Sclerosing diseases of the biliary tree

INSELSPITAL
UNIVERSITÄTSSPITAL BERN
HOPITAL UNIVERSITAIRE DE BERNE
BERN UNIVERSITY HOSPITAL

Reiner Wiest M.D.

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

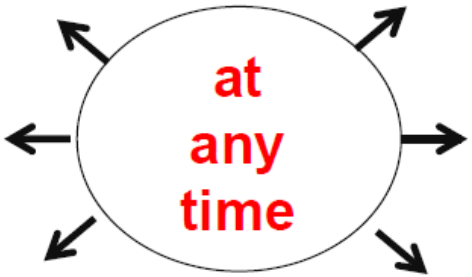
IBD-PSC: epidemiology, incidence, prevalence….?

- 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

What can cause sclerosing of biliary tree ?

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

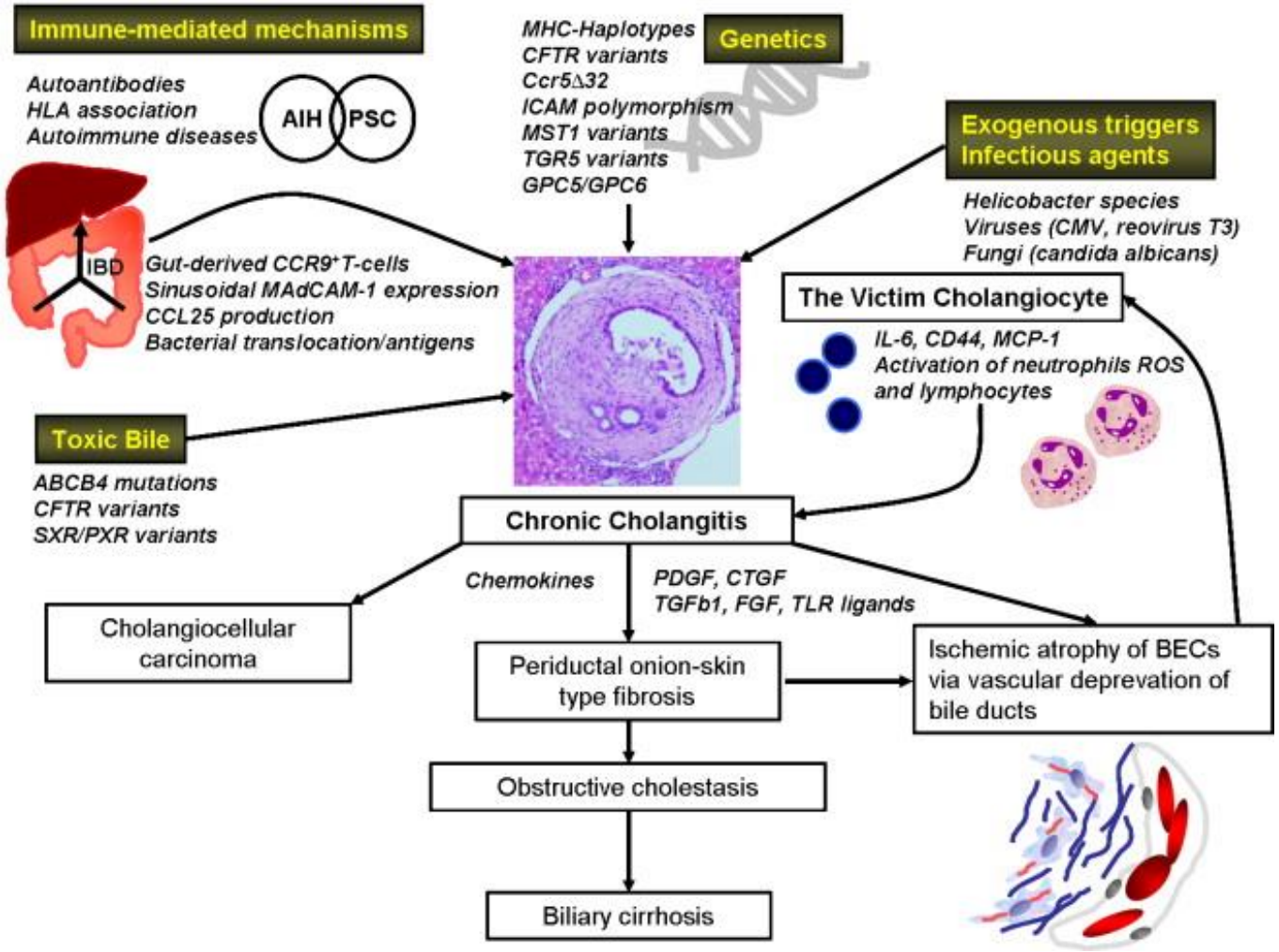
Others: Portal-hypertensive Biliopathy, Masto-, Histozytosis, Caroli, ...mimicking: amyloidosis, allograft rejection, hodgkin`s disease.....

Pathogenesis of Primary Sclerosing Cholangitis ?

PSC

Pathogenesis of Primary Sclerosing Cholangitis ?

PSC




No.1

Most difficult questions in the bible class history !

PSC

Which genes are shared between UC and 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

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 ?

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 $\alpha 4\beta 7$-CCR9+CD8+T-cells primed by retinoic dependent iDC

Eksteen B et al. Gastroenterology 2009

PSC

Factors modulating risk for PSC ?

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**

PSC

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

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

Mayo Risk Score for PSC?

PSC

Mayo Risk Score for PSC?

PSC

R= (0.0295 * (**age** in years)) + (0.5373 * LN(total **bilirubin** in mg/dL)) - (0.8389 * (serum **albumin** in g/dL)) + (0.5380 * LN(**AST** in IU/L) + (1.2426 * (points for **variceal bleeding**))

Points for variceal bleeding: 0 if none, 1 if present.

Each unit increase in the Mayo Risk Score (R) is associated with a 2.5-fold increase in the risk of death. The score shows very slight upward slope over time in stable patients, but during the terminal phase it shows an acceleration in progression (http://www.medal.org/)

R ≤ 0 = low" risk
R= 0-2 = "intermediate" risk
R > 2 = "high" risk

Kim et al. Mayo Proc 2000

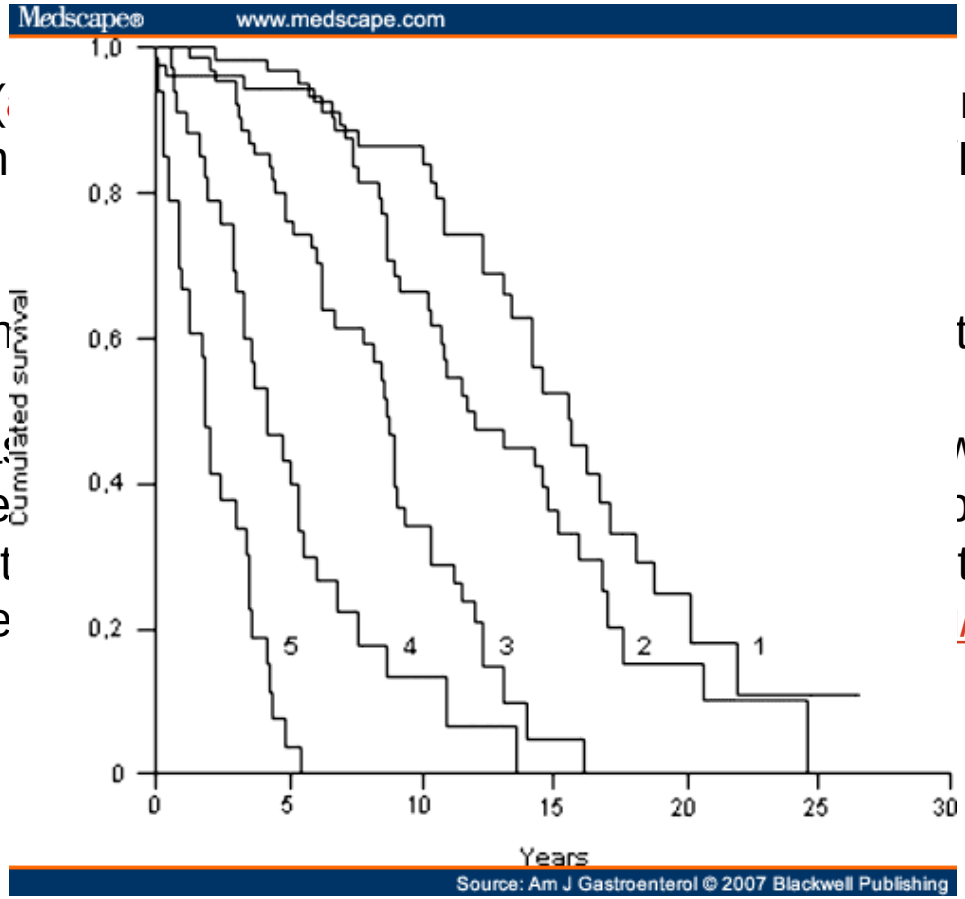
Mayo Risk Score for PSC?

PSC

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

Poin t.

