IBD interest group meeting – 16 September 2017

A unique UC phenotype

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4 key thoughts…

- The jaundiced IBD patient
- The role of the multi-disciplinary team
- When to transplant?
- What to do with the colon?

Clinical Case

- 24 year old male
- Family history of colorectal carcinoma (CRCa)
- Inflammatory bowel disease in 2010 (IBD)
  - Pan-colitis (mild)
  - Sigmoid/rectal < right sided inflammation
  - Ulcerative colitis (UC)
- Management
  - 5 ASA oral + suppositories

Clinical course

- Mostly asymptomatic, uncomplicated UC

- 2015
  - Severely fatigued
  - Yellow discoloration
  - Severe pruritus

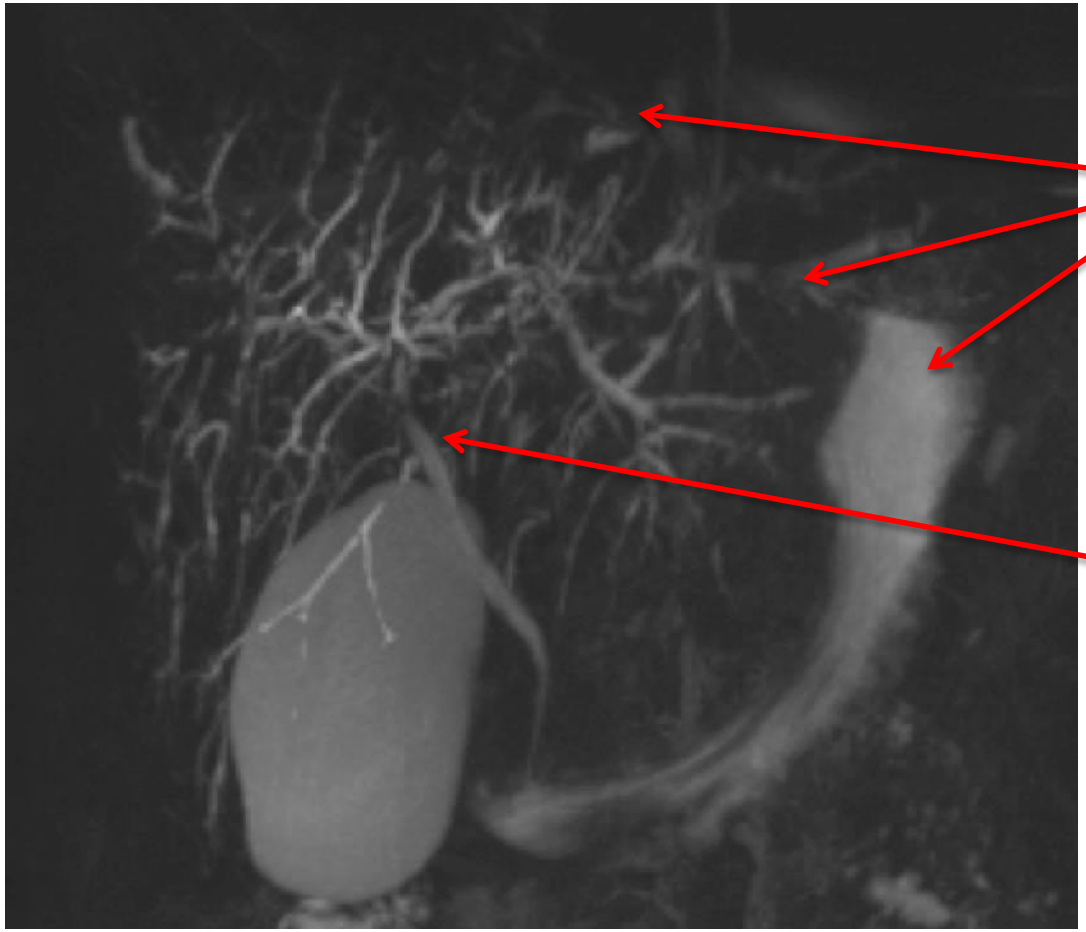
Investigations (2015)

