

EMA stakeholder interaction on the development of medicinal products for chronic non-infectious liver diseases (PBC, PSC, NASH)

Programme

3 December 2018

European Medicines Agency, Canary Wharf, London, United Kingdom



Definition, natural history and the lack of approved therapeutic interventions

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[@dougton](https://twitter.com/dougton)

The challenge of PSC....

Rare disease

- Few patients in mixed GI practice

Complex disease

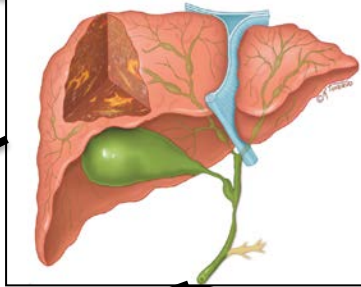
- Several phenotypes
- IBD Association (70%)

Young male patient population

- Median age of diagnosis <40yo

Lack of effective medical therapy

- 'Surgical' management of advanced disease



Patient experience

- Symptom burden
- Psychological impact

Cancer risk

- Cholangiocarcinoma (>20% 10yr)
- Colorectal (10x higher risk than UC)

Unfavourable natural history

- <50% transplant free survival at 10 yrs

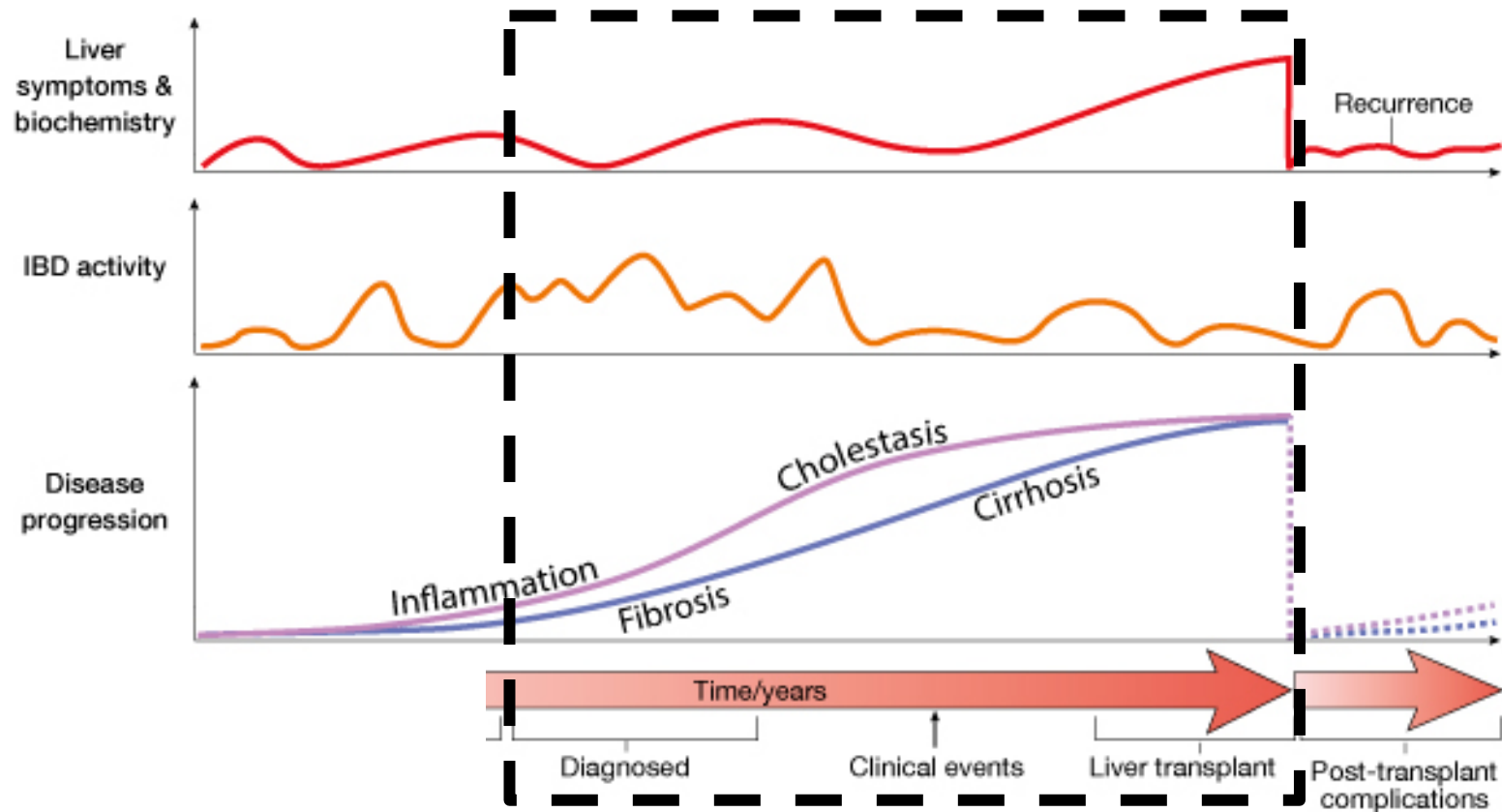
Current Definition of PSC

A diagnosis of PSC is made in patients:

- with **elevated serum markers of cholestasis** (ALP, GGT) not otherwise explained
- **Characteristic changes on cholangiography** (MRCP or ERCP)
 - multifocal strictures
 - segmental dilatations
- When **causes of secondary sclerosing cholangitis and other cholestatic disorders are excluded.**

