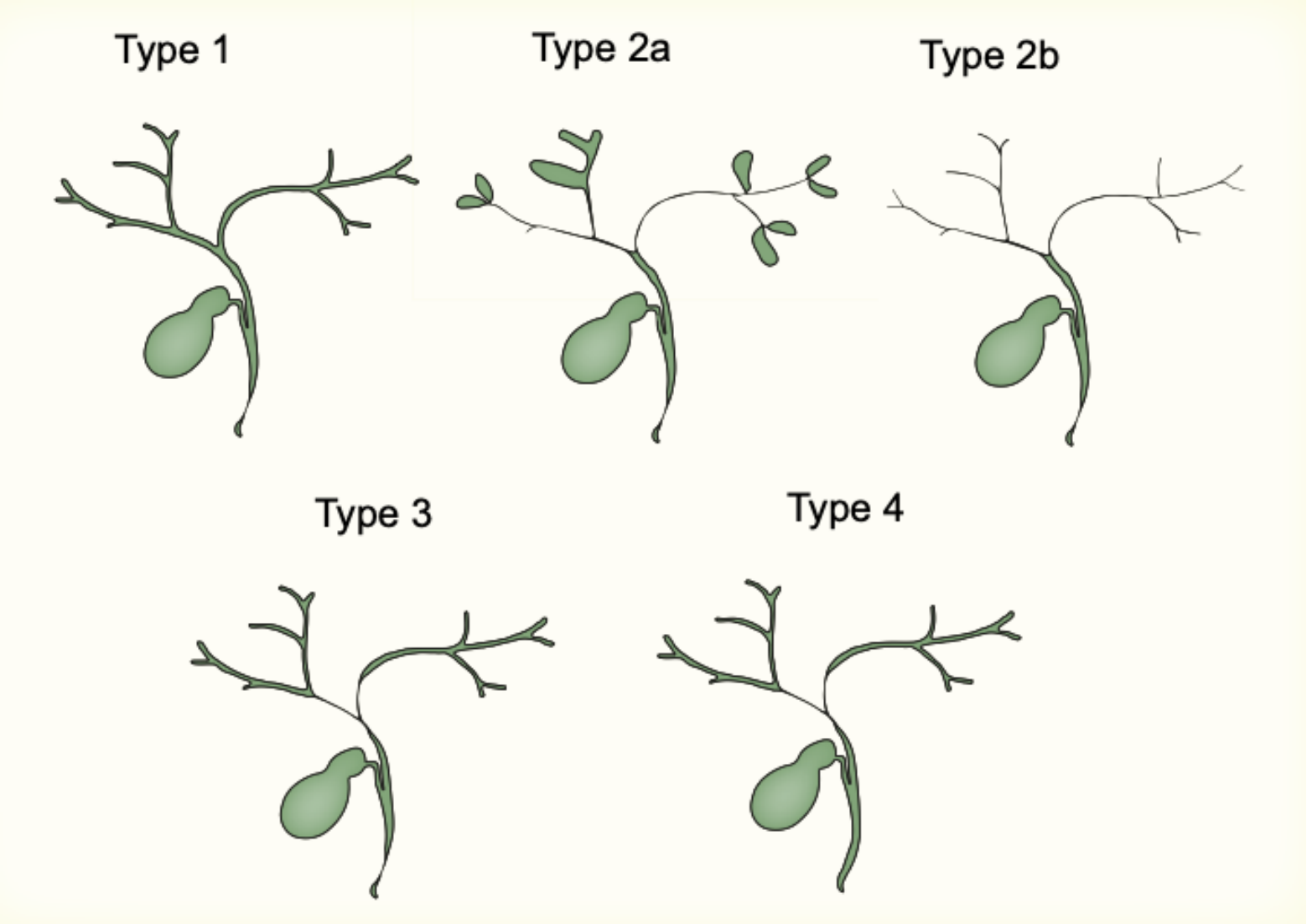
ischemic-type cholangiopathy + toxic bile