- Cholestatic picture
- Synthetic function preserved
- No recent drug history
- Hepatitis studies all negative
- Autoimmune studies negative
- Ferritin normal
- HIV negative
- Ceruloplasmin normal

TB	81
CB	70
ALP	798
GGT	524
AST	141
ALT	155
INR	1.16
ALB	39

Imaging

MRCP 2015



Beading and irregularities

Focal narrowing Dominant stricture

Hepatomegaly

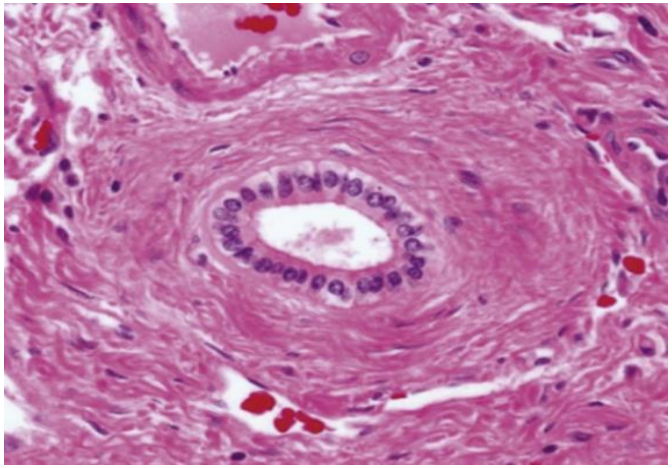
Primary sclerosing cholangitis (PSC)

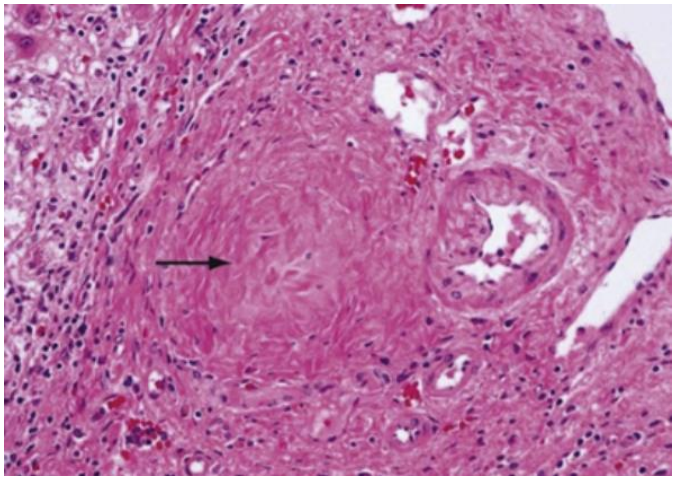
Primary sclerosing cholangitis (PSC)

- Chronic cholestatic liver disease
- Intra and extrahepatic bile duct
- Bile duct obliteration, cirrhosis and liver failure
- > 50% require liver transplant in 10-15yrs

Pathological themes in PSC

Histopathology





Progressive injury to small and large ducts

Inflammation confined to portal tracts

Concentric periductal fibrosis (onion skinning)

Loss of bile ducts and cirrhosis

Sleisenger and Fordtrans's Gastrointestinal and Liver disease. Chp. 68 10th edition