EASL Cholestatic Liver Disease Guidelines J Hepatol 2009

PSC Diagnosis: Clinical PSC



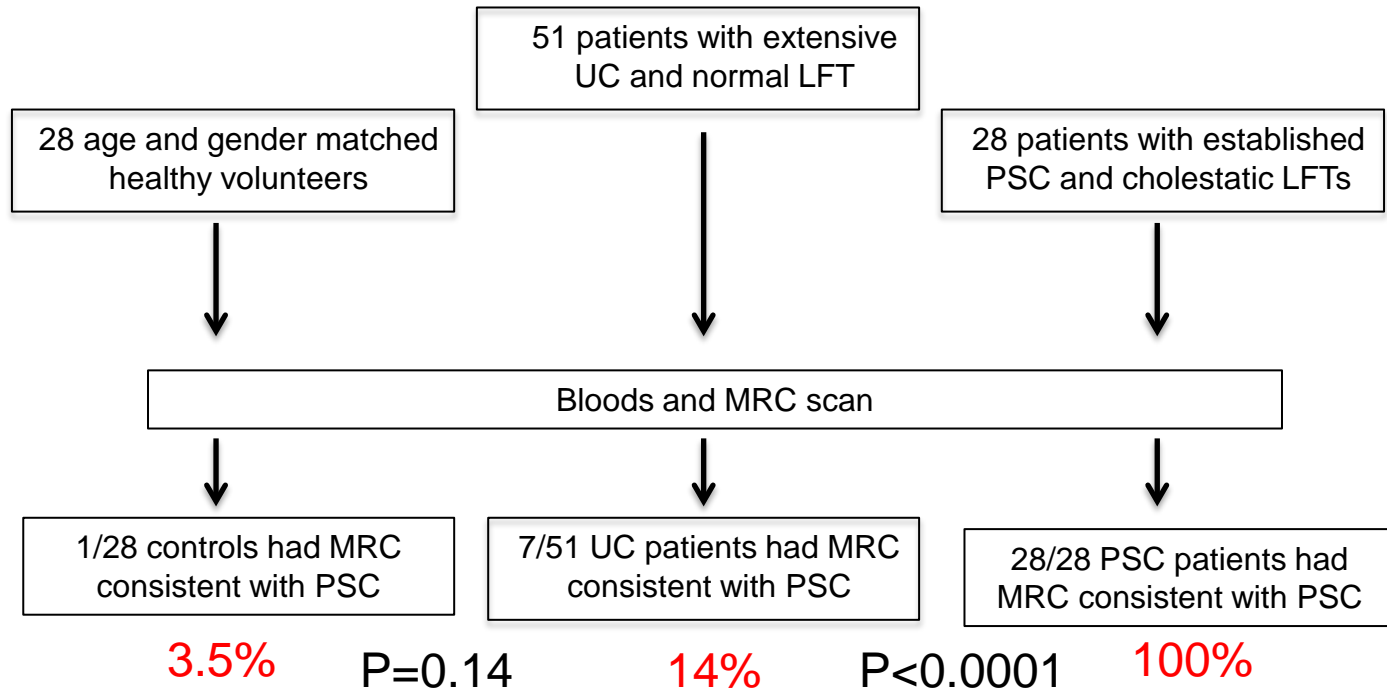
Tom H. Karlsen^{1,2,3,*}, Trine Folseraas^{1,3}, Douglas Thorburn^{4,5}, Mette Vesterhus^{1,6}

Journal of Hepatology 2017 vol. 67 ; 1298–1323

world class expertise  local care

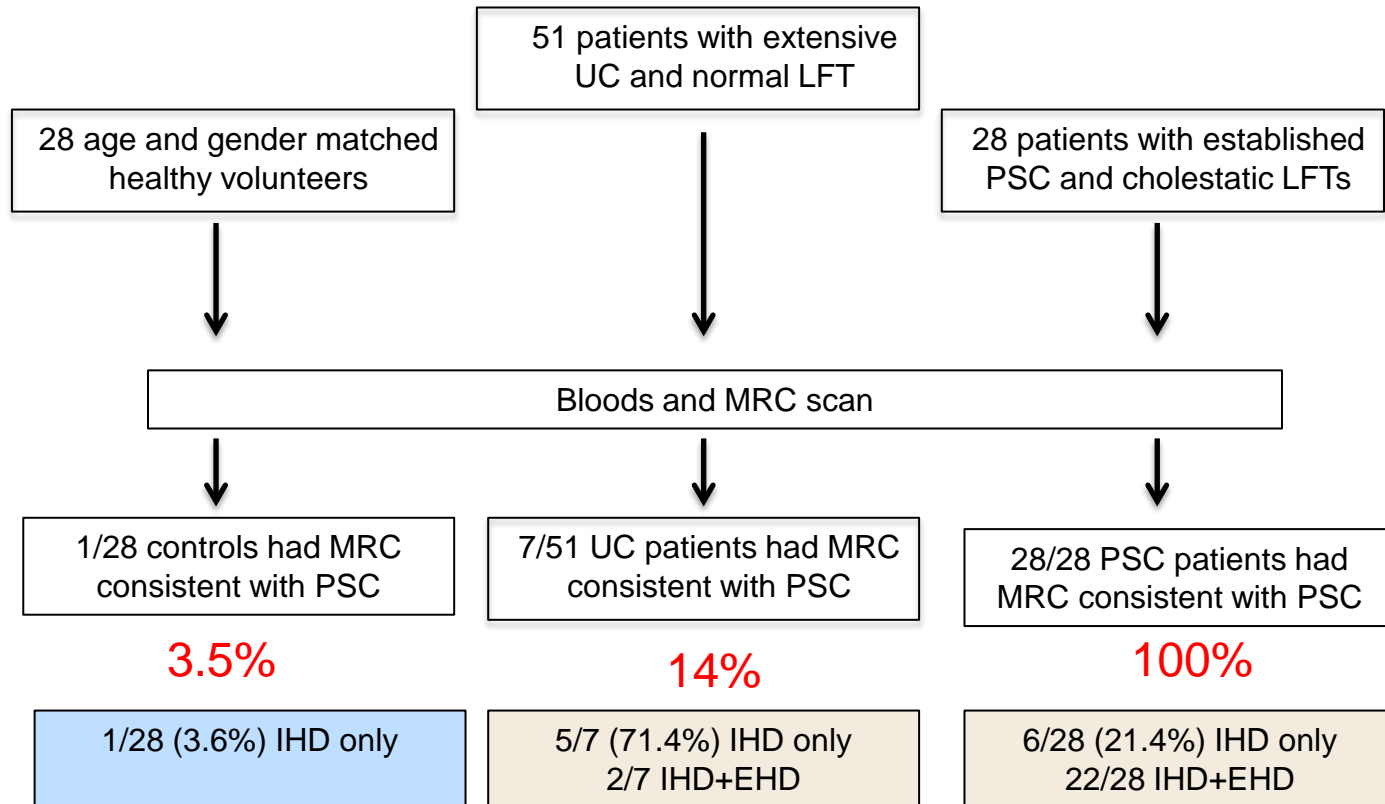
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Prevalence of subclinical PSC in patients with extensive UC and normal LFTs