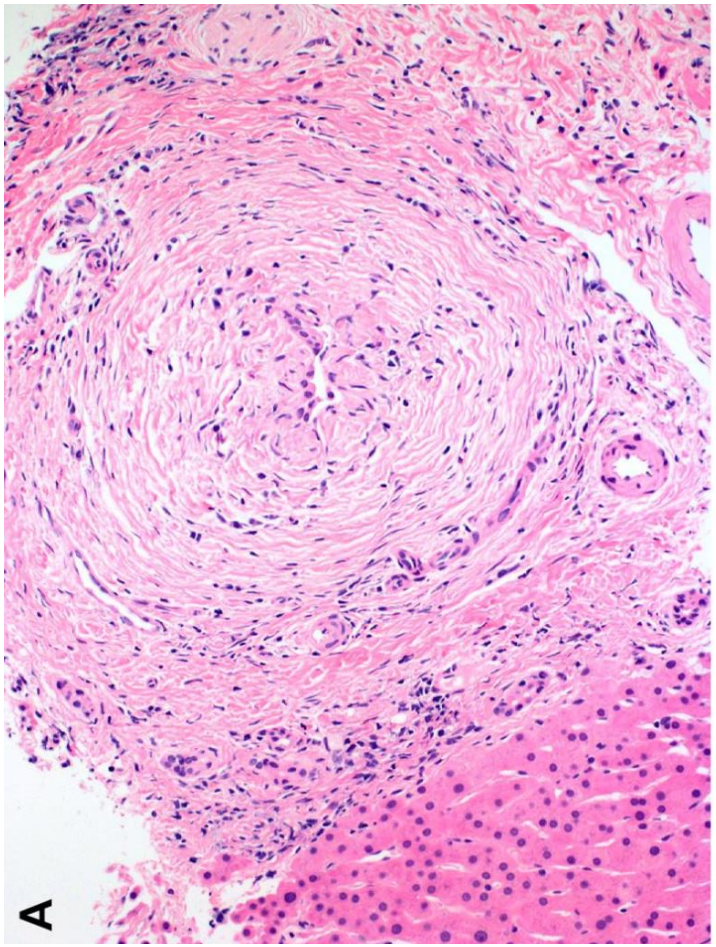
Often rapidly progressive disease, hepatic failure

- **Mean survival 17-40 months**
- **No evidence-based medical treatment**
- **Endoscopic removal biliary casts + UDCA 10-15mg/d only treat. options**
- **Liver transplant only curative measure in advanced stages**

Gudnason HO et al. Clin Exp Gastro 2017; Martins P et al. GE Port J Gastroenterol 2020

