NASJONAL KOMPETANSETJENESTE
for gastroenterologisk ultralyd

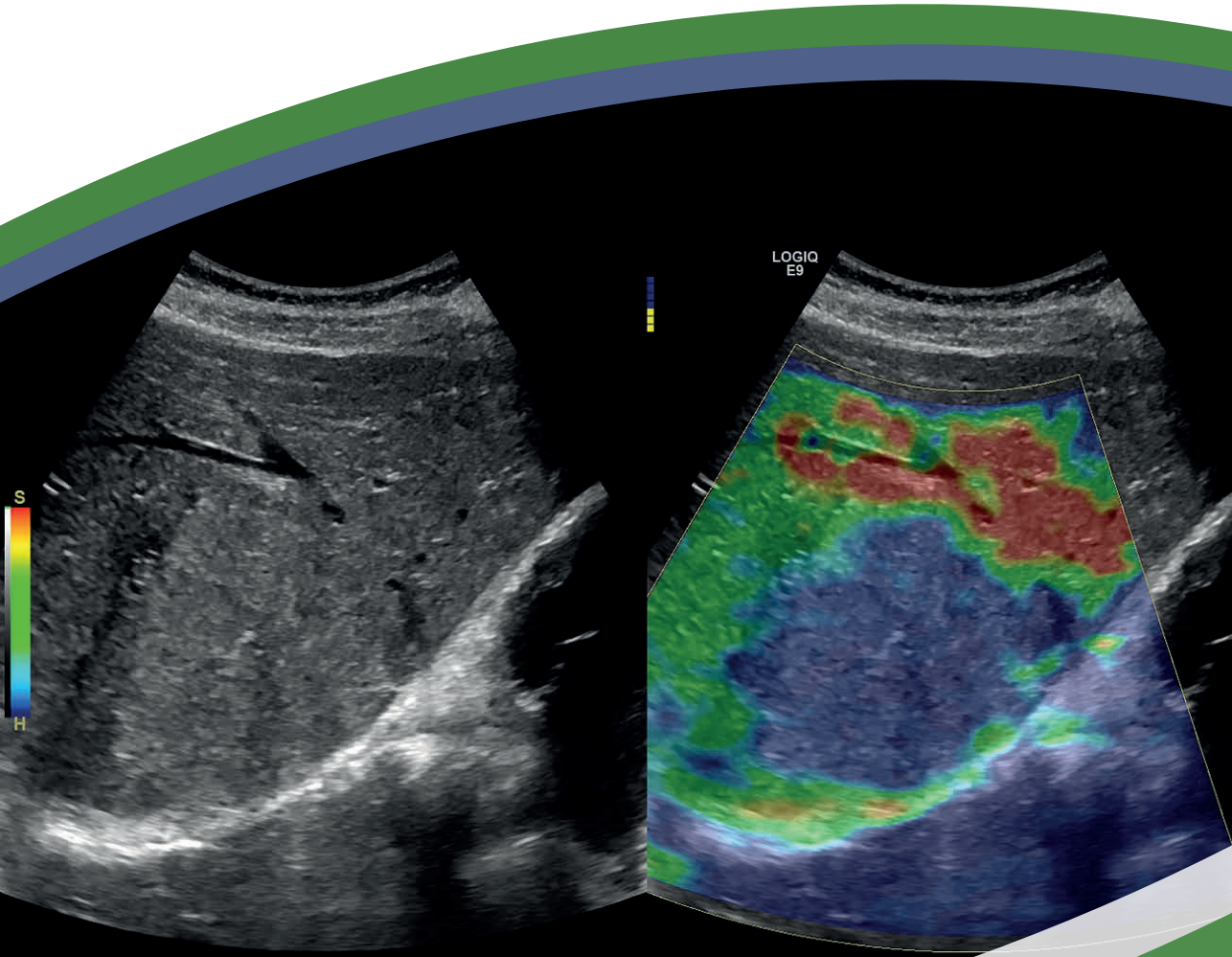
HELSE BERGEN
Haukeland universitetssjukehus

UNIVERSITETET I BERGEN

ABSTRACT BOOK

Symposium at Legenes Hus 3rd of December 2021

20th Anniversary of National Centre for Ultrasound in Gastroenterology



A symposium also in the Honour of
Professor Emeritus Trygve Hausken

Edited by: Tina M. Veberg and Odd Helge Gilja
Cover image front page: A strain elastogram of FNH of the liver. Photo: OH Gilja Cover design: Tina M. Veberg

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Preface

Dear ultrasound friends,

It is with great pleasure we welcome you to the 20-years Anniversary Symposium of National Centre for Ultrasound in Gastroenterology (NCUG) in Bergen. NCUG is based at Division of Gastroenterology, Department of Medicine, Haukeland University Hospital, and for 45 years now ultrasound has been used in this clinic to diagnose patients with digestive diseases. During these years ultrasound has become an increasingly important tool for the doctor who wants rapid and efficient work-up of the patients with abdominal complaints. Furthermore, EUS-guided interventions have become a crucial tool in the management of complicated lesions of the GI tract and surrounding organs.

Today, ultrasound has become a natural part of the education of gastroenterologists in Norway, not at least thanks to continuously strategical work by NCUG to implement ultrasound in the specialist curriculum. Education is a key pillar in NCUG. This was further consolidated when we in 2014 received accreditation as a European Ultrasound Learning Centre (ULC) by the European Ultrasound Federation (EFSUMB). Moreover, NCUG was in 2017 awarded the Euroson Congress to be held in Bergen, but unfortunately this event had to be cancelled due to Covid, only 3 months before taking place.

Science is the other important pillar of NCUG activity. We are proud to report that we over the years have published 385 scientific papers in referee-based journals. We have contributed to 28 international guideline papers and 13 international position papers clearly demonstrating the impact NCUG authors have on scientific content and clinical standards of good practice. Furthermore, we have published over 100 articles on popular science. Moreover, NCUG has published 3 major ultrasound books and 5 conference proceedings on ultrasound. Our PhD- and Post-Doc students are highly important for the success of NCUG regarding scientific contributions. Senior doctors in NCUG have supervised 26 PhD students and mentored 5 Post-Doc candidates leading to significant steps ahead to improve patient diagnostics.

International collaboration throughout the globe has fertilized our work in Bergen in so many ways. In USA, we have collaborated with researchers at University of Washington, Seattle, at Jefferson in Philadelphia and at Rush University in Chicago. In Adelaide, Australia we have a longstanding cooperation on how to use ultrasound to disclose secrets of GI motility. At Black Lion Hospital in Ethiopia and Mnazi Mmoja Hospital at Zanzibar, we have contributed arranging post-graduate courses, to lecturing, and to supervision of fellows. In Europe, our most important collaboration has been with Universities in Denmark, Italy, Holland, Germany, and Romania. We feel privileged to have such a broad network of experts to collaborate with.

Looking ahead, NCUG have many plans to disseminate ultrasound knowledge and practical skills, not only to the 4 health regions of Norway, which is our main mission, but also to the international community around the globe. We are now in the midst of an 8-year action plan where we combine “super-user courses” (teach-the-teacher) of key regional doctors with tailored post-graduate courses at local/regional hospitals. Furthermore, we are building a large digital database of ultrasound lectures, instructive videos, and course material to be utilized by other doctors and hospitals in Norway.

The present symposium is also in the honour of Prof. Emeritus Trygve Hausken, who has been a key person in the development of NCUG during all 20 years. Prof. Hausken is world famous for his application of a soup meal (Toro clear meat soup) in combination with ultrasound scanning to test patients with dyspepsia. Furthermore, he has performed highly original research on transpyloric flow using methods like pulsed and color Doppler, and estimation volume meal flow using 3D ultrasound. But most importantly, I want to extend my gratitude to Trygve for being such a good colleague and friend, with whom I have shared so many great moments around the globe.

Finally, I want to say a few words of thanks. First, to my predecessor in this chair, Prof. Emeritus Svein Ødegaard, who so generously showed me “the light in the dark”, and inspired me to enter the exciting field of ultrasound, both with respect to teaching and science. Without the stable financial support from our National Health Authorities (HOD), NCUG would not have existed. We are also grateful for the support of Helse Bergen, who has given support and local space for our activities. We thank NIH of USA, The Norwegian Cancer Society, The Norwegian Research Council, and Helse Vest for monetary support to our research.