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



Kim et al. Mayo Proc 2000

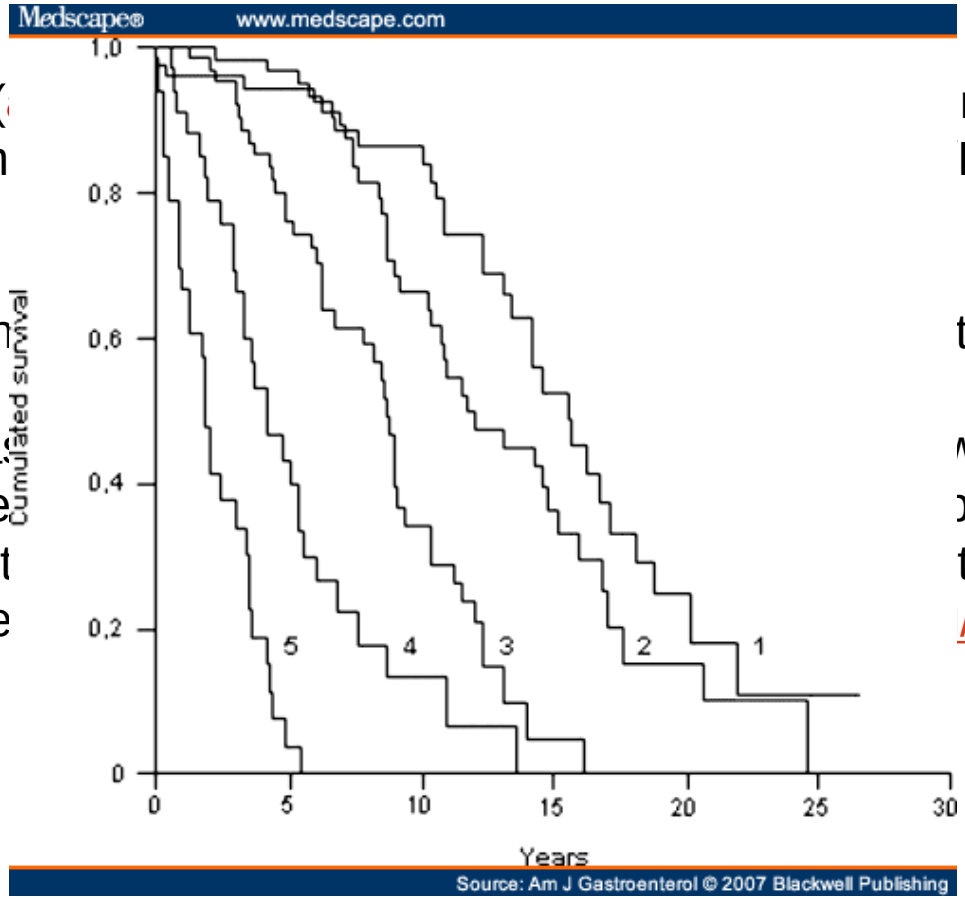
Mayo Risk Score for PSC?

PSC

R= (0.0295 * (n 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 /)



Kim et al. Mayo Proc 2000

Lab tests of Primary Sclerosing Cholangitis ?

9

Lab tests of Primary Sclerosing Cholangitis ?

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

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

Lab tests of Primary Sclerosing Cholangitis ?

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

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

Other lab tests?

PSC

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

PSC

Diagnosis of Primary Sclerosing Cholangitis ?

PSC

Diagnosis of Primary Sclerosing Cholangitis ?

-Lab: CHOLESTASIS (not other wise explained…)

PSC

Diagnosis of Primary Sclerosing Cholangitis ?

-Lab: CHOLESTASIS (not other wise explained…)

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

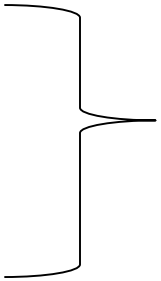
- ERC(P)

PSC

Diagnosis of Primary Sclerosing Cholangitis ?

-Lab: CHOLESTASIS (not other wise explained…)

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



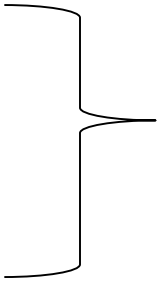
abnormal cholangiogram
(strictures / dilatations)

PSC

Diagnosis of Primary Sclerosing Cholangitis ?

-Lab: CHOLESTASIS (not other wise explained…)

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



abnormal cholangiogram
(strictures / dilatations)

What is small duct PSC ?

PSC

11

What is small duct PSC ?

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

What is small duct PSC ?

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 ?

What is small duct PSC ?

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)


No.1

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

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

Most common complications of PSC ?

PSC

Most common complications of PSC ?

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

Most common complications of PSC ?

PSC

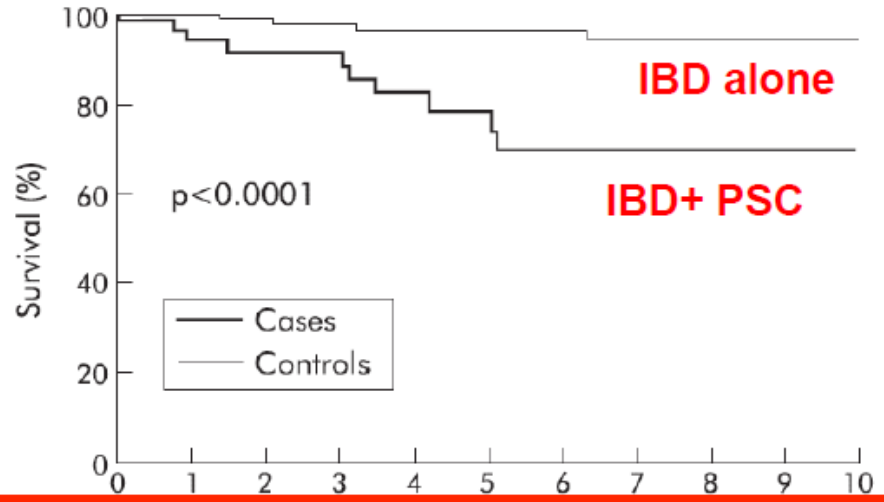
- **Cholangiocarcinoma = most common cause of death**
  (0.6-1.5%/year and up to 20% life-time risk in PSC
  up to 50% diagnosis in 1st year after PSC-diagnosis)

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

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

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)

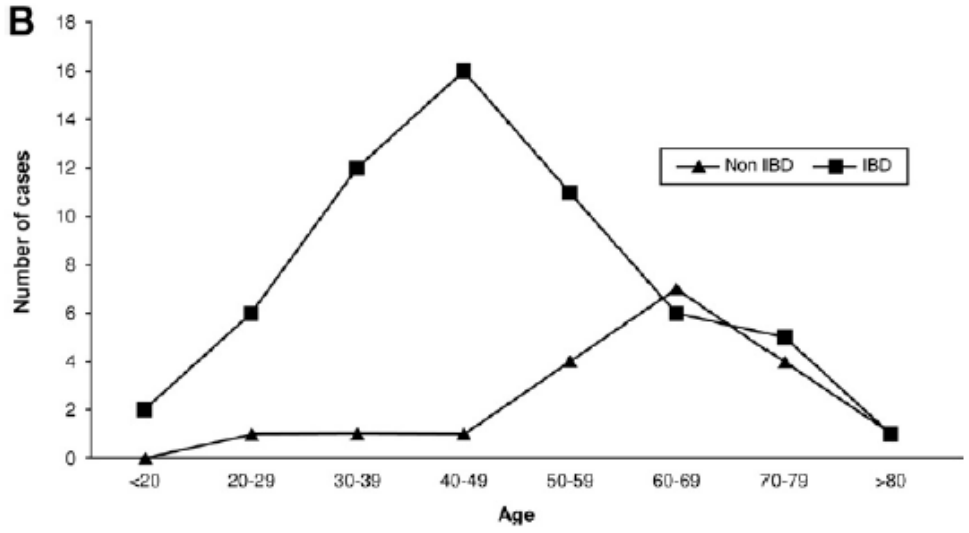
Adjusted
Age, duration,
rectal sparing etc.

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

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%)

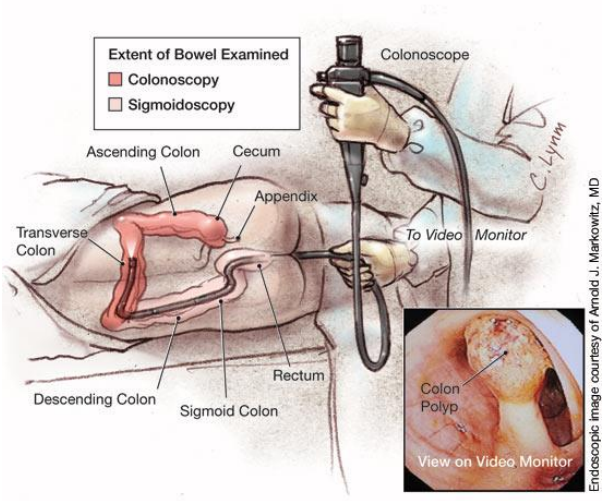
p<0.05

Rudolph G et al. J.Hepatoll. 2010

Ngu et al. ClinGastroHepatol 2011

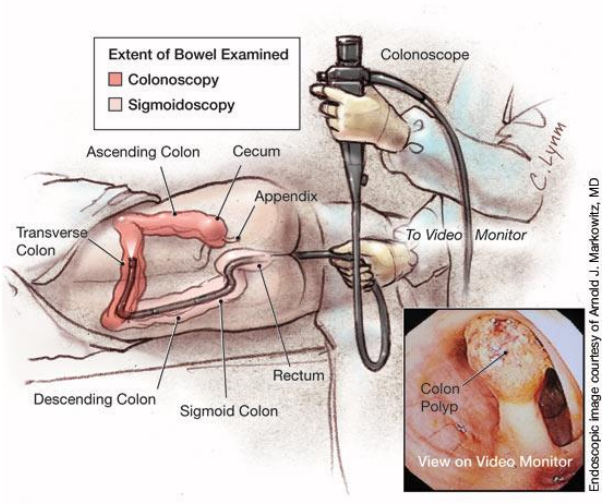
Colon and PSC:
When colonoscopy in PSC ?

PSC



Colon and PSC: When colonoscopy in PSC ?

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 ?

Characteristic features of IBD in PSC ?

- **Rectal sparing**
- **Mild course**
- **Back-Wash-Ileitis**

Impact of PSC on Colorectal Cancer Risk in IBD ?

Impact of PSC on Colorectal Cancer Risk in IBD ?

Cumulative risk (dysplasia and/or CRC): after 25 years

with PSC vs. Without PSC: 50% vs. 10%, p<0.01

OR 5.1 (95% CI 3.58 -6.41)

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)

Impact of PSC on Colorectal Cancer Risk in IBD ?