Danke für die Aufmerksamkeit


Type 1
Type 2a
Type 2b
Type 3
Type 4



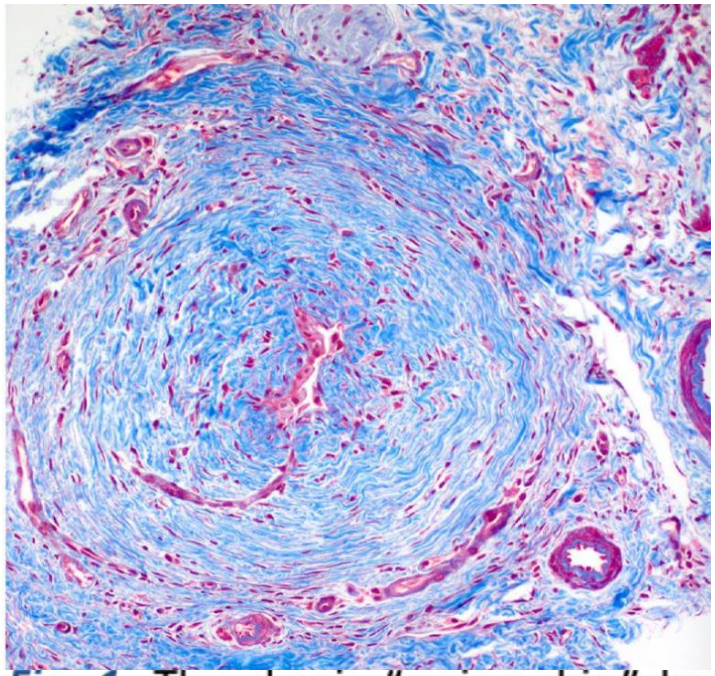
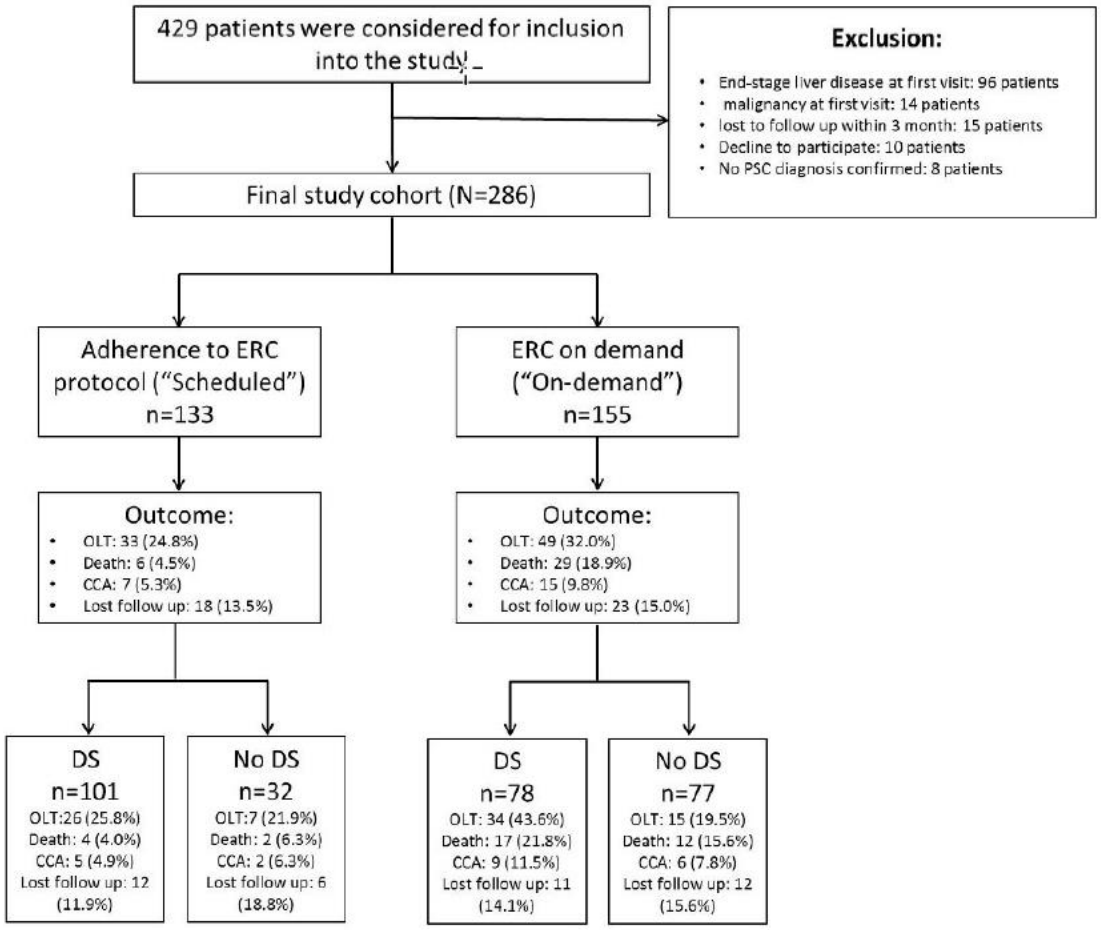


Fig. 1. The classic "onion-skin" lesion of PSC characterized by concentric fibrosis around a bile duct. There is marked luminal narrowing with epithelial degeneration and atrophy. Minimal lymphocytic infiltrates and mild ductular reaction are noted in the portal tract


429 patients were considered for inclusion into the study
Exclusion:
End-stage liver disease at first visit: 96 patients
malignancy at first visit: 14 patients
lost to follow up within 3 month: 15 patients
Decline to participate: 10 patients
No PSC diagnosis confirmed: 8 patients
Final study cohort (N=286)
Adherence to ERC protocol ("Scheduled") n=133
ERC on demand ("On-demand") n=155
Outcome:
OLT: 33 (24.8%)
Death: 6 (4.5%)
CCA: 7 (5.3%)
Lost follow up: 18 (13.5%)
Outcome:
OLT: 49 (32.0%)
Death: 29 (18.9%)
CCA: 15 (9.8%)
Lost follow up: 23 (15.0%)
DS n=101
OLT:26 (25.8%)
Death: 4 (4.0%)
CCA: 5 (4.9%)
Lost follow up: 12 (11.9%)
No DS n=32
OLT:7 (21.9%)
Death: 2 (6.3%)
CCA: 2 (6.3%)
Lost follow up: 6 (18.8%)
DS n=78
OLT: 34 (43.6%)
Death: 17 (21.8%)
CCA: 9 (11.5%)
Lost follow up: 11 (14.1%)
No DS n=77
OLT: 15 (19.5%)
Death: 12 (15.6%)
CCA: 6 (7.8%)
Lost follow up: 12 (15.6%)