Bergen, primo November 2021

Prof. Dr. med. Odd Helge Gilja

Director of NCUG

Congratulations from EFSUMB

Dear colleagues of the National Centre for Ultrasound in Gastroenterology (NCUG) at Haukeland University Hospital,
dear friends of ultrasound,

It is my great pleasure and honour to extend my warmest congratulations and high appreciation to the Norwegian National Centre for Ultrasound in Gastroenterology (NCUG) at Haukeland University Hospital on the occasion of its 20th anniversary. The Department of Clinical Medicine with its Gastroenterology Division at Haukeland University Hospital recognized the importance of ultrasound for gastroenterology at a very early stage, following the concept of clinical ultrasound developed in Germany by Professor Gerhard Rettenmaier in 1976. Rettenmaier and the founders of the GI Ultrasound Group in Bergen recognized that ultrasound should be the direct continuation of clinical examination with technical means and therefore does not belong in the hands of radiologists alone, but primarily in those of clinical specialists. When the later founder and chair of NCUG Svein Ødegaard returned to Bergen in 1981 from his three-year study visit in Germany, he succeeded in forming, together with Ole Martin Pedersen, Bjarte Börkje, Christen Bang, Trygve Hausken, Arnold Berstand and later Odd Helge Gilja, a powerful and enthusiastic group of gastroenterologists with special interest and expertise in ultrasound. It is interesting and noteworthy that in the second half of the 1980s, in addition to transabdominal ultrasound, endoscopic ultrasound was also advanced in Bergen. Morphology and function of the gastrointestinal tract were particularly in focus, and the term "Functional Sonography" was born. Thus, scientific pioneering work was done in this powerful GI ultrasound group, which could be published in high-ranking gastroenterological journals from the 1990s onwards. It was only logical that in 2001 the

National Centre for Ultrasound in Gastroenterology at Haukeland University Hospital was founded as the result of this successful development, which included not only research but also training of young gastroenterologists in ultrasound techniques. I am not aware of anything comparable in the world - an institute and network dedicated solely to researching and disseminating the use of ultrasound techniques in gastroenterology. Success has proven the founders around Professor Svein Ødegaard right: new names continue to appear in publications from the NCUG; in addition to studies on sonographic assessment of motility of the gastrointestinal tract, noteworthy publications have emerged in other research fields, particularly on transendoscopic miniprobe ultrasound and 3D (endoscopic and transabdominal) US; pancreatic structure, elasticity, and perfusion in patients with cystic fibrosis; on comparison of abdominal and endoscopic ultrasound in patients with chronic pancreatitis; sonoporation; and on the role of various ultrasound technologies for the diagnosis and activity assessment of Crohn's disease and on strain elastography of the pancreas and shear wave elastography of the liver. Also of note are the publications comparing the value of multiparametric ultrasound with various established methods in gastroenterology (endoscopy, manometry, scintigraphy, pancreatic function tests, MRI). I am very happy that the NCUG has also always experienced inspiration within its worldwide network from the close cooperation with the gastroenterological ultrasound experts in Germany, especially with Gerhard Rettenmaier, Harald Lutz, Karl-Heinz Seitz, Christoph F. Dietrich and Dieter Nürnberg.

The European Federation of Societies for Ultrasound in Medicine and Biology (EFSUMB) is closely linked to NCUG: in 2014 NCUG was accredited as European Ultrasound Learning Centre (ULC) - a recognition NCUG lives up to through a variety of educational activities: ultrasound textbooks were created here, among them “Basic and new aspects of Gastrointestinal Ultrasonography” (2005), “Atlas of Endoscopic Ultrasonography” (2007) and “Introduction into abdominal sonography” (2009). Several educational conferences and workshops took place over the years, among them EUROSON schools, and a nation-wide ultrasound training programme has been set up. NCUG was successful with his endeavour to integrate ultrasound in the curricula of medical faculties in Norway. It is no exaggeration to say: NCUG is the centre of educational activities in gastroenterological ultrasound not only in Norway but far beyond. For this reason, too, it was very sad and disappointing that the EUROSON congress in Bergen, planned and magnificently prepared for 2020, could not take place due to the COVID-19 pandemic. Nevertheless, I would like to thank here all who

worked hard at NCUG and beyond in Bergen and in Norway for this event. I sincerely hope that Norwegian Ultrasound Society (NFUD) together with NCUG will have the strength and confidence to prepare and then host another EUROSON congress soon. The chair of NCUG, Professor Odd Helge Gilja has done a great job as Executive Board member (2002 – 2019) and in particular as President of EFSUMB (2015 – 2017). Among other important achievements, he started and coordinated the EFSUMB guideline project on Gastrointestinal Ultrasound (GIUS), which was recently completed. The 7 guidelines and position papers have received great recognition in the European ultrasound and gastroenterology community and worldwide. So far, the first part of this guideline series has already been cited 112 times, the one on IBD 78 times and the one on appendicitis and diverticulitis 43 times.

EFSUMB will also soon be able to celebrate a jubilee: February 11, 2022, marks the 50th anniversary of the founding of EFSUMB. A small group of ultrasound enthusiasts who met in Basel in February 1972 has grown into a society with a strong membership, which despite political upheavals, in different political systems and under very different economic conditions, and in the face of the rise of other imaging modalities has defied numerous centrifugal forces and grown together into a strong-minded, lively and influential European Ultrasound Family. The Norwegian Ultrasound Society (NFUD) joined EFSUMB in 1975 and has contributed in many ways to make EFSUMB in 2021 a strong player in the European scientific and educational landscape.

On behalf of the European ultrasound family, I warmly greet you on your anniversary. I thank Professor Odd Helge Gilja and NCUG for the opportunity to join you in celebrating NCUG's proud history. EFSUMB looks forward to further inspiration from NCUG and continued successful collaboration on educational, research and publication projects!

Kjære venner av Nasjonal kompetansetjeneste for gastroenterologisk ultralyd:
Lykke til det neste tiåret!

November 14th, 2021

Prof. Dr. med. Christian Jenssen

European Federation of Societies for Ultrasound in Medicine and Biology (EFSUMB)

President 2021 - 2023

A salutation from WFUMB to NCUG 20-years jubilee

National Centre for Ultrasound in Gastroenterology (NCUG) has put its mark on the earth and left an impressive signature on the medical ultrasound sky. On behalf of the World Federation of Ultrasound in Medicine and Biology (WFUMB), it is my privilege as Past-President to congratulate the entire NCUG organization with this impressive jubilee and not just the institution per se but in particular also all the dedicated persons affiliated with NCUG, past and present. NCUG with its longstanding scientific and educational activities has contributed strongly on the international arenas of science and education and heavily influenced the way modern medicine is understood and practiced not only in Scandinavia but throughout the world.

Under the visionary leadership of previous director and founder, Prof. Svein Ødegaard, and current director, Prof. Odd Helge Gilja, NCUG has matured from a national center of excellence and now stands out on the international arena as a beacon of ultrasound knowledge and a true international center of excellence. This is evidenced by the large number of publications and PhD dissertations that has received considerable international attention and exerted invaluable and lasting impact on the medical ultrasound community worldwide. NCUG researchers have contributed to a vast number of international guidelines and clinical recommendations, thus influencing how doctors should practice ultrasonography in daily routine.

The most important impact of NCUG, however, lies beyond statistics and sheer numbers, impressive as they may be, and has to do with the way we understand and teach medicine. From a classical perception of medicine a profession practiced in different “pillars” of medical specialties, ultrasound today has brought about a total paradigm shift in modern medicine, which implies that the individual patient may be both diagnosed and treated by a clinician with expertise in multiparametric ultrasound and need not be referred to several diagnostic procedures in different departments.

In this game-changing shift of paradigm NCUG has played an important role and undertaken scientific leadership not only in Norway but on the international scene of medicine. The impact of this influence is reflected in the fact that NCUG faculty has been very active internationally with the current director serving as EFSUMB President 2015-2017 and recently in WFUMB as chairman of the Education Committee and current leader of Center of Education (COE) Task Force Group. In this way NCUG has helped pave the way for new COEs around the globe and contributed to many post-graduate courses in low-resourced areas of the world.

Additionally, NCUG researchers contributed extensively to the newly released comprehensive textbook “WFUMB Ultrasound Book” including co-writing several chapters and having one of the editors coming from NCUG. It is my sincere hope that NCUG through adequate funding, manpower and intellectual capacity will continue its excellent work and, in the future, will inspire to excellence in ultrasound through education and research for the benefit of both patient care and the entire medical community, not only in Norway, but also in parts of the world with enormous needs of ultrasound equipment and competence.

