

HEPATIC CYSTS

Occurrence and effect of single-session alcohol sclerotherapy

Trond Bjerke Larssen

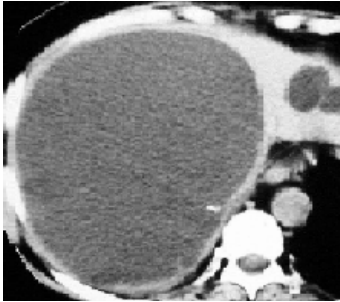


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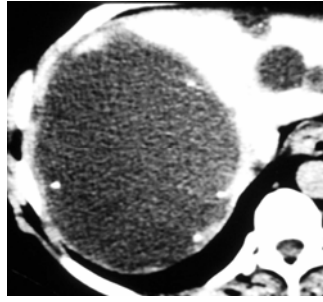
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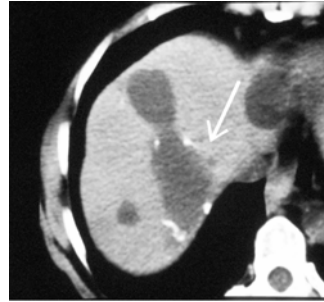
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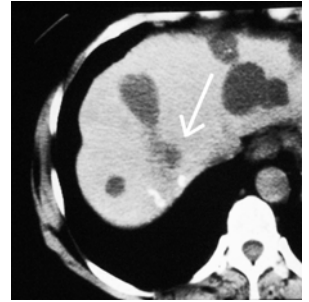
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Trond Bjerke Larssen



SECTION FOR RADIOLOGY, DEPARTMENT OF SURGICAL SCIENCES
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2. List of abbreviations, errata

ADPKD	Autosomal dominant polycystic kidney disease
ADPLD	Autosomal dominant polycystic liver disease without renal involvement
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
CT	Computed tomography
GT	Glutamyl transpeptidase
HCC	Hepatocellular carcinoma
HU	Hounsfield Units
HUS	Haukeland University Hospital
LDH	Lactic dehydrogenase
mHz	Megahertz
MRI	Magnetic resonance imaging
US	Ultrasound

Errata:

Paper III. Patients and methods: The sentence “From December **1995** to June 1999 all sclerotherapy procedures in symptomatic, non-parasitic, non-neoplastic liver cysts were performed with a time of ethanol exposure of 10 minutes” should be corrected to “From December **1996** to June 1999 all sclerotherapy procedures in symptomatic, non-parasitic, non-neoplastic liver cysts were performed with an ethanol exposure of 10 minutes”.

Paper V. Results, para.3: The sentence “Of the 174 affected individuals, 14 had polycystic livers (3.5%)” should be “Polycystic liver disease was found in 14 cases (0.9% of all livers and 8.1% of 174 livers containing cysts)”.

3. List of original papers

This thesis is based on the following papers, referred to in the text by their Roman numerals:

Paper I

Larssen TB, Viste A, Jensen DK, Sondenaa K, Rokke O, Horn A. Single-session alcohol sclerotherapy in benign symptomatic hepatic cysts. *Acta Radiol* 1997;38(6):993-7.

Paper II

Larssen TB, Jensen DK, Viste A, Horn A. Single-session alcohol sclerotherapy in symptomatic benign hepatic cysts. Long-term results. *Acta Radiol* 1999;40(6):636-8.

Paper III

Larssen TB, Rosendahl K, Horn A, Jensen DK, Rorvik J. Single-session alcohol sclerotherapy in symptomatic benign hepatic cysts performed with a time of exposure to alcohol of 10 min: initial results. *Eur Radiol* 2003;13(12):2627-32.

Paper IV

Larssen TB, Rorvik J, Horn A, Karwinski B, Skadberg O, Pedersen OM, Rosendahl K. Biochemical and cytologic analysis of cystic contents in benign non-parasitic symptomatic hepatic cysts before and after ethanol sclerotherapy. *Acta Radiol* 2004;45(5):504-9.

Paper V

Larssen TB, Rorvik J, Hoff SR, Horn A, Rosendahl K.. The occurrence of asymptomatic and symptomatic simple hepatic cysts. A prospective, hospital-based study. *Clinical Radiology* 2005;60:1026-1029.

4. Background

4.1. Introduction

The term fibropolycystic disease of the liver encompasses a spectrum of disorders, from simple hepatic cysts to more complex entities such as hepatic fibrosis (Table 1). In this thesis I have addressed simple hepatic cysts, with or without symptoms. Various terms have been used for simple hepatic cysts, such as biliary cyst, non-parasitic cyst of the liver, benign hepatic cyst, congenital hepatic cyst, unilocular cyst of the liver, solitary cyst of the liver¹, or dysontogenetic liver cyst². The term solitary cyst is often inappropriate, since simple (i.e. thin-walled, fluid-filled) cysts of the liver commonly present as two or more¹. In the following I have used the terms simple liver (or hepatic) cyst(s) for ten cysts or less³, and polycystic liver disease for more than ten cysts.

Traditionally, symptomatic cysts have been treated by open surgery. During the past two decades the less invasive method of laparoscopic fenestration and the even less traumatic method of sclerotherapy have been introduced. Because symptomatic liver cysts are rare, little has been published about either method and the number of patients is low. To our knowledge, random trials comparing sclerotherapy and laparoscopic surgery have not been published. However, sclerotherapy has been practised with considerable variation as regards the selection of sclerosing agent, the volume of sclerosant applied, the time of exposure of the cyst to the sclerosant as well as the use of one single session or multiple sclerotherapy sessions. This may explain why the use of sclerotherapy has not gained a wider acceptance. Leading liver surgeons have expressed an interest in further research being carried out concerning standardisation and simplification of the method of sclerotherapy^{4,5}.

In this study we have aimed at assessing the short- and long-term effects of procedural adjustment, so that sclerotherapy would be more acceptable to the patient and more efficient. For example, we have studied the effect of decreasing the number of sessions of ethanol injection and the time of ethanol exposure. We also wanted to study the mechanism of reaccumulation of cyst fluid. Finally, we wanted to assess the number of patients with asymptomatic and symptomatic liver cysts in patients referred to the Radiology Department of a Teaching Hospital.

Table 1. Fibropolycystic disease of the liver ⁽¹⁾

	Heredity	Patients age at clinical presentation	Hepatic pathology
Adults			
Simple hepatic cysts	Not known	40-80 years	Cysts, few
Autosomal dominant polycystic disease of the kidneys with hepatic involvement (ADPKD) ⁽²⁾	Dominant	30-50 years	Cysts, multiple
Autosomal dominant polycystic hepatic disease without renal involvement (ADPLD)	Dominant	30-50 years	Cysts, multiple
Carolis disease ⁽³⁾ and extrahepatic bile duct cysts (choledochal cyst; choledochocele)	Not known	Adolescence or young adult	Dilated biliary ducts
Congenital hepatic fibrosis	Recessive	Childhood or adult	Fibrosis Dilated biliary ducts
Children			
Infantile	Recessive	3-6 months	Fibrosis
Neonatal	Recessive	1 month	Dilated biliary ducts Fibrosis
Perinatal	Recessive	Birth	Dilated biliary ducts Fibrosis Dilated biliary ducts

⁽¹⁾ Modified after Sheila Sherlock⁶.

⁽²⁾ Between 30%⁷ and 88%⁸ of patients suffering from ADPKD also have polycystic disease of the liver.

⁽³⁾ Carolis disease: Cyst-like dilatation of intrahepatic biliary ducts. Choledochal cyst: Dilatation of extrahepatic biliary ducts. Choledochocele: Dilatation of the distal common bile duct localised within the duodenal wall ⁶.

4.2. Embryology

In 1906, Moschcowitz suggested that non-parasitic hepatic cysts were caused by a maldevelopment of biliary ducts during intrauterine life⁹. At three weeks gestational age, a

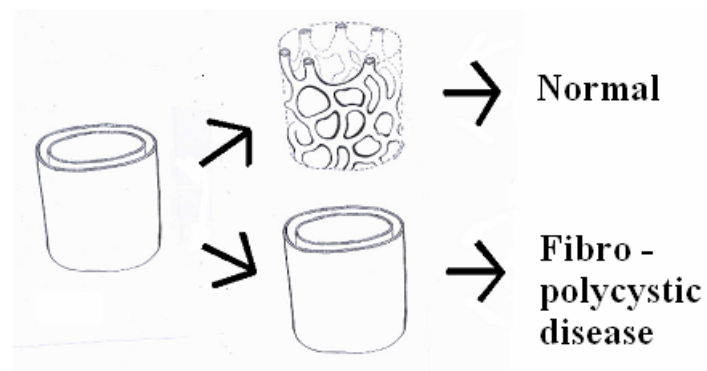
diverticulum appears at the anterior wall of the foregut. This diverticulum differentiates into two parts, one forming the fetal liver and the other forming the extrahepatic biliary tract, including the gallbladder ¹⁰. The primitive liver cells grow to create sheets of cells. At six weeks the first bile ductuli appear within these sheets of cells. At 9-10 weeks intrahepatic biliary ductuli appear as a single layer of epithelial cells surrounding the primitive portal tracts. At thirteen weeks a second layer or sheet of cells appears. This results in a double cylinder, with a slit-like lumen between the layers, as shown in figure 1. This double cylinder is the ductal plate ¹⁰, named so by Hammar in 1926 ¹¹. After thirteen weeks this double plate changes its configuration into a network of tubules representing a more advanced stage of embryonic bile ducts (figure 1), but still located periportal. Ductal plate malformations exist when there are either too few or too many double cylinders ¹². Liver cysts and other manifestations of fibropolycystic disease of the liver are all the result of an excess of ductal plates; on the other hand, in intrahepatic biliary atresia, there are too few bile ducts, since all ductal plates have been destroyed ¹².