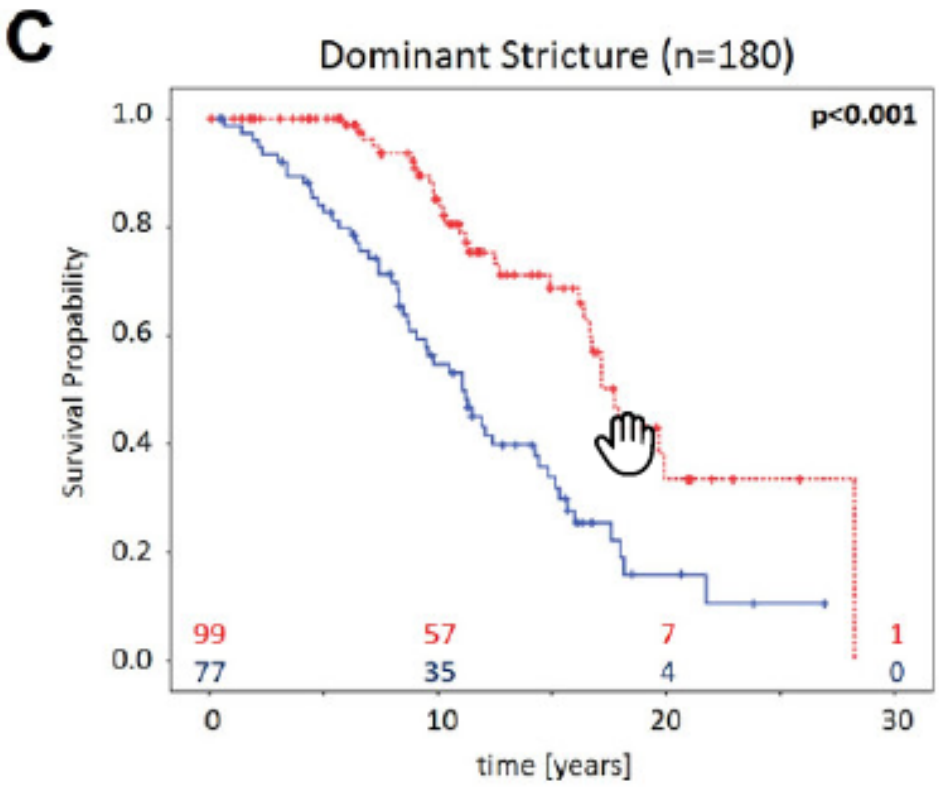


Figure 4 Kaplan-Meier analysis. Kaplan-Meier estimation confirmed the significant difference in transplantation-free survival between scheduled (red) and on-demand groups (blue) (17.9 vs 15.2 years; log-rank: p=0.008) (A). Further subgroup analysis revealed superior survival due to scheduled endoscopic intervention only in patients with the presence of DS (17.8 vs 11.1 years; log-rank: p<0.001) (B), whereas in patients without DS, transplantation-free survival was not affected by scheduled endoscopic surveillance (21.0 vs 18.7 years; log-rank: p=0.8) (C).

Rupp C et al
Gut 2019

Predominant aetiology of secondary sclerosing cholangitis	Disease
Chronic obstructive	Choledocholithiasis
	Cholangiocarcinoma, other benign and malignant neoplasms
	Portal hypertensive biliopathy
	Surgical trauma (*e.g.*, during cholecystectomy)
	Anastomotic stricture after surgery (*e.g.*, liver transplantation, hepaticojejunostomy)
	Chronic pancreatitis
Immune-mediated	IgG4-related cholangitis
	Hepatic sarcoidosis
	Eosinophilic cholangitis
	Mast cell cholangiopathy
	Hepatic allograft rejection
Infectious	Recurrent pyogenic cholangitis
	Chronic biliary infestation (liver fluke, ascaris)
	Histiocytosis X
	Cryptosporidiosis, microsporidiosis
	Cytomegalovirus
	AIDS-related cholangiopathy
Ischaemic	Non-anastomotic strictures after liver transplantation
	Hepatic artery thrombosis (*e.g.*, after liver transplantation)
	Transarterial chemotherapy / embolisation therapy
	Sclerosing cholangitis of the critically ill patient including COVID-19-related cholangiopathy
	Systemic vasculitis
Hereditary	Cystic fibrosis-associated cholangiopathy
	ABCB4 deficiency (histological)
Toxic	Ketamine

Histologic features compatible with PSC should be observed to confirm a diagnosis of small duct PSC. These include periductal fibrosis (observed in fewer than half of samples), fibro-obliterative cholangitis (observed in only 5-10% of samples), ductular reaction, periductal inflammation, ductopenia and variable amounts of portal inflammation.[16,33] There is, however, great controversy regarding how typical the histology findings should be to ensure a diagnosis of small duct PSC, as not even periductal fibrosis can be considered pathognomonic of PSC. Based on specific genetic associations, small duct PSC may represent very early stages of PSC in patients who also have IBD, but not in those without.[53] Although ulcerative colitis (UC) is still the most common type of IBD associated with small duct PSC, we tend to see a larger proportion of patients with Crohn's disease among those with small duct disease, and the male preponder-