Culver EL et al, JCC 2017.

Prevalence of subclinical PSC in patients with extensive UC and normal LFTs



Culver EL et al, JCC 2017.

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Outcome of Subclinical PSC-UC

Follow Up [median years(months), range] **8.8yr (106mo)**, 30-116m

| | MRC evidence of subclinical PSC |
|--|--|
| Persistently abnormal liver function | 4/11 (36.4%) |
| Radiological evidence of progression | 2/11 (18.2%) to involve IHD+EHD |
| Decompensation of PSC | 0/11 |
| Liver Transplant for PSC | 0/11 |
| Surveillance colonoscopy low grade adenoma | 1/7 (14.3%) with UC - resected |
| Cholangiocarcinoma | 1/11 (9.1%) after 7.2yrs |
| Death | 2/11 (18.2%) |

Culver EL et al, JCC (abstract) 2017.

Sub-clinical PSC

Lunder et al Gastro 2016

IBSEN Cohort - 756 patients diagnosed with IBD Jan 90 – Dec 93

470 attended for 20yr f/u assessment, including 322 (68%, 222 UC, 100 CD) underwent MRCP

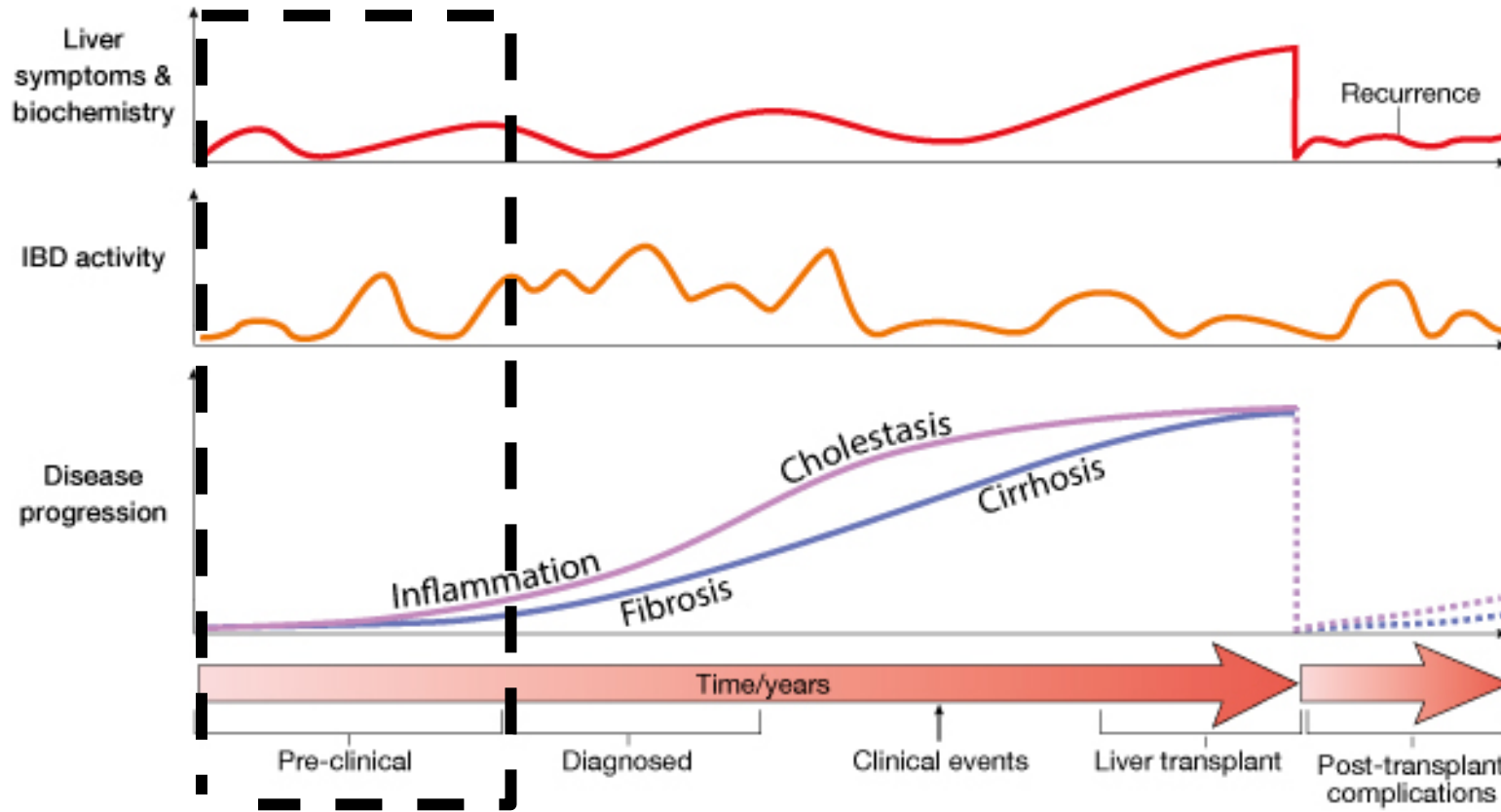