Cumulative risk (dysplasia and/or CRC): after 25 years

with PSC vs. Without PSC: 50% vs. 10%, p<0.01

Surveillance colonoscopy at 1-2 years interval in PSC with IBD

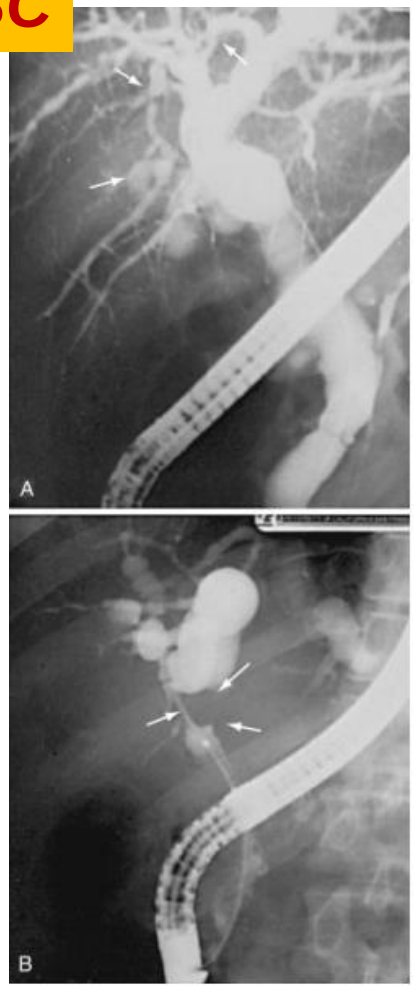
- younger at onset of IBD

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

Brackmann S et al. Scand J Gastro 2008 Shetty Am J Gastroenterol 1999

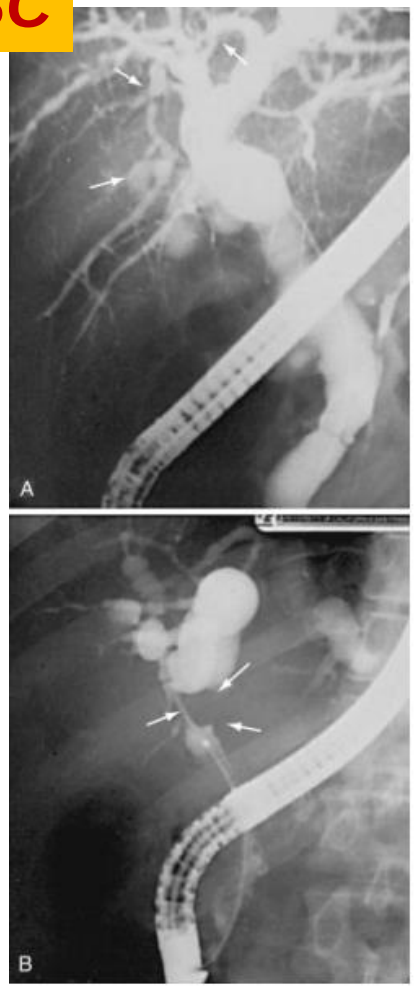
When to go for ERCP ?

PSC



When to go for ERCP ?

PSC



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

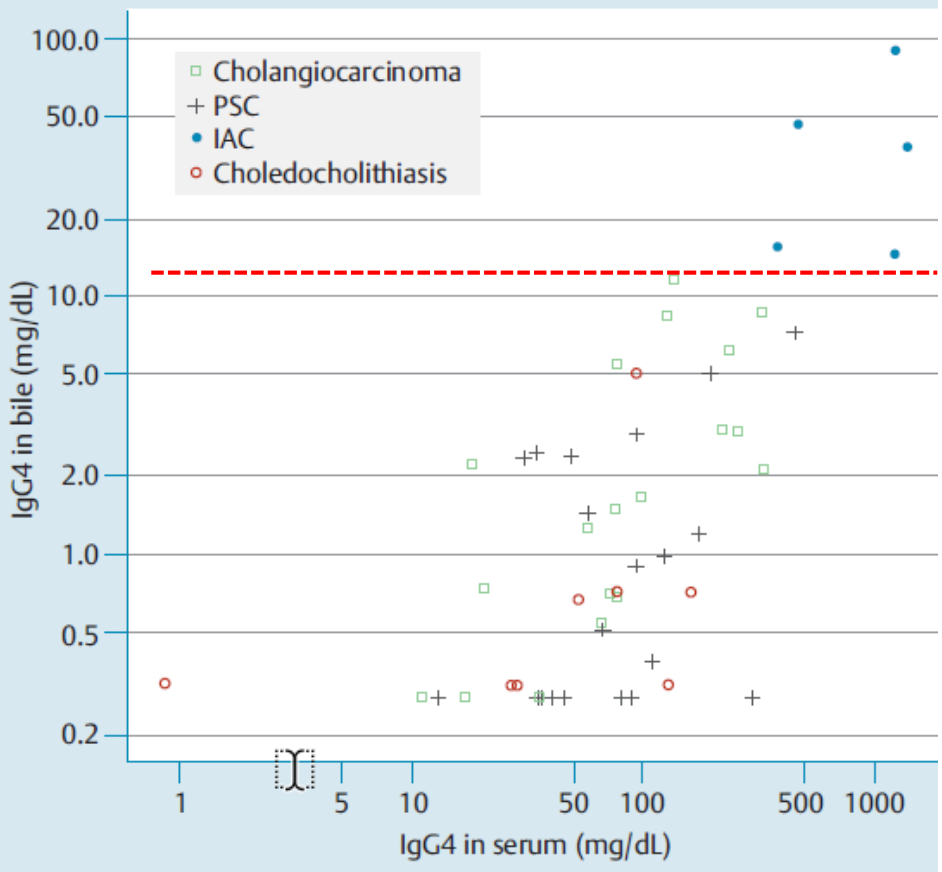
  -clinically relevant or worsening symptoms
  jaundice, cholangitis, pruritus, weight loss
  -rapid increase of AP and/or bilirubin
  -new or progression of known dominant stricture (MR)

- **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 ?

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

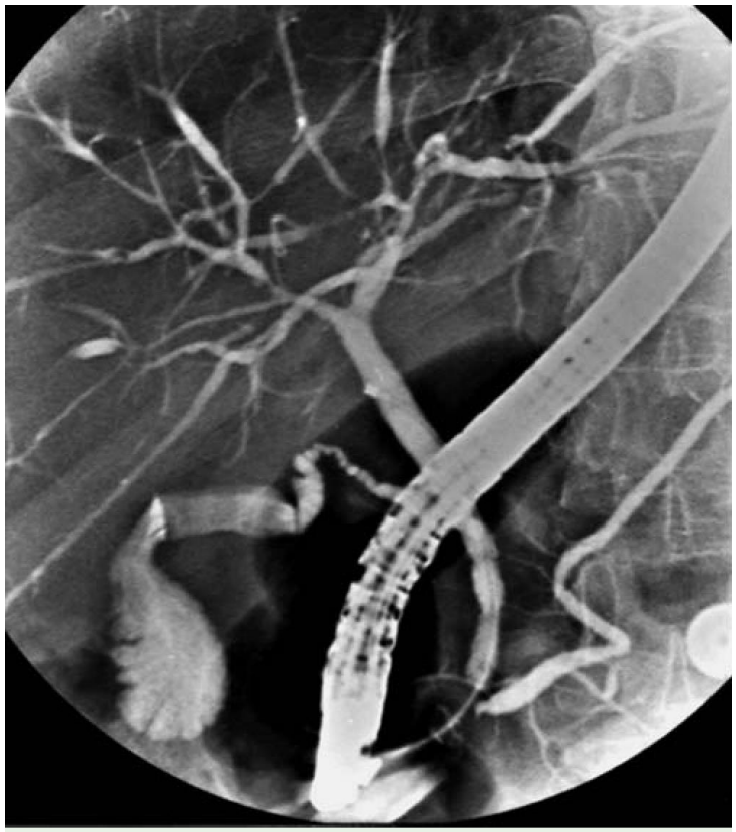
Vosskuhl, Lankisch et al. Endoscopy 2012

ERCP-findings: Amsterdam-classification

PSC

ERCP-findings: Amsterdam-classification

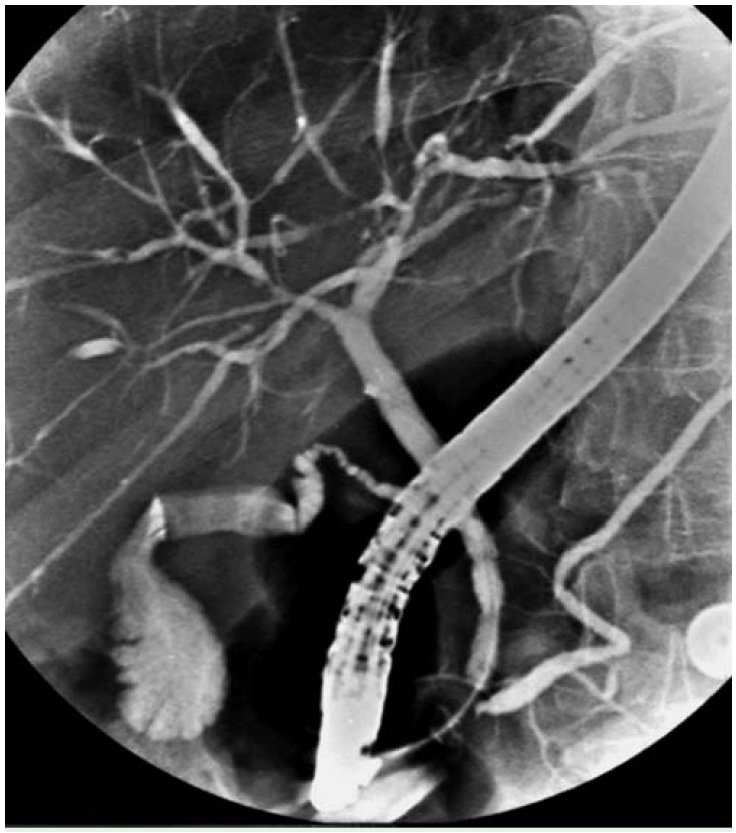
PSC



ERCP-findings: Amsterdam-classification

PSC

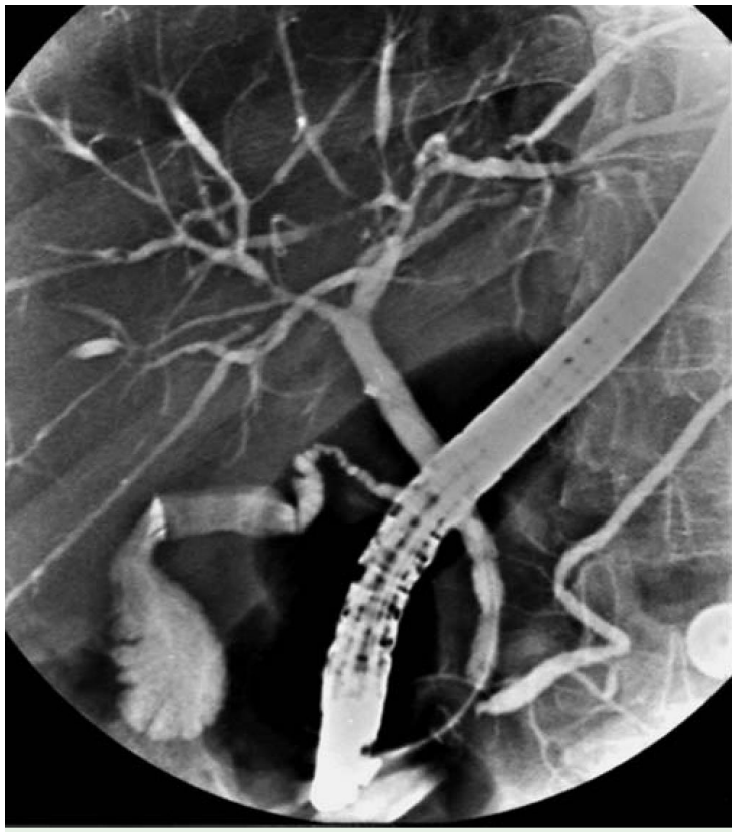
Full occlusion cholangiogramm mandatory:
Type I (intra- and extrahepatic)