Copenhagen, primo November 2021

Acs. Prof. Dr. med. Christian Pállson Nolsøe

World Federation for Ultrasound in Medicine and Biology (WFUMB)

Past- President

A man of honour. Homage to a Pioneer.

Professor, Dr.med. Trygve Hausken, who was expected should stay young forever, has retired.

If you want a co-worker and a friend who is hard working, reliable, friendly, helpful, always sharing his knowledge and never craving for fame and glory, Trygve is the one.

Trygve came to the Department of Medicine, Haukeland Hospital with clinical experience, endoscopy skills, many fruitful ideas and a special interest for patients with digestive trouble. Thus, he was ready for more, and he turned his thoughts to clinical as well as basic research. The GI-unit had already included both transabdominal and endoscopic ultrasound as diagnostic tools, and Trygve started using real-time ultrasound in studying gastrointestinal physiology and motility, especially gastric emptying. He presented his work at ultrasound and GI-meetings in many countries, and his papers were accepted in high quality journals.
His research work and doctor's degree (1992) formed the basis of subsequent projects, publications and theses. Furthermore, his methods were implemented in daily clinical work, sometimes giving more precise information than other examinations.

Trygve was a welcome guest everywhere. As a visiting researcher to Professor Rettenmaier's group in Böblingen, West-Germany, he was trained by Dr. Karlheinz Seitz in using Doppler technology in abdominal vessels. Later, Trygve got the idea to use Doppler to also study gastric emptying. Thus, he published the first paper in how to study transpyloric flow with Doppler. His visit to University of Washington, Seattle, USA resulted in papers within 3D ultrasound imaging, also being evaluated as best published paper that year. There is a saying in our group in Bergen, "Ultrasound makes the World go around". Trygve has been everywhere, including many flights to Australia with the Famous Bergen (Toro) Meat Soup in his suitcase.

Professor Trygve Hausken's eminent work has been crucial for establishing National Centre of Gastroenterology (NCUG) in 2001. Congratulations to both of you.

Trygve had some challenges, and the reason for this was that he could never say "No" to anybody!

Thank you my friend and stay cool.

Svein Ødegaard

Former Director, Department of Medicine and

National Centre for Ultrasound in Gastroenterology

Professor em, Dr.med. University of Bergen

Programme

0845 Registration, Coffee
0900 Welcome Address by Odd Helge Gilja

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Chairs: Odd Helge Gilja and Roald Flesland Havre

0915 New techniques in interventional US with focus on Fusion
Christian Nolsøe
0940 CEUS in ultrasound-guided interventions
Christian Jenssen
1005 EUS guided biliary access and interventions
Khanh Cong Do Pham

1040 Coffee break

Session 2 Liver

Chairs: Geir Folvik and Mette Vesterhus

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Fabio Piscaglia
1125 Ultrasound evaluation of PSC
Mette Vesterhus
1150 Ultrasound and elastography in liver cirrhosis
John Willy Haukeland

1215 Lunch

Session 3 Pancreas

Chairs: Georg Dimcevski and Trond Engjom

1315 Cystic neoplastic lesions of the pancreas - the percutaneous option of ultrasound
Karlheinz Seitz

1340 Therapeutic EUS using RFA in pancreatic tumors
Roald Flesland Havre

1405 Sonoporation in pancreatic cancer (PDAC)
Ingrid Kvåle Nordaas

1430 Coffee break

Session 4 GI tract

Chairs: Trygve Hausken and Odd Helge Gilja

1500 Bowel wall ultrasound: from bench to bedside
Kim Nylund

1525 New ultrasound index in Crohn's disease
Fredrik Bjorvatn Sævik

1550 Gastric Ultrasound in Functional Gastrointestinal disorders
Elisabeth K. Steinsvik

Session 1: Interventional Ultrasound

New techniques in interventional US with focus on Fusion

Christian Pállson Nolsøe[1,2]

1) Dep of Surgery, Zealand University Hospital, Køge, Denmark
2) Copenhagen Academy for Medical Education and Simulation (CAMES), University of Copenhagen, Denmark

State of the art ultrasound anno 2021 along with all its newest technical refinements such as fusion, CEUS and elastography plus the more classic add-on technologies represented by Doppler and 3D/4D imaging has established itself as a fully developed and equivalued alternative to other available cross-sectional imaging modalities. Ultrasound can no longer be viewed as a single tool based on "simple" grey-scale imaging but rather it must be regarded as a sophisticated box of tools with potential of adding a combination of multiple ways of depicting the same target, including functional imaging such as stiffness and viability. The term "multiparametric ultrasound" (MPUS) has been suggested to indicate this diversity of approaches, which can be brought into play utilizing the same piece of equipment i.e., an US scanner in the clinical work-up of the individual patient. MPUS of course provokes associations with similar terms in CT and MRI lingo, but it also elegantly frames the full potential of State of The Art US along with its range of techniques of US-based new technologies and explains why US, in many aspects, is equal to CT and MRI, and for some indications e.g., contrast studies and fusion techniques in intervention, and in cases of renal insufficiency, is even superior.

Interventional ultrasound has countless well-established applications and at the same time continuously inspires users to develop impressive new procedures to the benefit of patients and the medical community.
Fusion ultrasound is an excellent example of this trend and represents a newer application of medical imaging, whereby dynamic real-time ultrasound images are presented simultaneously with corresponding sectional image obtained from other imaging modalities, such as CT or MRI. PET-CT is a known medical example of image fusion based on these principles.
Image fusion can be carried out between all types of image modalities provided their geometrical congruence do not vary considerably (Fig 1). In addition, fusion of an on-going ultrasound examination with a previously acquired one of the same structures, can be performed.

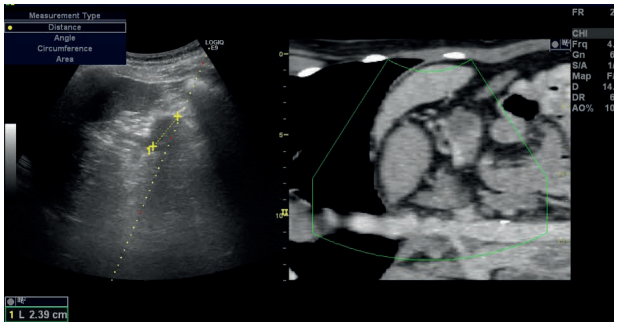

Figure 1 illustrates principle of ultrasound-CT fusion guided biopsy. Right-side image is previously recorded CT. Leftsided image is realtime US with puncture line going through the target of 2.4 cm echo poor solid mass in head of pancreas.

The basic advantage of image fusion with ultrasound is the ability to combine the dynamic features of ultrasound with the virtues of CT and MR imaging. Fusion ultrasound may also facilitate guiding of interventional procedures and can be used in combination with CEUS.

By ultrasound-CT fusion the ultrasound system generates a virtual CT image identical to the US image (or at least intended to be so) from the 3D coordinates using a local electromagnetic field and position sensors fitted to the ultrasound transducer. Prior to the ultrasound-CT fusion procedure the patient´s CT images must be loaded into the US scanner via the hospitals intranet or downloaded from a portable medium such as CD, DVD or USB stick. Selecting a focal plane with unique anatomical structures in the volume of CT images enables the examiner to identify a corresponding ultrasound image by scanning the patient. When the image planes are identical the CT and ultrasound imaging planes are locked to each other by the examiner. Thus, an ultrasound-CT fusion examination presents a dynamic ultrasound image alongside a corresponding CT image, or as a composition in which the CT image is superimposed on the active ultrasound image. Fusion technique may include the combination of CEUS with CT, MR or PET-CT imaging.

Fusion and CEUS, and especially the combination of the two, in our experience have become decisive factors in liver imaging to detect and classify focal lesions. These technologies increase the sensitivity of the detection of lesions and enable immediate differential diagnosis between malignant versus benign lesion such as hemangiomas and focal nodular hyperplasia.
The introduction of ultrasound contrast agents has had an overwhelming impact on modern medicine. CEUS, often in combination with fusion, has dramatically expanded the field of diagnostic and therapeutic ultrasound and opened a whole new world in patient management. Specifically for interventional ultrasound this has made previously impossible case doable. In liver imaging CEUS has become a game changer due to excellent time resolution and use of CEUS has changed the classic indications for biopsies so biopsy in the future should be reserved to a limited number of equivocal cases. CEUS in many aspects is comparable to CECT and CEMRI and CEUS has changed the algorithms for medical imaging and image guided interventions in the high-income societies of the industrialized world. CEUS seems advantageous compared to contrast enhanced CT in evaluation of benign liver lesions. Hemangiomas vary in the time they take to present the characteristic filling pattern. In some cases, the centripetal filling is over and done already in the arterial phase which may disturb optimal recording with CT. CEUS allows repeated visualization of the filling behavior of a lesion by bursting the contrast microbubbles in the image field. However, US-guided biopsies including use of fusion CEUS, will be required in case of complex scenario or equivocal findings, and it is also anticipated that it will continue to serve as a Gold-Standard in the increasing use of multi-modality investigations such as PET-CT.