HEPATOLOGY

AASLD
AMERICAN ASSOCIATION FOR

HEPATOLOGY, VOL. 65, NO. 3, 2017

AUTOIMMUNE, CHOLESTATIC AND BI

Validation of the Prognostic Value o Histologic Scoring Systems in Prima Sclerosing Cholangitis: An International Cohort Study

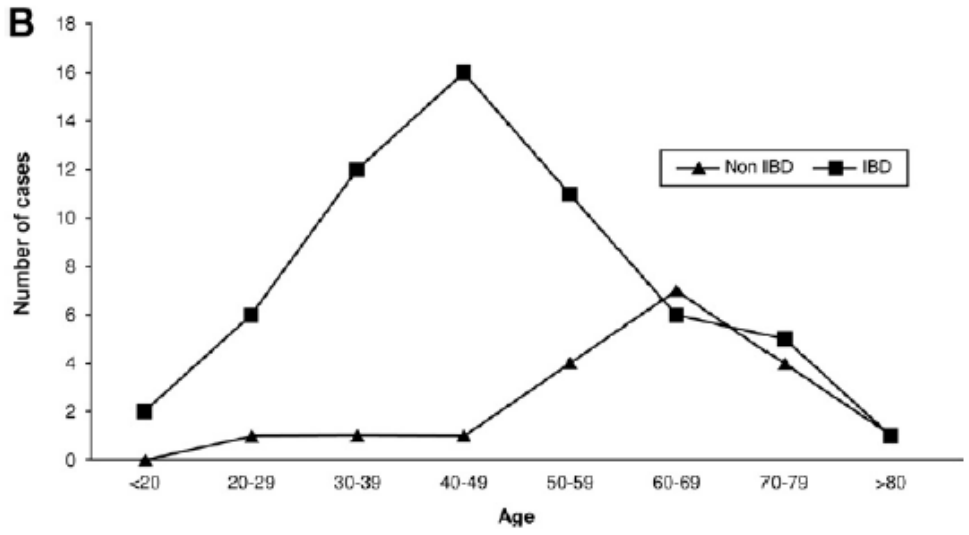
Elisabeth M. G. de Vries,[1*] Manon de Krijger,[1*] Martti Färkkilä,[2] Johanna Arola,[3] Peter Schirmacher,[4] Daniel Gotthardt,[5]

Nakanuma-Histo-Score with strongest predictive value

Prognosis of PSC in dependency on IBD

- 171 PSC pts. followed prospectively up to 20 years
- 97/171 dominant biliary stricture

- 79 PSC pts. Canterbury NewZealand



	Death/ OLT
PSC+ IBD	26/60 (43.3%)
PSC alone	3/19 (15.7%)