The PSC-IBD relationship

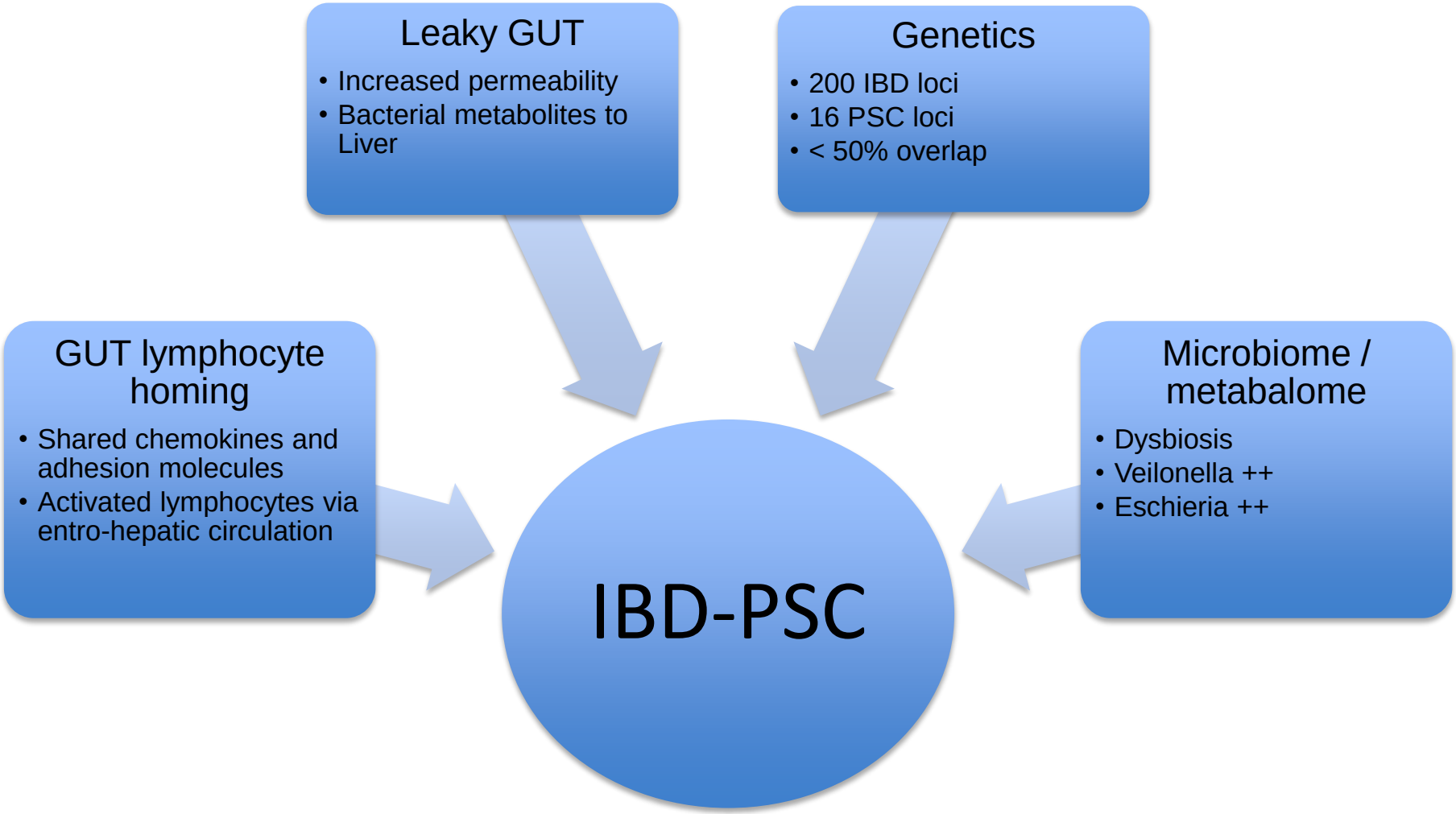
- Strongly associated to inflammatory bowel disease (IBD)

- 67% to 73% of patients with PSC have IBD
  - 85 to 90% have UC
  - 10 to 15% have CD