Advantages of fusion and CEUS in relation to interventional ultrasound:

The potential benefits of using fusion and CEUS in relation to ultrasound guided interventional procedures are considerable and this has recently been investigated and confirmed in a systematic review published in JUM: “Use of Ultrasound Contrast Agents in Relation to Percutaneous Interventional Procedures A Systematic Review and Pictorial Essay “. Likewise, the recommended usage of UCAs in interventional US is listed and described in detail in the latest published CEUS Guidelines: “The EFSUMB Guidelines and Recommendations for the Clinical Practice of Contrast-Enhanced Ultrasound (CEUS) in Non-Hepatic Applications: Update 2017”.
US-guided ablation of non-operable malignant liver lesions with RF or similar techniques such as laser, cryo and microwaves (MW) is a state-of-the-art treatment in many parts of the world that can be performed either percutaneously, laparoscopically, intraoperatively during laparotomy or in combination with liver surgery. Ultrasound remains the most used guiding modality for these procedures for obvious reasons.
Dedicated devices for US-guidance of such procedures are rapidly evolving and fusion CEUS performed before and after the ablation procedure improves the treatment results. By utilizing the

so-called GPS principle, fusion ultrasound may even make it possible to perform simultaneous ablation of multiple liver metastases which can provide substantial timesaving with MW ablation of several tumors (Fig 2)

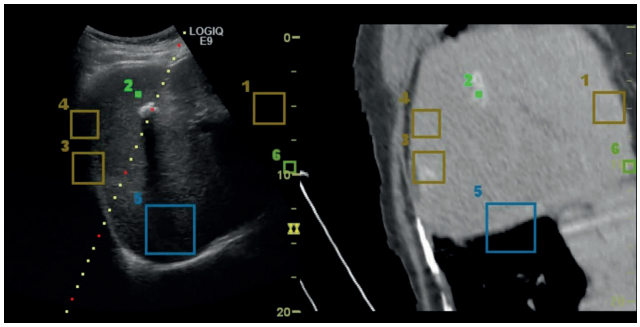

Figure 2 illustrates principle of GPS ultrasound-CT fusion guided ablation.

A total of 6 metastases is marked with US. When a metastasis is in focus the puncture-line can be manipulated to go through it and the square turns into a dot. The further away from focus the bigger the square becomes.

For practical consideration related to the intervention per se, any fusion CEUS guided intervention can be performed like the routine US-guided version of the procedure. In some cases, it may be necessary to use two contrast injections, one to plan the procedure and a second to perform it. Alternatively, an infusion pump may be used with continuous infusion throughout the procedure. CEUS and fusion has several overtly obvious applications related to ultrasound guided biopsy and may in some cases even be indispensable. Potential indications for CEUS guided biopsy, with or without fusion, are 1) Biopsy from perfused and thus viable areas and 2) biopsy of poorly visualized or downright “invisible” lesions, 3) avoid biopsy from lesions if CEUS study unequivocally shows benign lesion e.g. hepatic hemangioma and thereby potentially reduce morbidity and complications rate.

In adition to these indications related to biopsy fusion and CEUS may be beneficial in relation to interventional ultrasound in terms of all aspects of US-guided ablation and thus, in our department, we use CEUS, often in combination with fusion, in pre-ablation evaluation and procedure planning, in placement of ablation needles, and in immediate post-ablation control of tumor necrosis as well as in long-term follow-up (Fig 3).

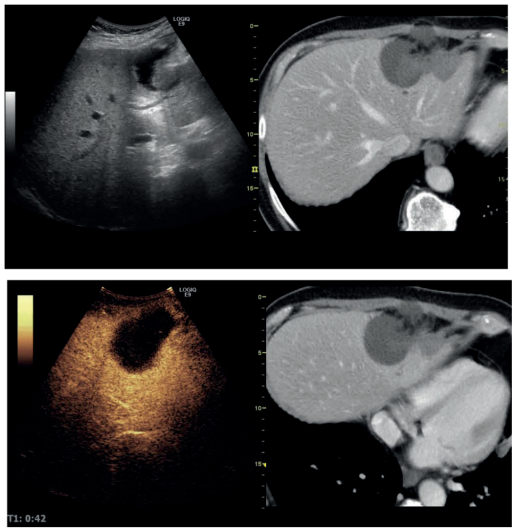

Figure 3 illustrates the principle and also the diagnostic value of CEUS - CT fusion in follow-up 3 month after MW ablation of liver metastasis.

In upper panel US shows cystic lesion with solid part. Latter could represent residual tumor or necrosis.

In lower panel CEUS demonstrates no contrast uptake and thus proves non-viability of the solid part

Fusion CEUS may also Improve visualization of poorly depicted fluid collections and finally, CEUS may be helpful in diagnosis of bleeding as a complication to interventional procedure and for guidance of percutaneous transhepatic cholangiography and in control of correct catheter placement in drainage procedures such as abscesses and nephrostomies.

The presence of malignant liver lesions leading to therapeutic consequences such as liver surgery, RF-ablation or chemotherapy is subject to verification before treatment is initiated. Liver surgery in many centers nowadays may be performed based on noninvasive diagnostic imaging in cases with typical enhancement patterns on both CT and CEUS and here fusion imaging can add considerably by improving visualization in case of less conspicuous lesions on CEUS alone.

CEUS is a very powerful tool due to the excellent time resolution and the possibility to keep a suspected lesion in the scanning plane throughout the entire contrast study, which frequently results in CT negative metastases being diagnosed and even biopsied with CEUS. Biopsy may be reserved to a limited number of cases such as when discrepancy exists between different imaging modalities. In our department, this would be the case when for instance a malignant diagnosis cannot be made with at least two imaging modalities and a fusion CEUS guided biopsy may then be indicated. In case of non-operability, a biopsy also often remains mandatory to confirm malignancy before initiation of chemotherapy due to oncology protocols.

Non-invasive diagnostic methods such as CEUS will change the classic indications for biopsies and reduce the number of diagnostic biopsies.

In general, new image modalities, such as PET-CT and MRI with liver specific contrast, beyond doubt, improve sensitivity in detection of malignancy, but they also generate false positive findings that require biopsy verification. In this scenario fusion with PET-CT-US and CEUS can be of tremendous help in finding the lesion and enabling CEUS and/or fusion guided biopsy. No doubt CEUS and US fusion with other modalities will be generally available and increase the demand for US-guided procedures. Differentiation between metastasis of carcinomas, lymphomas and HCC in the liver illustrates the need to obtain a firm diagnosis based on histology, since the very different treatments and prognosis depend on a correct classification, which, in most cases in our institution, include US-guided biopsies.

Dedicated US-transducers for endoscopic and endoluminal US adopting CEUS and fusion technology will be combined with other modalities and provide a range of new diagnostic and therapeutic possibilities in gastro-intestinal diseases as well as other clinical areas such as for instance urology and gynecological.

According to WHO, 2/3 of the world's population has no access to medical imaging. US and CEUS have the potential to rectify this inequality, and if CEUS were an integral part of ultrasound it would be realistic to bring State of the Art medical imaging all over this world.

Just imagine how very limited would be the value and reduced the impact of CT or MRI without contrast agents available! This is the scenario ultrasound must face in many countries without UCAs approval.

WFUMB (http://www.wfumb.org) has as its overall purpose to bring the use of medical ultrasound to every corner of the world. Used together with all its technical refinements, including fusion and CEUS and fusion CEUS-guided intervention, ultrasound emerges as a multipotent imaging tool second to none and capable of providing State of The Art imaging to the entire world.

Conclusion:

Fusion imaging and CEUS probably will reduce traditional indications for interventional procedures such as biopsies. However, both CEUS and fusion also at the same time will extend the use of interventional US with new applications and support existing applications. Interventional US will, overall, remain of crucial importance involving more complex and dedicated techniques.