ERCP-findings: Amsterdam-classification

PSC

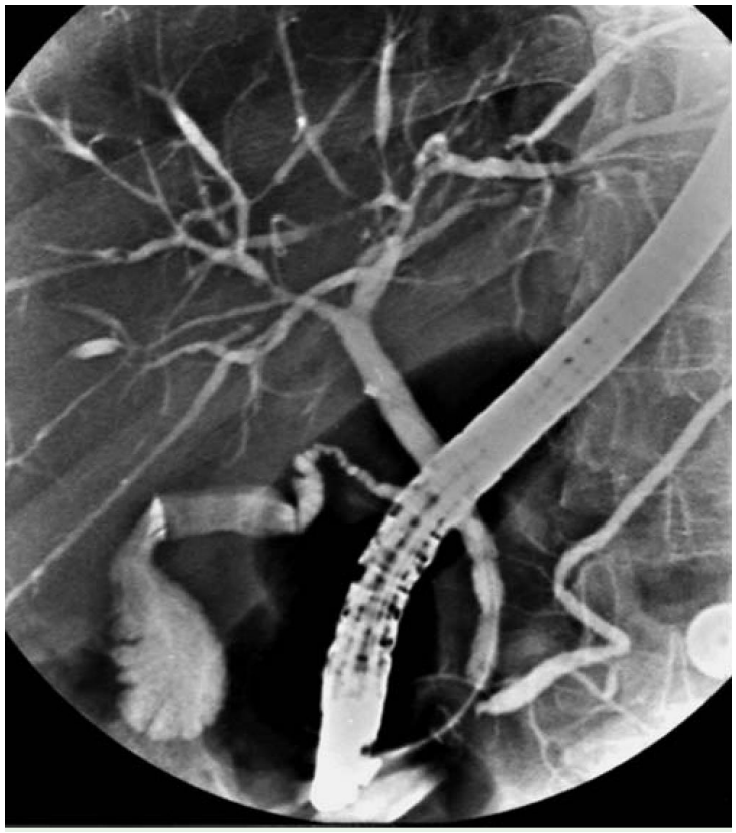
Full occlusion cholangiogramm mandatory:
Type I (intra- and extrahepatic)