- Patients with IBD
  - PSC in 2 – 8% of UC
  - PSC in 3% of CD

Sleisenger and Fordtrans's Gastrointestinal and Liver disease. Chp. 68 10th

Pathogenesis of PSC-IBD

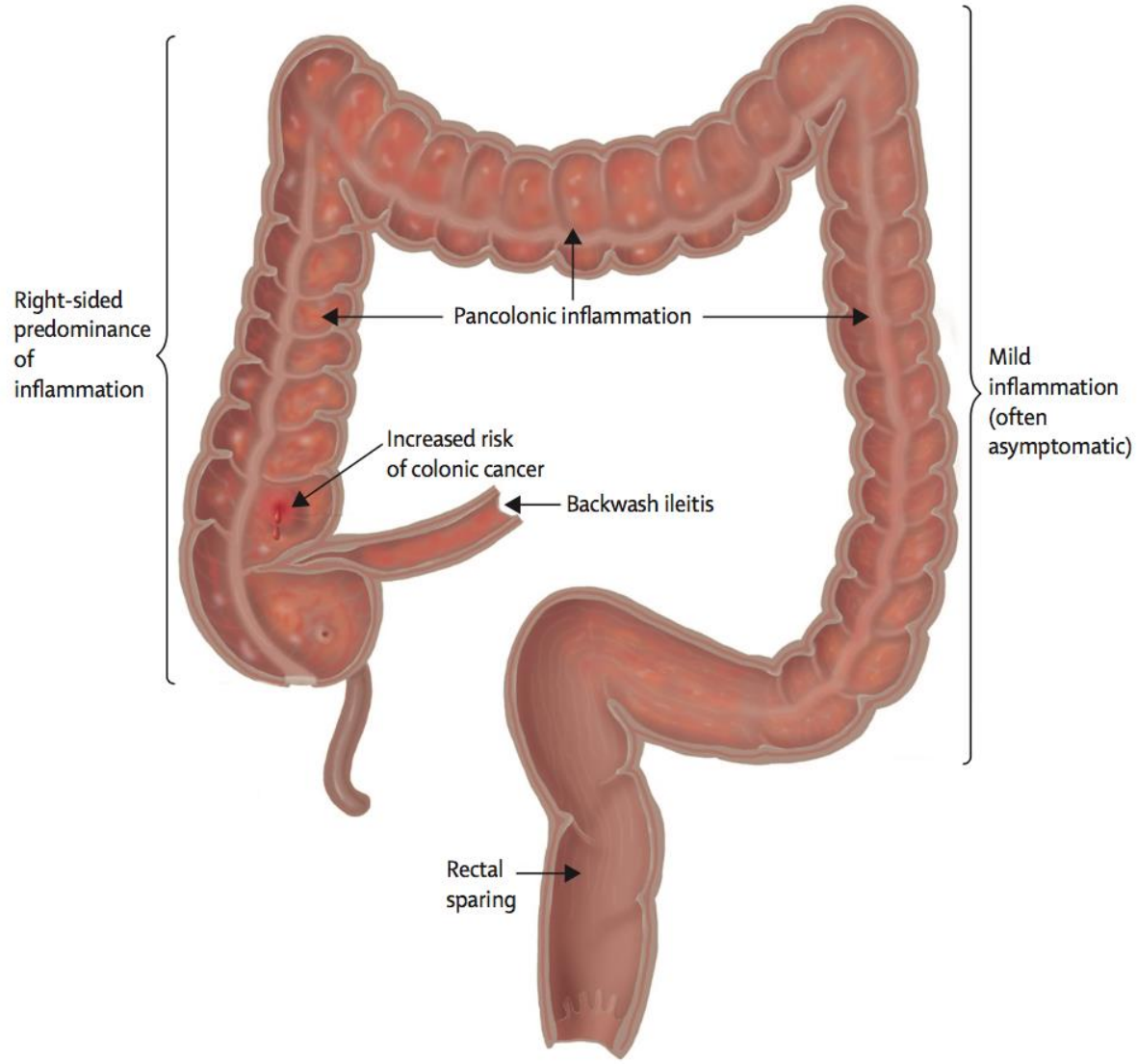


PSC-UC demographics

- Incidence is higher in young males
- Mean age for IBD diagnosis is significantly earlier
  - 24.5yrs vs. 33.8yrs
- The PSC occurs at a younger age
  - 33.6yrs vs. 58.9yrs ($p<0.001$)