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Notes:

CEUS in ultrasound-guided interventions

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Introduction

Ultrasound is increasingly used for guidance of percutaneous and transluminal diagnostic and therapeutic interventions. Compared to guidance by fluoroscopy, CT or MRI, US guidance can also be use d at the bedside, is widely available, inexpensive and can be performed without radiation exposure. However, the main advantage over intervention guidance by radiological cross-sectional imaging modalities (CT, MRI) is that ultrasound is a real-time procedure [(1, 2)]. In addition, endoscopic ultrasound (EUS) also allows interventional access to compartments that are not accessible, difficult to access or only accessible with high risk with percutaneous access, for example in the mediastinum, perirectal space and in the deep abdomen and retroperitoneum [(3, 4)]. However, disadvantages of guidance by B-mode ultrasound can be the superimposition of target structures by air/gas reflexes, their poor differentiation from the surrounding area, the lack of differentiation between vital tissue and necrosis and the lack of contrast of luminal and vascular structures. Apart from superimposition of target structures, these disadvantages can be very elegantly overcome using ultrasound contrast agents (UCAs). The intracavitary application of UCAs in the renal collecting system was first reported in 1986 [(5)], then in 2004 also the biopsy of focal liver lesions not visible on B-scan under direct guidance by intravenous injection of UCA [(6)]. Contrast-enhanced ultrasound (CEUS) has established itself as an indispensable complement to B-mode ultrasound and Doppler techniques within the last two decades. UCAs are characterised by their excellent tolerability with a frequency of severe (pseudo-)allergic reactions of approx. 0.007 – 0.015% when used intravenously [(7-9)]. Moreover, they can be used repeatedly without any toxicity. Although intracavitary use, except for voiding sonography, is not approved by regulatory authorities, it is nevertheless extremely safe with no side effects reported so far.
The possible applications of CEUS-assisted interventions, which are now reported mainly in case series and retrospective studies, are diverse and have expanded considerably in recent years [(10, 11)].

CEUS-guided biopsy

There are four main indications for CEUS-guided biopsy of focal lesions [(10, 12-14)]:

1) Improved pre-interventional characterisation of potential biopsy targets through CEUS
2) Improved visualisation of target lesions that are difficult or impossible to delineate in B-mode US.
3) Reduction in the rate of false-negative biopsies through better differentiation of vital and necrotic tumour parts
4) Reduce the complication rate of percutaneous biopsies and rapid detection and risk assessment of intervention-related bleeding.

The improvement of pre-interventional characterisation of focal liver lesions is well established in numerous multicentre prospective studies and helps to select the most suspicious and easily accessible one in the presence of multiple lesions. Furthermore, it may lead to the omission of invasive histological work-up in a substantial proportion of focal liver lesions [(10)]. Percutaneous biopsy of focal liver lesions has a relevant risk of major bleeding of 0.56% in a multicentre German study [(15)]. Other examples of avoiding potentially risky biopsies by clearly characterising the potential target lesions by CEUS are mucocele of the appendix and bronchogenic cyst. The percutaneous biopsy of a mucocele can cause a potentially fatal peritoneal pseudomyxoma, the endosonographic fine-needle aspiration biopsy of a bronchogenic cyst is associated with a very high risk of a life threatening mediastinitis. Both lesions, which often appear to be solid in B-mode ultrasound, can be clearly identified as cystic by CEUS, and thus biopsy can be avoided. Conversely, by intranodal or subcutaneous injection of UCAs, it is possible to select metastatically affected sentinel lymph nodes in breast carcinoma for targeted biopsy [(16, 17)].
Improving the visualisation of poorly demarcated liver lesions as well as lung tumours within atelectasis by CEUS can improve the technical success rate of US-guided biopsy Convincing prospective data give proof of an increase in the rate of adequate biopsies from tumours with necrotic parts by 10% - 15% through CEUS guidance [(10, 11, 18)].

Other CEUS-assisted diagnostic interventions

Other CEUS-assisted diagnostic interventions, except for voiding sonography for the detection of vesicourethral reflux, have been reported mainly in single cases or small case series. Examples include diagnosis and intervention planning in Zenker's diverticulum, assessment of tube patency in the context of infertility diagnosis, use of UCAs in the biliary system (ERCP, PTCD) and for visualisation of (residual) calculi or obstruction and for intervention guidance, in cystic pancreatic lesions after puncture to detect communication with the pancreatic duct system, CEUS-guided diagnosis of hepatic hydrothorax and CEUS-guided ultrasound fistulography, especially of perianal fistulas.

CEUS-guided tumour ablation

CEUS has become a very important tool for the management of percutaneous ablation of malignant tumours of the liver, kidney and other organs, and is increasingly used for monitoring the success of radiological ablation procedures (transarterial chemoembolization (TACE) [(10, 11, 19-24)]. The focus here is on improved visualisation and delineation of the ablation target, direct guidance of the ablation procedure with immediate detection of both residual vital tumour tissue and bleeding complications, as well as evaluation of the ablation success in the follow-up. CEUS appears to be equally accurate or even superior to CT in the detection of residual vital tissue during the ablation procedure [(20, 21)]. In a recently published meta-analysis, the sensitivity of CEUS for the detection of residual tumour tissue after locoregional therapy (TACE, ablation) of HCC was 85%. Specificity and accuracy were both found to be very high at 94% [(19)].

CEUS-assisted drainage procedures

The intracavitary use of UCAs as an alternative or supplement to fluoroscopy has become established for numerous drainage procedures in recent years. This applies to percutaneous transhepatic cholangiodrainage (PTCD) [(2, 25)] as well as to percutaneous nephrostomy [(2, 26, 27)]. The procedure is used for better visualisation of the duct structures to be drained, especially if these are not clearly dilated, to detect the obstruction plane, but also to detect

leaks or dislocations in the follow-up. In percutaneous abscess drainage, CEUS has proven useful for improving pre-interventional visualisation of the abscess contours (Fig. 1, Fig. 2a), for checking correct needle and catheter placement, for detecting or excluding communications (e.g., with the biliary tract system, renal collecting system, pancreatic duct and intestinal structures). Compared to fluoroscopy, checking the size of the abscess and function and position of the drainage catheter in the post interventional care is significantly simplified (Fig. 2b) [(2, 11, 28, 29)].

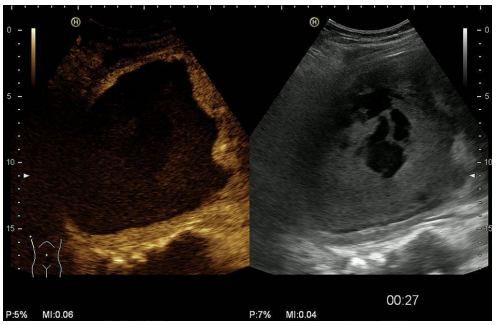


Figure 1: Characterisation of a liver abscess using intravenous CEUS: die to solid-appearing contents, in B-Mode the liver abscess seems to be considerably smaller than with CEUS.

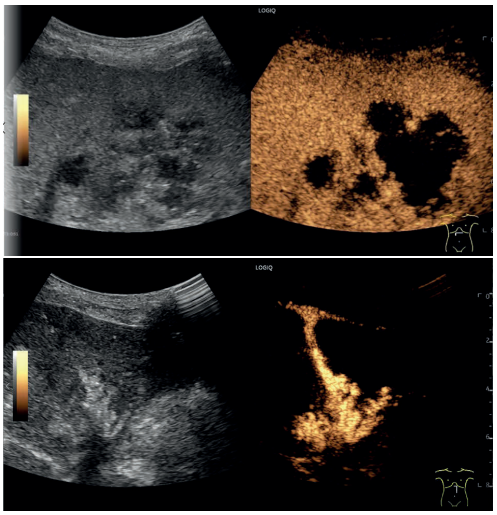


Figure 2: CEUS-guided abscess drainage.

Intravenous CEUS helps to delineate the abscess with several communicating cavities (a). On follow-up, application of UCA via the pigtail catheter reveals leakage into the peritoneal cavity along the catheter (b)

CEUS-assisted injection therapy and vascular therapy

Vessels, vascular pathologies, and vascular leaks can be excellently visualised by CEUS. Case studies described the use of CEUS in obliteration of visceral and groin pseudoaneurysms (Fig. 3) [(30)] and to guide neurolysis of the coeliac plexus [(31)]. The successful intraoperative use of CEUS in the revision of endoleaks after surgery for abdominal aortic aneurysms [(32, 33)] was also reported.