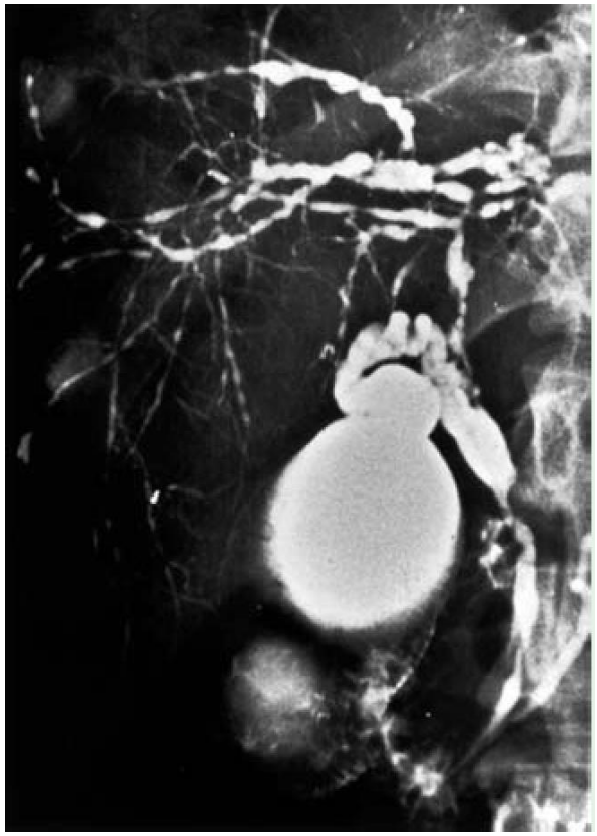


ERCP-findings: Amsterdam-classification

PSC

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

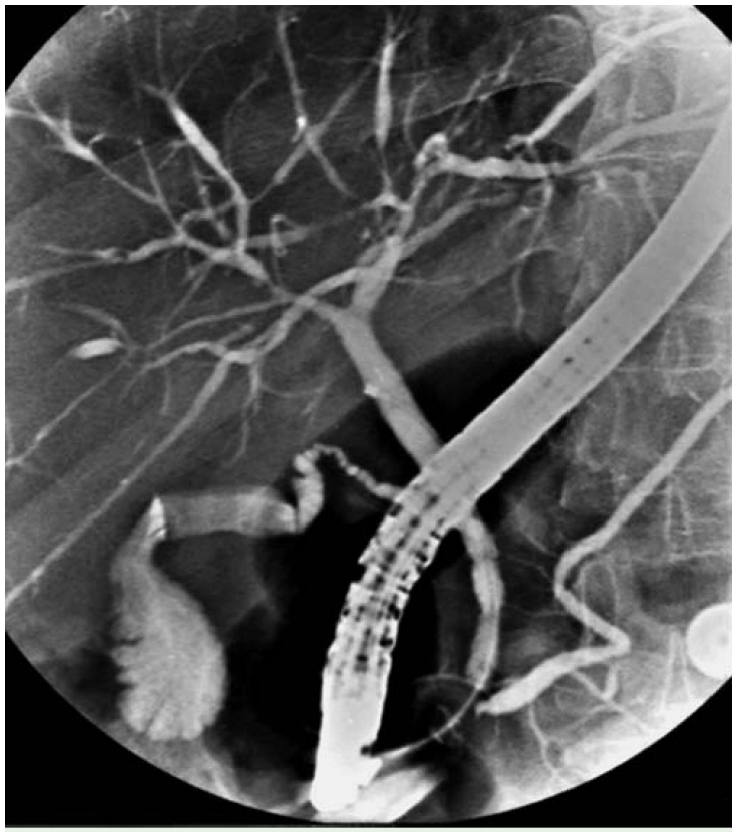




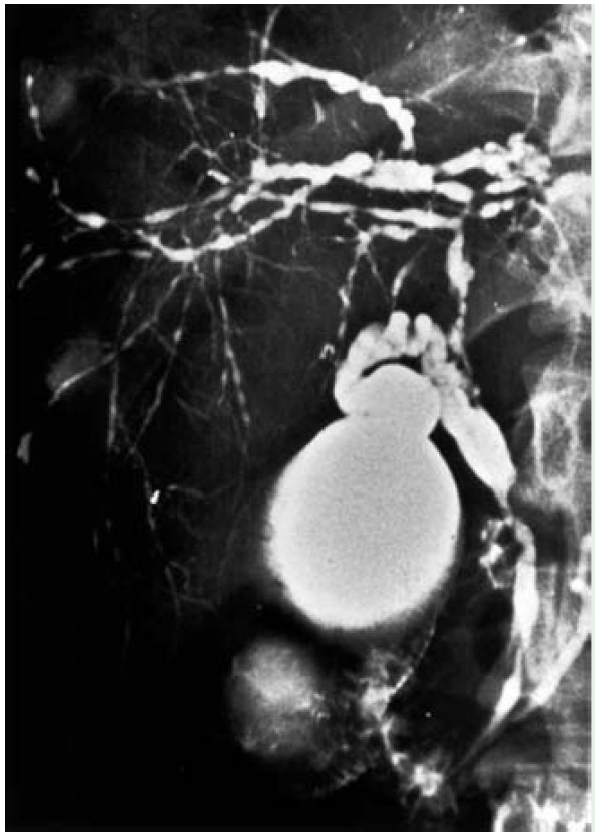
ERCP-findings: Amsterdam-classification

PSC

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



Type II intra-
Type III extrahepatic



ERCP-findings: Amsterdam-classification

ERCP-findings: Amsterdam-classification

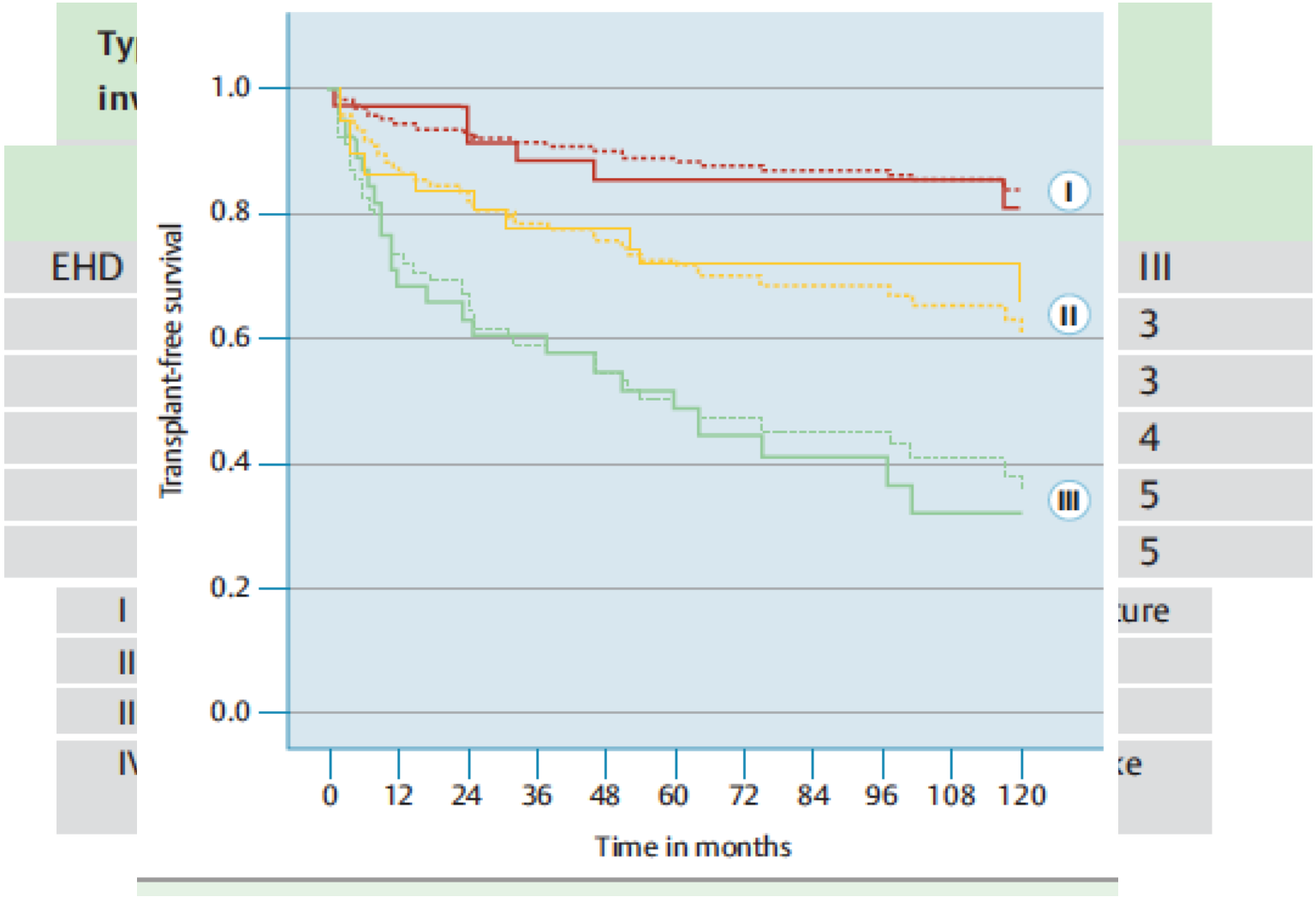
Type of duct involvement	Cholangiographic abnormalities
Intrahepatic	
0	No visible abnormalities
I	Multiple caliber changes; minimal dilatation
II	Multiple strictures; saccular dilatations, decreased arborization
III	Only central branches filled despite adequate filling pressure; severe pruning
Extrahepatic	
0	No visible abnormalities
I	Slight irregularities of duct contour; no stricture
II	Segmental strictures
III	Strictures of almost entire length of duct
IV	Extremely irregular margins; diverticulum-like outpouchings

ERCP-findings: Amsterdam-classification

Type of duct involvement	Cholangiographic abnormalities			
	IHD			
EHD	0	I	II	III
0	–	2	3	3
I	1	2	3	3
II	2	3	3	4
III	3	3	4	5
IV	3	3	4	5

I	Slight irregularities of duct contour; no stricture
II	Segmental strictures
III	Strictures of almost entire length of duct
IV	Extremely irregular margins; diverticulum-like outpouchings

ERCP-findings: Amsterdam-classification



23

Dominant stricture ?
- definition, frequency, risks

PSC

23

Dominant stricture ?
- definition, frequency, risks

PSC

Definition: stenosis with a diameter of

<1.5 mm in the CBD

< 1 mm in the right or left hepatic duct (within 2 cm to hilus)

Mostly associated with increased cholestasis and pruritus

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

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

ERCP: management of dominant stricture ?

PSC

ERCP: management of dominant stricture ?

PSC

- 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 every 1-4 weeks, CBD 8mm, DHR/L 6 mm till success
- **Stenting**: Perforation rate higher and hence,

  only in selected cases and only short-term (1-2 weeks)

PSC and CCA: epidemiology, risk, prognosis

PSC

PSC and CCA: epidemiology, risk, prognosis

PSC

- Life-time risk up to 15-20% (=400-fold increased)
- 10-year cumulative risk: 6-9%
- 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

Most common location of CCA in PSC ?

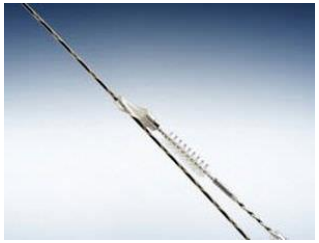
Most common location of CCA in PSC ?

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

Stricture – diagnostics – Brush ± FISH ± Cholangioscopy ?

Stricture – diagnostics – Brush ± FISH ± Cholangioscopy ?

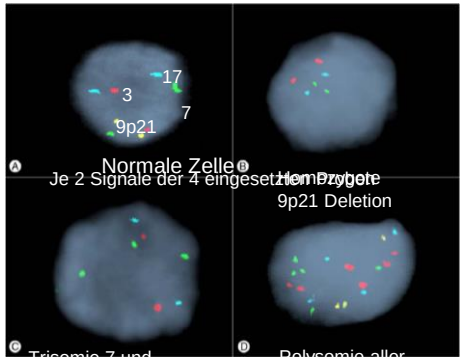
Brush-cytology:



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%)

PSC and Gallbladder: Polyps and Cancer

PSC

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

- 102 PSC patients undergoing cholecystectomy
- 8 GB adenocarcinoma

Buckles AJG 2002

- 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

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

Annual ultrasound recommended

Any mass lesion (> 10 mm): cholecystectomy

- 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

PSC Surveillance – How ?

PSC Surveillance – How ?

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

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

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

Medical Treatment of PSC ? UDCA – others ?

PSC

Medical Treatment of PSC ? UDCA – others ?

PSC

- still no evidence that UDCA is beneficial in improving symptoms or transplant-free survival.

Medical Treatment of PSC ? UDCA – others ?

PSC

- still no evidence that UDCA is beneficial in improving symptoms or transplant-free survival.

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

Medical Treatment of PSC ? UDCA – others ?

PSC

- still no evidence that UDCA is beneficial in improving symptoms or transplant-free survival.

- **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)

Medical Treatment of PSC ? UDCA – others ?

PSC

- still no evidence that UDCA is beneficial in improving symptoms or transplant-free survival.

- **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)

- Corticosteroids, Immunosuppresants for AIH (overlap-patients)

Potential future Medical Treatment of PSC?

PSC

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

Liver Transplantation in PSC: when, how...

PSC

Liver Transplantation in PSC: when, how...

PSC

- 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

Liver Transplantation in PSC: when, how...

PSC

- 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

- **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
- UC: Colectomy seems to protect from recurrence of PSC (controversial, selected cases, question when)

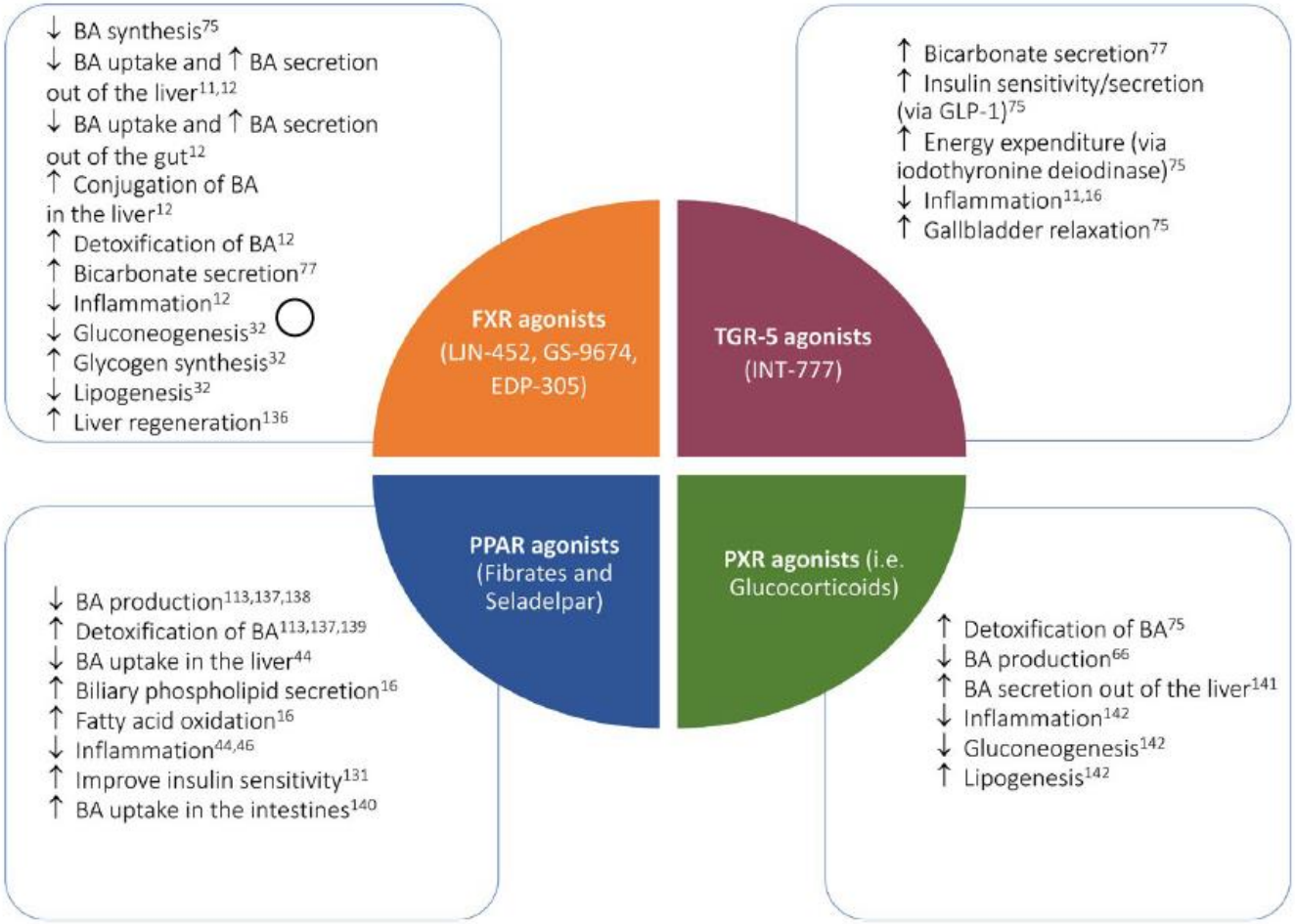
Liver Transplantation in PSC: when, how...