The initial ductal plates are observed in the central part of the liver. As the liver develops, new ductal plates appear towards the periphery of the liver. As a result of this, early stages of ductal plates are present towards the periphery of the liver, while more mature stages are located centrally. Therefore, when examining the liver of the fetus, all stages of intrahepatic bile ducts are seen, with the more primitive, recently made structures located peripherally. Thus, in a diseased organ, the amount of associated fibrosis and the level of biliary duct affection will demonstrate different variants of fibropolycystic disease (Table 1).

The production of bile begins at 12 weeks. Adult biliary ductal cells are characterised by cytokeratin 19. Fetal biliary ductal cells contain this substance from 9-10 weeks. The same cytokeratin is found in the walls of hepatic cysts ^{13;14}.

Figure 1. The ductal plate - the embryonic bile duct at thirteen weeks.

The embryonic bile duct at thirteen weeks has the form of a double cylinder (the ductal plate) consisting of two sheets of single-layered epithelium surrounding the portal vein branches. After thirteen weeks the ductal plates change into a network of biliary ductuli. If this reconstruction does not take place, an excess of primitive biliary channels (ductal plates) will result in fibropolycystic disease (polycystic disease of the liver, Carolis disease or other manifestations).



4.3. Genetic aspects.

While the infantile forms of hepatic fibropolycystic disease are autosomal recessive (Table 1), the mode of heritage for the juvenile forms (choledochal cyst and Carolis disease) is unknown. The adult form of hepatic fibropolycystic disease includes two variants of polycystic liver disease, both following an autosomal dominant heritage. First, polycystic liver disease is associated with autosomal dominant polycystic kidney disease (ADPKD). The autosomal dominant heritage of ADPKD was demonstrated by Dalgaard in 1957¹⁵. In 1985 the first gene for this disease was localised to the short arm of chromosome 16¹⁶. Second, another variant, autosomal dominant polycystic liver disease (ADPLD) was reported by Pirson in 1996¹⁷. ADPLD is not associated with renal involvement. The prevalence of ADPLD in the general population is not known¹⁸. In 2000 the gene for ADPLD was localised to chromosome 19 by Reynolds¹⁹. The mode of heritage for simple hepatic cysts is not known⁶.

4.4. Pathology

Liver cysts are surrounded by a thin fibrous capsule, lined by an inner, single layer of cuboidal epithelium²⁰, identical to that found in bile ducts within the portal triads (figure 2). When examined immunohistochemically, this epithelium has the characteristics of biliary duct epithelium, containing cytokeratin 19¹³. It shares several properties with the biliary duct epithelium, including a response to secretin²¹.

In 1918, von Meyenburg described biliary hamartoma as a pathologic entity from which cysts in polycystic liver disease develop, designated as von Meyenburg complexes^{8;22}. These complexes, also called microhamartomas, usually measures less than 5 mm⁶, and consist of multiple, small bile ducts embedded in a fibrous stroma. They represent ductal plate malformations¹², and are associated with fibropolycystic disease²³. In a series of 2843 autopsies, von Meyenburg complexes were found in 5.6% of normal livers, in 44% of livers containing at least one hepatic cyst, and in 97% of livers showing autosomal dominant polycystic kidney disease (ADPKD)⁸.

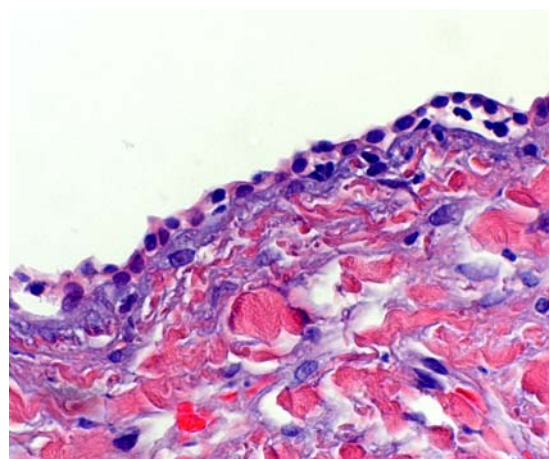


Figure 2. This histopathologic image demonstrates the wall of a liver cyst covered by a single layered cuboidal epithelium, which has evolved from the epithelium of aberrant embryonal biliary ductuli. (Courtesy of Ole Johan Halvorsen, MD, Department of Pathology, Haukeland University Hospital)

4.5. Epidemiology

Simple, asymptomatic cysts are the most frequently occurring focal liver lesion, with a reported prevalence varying between 1% in autopsies²⁴ to 2.5-18% when based on imaging²⁵⁻²⁷. These are seldom diagnosed before the age of 40 years, after which the prevalence increases gradually with age²⁷, without significant differences between the sexes²⁷. Polycystic liver disease is less frequent than simple hepatic cysts, but the prevalence of polycystic liver disease as well as of simple hepatic cysts in the general population is not known. That there are at least two different definitions of polycystic liver does not make the investigation of this topic easier¹⁸. The majority of patients presenting with polycystic liver disease suffer from autosomal dominant polycystic kidney disease (ADPKD) with a reported prevalence of 0.1%²⁸. The occurrence of liver cysts in ADPKD vary from 30 to 88% in different studies^{7;8;29}.

Since the occurrence of symptomatic liver cysts is low, true population-based data are sparse. A report from Sanfelippo in 1974, based on 88 000 explorative laparotomies, revealed symptomatic liver cysts in 0.2% of the cases³⁰. Between 80 and 90%^{31;32} of symptomatic liver cysts, both polycystic and simple, occur in women^{31;32}. The reason for this is unclear, but gestational hormones³³ and estrogen may play a role³⁴. Women who have never been pregnant and who have not used estrogen medication have a lower statistical risk of symptomatic hepatic cysts in autosomal dominant polycystic renal disease³⁵.

4.6. Symptoms

Simple liver cysts only rarely cause acute abdominal symptoms. When this occurs, it is due to spontaneous or traumatic rupture, to hemorrhage into hepatic cysts³⁶, or to torsion of an exophytic cyst or secondary infection. The most common symptoms are chronic pain, abdominal mass and early satiety due to compression of the stomach, although jaundice and respiratory problems have also been reported³⁷⁻⁴⁴. When chronic, even moderate symptoms may result in a permanent reduction in the patients' quality of life.

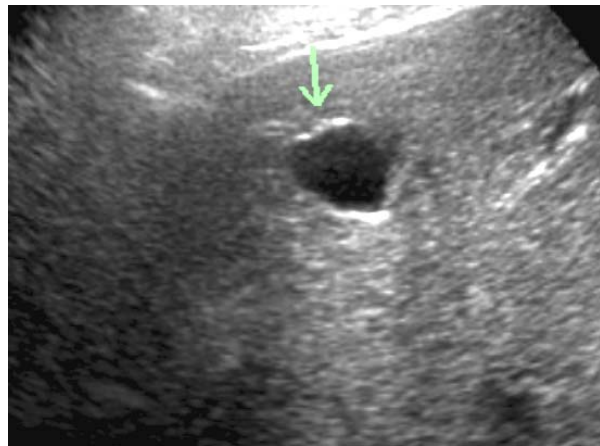
In polycystic liver disease, symptoms may be severe when the degree of hepatomegaly is extreme^{45;46}. Such symptoms are: lower extremity edema due to inferior vena cava compression; ascites secondary to hepatic venous outflow obstruction; portal hypertension with esophageal varices; severe nutritional problems due to compression of the stomach and gastrointestinal tract; and severely reduced quality of life^{47;48}.

Several case reports have been published on cystic disease of the liver complicated by malignancy such as adenocarcinoma⁴⁹, squamous cell carcinoma⁵⁰ and cholangiocarcinoma^{51;52}. It has been claimed that there is an association between polycystic liver disease and cholangiocarcinoma⁵¹. According to one author, the most frequent complication in autosomal dominant polycystic liver disease with renal involvement is the infection of liver cysts, with cholangiocarcinoma as the second most frequent complication²⁸.

4.7. Diagnosis

The diagnosis of liver cysts is based on cross-sectional imaging, including ultrasound (US), computed tomography (CT) and magnetic resonance imaging (MRI). The main differential diagnoses are pyogenic abscess, amoebic abscess, hydatid cysts and necrotic neoplasm⁵³.

Figure 3. Ultrasound of the liver showing a simple, thin-walled cyst with anechoic contents and posterior echo enhancement.



Ultrasound (US) has been known for its great potential in differentiating cystic abdominal lesions from solid ones since the early period of US technology⁵³⁻⁶⁰. US has been the method of choice for investigating the liver for about three decades^{55;55;59;61-67;67}. A high spatial resolution enables a detailed characterization of liver cysts⁶⁸. The sonographic criteria of a cyst are a thin, not discernable wall, anechoic cystic contents and posterior echo enhancement (figure 3). Based on these criteria, high diagnostic accuracy has been reported^{66;69-71}. The major limitations of US occur in obese patients and in patients with severe deformities, such as kyphoscoliosis.