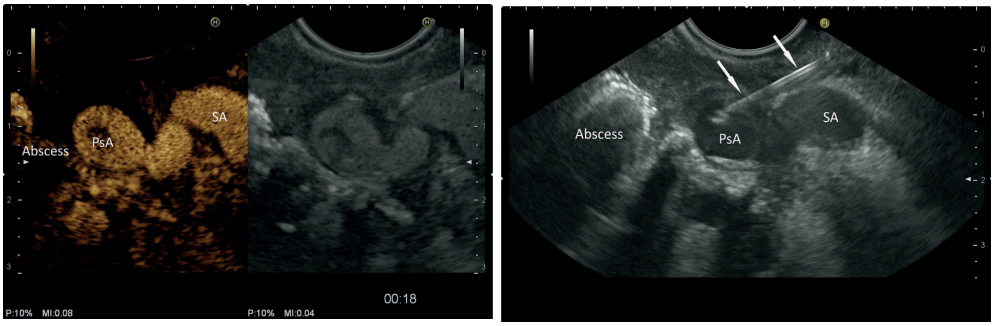
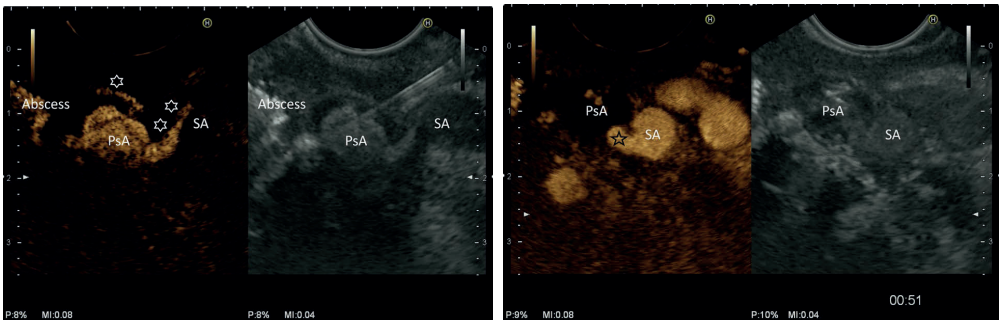


Figure 3: Contrast-enhanced EUS-guided injection treatment using thrombin of a visceral pseudoaneurysm of the splenic artery following pancreatic tail resection complicated by infected fluid collection, treated by EUS-guided drainage: intravenous CEUS delineates a small pseudoaneurysm (PsA) of the splenic artery (SA) near the drained abscess cavity (abscess) (a). EUS-guided puncture of the pseudoaneurysm using a 22 Gauge aspiration needle (b; needle marked with arrows) and injection of thrombin solution with one droplet of the UCA SonoVue® into the pseudoaneurysm (c). Injection rate is controlled by intracavitary CEUS by avoiding too much leakage of thrombin-UCA-solution into the abscess cavity (*) and into the splenic artery (**). After completion of EUS-guided obliteration treatment intravenous injection of the UCA reveals nearly complete obliteration of the pseudoaneurysm. Only a tiny perfused residual cavity (*) remains (d).



Conclusions

The intravenous and intracavitary application of UCAs as well as the combination of both approaches can improve the efficiency and safety of percutaneous and transluminal diagnostic and therapeutic interventions as well as their follow-up. They expand the possible spectrum of (E)US-guided interventions and offer numerous advantages over CT-, MR- and X-ray-guided interventions due to mobility, simpler technical implementation and integration into clinical algorithms, independence from large-scale equipment, bedside implementation, unproblematic repeatability, lower complication potential of the contrast agents used and absence of radiation exposure. However, prospective studies are hardly available, presumably because many of the advantages mentioned are so obvious that integration into clinical routine often seems self-evident even without scientific evidence.

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Notes:

EUS-guided biliary access and interventions

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ERCP is the gold standard for biliary drainage. ERCP is a well-established procedure that offers transpapillar biliary decompression of bile ducts and the gallbladder. In expert hands, ERPC has a high success rate of up to 80-90%, but in 5-10%, transpapilar biliary cannulation will not be possible[1]. Common causes include inaccessible papilla, tumor obstruction, or altered surgical anatomy.

Percutaneous transhepatic biliary drainage (PTBD) may be used when ERCP fails. PTBD has a high success rate of up to 90%, but adverse events occur in 35-77%, mostly clogging, infection, cholangitis, pain, and discomfort[2]. In addition, the bile cannot be used physiologically and must be emptied into a bag, which also needs maintenance. EUS-biliary drainage (EUS-BD) has been compared to PTBD and shows a comparable success rate but has less need for reintervention[3,4]. Surgical biliary decompression, with hepatico-enteral anastomosis, is the third option with a high risk of complication and mortality. Compared to the techniques mentioned above, EUS guided biliary access, and drainage offers an alternative route when ERCP, PTBD have failed, or surgery if not possible[5–7].
Depending on the anatomy, EUS can gain access or drain bile directly. The different entry points for EUS are from the stomach or the duodenum (Fig1).

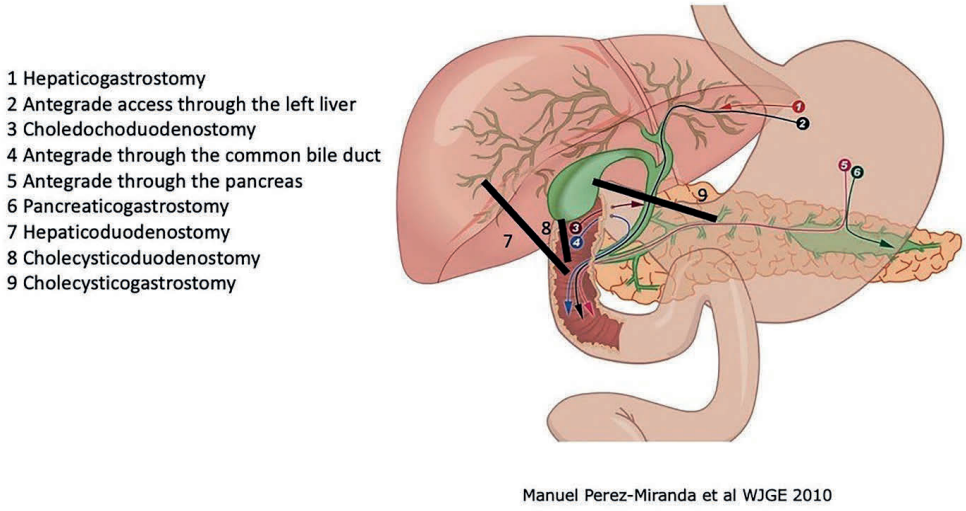

Fig 1. The different access points to the bile ducts with EUS

It is usually possible to access the left liver (segment II and III) and the hilum from the stomach. The gallbladder can be accessed from the bulb or the antrum. From the bulb, the right liver, cystic duct, and the common bile duct are in close vicinity and therefore accessible to therapy. The different techniques require significant skills in both ERCP and EUS. The risks of complication are high, most notably being bile leakage, which may be fatal. One of the crucial factors that have made EUS-guided interventions possible is the development of dedicated stents and specialized tools and accessories, which have made EUS biliary procedures safer.

For most EUS-guided biliary drainage, the basic steps are the same. First, a good scope position is required, and the dilated bile ducts are identified on EUS. Usually, a 19G FNA needle is used to puncture the bile duct. Bile is aspirated followed by contrast injection to achieve a cholangiogram (Fig 2). A 0.025 or 0.035 long guidewire is passed through the needle into the desired bile duct or anterogradely through the papilla to the duodenum (Fig 3).