26 (8.1%) had MRCP evidence of PSC

9 (2.8%) had been previously diagnosed with PSC

Features of this new PSC

- Predominantly intra-hepatic changes
- Similar/Higher prevalence in CD (v UC)
- Sub-clinical cases were 70% females

PSC: Sub-clinical PSC



Tom H. Karlsen^{1,2,3,*}, Trine Folseraas^{1,3}, Douglas Thorburn^{4,5}, Mette Vesterhus^{1,6}

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IPSCSG Definitions Paper 2019

Adult & Paediatric

Definite & Probable PSC

Large duct & small duct, AIH Overlap/Variant

Histopathology

Recurrent PSC

Clinical events

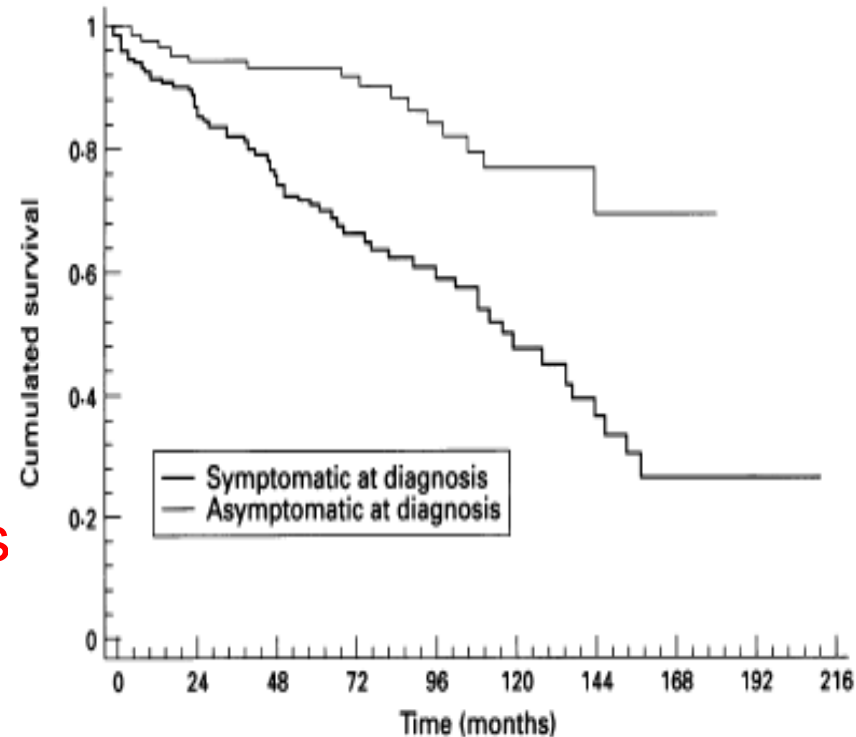
- PSC specific - Cholangitis, Dominant Stricture
- Genaralised - Cholangiocarcinoma, HCC

Clinical endpoints

Colitis

Natural history of PSC

- 305 Swedish patients
- 27% intra:6% extra:67% both
- Median follow-up 63 months:
 - 74% (227) alive
 - 15% (45) dead
 - 11% (34) OLT
- Median survival from diagnosis to death or OLT 12 yr