Computed tomography (CT). The CT-criteria for a simple liver cyst include a lesion containing homogenous fluid with a density of 0-10 Hounsfield Units (HU), surrounded by a thin, not discernable, non-enhancing capsule^{3;59;63;72;73} (figures 4 and 5). When these criteria are used, the diagnostic accuracy is high. However, statistical data are limited, since studies on the diagnostic efficacy of CT in diagnosing liver lesions are focused on malignant disease. A sensitivity greater than 90% in the detection of liver metastasis with diameters greater than

10 mm has been reported⁷⁴⁻⁷⁹. When CT findings are equivocal, US⁶³ or MRI⁷⁹ are utilized to distinguish cystic lesions from solid ones. In cases of patchy capsular enhancement or a thickened capsule, neoplasm or abscess is the more likely diagnosis. After a haemorrhage into a cystic cavity, CT may show high attenuation consistent with blood clots for 1-3 days following the event. In these cases, CT is more accurate than US.

Because CT, US and MRI alone are unable to differentiate between a simple liver cyst and a hydatid cyst, additional tests have to be performed if hydatid disease is suspected⁸⁰.



Figure 4. CT scan demonstrating a large liver cyst with a thin wall and homogenous contents.

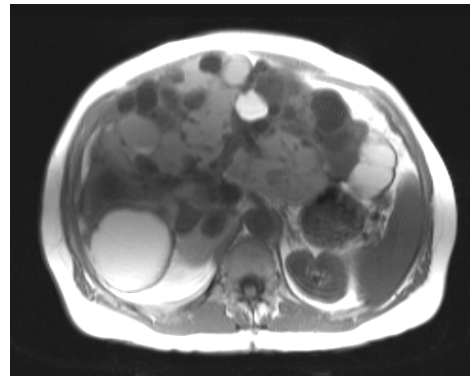
Figure 5
CT scan showing multiple liver cysts in polycystic liver disease.



Magnetic Resonance Imaging (MRI). Similar to CT, the MR-criteria for liver cysts include a thin, non-enhancing wall, not discernable from the surrounding liver tissue (figure 6). On T1- and T2-weighted images a liver cyst returns a low and a high signal, respectively^{63;81}. In a recent study⁷⁹ of candidates for liver resection, MRI was superior to CT in diagnosing cysts with diameters less than 10 mm. Nine cysts characterized as malignant or indeterminate by CT were all correctly characterized as cysts by MRI. MRI was thus the superior method for the staging of malignant disease of the liver⁷⁹. When a hemorrhagic cyst represents a

diagnostic problem on US and CT, MRI may provide characteristic diagnostic information^{3;63;82}.

Figure 6. Axial T1- weighted MRI in a 56-year-old female with polycystic liver disease. High intensity liver- lesions are consistent with cysts containing haemoglobin or haemoglobin degradation products. Low-intensity lesions represent cysts containing ordinary cystic fluid.



4.8. Treatment of liver cysts

Indications for treatment are chronic symptoms which lead to a general reduction of the quality of life, such as hepatomegaly, pain, local bulging, early satiety due to compression of the stomach, biliary duct compression, as well as acute abdominal symptoms caused by cystic rupture or hemorrhage into the cyst. Traditionally, surgery has been the method of choice for symptomatic liver cysts^{45;46}. During the past two decades, two different percutaneous methods have been described: laparoscopic fenestration^{5;80} and percutaneous sclerotherapy^{31;32;83;84}.

4.8.1. Surgery

The alternative surgical methods for treating symptomatic liver cyst are fenestration, liver resection and liver transplantation.

Fenestration (also termed de-roofing) is the surgical method most commonly used today, and consists of making an opening - a fenester or window - in the cyst. Thereafter the cystic fluid is drained into the peritoneal cavity from which it is resorbed and subsequently eliminated via the urine. This method can be performed laparoscopically. Some publications report favourable results of laparoscopic cyst fenestration both of simple cysts^{5;80;85} and polycystic liver disease⁸⁶. However, this number of studies is few. In addition, the quantity of patients in each study is low, and the times of observation are short⁵. Nor have random studies comparing different surgical methods with sclerotherapy been carried out⁵. In order to prevent recurrence, laparoscopic fenestration has been combined with the use of an omental transposition flap⁸⁷. Others have used a combination of laparoscopic fenestration and ethanol sclerotherapy^{88;89}. Only after the failure of laparoscopic fenestration should open surgical fenestration or other surgical methods be used. Fenestration performed in open surgery combined with liver resection is usually only appropriate in severe cases of polycystic liver disease^{45;46}.

Until recently, **Liver resection** has been the traditional surgical method for symptomatic liver cysts. In solitary or few cysts, partial or total cystectomy and more infrequently formal

hepatic resection was performed. The recurrence rate following partial cystectomy has been reported as from 0 to 37 %⁴. In polycystic liver disease, surgical treatment may be indicated when severe hepatomegaly reduces the quality of life severely or when complications such as jaundice occur, due to compression of biliary ducts⁹⁰. In the largest series published on liver resection combined with fenestration the mortality and morbidity rates were 3% and 58%, respectively. This report involved severe cases of polycystic liver disease⁴⁶.

Liver transplantation is a high risk and high cost procedure with a mortality ranging from 0-20%^{4;48;91-94}. For patients who survive and avoid severe postoperative morbidity, great improvement of the quality of life may be achieved^{29;48;93;95}. Lifelong immuno-suppressive treatment may be necessary⁴.

From a surgical point of view, polycystic liver disease may be subdivided into three categories: Type I, Type II and Type III⁴. In Type I, there are a few large cysts, well suited for laparoscopic fenestration as well as for sclerotherapy. Although the results of liver resection or total cystectomy for Type I polycystic disease are good, with postoperative morbidity of only 10%, few recurrences and only one postoperative death reported⁴, the procedure of choice should be sclerotherapy⁵.

In Type II polycystic liver disease, some segments of the liver are relatively free of cysts while others are diffusely involved, with large numbers of small cysts. If at least two adjacent liver segments are relatively free of cysts, surgery is worth considering. Liver resection combined with fenestration of multiple cysts is the method of choice. The reported preoperative mortality has been 0-20%⁴, whereas postoperative morbidity may be as high as 50%⁴.

In Type III polycystic liver disease, hepatomegaly is due to innumerable small cysts involving all of the liver segments, and liver transplantation may be the only therapeutic alternative^{29;48;93;95}.

4.8.2. Percutaneous interventional procedures.

The alternative methods are aspiration without or with sclerotherapy, using ethanol or other sclerosing agents. In 1983, Saini reported on 15 sole aspiration procedures on liver cysts in 13 patients. Within two years, all cysts had regained their original size⁹⁶. Some cysts recurred within two weeks. The exact interval before recurrence was not noted, but it became clear that cysts may recur rapidly following aspiration alone. If the symptoms disappeared after

aspiration and reappeared when the cyst recurred, surgery was considered necessary. This diagnostic procedure was initially used therapeutically, but still has considerable value in deciding whether to perform sclerotherapy.

Sclerotherapy.

In 1976, Goldstein⁹⁷, having been inspired by the work of Vestby^{98,99} on sclerotherapy of renal cysts by means of panthopaque, injected panthopaque in a large, symptomatic liver cyst. Although Goldstein's results were promising with no recurrence after eight or 16 months, no further work on sclerotherapy using panthopaque has been published. The first paper on liver cyst sclerotherapy using ethanol was published by Bean in 1985⁸⁴. He reported a good response to sclerotherapy of six cysts in six patients. His work was followed by others, who reported high success rates ranging from 70 to 100% using differing procedures (Table 2). Anderson⁸³, vanSonnenberg³² and Furuta¹⁰⁰ used multiple-session procedures, while other authors used a single-session procedure¹⁰¹. Moreover, the time of exposure to ethanol varied considerably among different authors. Although the results were promising, the method did not gain general acceptance among liver surgeons. In a review of the literature⁵ concerning nearly all studies on ethanol sclerotherapy^{31;32;83;84;101-105} and laparoscopic surgery^{85;87;106-114} published in English until 2001, the authors concluded that ethanol sclerotherapy probably was as effective as laparoscopic fenestration, having the advantage of fewer complications. They also concluded that a random controlled trial comparing ethanol sclerotherapy with laparoscopic surgery would be ideal, but that such a study would be difficult to conduct since symptomatic simple cysts are rare and long-term follow-up would be necessary⁵.

The use of minocycline hydrochloride as a sclerosing agent has been reported in three studies¹¹⁵⁻¹¹⁷. A total of 15 patients were treated for simple hepatic cysts. The results were promising, but the number of patients is limited, and further clinical research is necessary.

Table 2. Ethanol sclerotherapy of benign liver cysts: data from several different authors.

Author Year	Cysts / patients	Sessions per cyst	Time of exposure (minutes)	Maximum alcohol volume(ml)	Success rate (%)
Bean 1985	6/6	1	20	200	100
Kairaluoma 1989 ⁽¹⁾	15/8	1	60	100	100
Andersson 1989	9/9	1-8	10-20	100	89
Simonetti 1993	30	1?	20-30	20-30% of cyst vol.	70
Montorsi 1994	21/21	?	20-30	25% of cyst vol.	72
vanSonnen- berg 1994	14/ ⁽²⁾	1 –11 ⁽³⁾	20 –0	33-50% of cyst vol.	88
Tikkakoski 1996 ⁽¹⁾	59/25	1	60	100	97

- (1) The study published by Tikkakoski was carried out at the same institution (Oulu University Hospital, Finland) and includes the same patients as the study published by Kairaluoma. Tikkakoski added patients treated during the period 1987- 1992. Both of these authors applied 100ml alcohol for 20 minutes 3 times (3 times 100ml for a total of 60 minutes) in cyst with volumes over 1000 ml.
- (2) In vanSonnenbergs' study, 24 cysts in 20 patients were treated: 14 cyst with alcohol alone, 10 cysts with tetracycline, doxycycline or a combination of alcohol and tetracycline or doxycycline.
- (3) Using the multiple session procedure, one single cyst was treated by 11 different sessions corresponding to 11 doses of ethanol (33-50% of cyst volume x 11), and a cumulated time of exposure to ethanol of 330 minutes during 44 days of catheter drainage.