p<0.05

Rudolph G et al. J.Hepatoll. 2010

Ngu et al. ClinGastroHepatol 2011

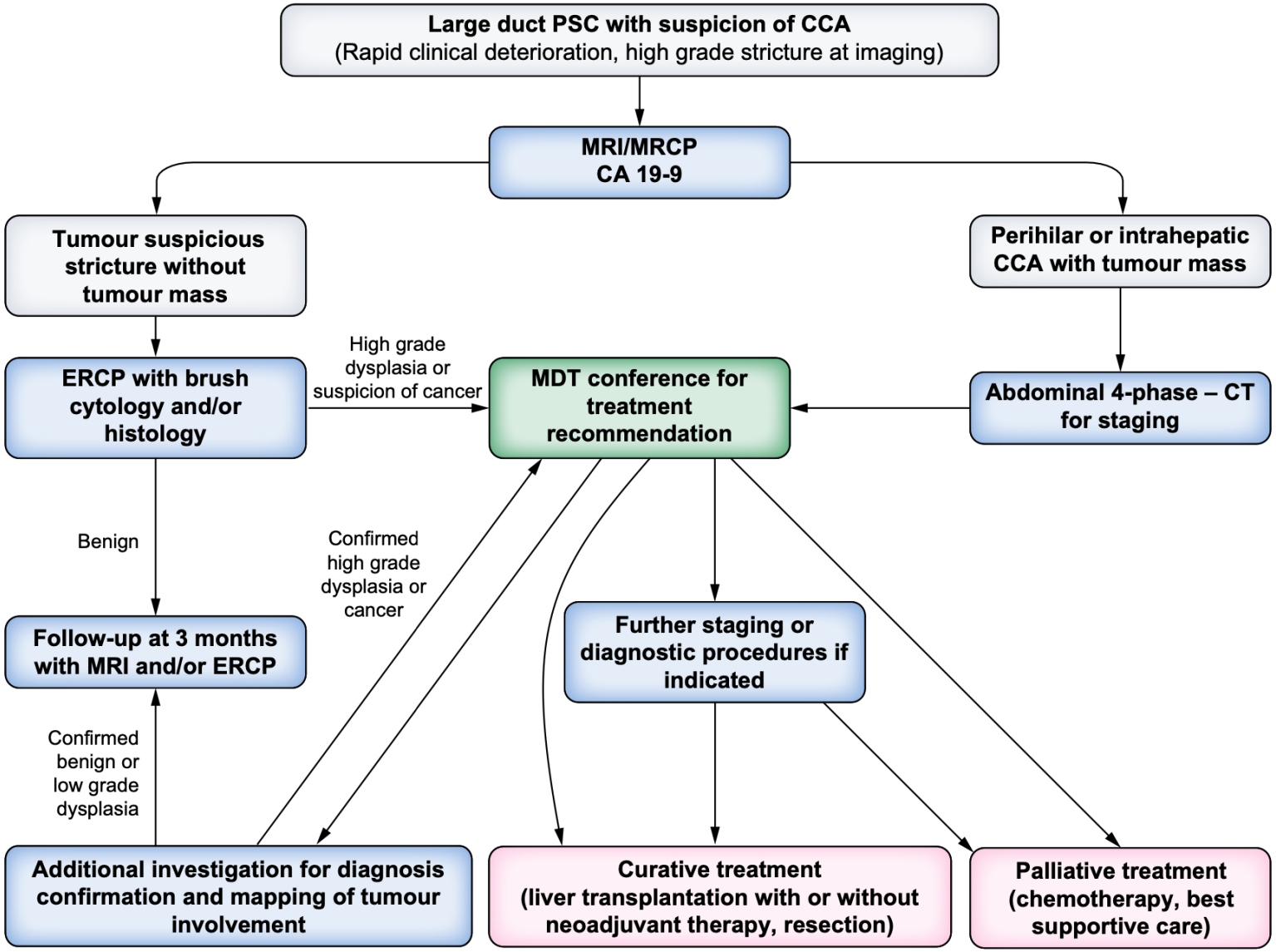
Non-invasive risk stratification in PSC

Level of applicability	Prognostic tools
High (High applicability, robust validation)	○ Baseline (early *vs.* advanced) disease stage as defined by biochemical (bilirubin, albumin, platelets, prothrombin time) and imaging analyses ○ Small duct PSC *vs.* classical PSC
Moderate (High applicability, further validation pending)	○ ALP ○ LSM by VCTE ○ ELF test ○ MRI/MRCP
Indeterminate (Insufficient applicability and/or validation)	○ Age, gender and type of IBD ○ AIH features ○ IgG4 serum levels ○ PSC-specific prognostic scores* (except for Mayo Risk Score in advanced PSC)

Unusual cholangiographic features

Some PSC patients may present with cystic dilatations of intrahepatic bile ducts simulating Caroli's disease [10]. Of note, the fusiform and small cystic dilatations of intrahepatic (mostly peripheral) bile ducts, as observed in patients with congenital hepatic fibrosis and autosomal recessive polycystic kidney disease, should not be misdiagnosed as PSC [11].

Another differential diagnosis is the peculiar cholangiographic phenotype of adult forms of ABCB4/MDR3 deficiency which may be characterized by large unifocal or multifocal spindle-shaped intrahepatic bile duct dilatations with or without apparent bile duct stenosis [12,26]. This diagnosis should be suspected on familial clustering of excessive gallstone disease and often a history of prior cholecystectomy at age <40 years and associated intrahepatic cholestasis of pregnancy, and is confirmed by *ABCB4* genotyping.