Broome *et al* Gut 1996

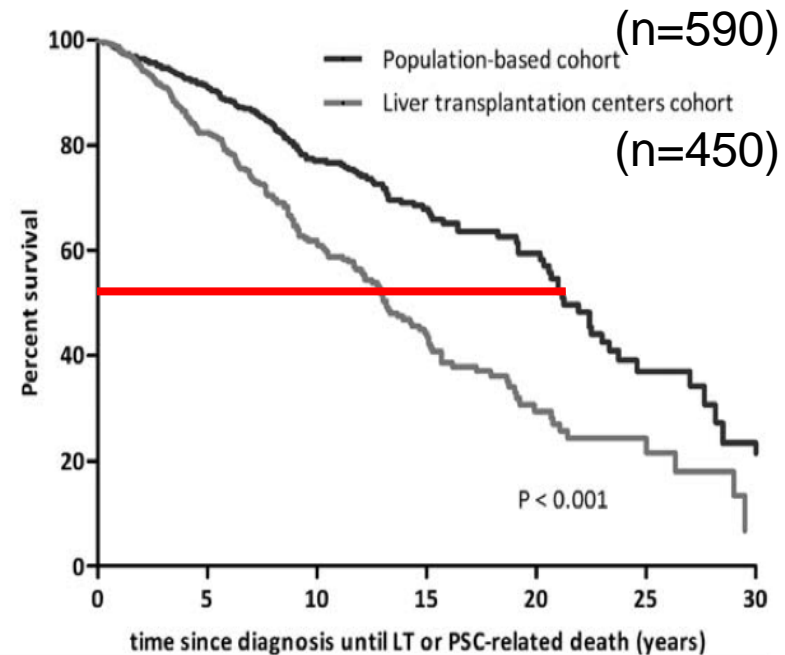
Natural History PSC

| | Wiesner, 1989 | Farrant, 1991 | Broome, 1996 |
|-------------------------|------------------|------------------|-----------------|
| Centres, country | 1, USA | 1, UK | 8, Sweden |
| No | 174 | 126 | 305 |
| Follow-up | 6.0 yrs | 5.8 yrs | 63 mo |
| Median survival | 11.9 yrs | 12 yrs | 12 yrs |
| Survived | 98 (56%) | 80 (63%) | 227 (74%) |
| Death | 59 (34%) | 28 (22%) | 45 (15%) |
| Cirrhosis | 43 | 18 | 33 |
| CCa | 11 | 2 | 12 |
| Liver Transplant | 17 (10%) | 26 (21%) | 34 (11%) |
| Cirrhosis | | 24 (92%) | |
| Malignancy | | 2 (8%) | |
| QoL | | 0 | |

Natural History of PSC

44 Dutch hospitals covering 50% of the population
Median FU 92 mo.
Median survival from diagnosis until LT or PSC-related death:

- 21.3 yrs all PSC
- 13.2 yrs OLT centers (P < 0.0001)



| | | | | | | | |
|------------------|-----|-----|-----|-----|----|----|---|
| patients at risk | 590 | 378 | 206 | 104 | 50 | 18 | 5 |
| | 422 | 266 | 143 | 67 | 26 | 9 | 0 |

Boonstra *et al.* Hepatology 2013

Natural History PSC

| | Wiesner, 1989 | Farrant, 1991 | Broome, 1996 | Boonstra, 2013 | Weissmuller 2017 |
|-------------------------|------------------|------------------|-----------------|-------------------|---------------------|
| Centres, country | 1, USA | 1, UK | 8, Sweden | 44, Holland | 37, Multiple |
| No | 174 | 126 | 305 | 590 | 7,121 |
| Follow-up | 6.0 yrs | 5.8 yrs | 63 mo | 92 mo | |
| Median survival | 11.9 yrs | 12 yrs | 12 yrs | 21.3 yrs | 14.5 yrs |
| Survived | 98 (56%) | 80 (63%) | 227 (74%) | 399 (67%) | 4505 (63%) |
| Death | 59 (34%) | 28 (22%) | 45 (15%) | 73 (12%) | 920 (13%) |
| Cirrhosis | 43 | 18 | 33 | 13 | <330 |
| CCa | 11 | 2 | 12 | 24 | 590 |
| Liver Transplant | 17 (10%) | 26 (21%) | 34 (11%) | 94 (16%) | 1696 (24%) |
| Cirrhosis | | 24 (92%) | | | |
| Malignancy | | 2 (8%) | | | |
| QoL | | 0 | | | |

Natural History PSC

| | Wiesner, 1989 | Farrant, 1991 | Broome, 1996 | Boonstra, | Weissmuller , 2017 | Andersen, 2017 |
|-------------------------|---------------|---------------|--------------|-------------|--------------------|----------------|
| Centres, country | 1, USA | 1, UK | 8, Sweden | 44, Holland | 37, Muliple | 1, Norway |
| No | 174 | 126 | 305 | 590 | 7,121 | 138 |
| Follow-up | 6.0 yrs | 5.8 yrs | 63 mo | 92 mo | | |
| Median survival | 11.9 yrs | 12 yrs | 12 yrs | 21.3 yrs | 14.5 yrs | |
| Survived | 98 (56%) | 80 (63%) | 227 (74%) | 399 (67%) | | |
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| Cirrhosis | 43 | 18 | 33 | 13 | | |
| CCa | 11 | 2 | 12 | 24 | | |
| Liver Transplant | 17 (10%) | 26 (21%) | 34 (11%) | 94 (16%) | 1696 (24%) | |
| Cirrhosis | | 24 (92%) | | | | 53 (38%) |
| Malignancy | | 2 (8%) | | | | 60 (43%) |
| QoL | | 0 | | | | 25 (18%) |