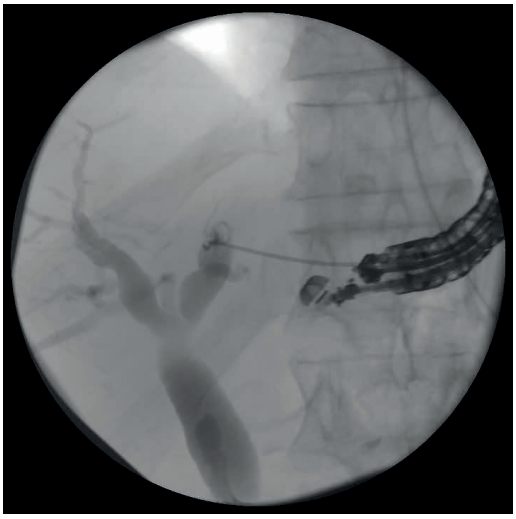

Fig 2: Cholangiogram with EUS via the left liver

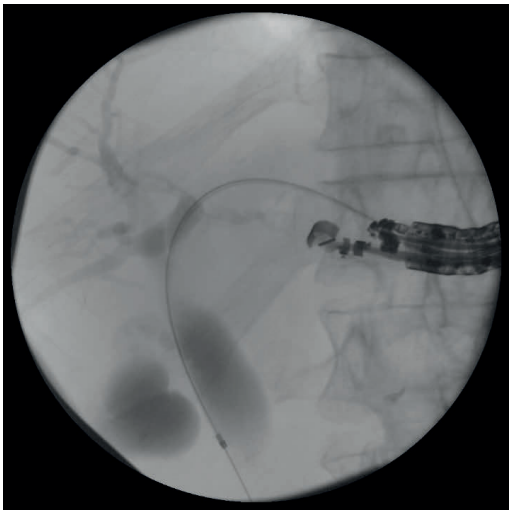

Fig. 3: Insertion of a guidewire into the duodenum through the left liver and dilatation with a 5Fr ring knife

From there on, the options are to drain directly, do EUS-ERCP rendezvous (Fig 4), or antegrade stenting. We may use a stiff balloon, dilatation catheter, a needle knife, cystotome, or ring knife for dilatation of the biliary enteric fistula. Dilatation should be just 1-2 French below the chosen stent's introducer size to minimal bile leakage. Stent placement should be done under combined fluoroscopic and endoscopic guidance (Fig 5).

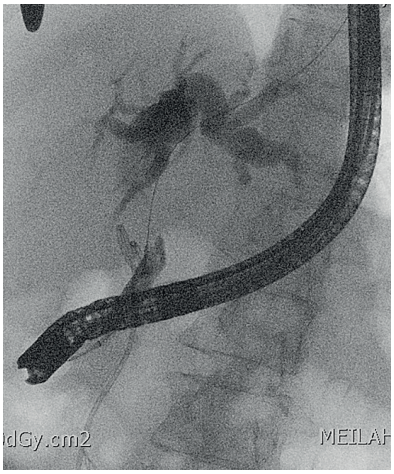

Fig 4: EUS-ERCP Rendez vous procedure. The transpapilar guidewire is caught with the duodenuopscope for stenting in a case with a tumor in the head of the pancreas.

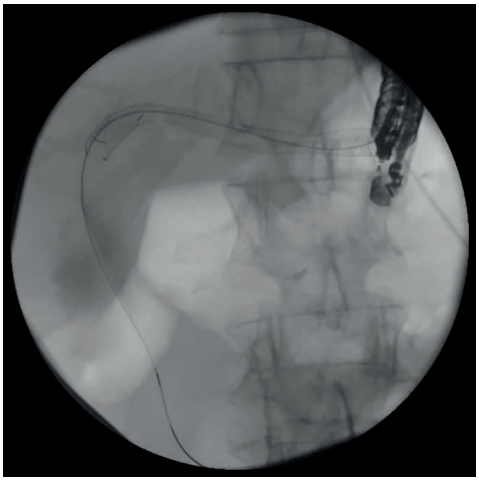

Fig 5 Release a semi-covered stent to anastomose the left side bile ducts to the stomach (Hepaticogastrostomy)

With the devolvement of electrocautery enhanced lumen apposing metallic stent (LAMS), EUS-guided cholecysto-enterostomy and choledochoenterostomy have become much faster and more convenient chosen stent's With LAMS, one single operator can efficiently perform drainage, even without fluoroscopy. Depending on the size, LAMS can serve as a port through which it is possible to do further therapy efficiently. An example is EUS guided cholecystico-duodenostomy with a LAMS for acute calculous cholecystitis; then electro hydrolithotrypsy can be used to fragmentize stones (Fig. 6).

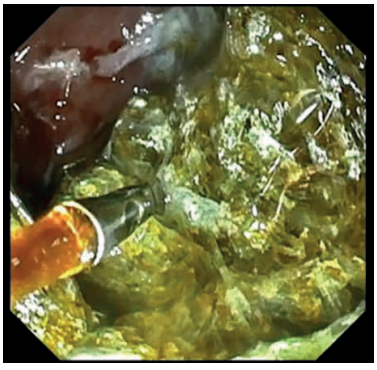

Fig 6 Fragmentation with electro hydrolithotripsy of a 3 cm gall stone inside the gall bladder through a LAMS

After cleaning the gallbladder, the LAMS can be removed. Hepaticogastrostomy can also do direct cholangioscopy for diagnostic purposes (Fig 7, 8).
EUS-BD allows many acrobatic solutions to access the bile ducts, with exceptional high technical and clinical success rates. In our opinion, EUS biliary drainage should be the 2nd choice of biliary decompression after failed ERCP. The drawback is a long learning curve and a lack of training centers.

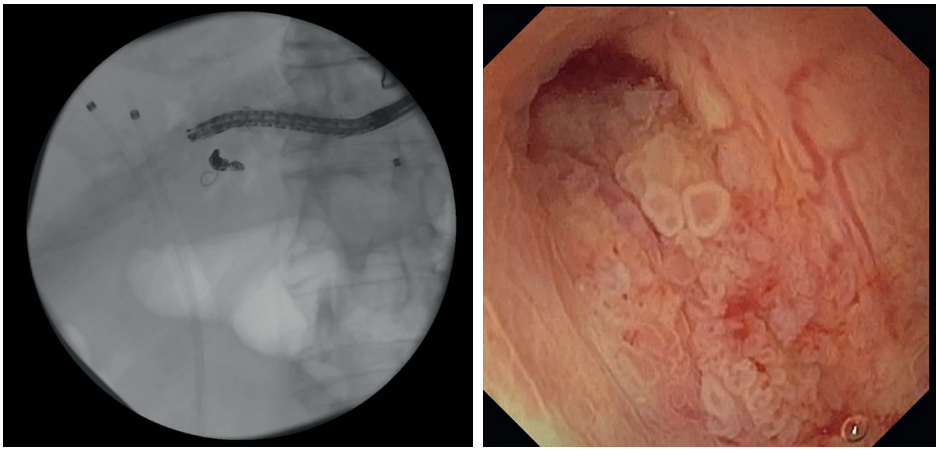

Fig 7+8 Cholangioscopy for biopsy through a hepaticogastrostomy in a patient with intraductal papillary neoplasia of the bile ducts.

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Notes:

Session 2: Liver

How to diagnose small HCC with CEUS

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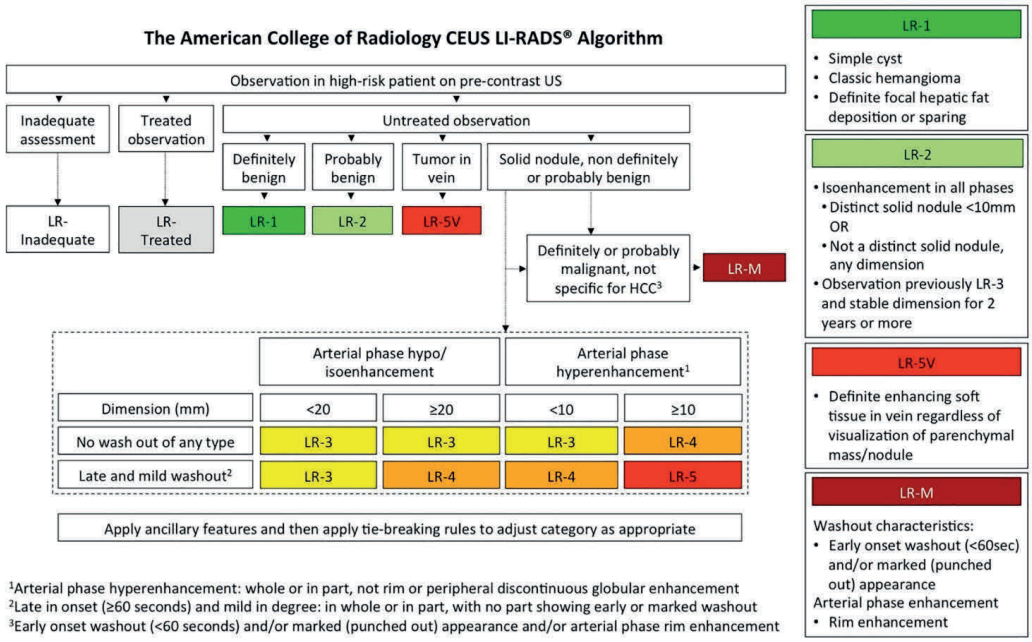
Hepatocellular carcinoma (HCC) is the most common complication of compensated cirrhosis leading to death, and is reported to be present in 70 to 90% of cases of HCC according to the etiology. The development of HCC in cirrhosis is held to arise through a progressive stepwise carcinogenesis in around 90% of the cases. The transformation occurs in the instance of cirrhosis and starts from microregenerative nodules, evolving in macroregenerative nodules (>5 mm), which may eventually develop low grade and subsequently high grade dysplasia and finally turn into an established malignancy. Accordingly, patients at risk for HCC, corresponding to those with cirrhosis or with other few selected risk factors must be submitted to 6-month interval surveillance for early tumor detection. Aim of surveillance is to detect HCC as early as possible, since patients in the very early stage (corresponding to Barcelona Clinic for Liver Cancer BCLC 0 stage, those with perfectly preserved liver function and single HCC <2 cm) or early stage (tumor within the Milan criteria, mainly <3 cm) have the highest likelihood of receiving curative treatments, including surgery and transplantation, and longest survival. Once a focal hepatic nodule is detected during HCC surveillance with ultrasound (US), a diagnostic imaging test including contrast-enhanced CT, MRI, or contrast-enhanced ultrasound (CEUS) is performed since a definitive diagnosis of HCC can be achieved with imaging alone, without histological confirmation provided the nodule has arisen in cirrhosis and displays a typical enhancement pattern.