Joo M et al. J Surg Path 2009;33:854-862

The unique PSC-UC phenotype



Quiescent to mildly symptomatic

Lower grade inflammation (Right > Left)

Reduced steroid use

Decreased rate of hospitalization

Inversely related PSC : IBD activity

Gut and Liver, Published online April 6, 2017

The colon concern in PSC-UC

Increased risk of colorectal neoplasia in patients with primary sclerosing cholangitis and inflammatory bowel disease: a meta-analysis of 16 observational studies

Han-Han Zheng[a,b] and Xue-Liang Jiang[b]

PSC-UC versus UC alone

- 3 fold risk of colorectal neoplasia and cancer

- Dysplasia – OR 2.98 (95% 1.54 – 5.76)
- Cancer – OR 3.01(95% 1.44 – 6.29)

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Biliary Cancer risk in PSC-IBD

Duration of Inflammatory Bowel Disease Is Associated With Increased Risk of Cholangiocarcinoma in Patients With Primary Sclerosing Cholangitis and IBD

- 33% increased risk per 10 years of IBD
- Not modified by colectomy
- Associated with hepatocellular Ca

Am J Gastroenterol. 2016 May ; 111(5): 705–711. doi:10.1038/ajg.2016.55.

Management – UC component

- Step up approach – mostly responds to 5-ASAs (lowers the cannilicular enzymes)

- Surveillance is the key
  - Annual colonoscopy
  - Annual imaging of the gall bladder (+Ca 19.9)
  - 6 monthly HCC screening when cirrhotic
  - Regular bone marrow density testing

Lancet 2013; 382: 1587–99

Management of the PSC component Ursodeoxycholic acid

- Low dose suggested an improvement in LFTs, not survival (used in Sweden)
  - Possible reduced risk of CRCa and CholangioCa

- High dose UDCA RCT was terminated.
  - Improved LFTS BUT increase in adverse events (sepsis)

Lancet 2013; 382: 1587–99

Management of the PSC component Immunomodulation

- No benefit

<u>Future work</u>

- Gut specific α4β7 (vedolizumab) targets to primed gut lymphocytes

- Small molecule inhibitors against CCR9

- ‘Mabs’ against fibrosis

Lancet 2013; 382: 1587–99

Management of the PSC component ERCP and Surgery

- Balloon dilation with/out stent placement

- Orthotopic liver transplantation (OLT)
  - Only potential cure
  - Survival rates of 85% at 5 years / 70% at 10 years
  - Without OLT – symptomatic patients die within 12-15 years.
  - Less based on MELD scores

Lancet 2013; 382: 1587–99

Course of IBD after liver transplant (LT)

- Worsening of colitis in 30% of patient
- Colectomy rate post LT 4 -20%
- Higher rate of overall clinical IBD activity
- 3 fold increased risk in CRCa