In the treatment of polycystic liver disease, the comparative roles of ethanol sclerotherapy and laparoscopic surgery have not been clarified in the review study⁵. The use of laparoscopic fenestration in these patients was limited. Another study⁸⁶ has concluded that although the exact role of laparoscopic cyst fenestration in the treatment of polycystic liver disease remains unclear, the method appears to be of benefit to a limited, selected number of patients. In this study, this therapy is recommended in massive hepatic cystic disease when the cysts are not well suited for percutaneous sclerotherapy.

Only a few case reports have been published regarding the use of ethanol sclerotherapy in the treatment of multiple medium and large size cysts in polycystic liver disease ^{118;119}. More research is needed to explore this problem.

5. Aims of the study

To examine the short- and long-term effect of single-session ethanol sclerotherapy on the size of benign liver cysts;

-to examine the effect of single-session ethanol sclerotherapy on benign liver cysts performed with a short exposure (10 minutes) of the cyst wall to ethanol;

-to evaluate the results of single-session ethanol sclerotherapy of benign liver cysts on the patients symptoms;

-to examine the cystic contents before and after ethanol sclerotherapy by cytologic and biochemical methods in order to investigate the post- sclerotherapy re-collection of fluid within the cysts;

-to examine the occurrence of symptomatic and non-symptomatic hepatic cysts in a University Hospital patient population.

6. Material and methods

6.1. Patients

The present work consists of two major study groups, one consisting of 28 patients with symptomatic liver cysts (Part I, Papers I-IV) and one consisting of 1541 consecutive patients referred for diagnostic ultrasound examination of the abdomen (Part II, Paper V).

6.1.1. Patients. Part I.

A total of 28 patients (24 females and 4 men) aged 33-83 (mean 67) years, admitted to the surgical outpatient clinic at Haukeland University Hospital (HUS) for various symptoms related to liver cysts, were included in the study during the years 1993-2002. Data on patients and the Paper in which they appear are listed in Table 3.

Table 3. Patients with simple (S) or polycystic liver cysts (P) included in papers I-IV treated by ethanol sclerotherapy during the period from March 1993 to November 1999 and from May 2002 to September 2002. Patients listed twice or more had more than one cyst treated.

Patient number	Type of cyst	Sex/age	Date (month/year)	Included in paper	Time of exposure (minutes)	Cyst volume (ml)	Final Time of observ (ml/months)	volume/
1	S	F 71	3 / 93	I, II	7	1752	0 / 67	
2	S	F 63	2 / 94	I	20	4800	959 / 7	
3	S	F 74	3 / 94	I,II	20	275	0 / 54	
4	S	F 82	4 / 94	I,II	8	2000	0 / 53	
5	P	F 38	5 / 94	I	20	680	29 / 8	
6	P	F 33	1 / 95	I,II	20	200	0 / 43	
7	S	F 76	3 / 95	I,II	20	450	0 / 42	
8	P	F 40	3 / 95	I,II	20	210	42 / 12	
9	P	M 69	3 / 95	I,II	10	2700	188 / 41	
10	P	F 61	8 / 95	I,II	20	680	21 / 36	
11	S	F 73	2 / 96	II	20	2418	0 / 30	
12	S	F 75	8 / 96	II	20	2000	0 / 24	
13	S	F 60	12 / 96	II, III	10	1800	35 / 47	
14	S	F 46	1 / 98	III	10	394	4 / 37	
15	S	F 61	2 / 98	III	10	30	0 / 32	
16	P	F 44	4 / 98	III	10	1920	523 / 31	
16	P	F 44	5 / 98	III	10	390	0 / 29	
17	S	F 58	9 / 98	III	10	330	0 / 13	
18	P	F 58	5 / 99	III	10	840	139 / 17	
18	P	F 58	6 / 99	III	10	110	8 / 16	
18	P	F 58	6 / 99	III, IV	10	167	85 / 16	
19	S	M 58	6 / 99	III	10	4110	86 / 14	
16	P	F 45	6 / 99	IV *)	----	----	----	
20	S	F 62	8 / 99	IV	----	----	----	
21	S	F 77	10 / 99	IV	----	----	----	
22	S	F 71	11 / 99	IV	----	----	----	
23	S	M 83	11 / 99	IV	----	----	----	
24	P	F 56	5 / 02	IV	----	----	----	
25	P	F 67	6 / 02	IV	----	----	----	
26	P	F 53	6 / 02	IV	----	----	----	
27	P	F 40	6 / 02	IV	----	----	----	
28	S	M 86	9 / 02	IV	----	----	----	

* **Study IV** did not involve data on time of exposure for each cyst, cyst volume or time of observation.

In cases of equivocal abdominal symptoms, a positive aspiration test was required before inclusion. All aspiration tests were performed by an experienced radiologist. A positive test was defined as the disappearance of abdominal symptoms after the evacuation of the cyst.

The criteria for inclusion in the study were cyst-related symptoms as judged by an experienced gastrointestinal surgeon and one or more symptomatic liver cysts diagnosed by imaging.

The criteria for exclusion from the study were: hydatid cyst; neoplastic cyst; cyst-like ectasies of the intrahepatic biliary ducts (Carolis disease); coagulopathy; or polycystic liver disease with innumerable small cysts but without large or medium-size cysts suitable for sclerotherapy.

After contrast injection and before the instillation of ethanol, the following three criteria had to be met: 1) no communication between the cyst and the biliary tree; 2) no intraperitoneal leakage of contrast; 3) the ability to aspirate the contrast from the cystic cavity.

Informed consent concerning ethanol sclerotherapy was given by all patients.

6.1.2. Patients, Part II

A total of 1541 patients (869 females and 672 males), aged 0-99 (mean 57.7) years, referred for abdominal ultrasound to the Department of Radiology, Haukeland University Hospital were included during the period 21 January 2000 to 11 November 2000. A referring Department was registered for 1240 of the patients: 404 patients from the Department of Oncology (all patients had either active or healed malignant disease); 290 patients from the Department of Internal Medicine; 243 patients from the Department of Surgery; 100 patients from the Department of Paediatrics; and 243 patients from other departments (Departments of Neurology, Dermatology, Rheumatology, Psychiatry and Emergency).

6.2. Methods - Part I.

6.2.1. Study design.

Part I was a prospectively conducted, observational and experimental study. The clinical examinations prior to inclusion were done by an experienced gastrointestinal surgeon, who classified symptoms as mild, moderate or severe. Pre-procedure liver function tests were taken. If there was no suspicion of liver tissue damage at that time, these tests were not repeated at clinical follow-up. To investigate the short- and long-term effect of 20 minutes exposure to ethanol, 13 patients were studied (Papers I and II), and to investigate the effect of 10 minutes exposure to ethanol, 7 patients were studied (Paper III). To investigate the cytologic and biochemical aspects of ethanol sclerotherapy, 11 patients were studied (Paper IV).

6.2.2. The effect of sclerotherapy.

The effect of sclerotherapy was evaluated by the measurement of the pre-and post-procedure cyst volume, by the registration of symptoms and through laboratory tests.

Measurements of cyst volume.

The cyst volume on the day of sclerotherapy was measured by direct measurement of the aspirated cystic contents. Measurements of cyst volume was performed using CT and the formula: $V = d1 \times d2 \times d3 \times 0.523$ before sclerotherapy and at follow-ups scheduled at 3, 6, 12 and 24 months. This method has been applied to uterine and ovary volume measurement using ultrasound¹²⁰.

Clinical evaluation of symptoms, and laboratory tests.

The patients were seen at an outpatient clinical consultation scheduled at 3 and 6 and 12 months after sclerotherapy. The symptoms were classified as improved, unchanged or deteriorated at each follow-up. The following liver function tests were taken before sclerotherapy: Alanine aminotransferase (ALT), aspartate aminotransferase (AST), glutamyl transpeptidase (GT), bilirubin, and alkaline phosphatase. Also hemoglobin, thrombocytes, cephotest and INR were taken. A test for hydatid disease was taken before sclerotherapy when this diagnosis was suspected.

Evaluation of side effects.

Procedural pain was evaluated by the radiologist during the procedure, and classified as absent, mild, moderate or severe. During our early work with ethanol sclerotherapy we tested for increased blood ethanol concentration one hour after the sclerotherapy procedure. The routine use of this test was discontinued due to low values of ethanol and absence of clinical signs of ethanol intoxication. We later determined ethanol intoxication by constantly evaluating the patients' apprehension and level of consciousness. Therefore, a specific ethanol measurement was only made if there was suspicion of ethanol intoxication based upon clinical evaluation, or if large cysts requiring the largest volume of ethanol were treated, particularly if the cyst wall was in close contact with large vessels.