PSC: Lack of Effective Therapy

Current Treatment of PSC

Symptoms

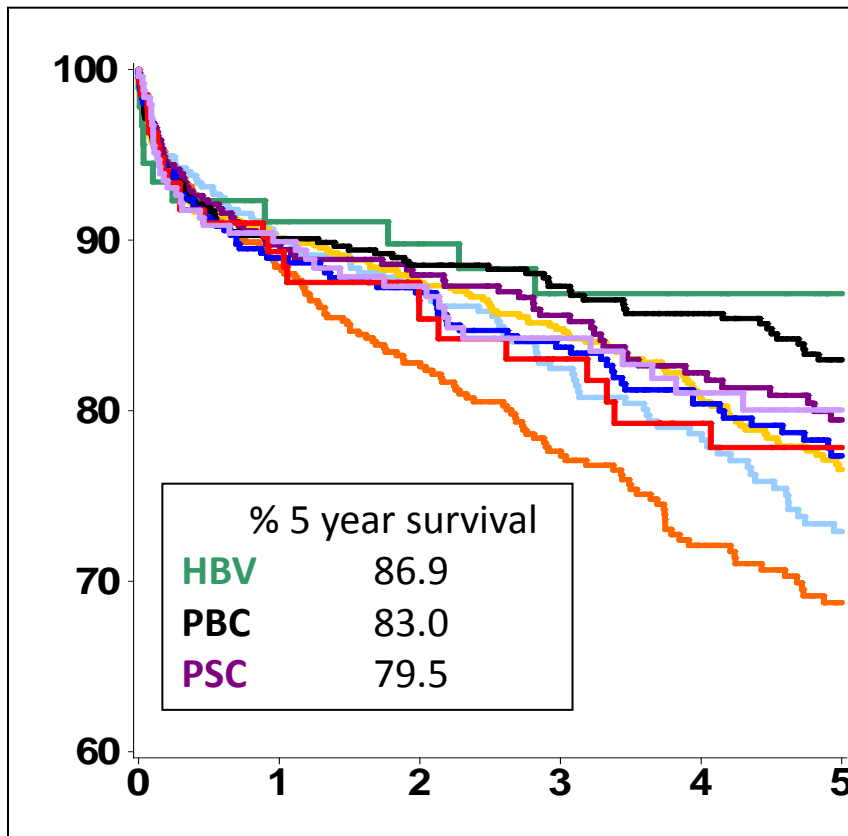
- Cholangitis
- Pruritus
- Pain
- Fatigue

Changing the course of the disease:

- Liver transplantation
- ??Therapeutic ERCP
- ??UDCA

PSC is an excellent indication for liver transplantation

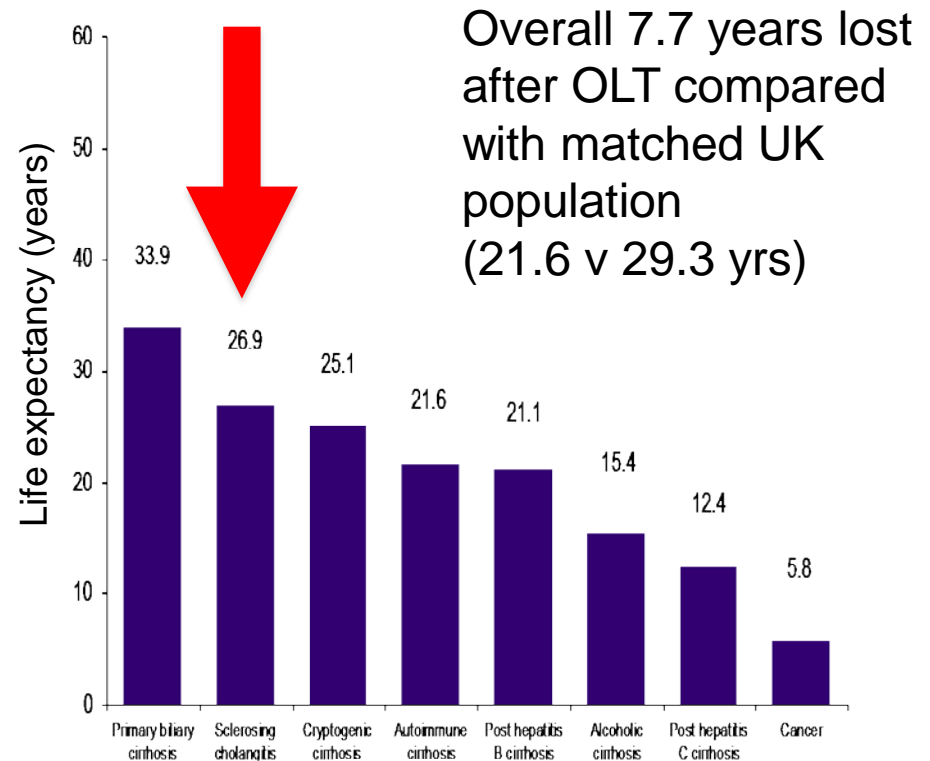
Risk adjusted transplant survival for adult first elective transplantation; 2000-11



Life expectancy of adult liver allograft recipients in the UK

K Barber, J Blackwell, D Collett, J Neuberger, on behalf of the UK Transplant Liver Advisory Group

Gut 2007;56:279-282. doi: 10.1136/gut.2006.093195



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Primary liver disease
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rPSC OLT: Significance of r-PSC

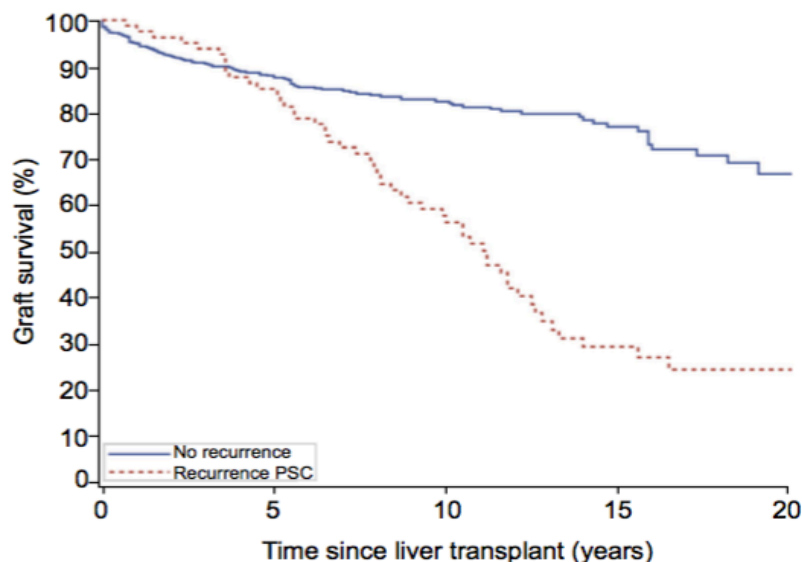
r-PSC in 14.3% of 679 UK PSC transplants 1990-2010;
Median FU 9yrs

rPSC associated with ***UC post-liver transplant***

(HR = 2.40, 95% CI 1.44–4.02) and ***younger age*** (HR = 0.78, 95% CI 0.66–0.93)

r-PSC increased risk of:

- Graft failure HR 8.15, 95% CI 5.59, 11.89
- Graft failure or death HR 4.71, CI 3.39, 6.56



| | 1 year survival | | 5 year survival | | 10 year survival | |
|-------------------|-----------------|--------------|-----------------|--------------|------------------|--------------|
| | In follow up | Survival (%) | In follow up | Survival (%) | In follow up | Survival (%) |
| rPSC (n = 81) | 80 | 98% | 67 | 84% | 39 | 56% |
| No rPSC (n = 530) | 493 | 95% | 372 | 88% | 208 | 82% |

Ravikumar et al *J Hepatol* 2015; 63(5):1139-46

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Therapeutic Efficacy of UDCA in PSC

Placebo Controlled Trials

| | Beuers (n=14) | Stiehl (n=20) | Lindor (n=105) | Mitchell (n=26) | Olsson (n=219) | Lindor (n=150) |
|-------------------|------------------|------------------|-------------------|--------------------|-------------------|-------------------|
| Dose (mg/kg/d) | 13-15 | 10-12 | 13-15 | 20 | 17-23 | 28-30 |
| LFTs | + | + | + | + | 0 | + |
| Histology | (+) | (+) | 0 | + | | |
| ERCP | | | 0 | | 0 | - |
| Survival | | | 0 | | 0 | - |

Pharmacological interventions for primary sclerosing cholangitis (Review) 2017

Saffioti F, Gurusamy KS, Hawkins N, Toon CD, Tsochatzis E, Davidson BR, Thorburn D

Ursodeoxycholic acid versus placebo for primary sclerosing cholangitis

Patient or population: people with primary sclerosing cholangitis
Settings: secondary or tertiary care
Intervention: ursodeoxycholic acid
Comparison: placebo

| Outcomes | Illustrative comparative risks* (95% CI) | | Relative effect (95% CI) | Number of participants (trials) | Quality of the evidence (GRADE) |
|--|--|--|--------------------------|---------------------------------|-------------------------------------|
| | Assumed risk | Corresponding risk | | | |
| | Placebo | Ursodeoxycholic acid | | | |
| Mortality Follow-up: 60 months | 72 per 1000 | 105 per 1000 (47 to 220) | OR 1.51 (0.63 to 3.63) | 348 (2 trials) | ⊕○○○ very low ^{1,2,3} |
| Serious adverse events | No trials reported the number of participants with serious adverse events or numbers of serious adverse events | | | | |
| Proportion of people with adverse events Follow-up: 60 months | 337 per 1000 | 358 per 1000 (237 to 498) | OR 1.22 (0.68 to 2.17) | 198 (1 trial) | ⊕○○○ very low ^{1,2,3} |
| Number of adverse events | No trials reported the number of adverse events. | | | | |
| Health-related quality of life Follow-up: 5 years Scale: SF-36 General Health Scale (Limits: 0 to 100; higher = better) | Mean in the placebo group was 61.10. | Mean in the ursodeoxycholic acid group was 1.30 higher (5.61 lower or 8.21 higher) | - | 198 (1 trial) | ⊕○○○ very low ^{1,2,3} |
| Liver transplantation Follow-up: 60 months | 123 per 1000 | 120 per 1000 (68 to 202) | OR 0.97 (0.52 to 1.81) | 348 (2 trials) | ⊕○○○ very low ^{1,2,3,4} |
| Any malignancy | No trials reported this outcome. | | | | |
| Cholangiocarcinoma Follow-up: 60 months | 43 per 1000 | 57 per 1000 (21 to 142) | OR 1.34 (0.48 to 3.68) | 348 (2 trials) | ⊕○○○ very low ^{1,2,3} |
| Colorectal cancer | No trials reported this outcome. | | | | |
| Cholecystectomy | No trials reported this outcome. | | | | |

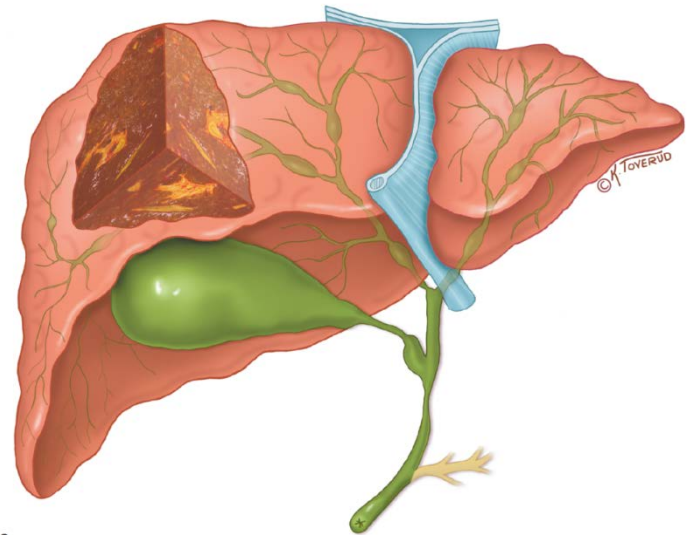
Summary

- EASL 2009 definition likely underestimates the prevalence of PSC, but the natural history of this subclinical disease remains to be established.
- New definitions for PSC are in development by the IPSCSG and should be finalized in 2019.
- Clinical endpoints in PSC arise over decades with event rates reported as 5.1 per 100 patient years for death and OLT and 1.4 per 100 patient years for HPB cancer.
- Liver transplant remains the only intervention shown to alter the natural history of the disease.