PSC

- 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

- **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
- UC: Colectomy seems to protect from recurrence of PSC (controversial, selected cases, question when)

Novel therapies in PSC - - - - >



Goldstein et al. Liver International 2018

What about osteoporosis in PSC ?

What about osteoporosis in PSC ?

237 PSC patients (74% with IBD)

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

What about osteoporosis in PSC ?

237 PSC patients (74% with IBD)

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

Risk factors for presence/development of osteoporosis in PSC ?

What about osteoporosis in PSC ?

237 PSC patients (74% with IBD)

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

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

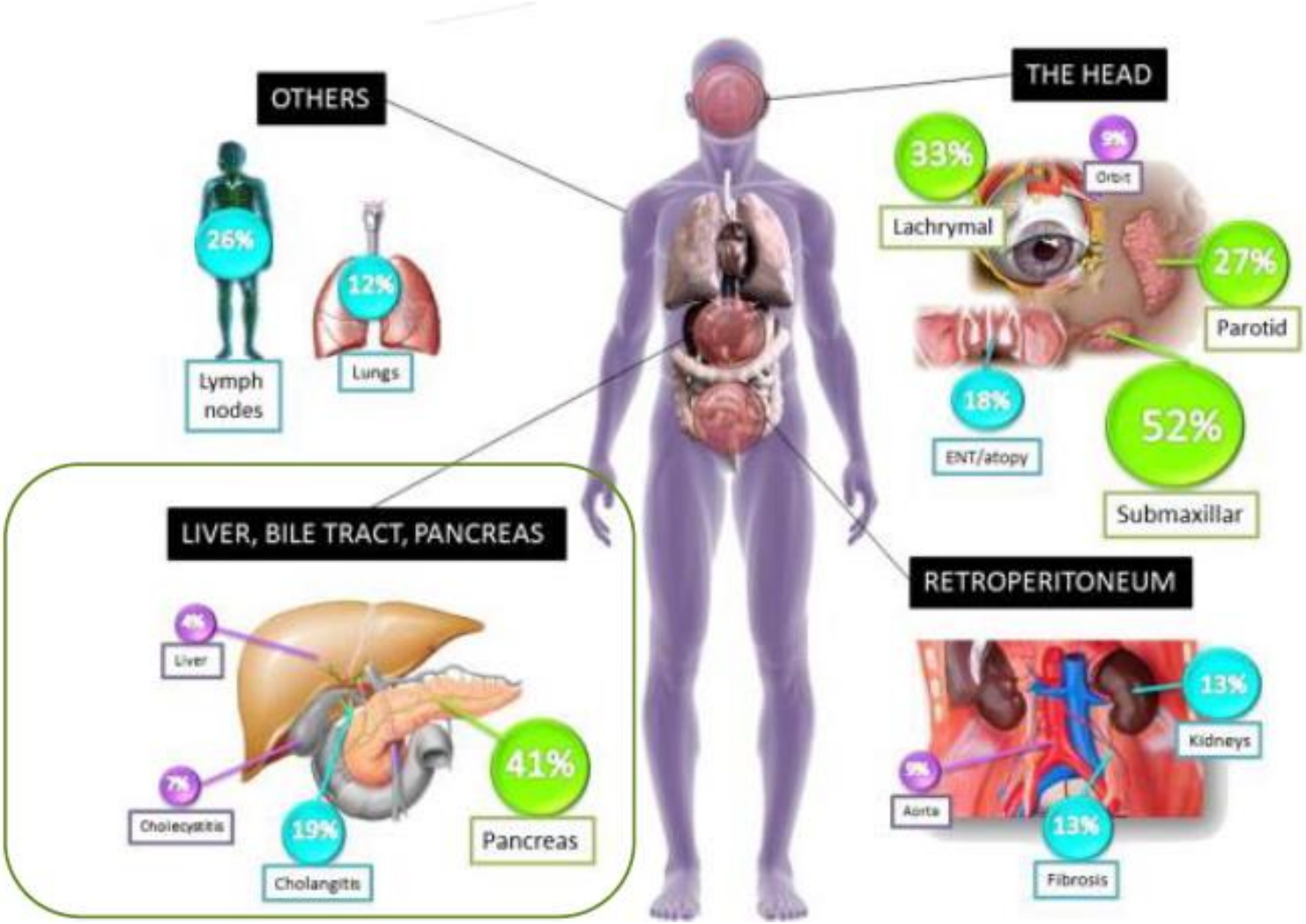
In cirrhosis and/or cholestasis every 2 years

At first diagnosis of PSC when risk factors or corticosteroids/OLT planned

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

Frequencies and types of IgG4-related diseases

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

% of total IgG normally

kDA size

IgG 4 and its specific features are…

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

IgG 4 and its specific features are…

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

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 - definition

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

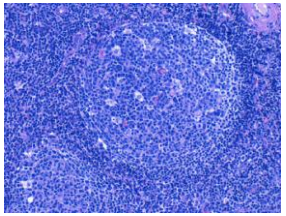
Adapted from: Chari ST, Takahashi N, Levy MJ, et al. A diagnostic strategy to distinguish autoimmune pancreatitis from pancreatic cancer. Clin Gastroenterol Hepatol 2009; 7:1097.

Microscopic characteristics in IgG4-hepatobiliary disease

IgG4

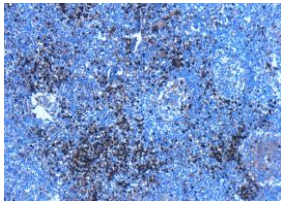
Microscopic characteristics in IgG4-hepatobiliary disease