Etiology of cystic fluid reproduction after sclerotherapy

To investigate the etiology of the re-filling of the cystic cavity, the cystic fluid of 11 cysts in 11 patients was examined on the day of sclerotherapy and 2-8 days (mean 4.5) later and analysed for cytologic and biochemical parameters. These eleven patients represented all patients referred for sclerotherapy during two periods, the first period from September 1998 to November 1999 and the second from May 2002 to September 2002. Two cysts were examined only by biochemical methods, since too many erythrocytes disturbed the cytologic examination. As a result, nine cysts were examined by cytologic methods and eleven cysts by biochemical methods.

The cytologic examination was made by qualified technologists using a manual semi-quantitative method by which the percentages of the different cellular components could be calculated. The biochemical analysis included CRP, orosomucoid and haptoglobin indicating acute inflammatory reaction, protein and albumin indicating capillary permeability, and bilirubin and alkaline phosphatase as indicators of cystic epithelial function.

In the last five patients, examined in 2002, blood was analysed for the same biochemical parameters on the day of sclerotherapy. The second blood sample was taken 2-3 days (mean 2.2) after sclerotherapy.

6.3. Sclerotherapy procedure

The patients were admitted to the hospital either the day prior to or early in the morning of the day the procedure was scheduled. For the first 22 patients, a premedication consisting of 50-100 mg pethidine and 0.6 mg atropine i.m. was administered 30-45 minutes before the start of the procedure and supplementary i.v. pethidine injections were given during the procedure if required. For the last 5 patients a different method of analgesia was used. This method differed in that an anesthetic nurse was present throughout the procedure, and no premedication was given. Sedation was achieved by midazolam (Dormicum; Roche) and pain control by means of short-term analgesics, usually alfentanil (Rapifen "Janssen-Cilag"), and more infrequently ketamin (Ketalar "Pfizer"), given intravenously during the procedure according to the individual patient's needs.

The patient was placed on an angiographic table and the local anesthetic lidocaine 10mg/ml (Xylocain "Astra Zeneca") was administered. Figures 7, 8A and 8B show the equipment used for the sclerotherapy procedure. Under ultrasound guidance, the needle tip was inserted into the cyst. An 18G, 20 cm needle (COOK, catalogue number SDN- 18- 20 -T) was preferred.

Puncture was made through 1-3 cm of liver tissue in order to reduce the possibility of leakage from the cyst. Thereafter a 90 cm Amplatz super stiff guide wire (MEDA, Amplatz extra stiff, 90 cm, catalogue number 1140 35 090) was introduced well into the cyst, initially under ultrasonographic guidance, and immediately after under fluoroscopic control (fig 7). A 7F dilator was used if necessary to reduce resistance, particularly in intercostal punctures. Thereafter a 7F, 30 cm pigtail catheter (Catalogue number 711007 030, PBN Medicals, Denmark) was inserted as far as possible into the cyst.

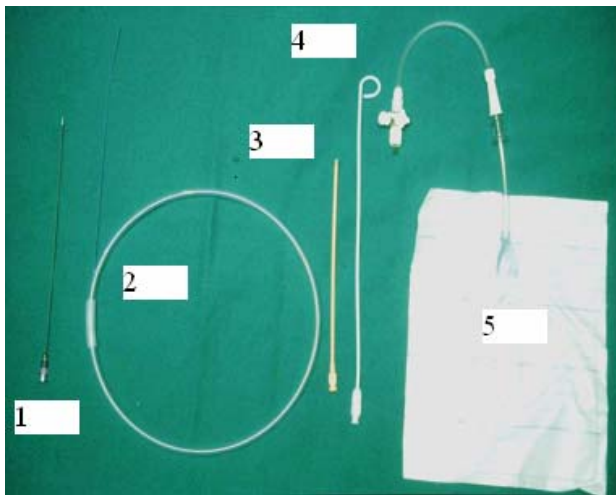


Figure 7. Equipment for the sclerotherapy procedure. An 18 g (1.2 mm) 20 cm long needle (1) is inserted under ultrasound guidance. The guide wire (2) is passed through the needle into the cyst. The needle is removed. A 7F dilator (3, yellow) is pressed through the abdominal wall. Next the 7F 30 cm long pigtail catheter (4) is introduced and connected with a drainage bag (5).

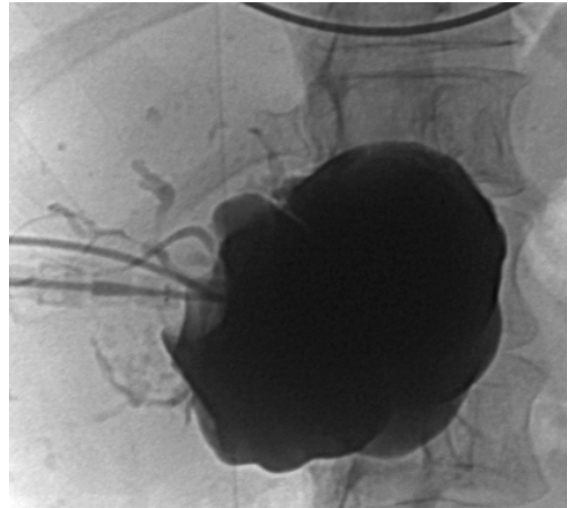
Figure 8A. Sclerotherapy procedure in the interventional radiology laboratory. The patient is placed on the angiographic table. Equipment for ultrasound-guided puncture combined with fluoroscopy-guided procedure is present. Cysts with volumes greater than 1000 ml are drained using an angiographic injector as illustrated in this figure.



Figure 8B. Cystic fluid is aspirated from the patient into the injector. When the syringe is full, the three way stopcock (arrow) is rotated, and the fluid is injected into the drainage bag. Thereafter the three way stopcock is rotated again to drain cystic fluid from the patient into the injector and so forth.

After emptying of the cyst, contrast (Omnipaque 300 mg J/ml mixed with an equal volume of saline) corresponding to about 50% of the cyst volume was injected. Radiographs were taken with the patient lying in three different body positions, to determine contra-indications such as communication with the biliary ducts, leakage of contrast into the peritoneal cavity, or problems related to aspiration of the injected contrast. Figure 9 is a radiograph of a liver cyst, demonstrating communication between cyst and biliary ducts visible at contrast injection. Sclerotherapy was therefore contra- indicated in this patient.

Figure 9. Injection of contrast into the cystic cavity. The cyst has been evacuated, and contrast has been instilled via the catheter. When ductal branches are filled with contrast – as was the case in this patient – a communication between the cyst and the biliary ducts was present, and the procedure was aborted.



After aspiration of the contrast, 96% ethanol was injected. The volume of ethanol ought to be 10 per cent of the cyst volume, but should never be more than 100 ml. The patient's position was slowly changed from supine to prone in clockwise and anti-clockwise directions a few times during the procedure to ensure contact between ethanol and every aspect of the cystic wall. Ethanol was left within the cyst for 10 minutes and then evacuated. In Papers I and II a new dose of the same volume of ethanol was injected once again - for another 10 minutes - during the same session. Thus, the total time of exposure to ethanol was 20 minutes, except for three patients (patients 1, 4 and 9 in Table 3). These three patients were exposed to ethanol for only 7, 8 and 10 minutes respectively because the procedure had to be shortened due to pain. In Paper III only one single dose of ethanol was given for 10 minutes. The volume of ethanol was the same: 10 per cent of the cyst volume, but never more than 100 ml.

Catheter- position was repeatedly controlled by fluoroscopy throughout the procedure. All ethanol was evacuated. The catheter was thereafter removed during continuous aspiration. However, this part of the procedure was changed after one patient experienced severe pain of long duration following the procedure (patient 3, Table 3) most likely due to localised chemical peritonitis caused by ethanol leakage during catheter withdrawal. Since then, we

irrigated the cyst with saline after aspiration of all ethanol. Saline was thereafter aspirated and the catheter removed, thus avoiding the leakage of ethanol into the peritoneum.

After the procedure the patient rested in bed for 4 hours. During our initial years of sclerotherapy all patients were hospitalised for at least 24 hours. Later, patients were usually able to leave the hospital the same evening, if symptoms were minimal.

Methods - Part II.

Study design – method:

Part II was a prospective, cross-sectional study. The ultrasound examinations were performed by 24 physicians (eight consultants, 16 residents) with experience in US varying from one to 20 years. A Toshiba Power Vision 7000 or an ATL HDI 5000 was used for adults, while children were examined using an ATL HDI 5000 machine. All the units were equipped with curved array and phased array sector multifrequency transducers. The ATL HDI 5000 ultrasound machine was equipped with three transducers used for examination of the liver. The transducer most commonly used had a curved array design and a frequency range of 2.0–5.0 MHz. The second transducers also had a curved array design, but with a frequency range from 4.0–7.0 MHz, suitable for small individuals and children, and one minicurved transducer with a frequency range from 2.0-4.0 MHz. The Toshiba PowerVision 7000 ultrasound machine was equipped with one curved array and one minicurved transducer, both with a frequency range of 3.0-6.0 MHz. All transducers of both machines were equipped with 128 piezo-electric crystals.

Criteria for a cyst were: focal liver lesion with anechoic contents; thin wall not distinguishable from the adjacent liver tissue; and posterior acoustic enhancement. The presence or absence of liver cysts was continuously recorded in a protocol at the ultrasound laboratory, and further details with regard to diameter and number of cysts were recorded in the radiology report. When the measurement of cyst diameter did not appear in the report, it was measured on the ultrasound images by the investigator.