<u>A PSC liver is somewhat protective</u>

Gut and Liver, Published online April 6, 2017

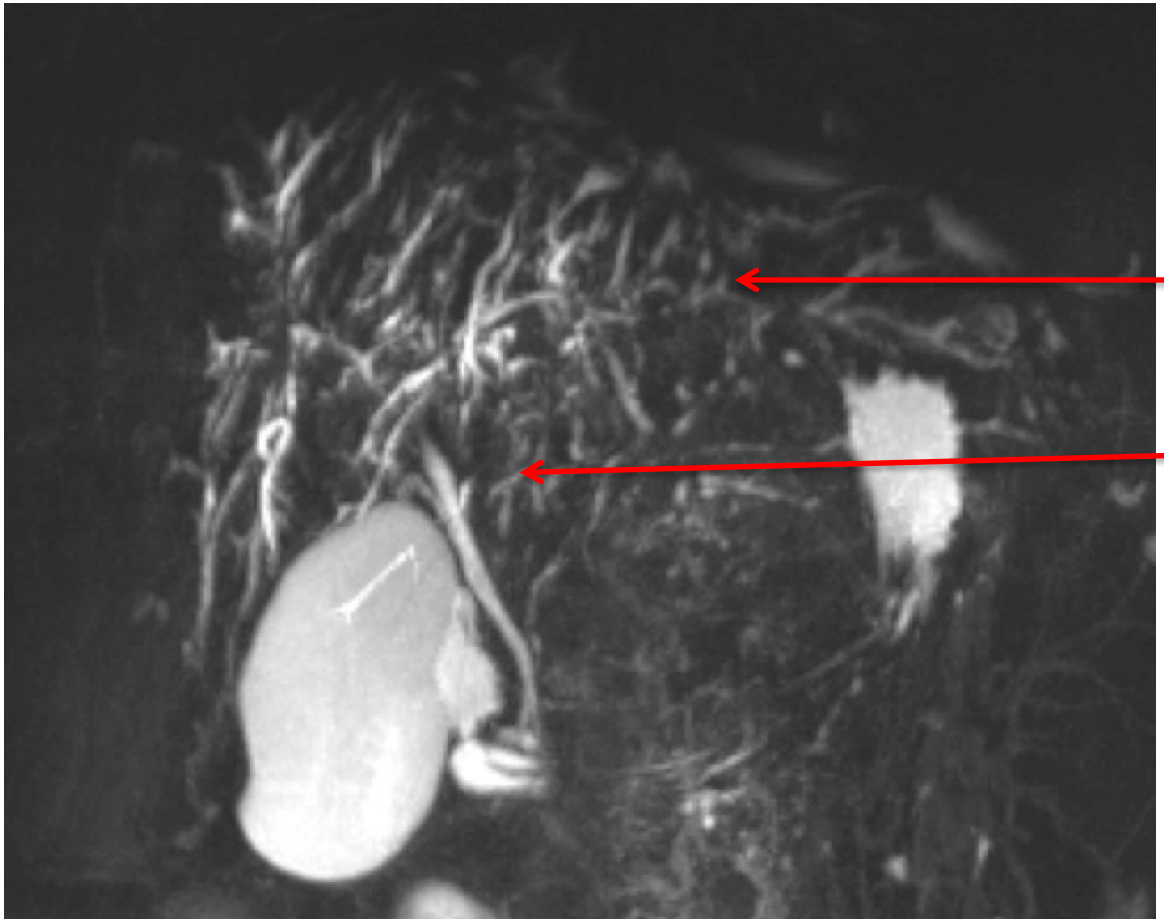
Case clinical progression (2017)

- Annual colonoscopy with random biopsies
  - chronic colitis with focal activity
- 6 monthly varices screen
  - Grade 1 oesophageal varices
  - Portal hypertensive gastropathy
- Co-managed with HPB and Liver
  - Prepared for OLT

	2015	2017
TB	81	60
CB	70	55
ALP	798	746
GGT	524	352
AST	141	118
ALT	155	164
INR	1.16	1.16
ALB	41	39
MELD	14	12

Case clinical progression

MRCP 2017



Massive hepatomegaly

Biliary fibrosis and obliteration

Marked narrowing of common hepatic duct

Features of portal hypertension

Splenorenal shunting

Clinical Questions?

1. When to do a liver transplant?
   - High risk surgery
   - MELD
   - Good baseline versus sick patient

1. Do we consider a subtotal colectomy before liver transplant
   - Risk of UC flaring
   - High risk of CRN / CRCa
   - Risk the graft – Tacro and stoma…
   - Risk for pouchitis

Conclusion

- Cholestasis in IBD must be fully investigated
- PSC -IBD shares a close, unexplained relationship
- The UC phenotype is unique
- OLT is the only cure
- Early multi-disciplinary team
- What one does with the colon is based on risk of cancer