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%



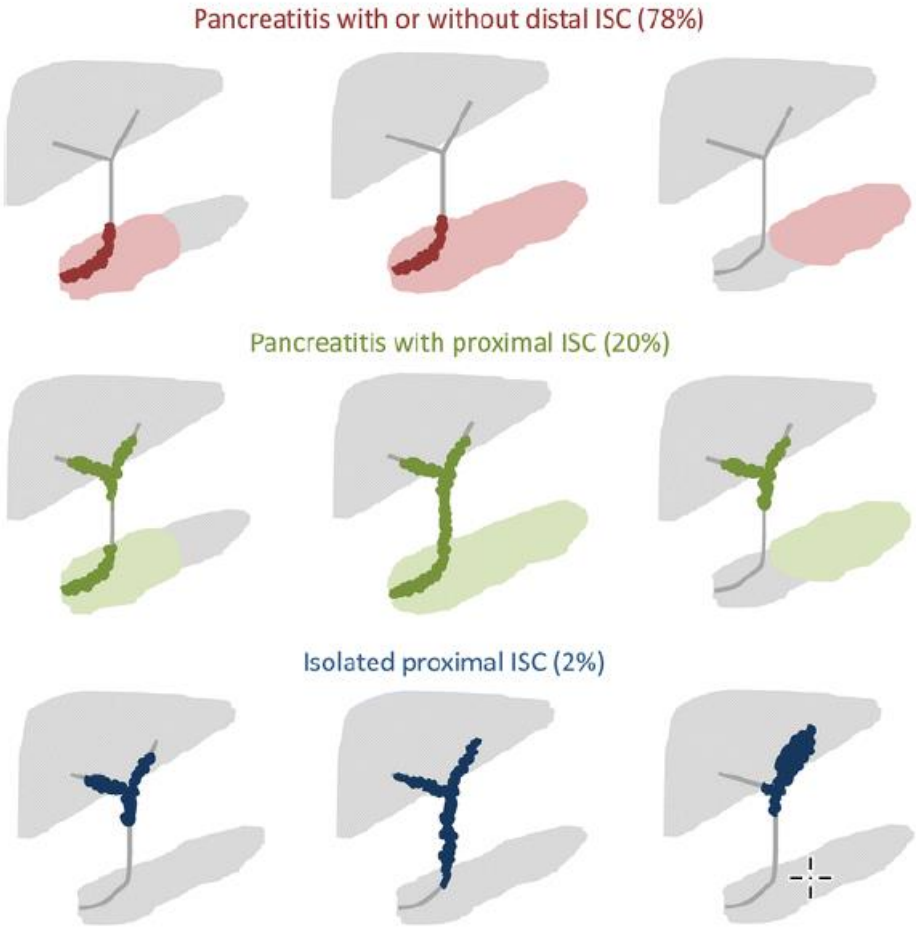
Brush cytology not sufficient

Biopsy to go for= cholangioscopy

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

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

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



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

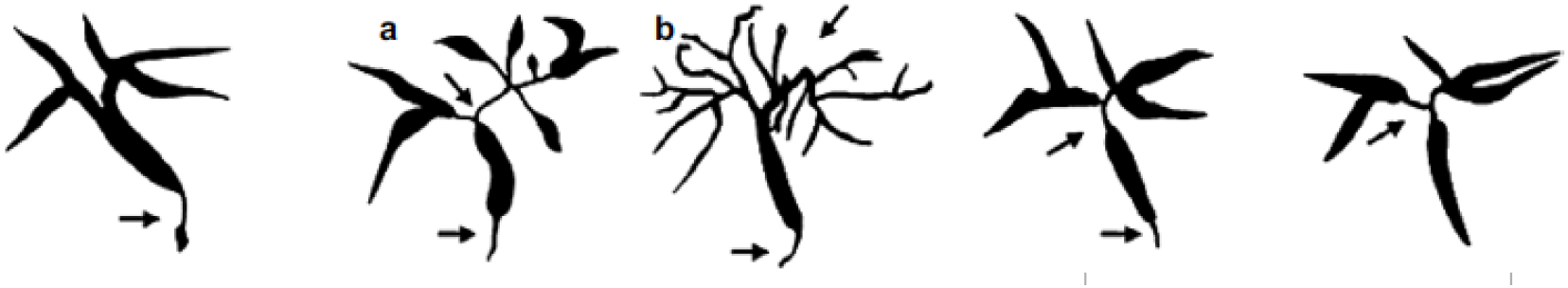
A: with
Pre-stenotic
dilatation

B: without
Pre-stenotic
dilatation

Hilar + CBD

Hilar alone

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



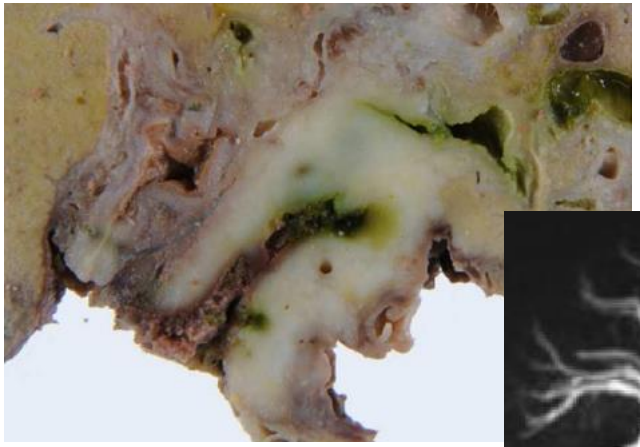
DD: pancreatic Ca,
Distal CCC, CP

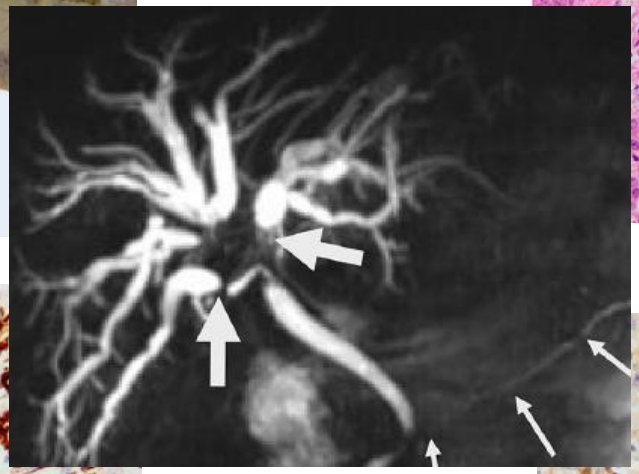
DD: PSC, SSC

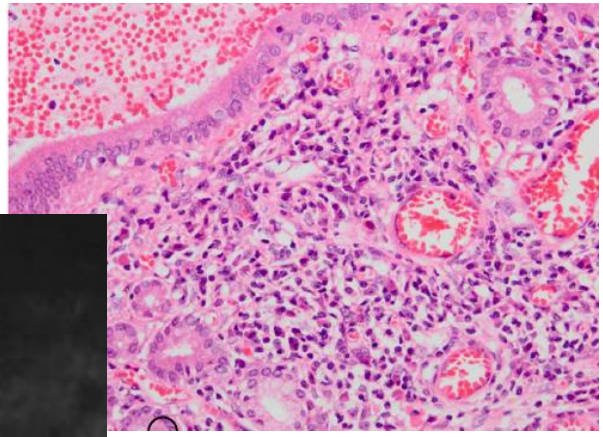
DD: Hilar CCA

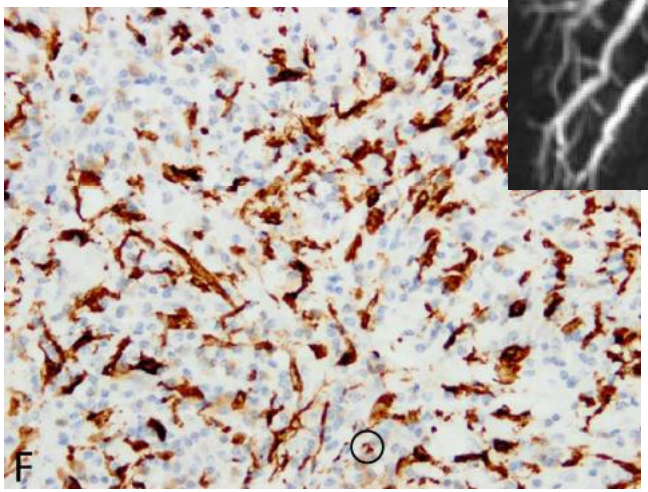
Okazaki et al. J.Hepatol 2014

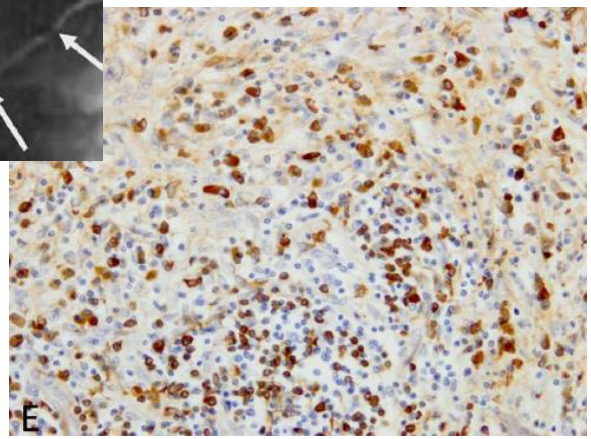
Type 3 – IgG-SC mimicking central CCC/Klatskin IV











Zen et al.
J.Gastroenterol 2016

IgG4-hepatobiliary disease – epidemiology, risk factors

IgG4

- **Most frequent extra-pancreatic manifestation of IgG4-related diseases**

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**

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**

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,**

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),**

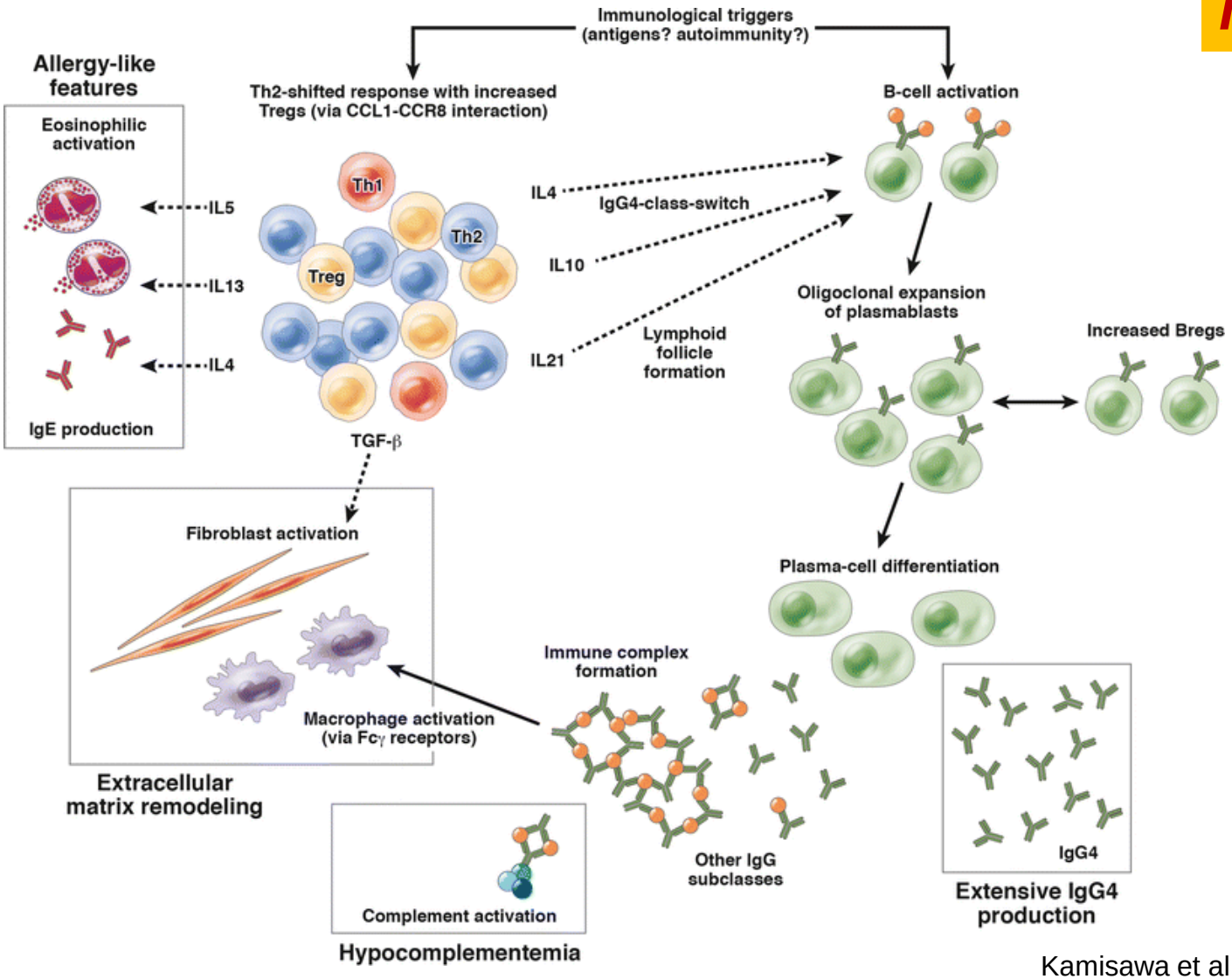
  allergy/atopy/eosinophlia, other autoimmune disease (thyroid, coeliac..)