6.3. Statistics

Differences in cystic volumes before and after ethanol liver cyst sclerotherapy were examined using the Wilcoxon Signed Ranks Test for non-parametric data (papers II-IV). Differences in cystic volumes before and after sclerotherapy according to time of exposure to alcohol (10 vs. 20 minutes) were examined using a non-parametric test for comparison of two groups (Mann-Whitney test). In Paper V the association between gender and the occurrence of cysts was examined using Fisher's exact test and logistic regression analysis. The ability of senior examiners and residents to diagnose liver cysts was tested using Fisher's exact test. The association between the occurrence of cysts, age of the patients and referring department was examined using logistic regression analysis.

7. Summary of results

Paper I.

During the period from March 1993 to August 1995, ten cysts in ten patients were treated using single-session ethanol sclerotherapy. After a mean observation time of 17.3 (7.8 - 42.0) months, the volumes of the cysts had decreased from a mean volume of 1375 (200 - 4800) ml to a mean volume of 126 (0 - 966) ml. This represents a mean volume reduction of 90.8 (77 - 100) %. In eight cysts, post-procedural re-accumulation of cystic contents was observed, but here too there was a satisfactory volume reduction some time later.

By protocol the cysts were supposed to be exposed to ethanol for 20 minutes, but due to pain the time of exposure was reduced to 7, 8 and 10 minutes, respectively in three patients (patients 1,3 and 9 in Table 3). Even though these large cysts, initial volumes 2700, 2000, and 1752 ml, were exposed for only 10 minutes or less, the volumes were reduced to 212 ml, 0 ml and 1 ml, a reduction in volumes of 92%, 100% and 100% after 18, 17 and 42 months respectively. Pain was severe in one patient and moderate in four others during or immediately following ethanol instillation. There were no other complications. There were no abnormalities in liver function tests following sclerotherapy.

Paper II

From March 1993 to November 1998, 23 cysts in 19 patients (18 female and one male) were treated by single-session ethanol sclerotherapy. Only patients with an observation period of a minimum of 12 months after single-session ethanol sclerotherapy were deemed eligible for the final analysis. Eleven patients with eleven treated cysts fulfilled this criteria. After an

observation period of mean 38.3 (12 - 67) months, cyst volumes were reduced from mean 1317 (200 - 2700) ml to mean 26 (0 - 188) ml, a volume reduction of mean 98 (93 -100)%. Thus, the post-sclerotherapy reaccumulation of fluid was followed by a significant volume reduction in 9 out of 10 patients. There were no complications.

Paper III

During the period from December 1996 to June 1999, 15 symptomatic liver cysts in nine patients (eight women and one man) were treated with a 10 minute exposure to ethanol. One 70-year-old woman did not turn up for follow-up control examination, and the 4 cysts in her polycystic liver were therefore excluded. One cyst was excluded because the 83-year-old female patient died from cardiac disease 7 months after the procedure. Only patients with an observation period of minimum 12 months after single-session ethanol sclerotherapy were found eligible for the final analysis. In 10 cysts in 7 patients with observation periods of median 23 (12-47) months, volumes were reduced from median 392 (30-4110) ml to median 21.5 (0-523) ml, a reduction of the median cyst volume by 95% ($p < 0.005$).

The only complication was pain during the procedure. During cyst aspiration, pain was severe in two procedures and moderate in two. During ethanol instillation pain was severe in one procedure and moderate in two. After evacuation of all ethanol, irrigation with saline and removal of the catheter, one patient experienced moderate pain, while no patients experienced severe pain. Liver function tests and clinical follow-up did not reveal any sign of damage to biliary ducts or liver parenchyma. All patients experienced relief of their clinical symptoms.

Paper IV

During the period from September 1998 to November 1999 and during an additional period from May 2002 to September 2002, cystic fluid from 11 cysts in 11 patients was examined on the day of sclerotherapy, and again 2-8 days later (mean 4.5). The fluid was analyzed for cytologic and biochemical parameters.

Biochemical parameters reflecting acute inflammatory reaction (C-reactive protein (CRP), haptoglobin and orosomucoid), cyst epithelial function (bilirubin and alkaline phosphatase), macromolecular leakage (protein and albumin), as well as parameters of hepatocyte function (alanine aminotransferase (ALT) and aspartate aminotransferase (AST)) were significantly elevated following sclerotherapy.

Cytologic signs of acute or subacute inflammatory reaction were absent before sclerotherapy, but present in all cysts after sclerotherapy. The number of cellular elements were increased in

all cysts and the relative percentages of different kinds of leucocytes could be calculated. In four cysts with an interval of two days between the first and the second sample 98-100% neutrophile granulocytes were present. In one cyst with an interval of two days and in all four cysts with an interval of six, seven or eight days the neutrophile granulocytes were partially replaced by lymphocytes and macrophages. In one cyst containing 100% lymphocytes before sclerotherapy, this was replaced by 98% neutrophile granulocytes and 2 % macrophages two days after sclerotherapy.

In the last five patients an analysis of biochemical parameters in the blood was performed both before and following sclerotherapy. Before and after sclerotherapy the median CRP value in blood was 7 and 71 respectively. In the same patients the corresponding CRP values in cystic fluid before and after sclerotherapy was 9 (range 0-10) and 10 (range 5-24), respectively. The second blood sample was taken 2-3 days (mean 2.2) after sclerotherapy. The other parameters only demonstrated minor differences in the values before and following sclerotherapy. There were no complications.

Paper V

From 21 January 2000 to 11 November 2000, 1541 patients referred for an abdominal ultrasound examination were included. Liver cysts were diagnosed in 174 (11.3%). No cysts were found in patients younger than 40 years of age. The occurrence increased with age ($p < 0.0005$). The occurrence in females was 12.5% (109/869) and in males 9.7% (65/672). This difference was not statistically significant ($p = 0.088$). The occurrence of liver cysts did not differ according to referring department ($p = 0,559$). Excluding 14 patients with polycystic liver disease (8.1% of 174 livers containing cysts and 0.9% of all livers), 322 cysts were recorded according to size in the remaining 160 patients: 91.9% with a diameter of 3 cm or less; 6.2% with a diameter between 3.1 and 6 cm; and 1.9% with a diameter greater than 6 cm. Symptomatic cysts occurred in six patients, representing 0.4 % of all 1541 livers and 3.5 % of all 174 livers containing cysts. These were all large cysts with a mean diameter of 115 (60 - 180) mm. In examinations performed by senior radiologists cysts were diagnosed in 16.1%, and in examinations performed by residents in 15.2% ($p=0.785$).

8. General discussion

Part I. Sclerotherapy of symptomatic liver cysts

Study design.

In principle, evaluation of new procedures and treatments ought to be performed using random controlled trials. However, in the present study the alternative standard treatment was surgery, a treatment associated with a higher morbidity and complication rate^{5;45}. Based on ethical considerations and on earlier reported encouraging results on sclerotherapy, we felt that an observational trial offering sclerotherapy to patients in need of surgery was justified¹²¹. Moreover, the low prevalence of the disease would have made it difficult to accumulate enough patients for a random controlled trial⁵.

Initially (Paper I and II), we examined the effect of single-session ethanol sclerotherapy using a time of exposure to ethanol of 20 minutes. Ethanol was left within the cyst for 10 minutes and then evacuated. A new dose of ethanol - the same volume – followed immediately, lasting for another 10 minutes, resulting in a total exposure to ethanol of 20 minutes. In three of the initial patients, ethanol was only injected once - for 7, 8 and 10 minutes, respectively, - because the patients experienced pain during the procedure. Although these cysts were large (2700ml, 2000ml and 1752 ml respectively) and the time of exposure was reduced, the sclerotherapy effect was still good, resulting in reductions of volume of 93%, 100% and 100% at follow-up observation after 41 months, 53 months and 67 months, respectively (Table 1, Paper II). Due to this favourable result, we decided to conduct another study using a 10 minute exposure to ethanol consecutively (Paper III). Ideally, the evaluation of 10 versus 20 minutes exposure could have been performed using a random design. To the present, we have found no reports on the effect of different sclerotherapy methods using a random design. This in part reflects the difficulties in obtaining enough cases. Two reports on ethanol sclerotherapy of simple renal cysts compare single-session with multiple-session procedure^{122;123}. In one paper, 82 cysts in 82 patients were reported. Forty-two cysts were treated by single-session and 40 by three different instillations of ethanol at 12 hour intervals. The mean follow-up periods were 12.9 and 15.4 months, respectively¹²². In another study, 19 renal cysts in 15 patients were treated by single instillations of ethanol and 13 cysts in 11 patients by repeated instillations of ethanol¹²³. Both these studies concluded that the results were better when more than one session was used. Another author recommended the use of multiple sessions for renal cyst ethanol sclerotherapy^{123;124}. In yet another study the long-term outcome of single-session sclerotherapy of 32 cysts in 32 patients was reported¹²⁵. The mean

follow-up observation period was 55 months. The mean cyst diameter was 7.8cm before and 1.7cm after sclerotherapy ($p>0001$). They concluded that single-session procedure of symptomatic renal cysts was efficient.

In the present study, we only included patients with significant symptoms who were judged by the gastrointestinal surgeon to be in need of surgery. During the study period, all patients suffering from symptomatic liver cysts were included. No patient also surgically treated was included except for patient 2, Table III (see below). No patients withdrew from the study after having given their informed consent.

