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**Title**

**Dominant stricture: time for a prospective multicenter study?**

**Current collaborators:**

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**Background/Rational**

Primary sclerosing cholangitis (PSC) is a chronic cholestatic liver disease of unknow origin, characterized by inflammation and fibrosing of the bile ducts, leading to strictures and dilatations. The natural history of the disease is developing biliary cirrhosis, end-stage liver disease, liver failure and death or need of liver transplantation (LT) (Hirschfield G et al. Lancet. 2013). Cholangiocarcinoma (CC) risk is also dramatically increased in patients with PSC (Bergquist A et al. J Hepatol. 2002).

Up to 50% of PSC patients develop a dominant stricture (DS) during the follow-up (Björnsson E et al. Am J Gastroenterol. 2004). Patient with a DS has a worse outcome then those without (Rudolph G et al. J Hepatol. 2009). The traditional definition of DS was a stricture < 1.5 mm in the common hepatic bile duct (CHBD) and < 1 mm in the hepatic duct (HD) within 2 cm from bifurcation (Stiehl A et al. J Hepatol. 2002). Recently, a new definition of DS combing patient´s symptoms (jaundice, biliary infection, pruritus or RUQ pain), laboratory tests (ALP, bilirubin), imaging (endoscopic retrograde cholangio-pancreatography ERCP and/or magnetic resonance cholangiopancreatography MRI-MRCP) and treatment (dilatation and stenting) has been proposed (Ponsioen C et al. Gastroenterology. 2021). This definition is referred as International PSC Study Group (IPSCSG).

According to ESGE-EASL Guidelines ERCP should be performed only in patients with: worsening of symptoms, worsening of liver tests and suspicious of a DS on ultra-sound (US) and/or MRI-MRCP (Aabbaken L et al. Endoscopy. 2017).

However, several issues need still to be elucidated:

1. The old DS definition was validated only for ERCP. The new definition of DS is based only on a Consensus Report.

ERCP and MRI-MRCP are completely different techniques. ERCP is usually performed with pressure injection of contrast medium using balloon occlusion technique. A strict comparison between ERCP

and MRI-MRCP findings has never been made. For these considerations, Venkatesh et al. (Venkatesh SK et al. Eur Radiol. 2021) has proposed to avoid the use of the term DS with MRI-MRCP, preferring the term high-grade stricture (i.e., a stricture with > 75% of luminal narrowing). This definition is referred as MR working Group (MRWG) of International PSC Study Group (IPSCSG) definition.

1. Patients with a dominant stricture can be asymptomatic and/or can present with normal laboratory tests (Björnsson E et al. Am J Gastroenterol. 2004).

**Aims of the study**

To evaluate:

1. Correlation between MRWG and IPSCSG definition of possible DS.
2. Accuracy of MRI-MRCP for screening and diagnosis of dominant stricture (IPSCSG), using ERCP as a gold standard.
3. Correlation between MRWG and IPSCSG definition of definite DS (response to endotherapy of symptoms and lab tests).
4. Diagnostic yield of the new definition compared to the old definition in predicting early outcomes:
   1. biliary inflammation and dysplasia.
   2. impact on symptoms and cholestatic liver tests: P-ALP, P-bil.

**Study design**

1. Prospective multi-center study.
2. All PSC patients (n=150) at ERCP examination for confirmation of diagnosis or in follow-up with a dominant stricture based on new definition: possible (MRI-MRCP or ERCP, symptoms, laboratory tests) and defined (response to endoscopic therapy).

**Endpoints**

1. MRWG and IPSCSG definition of DS.
2. improvement of symptoms: jaundice, biliary infection, pruritus or RUQ pain.
3. change in lab values: P-ALP and P-bilirubin or HelPSCore (M.Färkkilä et al UEG 2021). Also P-ALT, P-AST, P-GT, P-alb, P-TT%, INR are evaluated when needed.
4. presence of biliary inflammation and dysplasia.

**Data collection and variables**

Patients´ characteristics: gender, age, PSC diagnosis (year, MRI-MRCP, ERCP), overlap with AIH, co-morbidities (i.e., IBD).

Patient´symptoms before ERCP: SCCS-score (Munster K et al. Liv Int. 2020)

Patient´s lab test before ERCP: B-platelets, P-TT (or INR), P-ALP, P-AST, P-ALT, P-GT and bilirubin.

MRI-MRCP (performed max 3 months before ERCP) findings: quality of MRI-MRCP, 2 vs 3D, strictures (fixed, focal, diffuse), upstream dilatations, number, localization, severity, length).

ERCP findings: Amsterdam score or Helsinki-score, strictures (number, localization, length, upstream dilatations), dilatation, stenting, brush cytology finding (i.e., inflammation, biliary dysplasia).

Patient's symptoms (SCCS-score) and lab tests after 2-4 weeks: P-ALP, P-bil.

**Ethics**

All the patients included in the PSC registry study give a written informed consent and the PSC registry study protocol is approved by Helsinki University Hospital Ethical Committee IV, HUS/1566/2020.

**Time plan**

Study started the 1st October 2021. The study is open for collaboration with additional centers. Please contact us for more information.

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**Supplement 1. New definition of dominant stricture.**

A stricture is called a **possible dominant stricture (DS)** when it meets the following criteria before ERC:

1. **Imaging:** high-quality MRCP or ERC with narrowing of any length in extra-hepatic or first-order intrahepatic ducts, often-but not necessarily- with upstream dilatation.

**TOGETHER WITH**

1. **Symptoms and biochemistry:** significant worsening of cholestatic symptoms within last 2 months: jaundice, biliary infection, pruritus or RUQ pain **AND** **bilirubin and/or ALP:** absolute level of > 1.2 x ULN and recent increase, for example, > 1.2 x baseline **OR biochemistry alone:** bilirubin and/or ALP: increase within past 6 months, for example, > 1.5. x baseline, or absolute level of > 2 x ULN if no previous measurements within 6 months is available.

A stricture is called a **definite DS** when it meets the following criteria:

1. Difficulty to pass with a standard 5F catheter during ERC **OR**
2. Symptomatic and/or biochemical response (e.g., a > 20% drop in ALP and/or total bilirubin) to treatment 2-4 weeks after dilatation/stenting.