Pathogenesis of IgG4-sclerosing cholangitis

IgG4

Pathogenesis of IgG4-sclerosing cholangitis

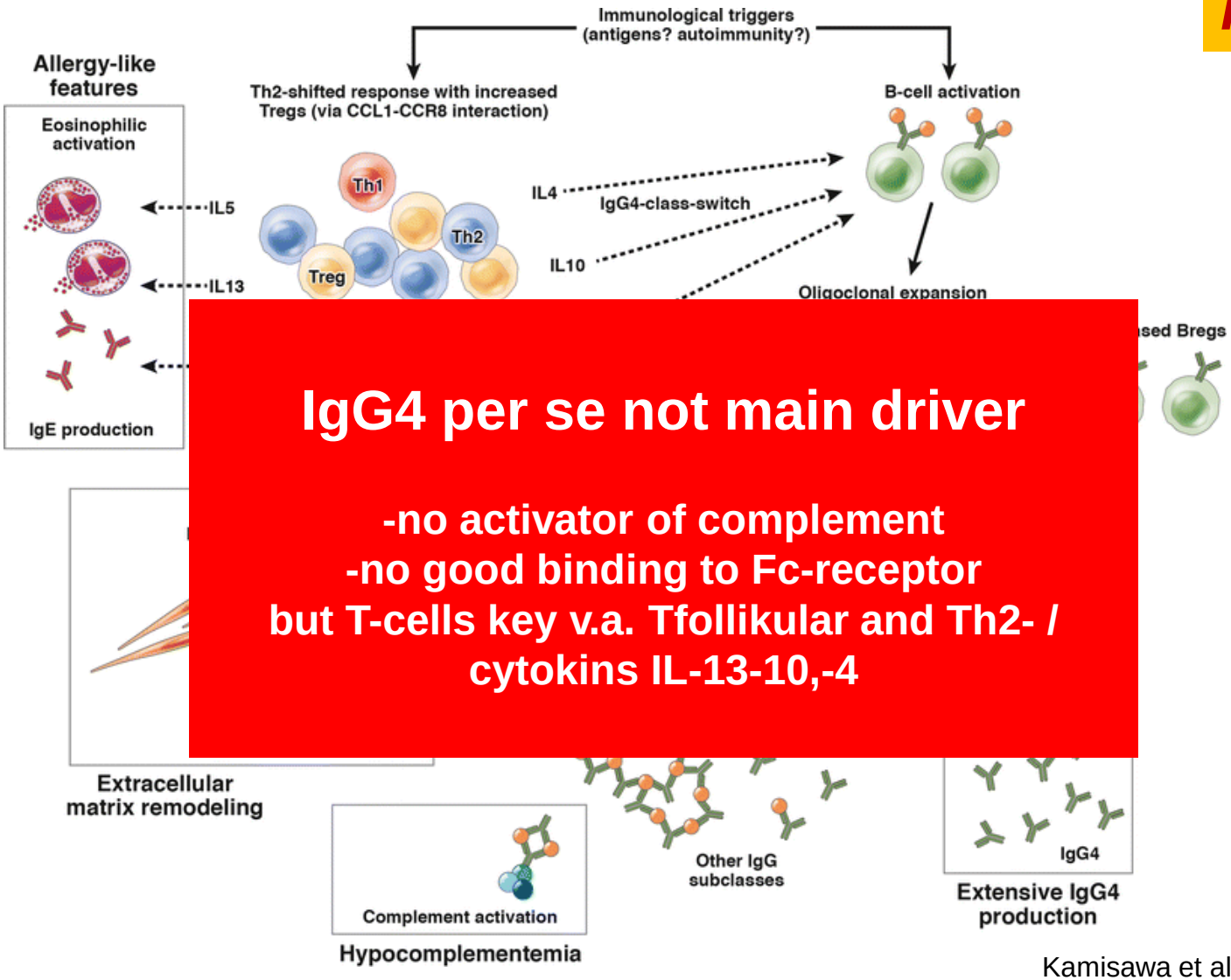
IgG4



Kamisawa et al. Lancet 2015

Pathogenesis of IgG4-sclerosing cholangitis

IgG4



IgG4 per se not main driver

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

Kamisawa et al. Lancet 2015

IgG4-serum levels- how useful ? Differentiate PSC

IgG4

IgG4-serum levels- how useful ? Differentiate PSC

IgG4

- > 1.4g/l: 65-80% of IgG4-SC (but 20% 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)

IgG4-serum levels- how useful ? Differentiate PSC

IgG4

- > 1.4g/l: 65-80% of IgG4-SC (but 20% 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

Typical ERCP-features in IgG4-sclerosing cholangitis ?

IgG4

Strictures in cholangiogramm:

- ✓ **Long + multifocal**

Typical ERCP-features in IgG4-sclerosing cholangitis ?

IgG4

Strictures in cholangiogramm:

- ✓ **Long + multifocal**
- ✓ **mild dilatations upstream**

Typical ERCP-features in IgG4-sclerosing cholangitis ?

IgG4

Strictures in cholangiogramm:

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

Typical ERCP-features in IgG4-sclerosing cholangitis ?

IgG4

Strictures in cholangiogramm:

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

How helpful for differential diagnostic purpose ?

Typical ERCP-features in IgG4-sclerosing cholangitis ?

IgG4

Strictures in cholangiogramm:

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

How helpful for differential diagnostic purpose ?

Typical ERCP-features in IgG4-sclerosing cholangitis ?

IgG4

Strictures in cholangiogramm:

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

How helpful for differential diagnostic purpose ?

Sensitivity 45% = forget it !

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

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

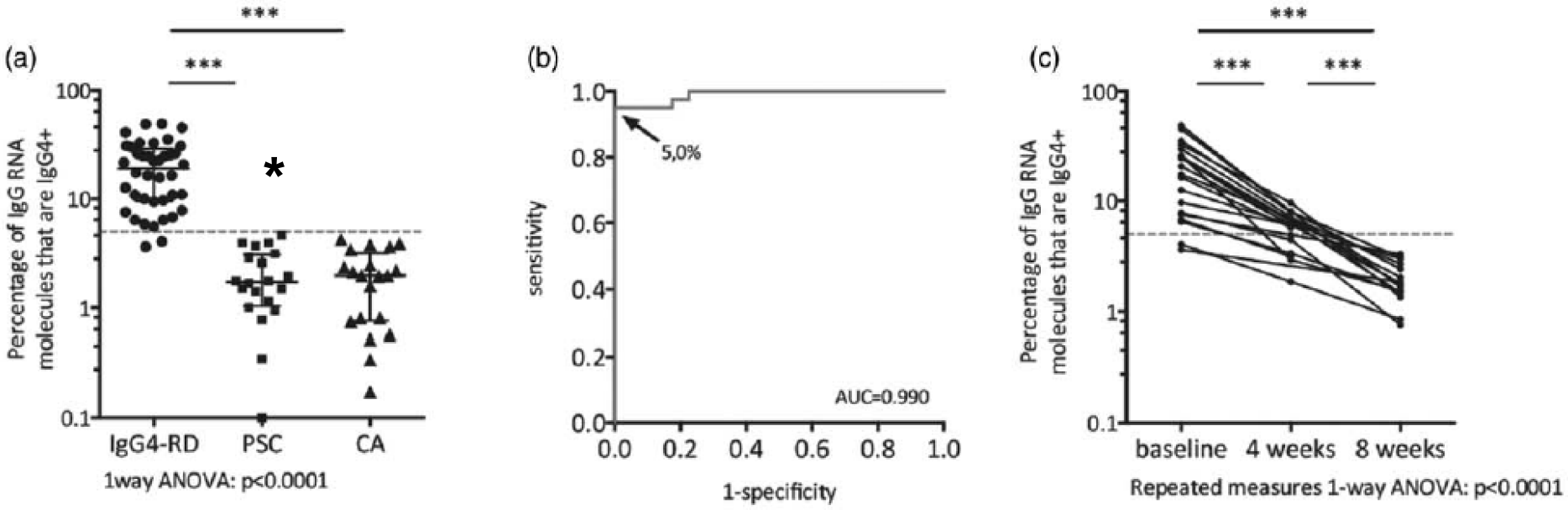
  E.g. in fibrotic stages
- ✓ IgG4-cells in other diseases

  e.g. malignancy, inflammation

How to differentiate PSC/CCA from IgG4-SC ?

How to differentiate PSC/CCA from IgG4-SC ?

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



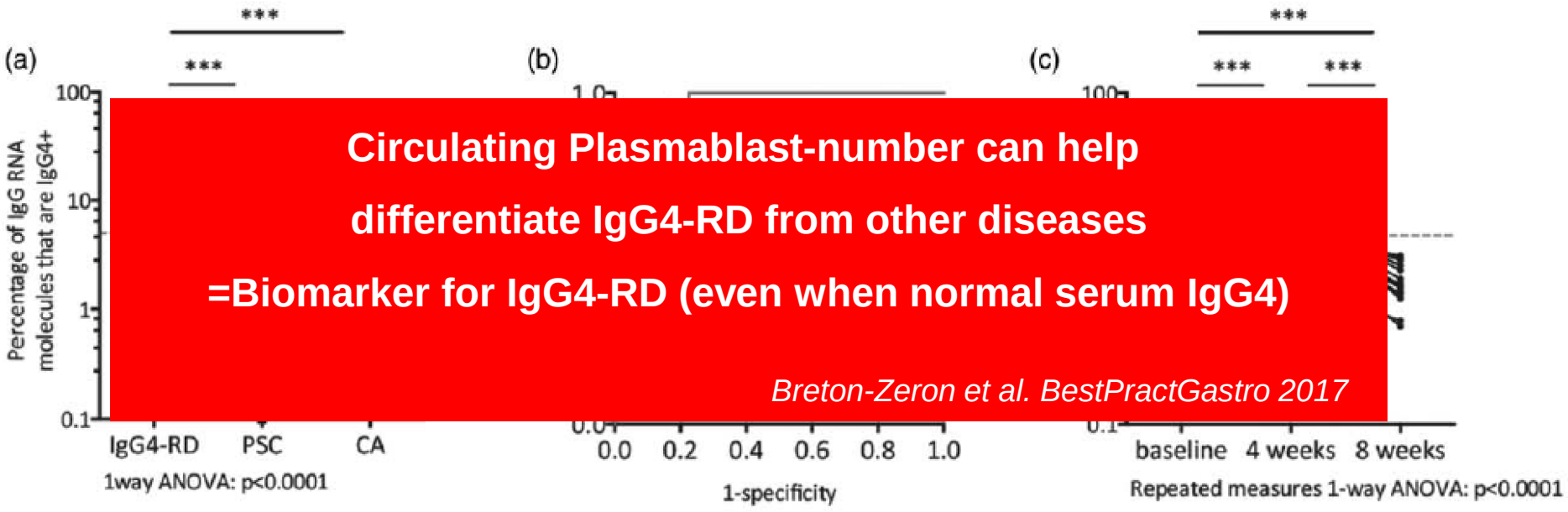
Sensitivity 94%, Specificity 99%

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

Breuers et al. Curr Opin Gastroenterol 2017

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

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

Maintenance therapy (2.5.-5 mg/d) for 3 years

reduces relapse rate compared to stop at 26 weeks (23% vs. 57%)

Treatment-success for IgG4-sclerosing cholangitis ?

IgG4

Treatment-success for IgG4-sclerosing cholangitis ?

IgG4

- 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)**

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

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

Danke für die Aufmerksamkeit