Another limitation of the study was the deviation from the follow-up protocol. The frequency of follow-ups had been established at 3, 6 and 12 and 24 months. The intervals did vary, as illustrated in figures 1 in Papers I, II and III. In spite of these variations, the sclerotherapy effect could still be evaluated. In one patient in Paper II the first follow-up was made 24 months after sclerotherapy. The volume reduction was 100 %, but since no examination was made at 3 or 6 months it was impossible to determine any presence or absence of a pattern of temporary post-procedural reaccumulation of fluid. Another patient included in Paper I was treated for a 4800ml cyst. She was seen at follow-up only once, at 7 months. By that time the volume of the cyst was reduced by 80%. Nevertheless, the surgeon operated on this patient one month later because her symptoms had not improved. After surgery her symptoms were unchanged.

Pre and post-procedure measurements of cyst volume

Accuracy of the method

In the present study the cyst volume was estimated on the basis of the three maximal diameters (90° angles) measured on the CT images, according to the formula of an ellipsoid: $\text{Volume (V)} = d1 \times d2 \times d3 \times 0.523$ ¹²⁰. This method has been used for the measurement of ovarian volume¹²⁰, and the reported accuracy is good¹²⁶. The method has also been used for the measurement of fetal urinary bladder volume for three decades^{127;128}. Still others have estimated liver cyst volume^{101;104} and renal cyst volume¹²⁵ by measuring one diameter .

The effect on cyst volume

The present studies showed that single-session ethanol sclerotherapy reduced cystic volume significantly over time. Our results support the initial observations of Kairaluoma, who in

1989 described that a single-session procedure was sufficient in spite of the refilling of the cyst after sclerotherapy, since the re-collected fluid was later resorbed. He claimed that this resorption and volume reduction lasted for more than one year¹⁰². Kairaluoma treated 15 cysts in eight patients. His first two patients were treated by a repeat sclerotherapy procedure, the initial procedure being repeated after one or two months. He did observe that there was a temporary re-collection of fluid during the first two months after the initial sclerotherapy procedure, but that the cyst thereafter decreased in size for at least two years. Due to this observation, he performed sclerotherapy only once, with satisfactory results, on the following six patients. In our study, all patients of Papers I, II and III who had a follow-up examination during the first two months after sclerotherapy (16 out of 19 patients) had a re-collection of fluid within the cyst (fig 1, Paper I, fig 1, Paper II and fig 1, Paper III). In all these patients this fluid was reduced in volume by 49-100% (median 95%) at later follow-ups. The post-sclerotherapy production of fluid within the cyst had also been observed by vanSonnenberg³² and Anderson⁸³ in series of 14 and 9 patients, respectively. However, we believe that their observations led to an erroneous conclusion. They recommended that a percutaneous catheter be left in place until the next day, and that a repeated sclerotherapy procedure be performed if drainage was more than 10 – 15 ml per 24 hours. This resulted in a maximum time of drainage of 44 days (Table 2), as one single cyst was treated by 11 different sessions during 44 days of catheter drainage³². In our series, however, we showed that the long-term effect was excellent after one single sclerotherapy procedure when the catheter was removed immediately. There was a 99% reduction of cyst volume after seven to 67 months follow-up. Thus, our studies have shown that the post-sclerotherapy re-collection of fluid is temporary.

Supplementary analysis:

To examine the effect of sclerotherapy in regard to the duration of ethanol exposure, we carried out a retrospective analysis on the total study population included in Papers I-III (Table 3). A total of 19 patients (22 cysts) were studied, 17 women (89.4%) and 2 men (11.6%) with a median age of 61.2 (32.5-81.7) years. The median volume of cystic fluid was 680 (30-4800) ml before and 6 (0-959) ml after sclerotherapy, a median volume reduction of 99.1% ($p < 0,005$). The median follow-up period was 30.8 (7.1 – 67.0) months.

We divided the study population into those who had received an exposure of 10 minutes or less to ethanol (10 patients, 13 cysts) and those who had received an exposure of 20 minutes (9 patients, 9 cysts). For the group who had received 10 minutes or less of exposure, the

median pre-procedure cyst volumes was 840 ml (30-4110 ml) and the median post-procedure volume was 8 ml (0-470ml), a median volume reduction of 732 ml (99.1%) ($p < 0.005$). The median time of observation was 30.5 (13.1 – 67.0) months. For the 9 patients (9 cysts) treated with 20 minutes exposure, the median volume was 680 ml (200-4800 ml) before and 0 ml (0-959ml) after sclerotherapy, a median volume reduction of 680 ml (100%) ($p < 0.005$). The median time of observation was 30.0 (7.1 – 54) months. The degree of cyst reduction did not differ between the two groups (Mann-Whitney test for non-parametric data, $p=0.896$), confirming that 10 minutes of exposure is sufficient for the procedure to be successful.

Clinical evaluation of symptoms

In the present study, 26 out of a total of 28 patients reported that their symptoms had improved following sclerotherapy. Evaluation of symptoms was assessed by a gastrointestinal surgeon, who obtained a clinical statement on the condition of each patient (patient opinion) prior to the procedure. This was repeated at all the follow-up examinations at an outpatient clinical consultation 3, 6 and 12 months after treatment. Although specific methods of assessing pain and nausea have been developed to impose some structure on the information we were collecting, none of these were found to embrace the subjective symptom complexity of liver cysts, which includes different types of pain, early satiety, shortness of breath, reduced physical mobility and fitness, and psychological problems. Thus, we chose to evaluate the symptoms in their entirety, classifying them as the patients' determination of improved, not changed or worsened. This may be seen to represent a weakness in the present study, but the examiner's extensive experience in evaluating clinical symptoms related to liver disease should in part outweigh these shortcomings. Our results are supported by those of others^{31;32;83;84;101;102;104}.

Evaluation of side effects.

Procedural pain.

Other than pain, there were no complications, a finding also reported by others^{31;32;83;84;101;102;104}. In March 1994, during the second year of this study, 27 ml of ethanol was used to treat a 275 ml cyst (patient number 3, Table 3). When the catheter was removed after aspiration of ethanol, the patient experienced severe pain which lasted several days. We concluded that this may have been due to the leakage of ethanol into the peritoneal cavity. Even though it was considered that all ethanol was evacuated from the cyst before the catheter was removed, some ethanol may well have remained within the catheter. This would be

sufficient to create a localised chemical peritonitis. Due to this experience we changed our procedure. At the end of each procedure, when all ethanol had been evacuated, we irrigated the cyst with saline before removing the catheter. After this change of procedure, we have never had a similar experience as that described above.

Also at the beginning of this study we observed that pain could be severe during cyst evacuation, before the application of ethanol, particularly in polycystic liver disease. We also observed that this pain during cyst evacuation was particularly severe in patients previously treated by liver surgery, and was probably the result of adhesions. This may well be similar to the experience of liver surgeons that laparoscopic fenestration of liver cysts is technically difficult if liver surgery has been done earlier, so that previous surgery is considered as a contra-indication for laparoscopic surgery^{120;129}.

As mentioned above, to improve pain control during the procedures, we reinforced the team with an anesthetic nurse who could provide the sedation and analgesics needed (Paper III). This improved pain control substantially, while still allowing the patient to change body position during the procedure.

Ethanol intoxication

Since ethanol intoxication was considered a potential side-effect, we examined our first patients (1993-1995, Paper I) for serum-ethanol one hour post-procedure. Because the values of ethanol observed were so low, the routine use of this test was discontinued (Paper I). Other authors have investigated the relationship between blood ethanol concentration, the volume of ethanol applied and the time of ethanol exposure. Kairaluoma et al found that the total volume of ethanol applied correlated significantly with the increase in blood ethanol content per kilogram body weight ($p < 0.025$, linear regression). Increased blood ethanol levels (maximum value 1.02 g/L) were measured by them in all eight patients treated for a total of 14 cysts¹⁰². As compared to our procedure, Kairaluoma et al and Tikkakoski et al used significantly longer exposure time (60 minutes), as well as higher volumes of ethanol^{31;102}.

Based on preliminary reports indicating a low risk for serious complications, and based on previous reports on the effect of ethanol on living cells, we chose ethanol as the sclerosing agent in the present study¹³⁰⁻¹³⁴. Several series - involving large series of patients - have been published on the potential hepatotoxic effect of ethanol tumor ablation therapy^{135;136}. In a multicenter study the rate of serious complications associated with this therapy was reported to be 0.1%¹³². In another study there were no fatalities in 2485 procedures in 207

patients¹³⁷. Some fatalities due to ethanol tumor ablation therapy have been noted^{132;138;139}. One 76-year-old man died from liver necrosis following percutaneous injection of 5 ml ethanol¹³⁸, while doses per session as high as 200ml have been given with no reported fatalities¹⁴⁰. In 333 high risk patients (large hepatocellular carcinoma, (HCC), liver cirrhosis) treated for hepatocellular carcinoma, there were 6 fatalities (1.8%): liver failure in one; rupture of HCC in one and rupture of esophageal varices in the remaining four^{141;142}. However, so far no serious complications have been reported as a result of liver cyst ethanol sclerotherapy^{31;32;83;84;101;102;104}. While other sclerosing agents, such as minocycline, have been used in small series, the results are difficult to compare to ours¹¹⁵⁻¹¹⁷.

Mechanism of sclerotherapy

In in-vitro experiments the toxicity of ethanol upon living cells is dependent upon the duration of exposure to ethanol and upon the concentration of ethanol¹³⁰. In animal experiments the effect of ethanol upon liver tissue has been investigated^{131;143}. Okano evaluated the sclerotherapeutic effect of different concentrations of ethanol in patients, concluding that a concentration below 40% is inefficient¹⁴⁴.