Large duct PSC with suspicion of CCA
(Rapid clinical deterioration, high grade stricture at imaging)
MRI/MRCP
CA 19-9
Tumour suspicious stricture without tumour mass
Perihilar or intrahepatic CCA with tumour mass
ERCP with brush cytology and/or histology
High grade dysplasia or suspicion of cancer
MDT conference for treatment recommendation
Abdominal 4-phase – CT for staging
Benign
Confirmed high grade dysplasia or cancer
Follow-up at 3 months with MRI and/or ERCP
Further staging or diagnostic procedures if indicated
Confirmed benign or low grade dysplasia
Additional investigation for diagnosis confirmation and mapping of tumour involvement
Curative treatment
(liver transplantation with or without neoadjuvant therapy, resection)
Palliative treatment
(chemotherapy, best supportive care)

PSC and Gallbladder: Polyps and Cancer

PSC

- 286 PSC patients: 18 (6%) GB mass lesion (21+9 mm)
- 10 cases (56%) GB cancer

Said K et al. J. Hepatol 2007

- 72 PSC patients (66 removed at LTx)
- > 50% abnormal histology of GB:
- Dysplasia in 37% and adenocarcinoma 14%

Lewis JT Am J Surg Pathol 2007

How to monitor for disease progression in PSC ?

- Non-invasive routine liver surveillance is suggested, based on:
  - Clinical review and standard serum liver tests including bilirubin, albumin, ALP, aspartate aminotransferase, platelets and prothrombin time, every 6 or 12 months depending on risk stratification, are recommended **(LoE 2, strong recommendation, 96% consensus).**
  - Liver elastography and/or serum fibrosis tests at least every 2 to 3 years are recommended **(LoE 3, strong recommendation, 96% consensus).**
  - Liver ultrasound and/or abdominal MRI/MRCP every year are suggested **(LoE 3, weak recommendation, 96% consensus).**

PSC Surveillance – How ?

- **Aim: Detection of early lesions**
- **No studies on optimal screening/surveillance strategies**
- **Yearly MR/MRCP most experts recommend**

No dominant stricture in MRCP

- Liver tests every 6 months
- annual CA 19-9 (cut-off-level?)
- MRCP if increasing AP/bilirubin

Dominant stricture in MRCP

- CA 19-9
- ERCP + Cytologie/ Biopsy
- MRT

Any doubts /suspect malignancy

- Cholangioscopy/Biopsy
- EUS/FNA

multicentric study.[94] However, the prognostic value of dynamic changes in these scores was not specifically assessed and inter-centre reproducibility remains an unsolved issue.[112] Lastly, some preliminary retrospective studies suggest the utility of 'MRCP+' as a prognostic tool for prediction of clinical outcomes in PSC.[113]

Despite the fact that sequential assessment of ductal changes

[94] **Lemoinne S, Cazzagon N**, El Mouhadi S, Trivedi PJ, Dohan A, Kemgang A, et al. Simple magnetic resonance scores associate with outcomes of patients with primary sclerosing cholangitis. Clin Gastroenterol Hepatol 2019;17:2785–2792 e2783.

[113] Ismail MF, Hirschfield GM, Hansen B, Tafur M, Elbanna KY, Goldfinger MH, et al. Evaluation of quantitative MRCP (MRCP+) for risk stratification of primary sclerosing cholangitis: comparison with morphological MRCP, MR elastography, and biochemical risk scores. Eur Radiol 2022;32:67–77.

How to handle pruritus in PSC ?

- It is recommended to exclude relevant bile du
in large duct sclerosing cholangitis as the ca
gressive pruritus. If present and reachab
strictures should be treated by endoscopic b
tation (or stenting, if balloon dilatation alon
cient) after brushing **(LoE 4, strong recomm
95% consensus).**

- Pharmacological treatment of moderate to s
tus in sclerosing cholangitis with bezafibrat
picin is recommended **(LoE 4, strong recom**

The formerly recommended first-line treatment of cholestasis-associated pruritus used to be cholestyramine (4-16 g/day, administered separately from other drugs), and in case of its ineffectiveness or intolerance, rifampicin (150-300 mg daily), naltrexone (12.5-50 mg daily) and sertraline (25-75 mg daily).[20,51] The evidence for the antipruritic effectiveness of the

What is the FITCH-trial ?

Fibrate for cholestasis-associated itch

[219] de Vries E, Bolier R, Goet J, Pares A, Verbeek J, de Vree M, et al. Fibrates for itch (FITCH) in fibrosing cholangiopathies: a double-blind, randomized, placebo-controlled trial. Gastroenterology 2021;160:734–743 e736.

Combination statin + fibrat = anti-cholestatic effects -_> use it!

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[221] Reig A, Sese P, Pares A. Effects of bezafibrate on outcome and pruritus in primary biliary cholangitis with suboptimal ursodeoxycholic acid response. Am J Gastroenterol 2018;113:49–55.

Potential future Medical Treatment of PSC?