Primary Sclerosing Cholangitis

Unexplained chronic and progressive disease of the biliary tree characterised by concentric, obliterative fibrosis leading to bile duct stricturing and eventually end-stage liver disease



Primary sclerosing cholangitis, the biliary tree, and ulcerative colitis *Gut*, 1967, 8, 435

M. E. C. THORPE, P. J. SCHEUER, AND SHEILA SHERLOCK

From the Departments of Medicine and Pathology, Royal Free Hospital, London

The requisites for the diagnosis of sclerosing cholangitis:

- (1) diffuse generalized involvement of the extrahepatic ducts
- (2) absence of previous biliary surgery
- (3) absence of gall stones
- (4) exclusion of carcinoma of the ducts by reasonably long follow up

Holubitsky & McKenzie, *Canad J Surg* 1964

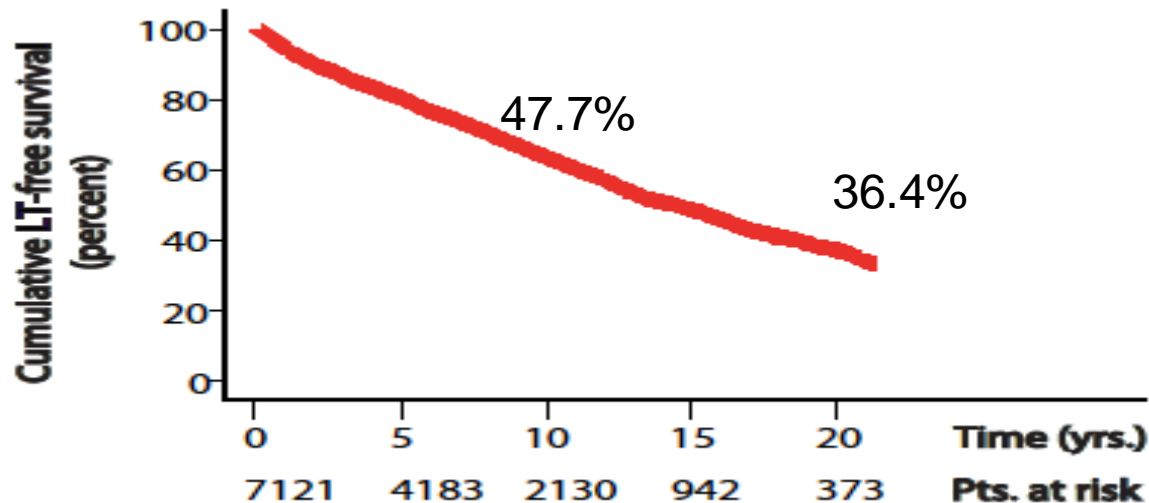
Warren, et al. *Am J Surg* 1966

EDITORIAL COMMENT It is well known that ulcerative colitis may be associated with a number of different diseases of the liver. This paper records sclerosing cholangitis as one possible mechanism of intrahepatic cholestasis. Sclerosing cholangitis is a general disease of the biliary system involving intra- and extrahepatic ducts and also the gall bladder. The diagnosis can only be made by laparotomy. The prognosis seems to be better that was originally thought.

PSC: Natural History

IPSCSG phenotype paper – 7,121 patients, 37 centres, 1980-2010

Male 65.5%, mean age of diagnosis 38yo, 70% with concomitant IBD



Median survival 14.5 years
Event rate 5.1 per 100 patient years

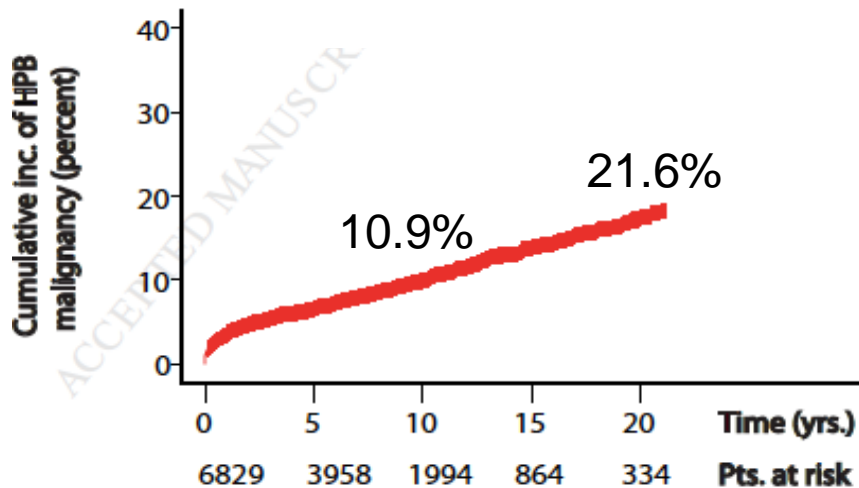
Weissmuller, Trivedi et al. Gastroenterology 2017

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PSC: HPB Malignancy

IPSCSG phenotype paper – 7,121 patients, 37 centres, 1980-2010



Cholangiocarcinoma

82% of malignancies

Incidence 1.4 cases/100 pt yrs

38% detected within 1st year of diagnosis

Incidence in 1st yr 2.6 cases/100 pt yrs