In Paper IV we studied the mechanism of ethanol liver cyst sclerotherapy, evaluated by cytologic and biochemical parameters before and after sclerotherapy. Cytologic signs of acute or subacute inflammatory reaction were absent in the fluid from all cysts before sclerotherapy and present in the fluid from all cysts following sclerotherapy. The biochemical parameters of acute inflammatory reaction CRP, orosomucoid and haptoglobine were significantly elevated in cystic fluid after sclerotherapy.

The same parameters were examined both in blood and in cystic fluid in only the last five patients included in Paper IV. In these patients there was a discrepancy between blood and cystic fluid as regards the most important biochemical parameter, CRP, the main indicator of acute inflammation. In blood, the median value of CRP was normal before sclerotherapy and significantly elevated after the procedure. In cystic fluid, CRP was only slightly elevated either before or after the procedure. A possible explanation for this could be that cystic fluid is avascular, whereas the CRP elevation in blood reflects the inflammatory reaction in the vascularised cystic wall. Of importance was also the observation that there were no signs of liver tissue damage found in blood when tested for ALT and AST values, nor were these values high in postsclerotherapy cystic fluid. This accords well with our experience that ethanol liver cyst sclerotherapy is a method of low risk, causing little or no damage to liver tissue. The re-collection of cystic fluid after sclerotherapy is probably due to macromolecular

leakage through increased gaps that occur between the endothelial cells in capillaries and venules. This agrees with the increase of protein and albumin concentration found in cystic contents following sclerotherapy. The significant differences in cystic fluid between pre- and post-sclerotherapy values of alkaline phosphatase and bilirubin might support the theory that there is a devitalisation of cystic epithelium when exposed to ethanol. Bilirubin and ALP may well leak from the adjacent liver tissue into the cystic cavity, due to ethanol damage of the cystic wall. We have not been able to find similar studies from other authors for the comparison of results.

The fact that fluid reaccumulates within the cyst after sclerotherapy and then not only is gradually resorbed but never reappears strongly indicates that this fluid is the product of a temporary inflammatory reaction in the cystic wall which has lost remaining vital epithelium.

ALT is the main biochemical indicator of liver cell function. The slight elevation of ALT indicates that the ethanol-induced damage has not only affected the cyst epithelium but also the adjacent liver tissue. This minor liver tissue damage is of no clinical significance. Severe liver tissue damage as a complication of ethanol liver cyst sclerotherapy has not been reported in the literature.

A control group, where cytologic and biochemical tests were taken both before and after catheterization of the liver cysts - without the use of ethanol - would have been desirable but was not attempted for ethical as well as practical reasons.

Part II. Occurrence of liver cysts.

Study design

The aim of this prospective, cross-sectional study was to evaluate the occurrence of liver cysts in our population, using high-resolution ultrasonography. To do so, we examined 1541 patients referred for an ultrasound examination at our hospital during the year 2000. In order to reduce the possibility of sampling bias, we used a large sample size over a study period of one year. We closely examined the data for inconsistencies due to sex, age and referring department. The data was also evaluated to determine variance due to different examiners.

All examinations were performed by one of 24 radiologists or radiology residents in a daily practice setting, and the patients were consecutively registered except for those days or periods when none of the 24 participating radiologists were present at the ultrasound

laboratory. Such periods occurred randomly throughout the study period. The data was well arranged with regard to age, sex and referring department, and the diagnosis of liver cysts did not differ significantly between radiologists and radiology residents. We therefore believe that we can make valid generalizations based upon our hospital-based sample. In accordance with guidelines from the Regional Ethics Committee, no informed consent was judged necessary for this clinical evaluation, since all data were made anonymous prior to analysis.

Accuracy of the results

The accuracy of ultrasonography in the detection of liver cysts is influenced by several factors related to the patient, to the ultrasound machine and technique used, and to the examiner. A restricted ultrasound view related to obesity, small-sized liver positioned far cranially in combination with bowel tympanism, an uncooperative patient and/or recent abdominal operation all tend to decrease the sensitivity. However, these factors may in part be outweighed by the correct positioning of the patients.

Image resolution depends on technical factors such as focusing¹⁴⁵, advanced computerised organisation of emission and receiver functions, emission frequency and post-processing capabilities. Even though we used high-resolution machines, they were probably insufficient in diagnosing cysts of 5 - 10 mm diameter at 4-10 cm depth except in lean, small-size patients optimally suited for US examination. Thus, our results are likely to underestimate the occurrence of very small liver cysts.

We found no statistically significant differences between radiology consultants and residents in the number of liver cysts detected, suggesting that reporting done by these two groups is consistent.

The occurrence of liver cysts.

In our hospital-based population we found that 11.3% of the patients had at least one liver cyst. In previous ultrasound studies of a similar design, the occurrence of hepatic cysts has varied between 2.5% during the period 1855-87²⁷, to 4.7% during the period 1990-92²⁵. These differences could be due to differences in the ultrasound machines used, to the experience of the examiners, or to true differences among populations.

In accordance with other authors²⁷ we did not find any significant differences in the occurrence of liver cysts according to sex. Some authors have reported on a female

dominance as regards symptomatic liver cysts^{31;32}; however, we did not see this. In 1974 Sanfelippo³⁰ reported on an occurrence of symptomatic liver cysts of 0.02% (15 in 88 000 explorative laparatomies). At that time, imaging technology was far less developed than presently, so Sanfelippo may well have underestimated the occurrence of non-symptomatic hepatic cysts; however, the rate of symptomatic liver cysts seems quite realistic.

The increasing occurrence of liver cysts with age was highly significant. The absence of cysts in individuals below the age of 40 is likewise highly significant. This observation is of great importance in tumor staging in young patients suffering from malignant disease. Regardless of the patients' age and regardless of the imaging modality applied, the diagnosis of cysts is uncertain when the diameter of the lesion is less than 10 mm. because of the averaging effect. If, for instance, a 5 mm lesion is found in the liver of a 30-year-old cancer patient, and it is impossible to decide by imaging methods whether this is a cyst or a solid lesion, statistically this is more likely to be a metastasis, whereas in an 80-year-old patient this lesion is statistically more likely to represent a cyst.

It is important, when staging cancer patients, to know if there is a correlation between the occurrence of liver cysts and the presence of malignant disease. No statistically significant correlation was found between the occurrence of liver cysts and the presence or absence of malignant disease. This finding is based upon the occurrence of liver cysts in Departments with both a high and a low occurrence of malignant disease. Only with regard to the Pediatric Department there was a difference in the occurrence of liver cysts compared to other Departments; cysts were completely absent in all children examined. This statistically significant difference is correlated to age and not to the presence or absence of malignant disease.

We found no differences between residents and senior radiologists in the detection rate of cysts. The high number of examiners with different levels of experience did not appear to have biased our results.

In his study, Gaines²⁷ excluded patients suffering from polycystic liver disease, whereas Carimani²⁵ included them. However, the conclusion for either of these studies as regards the occurrence of liver cysts would have been unchanged, since polycystic livers represent such a small proportion of the patients. All polycystic livers included in the present study fulfilled the criteria of more than 10 cysts as given by Ros³, who in turn refers to Bosniak¹⁴⁶.

Symptomatic cysts occurred in 3.5% of livers containing cysts. This is a high figure compared to the results of Sanfelippo (2 symptomatic cyst per 10 000 laparatomies, an occurrence of 0.02%). The number of patients treated for symptomatic liver cysts per year during the period 1993 – 2005 residing in the County of Hordaland was 0-5 patients (mean 3.1), i.e. 1 per 145 566 inhabitants per year (0.0007%). This corresponds better with the results of Sanfelippo.

9. Conclusions

1. Single-session ethanol sclerotherapy results in a significant reduction of cyst volume in benign, symptomatic liver cysts.
2. Following ethanol sclerotherapy a re-accumulation of fluid within the cyst is observed. This re-accumulation of fluid is temporary.
3. Neither repeated sclerotherapy procedures nor prolonged periods of catheter drainage are necessary.
4. Long term follow-up demonstrated that ethanol sclerotherapy not only has a temporarily palliative effect, but also results in long-lasting significant cyst volume reduction.
5. Our initial results indicate that it is possible to simplify the method of ethanol liver cyst sclerotherapy by reducing the time of exposure to ethanol from 20 to 10 minutes, thus reducing the volume of ethanol used.
6. Our results support the hypothesis that the post-sclerotherapy temporary re-accumulation of fluid within the cyst is the result of an inflammatory reaction.
7. The reduction in cyst volume achieved by sclerotherapy leads to an improvement in the patients' symptoms.
8. The occurrence of liver cysts in a hospital-based population is higher than reported in previous studies.
9. Symptomatic cysts occurred in 3.5% of livers containing cysts in our hospital patient population.

10. Future aspects

At our institution we now have treated 132 cyst in 60 patients. Twenty-five of these patients were suffering from polycystic liver disease. In some of these patients more than 10 cysts have been treated by ethanol sclerotherapy. Among these patients were candidates for liver transplantation. Preliminary results might indicate that in selected patients ethanol

sclerotherapy of multiple cysts might not only replace fenestration and liver resection, but even liver transplantation as the method of choice. We want to participate in further research in order to clarify this topic.

Paper III deals with the initial results of sclerotherapy performed with a short time of exposure to ethanol. Since 1999 we have continued this investigation by consecutively performing sclerotherapy with a reduced time of exposure to ethanol. We want to continue our research aiming at further simplification and standardisation of the method of ethanol sclerotherapy.

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