PSC

- **New form of UDCA:** 24-norUrsodeoxycholic acid (norUDCA) is the C23 homologue of the 3a,7b-dihydroxy C24 bile acid UDCA hydrophilic, anti-fibrotic,-inflammatory, -proliferative

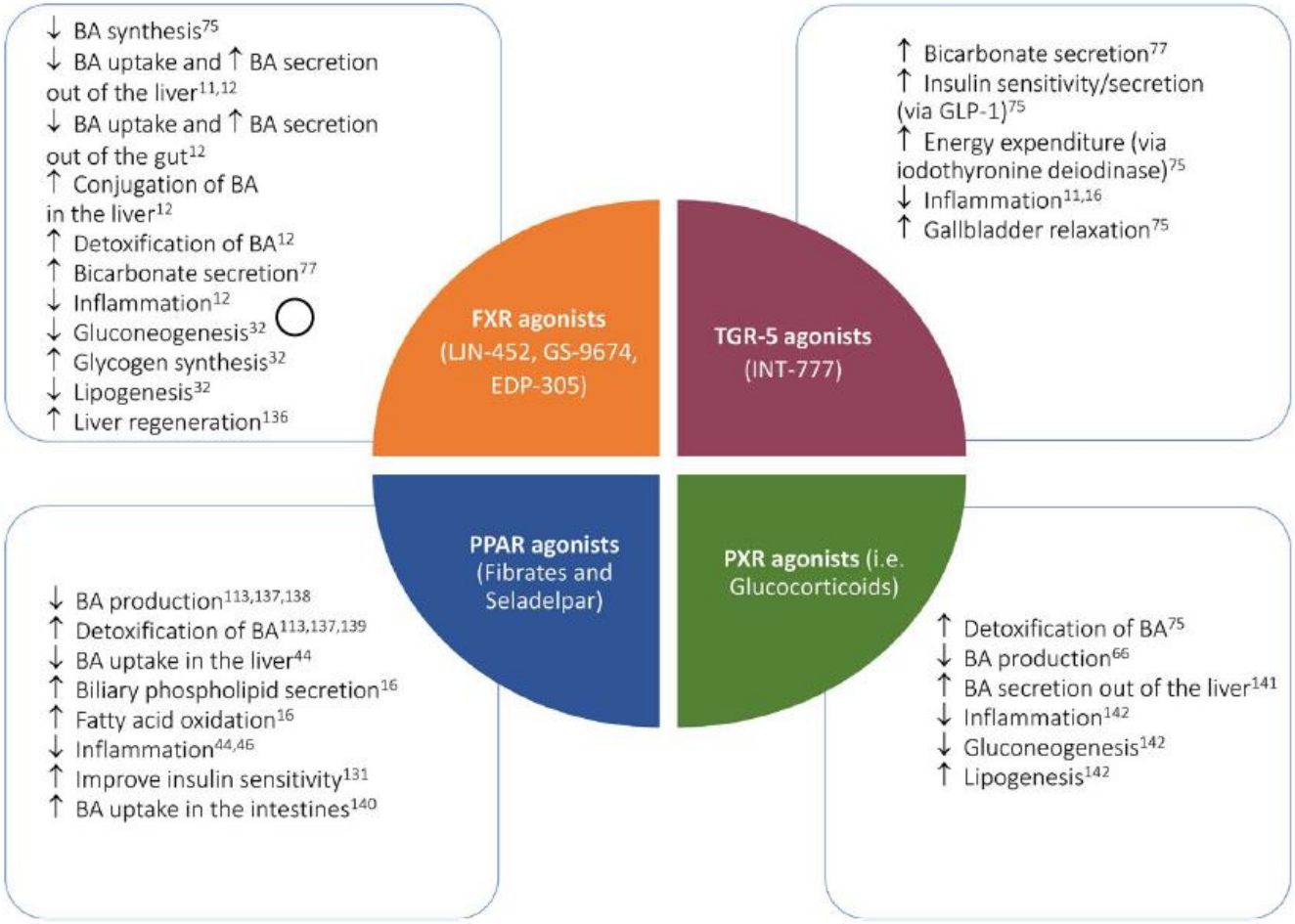
  Fickert P et al. J.Hep 2017
  Phase II – Phase III on-going

- **FxR-agonists: e.g. Obeticholic acid, INT-767 (Aesop-Phase II-trial)** also choloretic, cholangiocyte modulator, gut-barriere etc.

- **Vedolizumab : α4 β7 inhibitors / anti-Integrin (Trial ongoing)** aberrant gut-homing lymphocyte hypothesis focuses on the relationship between PSC and IBD.

Traumer M et al. Dig Dis Sci 2016

Novel therapies in PSC - - - - >



Goldstein et al. Liver International 2018