The challenge of contrast imaging techniques is to define and demonstrate the occurrence of the typical characteristics of HCC, rather than that of other malignancies which represent around 5% of liver nodules (corresponding to cholangiocellular carcinoma, mixed hepato-cholangiocellular carcinoma, metastasis and exceptionally other primary liver malignancies). Additionally, it would be relevant to grade the risk of other lesions, which do not still display the typical pattern of malignancy to already be an HCC. Such grading would help selecting which patients with cirrhosis deserve biopsy of the lesions (provided that the nodules can be reached with a needle) and which can rather be only submitted to strict monitoring.

An enhancement pattern typical for HCC with contrast enhanced ultrasound is now recognized by various international scientific societies, including the World and the European Federations of Societies for Ultrasound in Medicine and Biology (WFUMB and EFSUMB), the European Association for the Study of the Liver (EASL) and the American College of Radiology (ACR) among the most relevant. The pattern consists in Hyperenhancement in the arterial phase (non- rim and non- peripheral globular) follow by late (>60 seconds) and mild washout. The grading of the risk of other lesions according to the risk of being a non- hepatocellular malignancy or to be a lesions at a different grade of risks of HCC is only accepted by EFSUMB and the ACR. A group of international experts to develop CEUS Liver Imaging Reporting and Data System (CEUS LI-RADS) has been convened by the American College of Radiology (ACR) in 2014. After extensive discussions by the expert working group and based on feedbacks received in several international conferences a CEUS LI-RADS scheme was presented in 2016 and later updated as official CEUS-

LI-RADS version. According to this classification nodules at risk for HCC are categorized into 6 classes according to the contrast enhancing pattern: LR1 = benign, LR2 low risk of HCC, LR3 intermediate risk of HCC, LR4 probable HCC, LR5 corresponding to a diagnosis of HCC, LRM representing malignancy without a specific definition of the cellular nature (only 50% are HCC). The illustration of the different patterns will be presented and is illustrated in figure 1 and is recommended for the categorizations of lesions in patients with cirrhosis.

Figure 1. Scheme of CEUS LI RADS classification



Notes:

Ultrasound evaluation of PSC

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Primary sclerosing cholangitis (PSC) is a progressive immune-associated disease of unknown etiology and incompletely understood pathogenesis, characterized by biliary inflammatory and fibrotic stricturing as well as cholestasis[1]. Via a variable disease course, with fluctuating symptoms and liver enzymes, interspersed with intercurrent events such as gallstones, dominant strictures and bacterial cholangitis, PSC generally leads to liver cirrhosis and end-stage liver disease over time. The high risk of gallbladder cancer, cholangiocarcinoma, and colorectal cancer, justifies a focus on cancer surveillance in patient follow-up.

What is the role of ultrasound for the diagnosis, cancer surveillance and diagnosis, and prognosis, in PSC today? The diagnosis of PSC is based on typical findings on cholangiography; magnetic resonance cholangiopancreatography (MRCP) is the modality of choice. A recent (2021) position paper from the International PSC Study Group proposes that a compatible high-quality MRCP alone is sufficient for a probable diagnosis of PSC, whereas for a definite diagnosis one of three additional criteria should be fulfilled (elevated ALP, concurrent IBD, or histology compatible with PSC)[2]. Ultrasound is an integral part of the diagnostic algorithm[3], mainly to exclude other causes of cholestasis or other liver diseases and to identify cirrhosis or signs of portal hypertension but may also be the first imaging modality to identify bile duct dilatations, supporting a suspicion of PSC. Regarding cancer surveillance, gallbladder polyps in PSC may become malignant in about 50% of cases. Surveillance for gallbladder cancer may be performed by ultrasound, with excellent performance, or included in an annual evaluation by MRCP. Cholangiocarcinoma (CCA) is a major concern in PSC; patients carry up to 20% lifetime risk of CCA. While current surveillance strategies favour MRCP with contrast magnetic resonance imaging (MRI) at regular intervals and upon increasing or alarm symptoms[4], contrast-enhanced ultrasound may have a role in the often difficult diagnosis of CCA.

The major emerging role of ultrasound in PSC applies to prognostication. The establishment of biomarkers for the evaluation of prognosis, disease activity, and risk stratification, are highly warranted in PSC in order to lessen the burden of uncertainty reported by patients, provide personalized, risk-adjusted care and improve resource allocation, and improve patient selection as well as effect assessment in clinical trials, improving our chances of developing effective therapy. Spleen length, easily measured on an ultrasound scan, has been identified and validated as a prognostic marker in PSC[5], but the main focus is on liver elastography. Liver stiffness measurements may be performed using transient[6] or ultrasound elastography[7-9] in PSC and both are associated with histological fibrosis stage in PSC. Baseline as well as rate of change in liver elastography are strongly associated with clinical outcome in PSC and this has been validated in several independent studies. Transient elastography is most validated but ultrasound elastography integrated in a platform allowing a full evaluation of the liver may carry particular advantages in PSC by facilitating the identification of dominant stenosis. These frequently occur in PSC and have been shown to cause elevated liver stiffness not due

to fibrosis which is subsequently reduced upon endoscopic therapy. Recent clinical practice guidelines from the European Association for the Study of the Liver (EASL) advocate the use of elastography in the follow-up of patients with PSC[10].

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Notes:

Ultrasound and elastography in liver cirrhosis

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Detection of compensated Advanced Chronic Liver Disease

Advanced liver fibrosis and compensated liver cirrhosis are today referred to as compensated Advanced Chronic Liver Disease (cACLD) (1). The diagnosis of cACLD is frequently missed because of unspesific symptoms and lack of awareness both among patients and many physicians. However, timely diagnosis is crucial as treatment or removal of the underlying driving forces may halt the progression and even result in regression of liver fibrosis.

Direct and indirect signs of liver cirrhosis detectable by transabdominal ultrasound

Morphological changes. The accumulation of fibrosis and regenerative nodules may distort the normal configuration of the liver. Irregular surface and enlargement of the caudate lobe are early signs of liver cirrhosis. At later stages atrophy of the right lobe and hypertrophy of the left lobe are frequently seen.

Echogenicity. A healthy liver has a homogenous echo, whereas in liver cirrhosis, the echo is usually heterogenous and more rough.

Vascular changes. In parallel with progression of liver cirrhosis the portal vein pressure increases and the diameter of the portal vein may increase as well. The antegrade velocity is often reduced, less than 13 mm /sec is pathological. As portal hypertension progresses, the antegrade direction may reverse into retrograde flow. Theese aspects are evaluated by Doppler ultrasound.

Other signs of portal hypertension. Portal hypertension results in recruitment and de novo formation of portosystemic collaterals which might enlarge and give rise to varices. Both gastroesophageal varices and abberant vessels, for example splenorenal shunts or recanalization of the umbilical cord, can be detected with transbdominal ultrasound. Finally, in the context of liver cirrhosis, enlarged spleen which is easily assessed by ultrasound, indicates portal hypertension.

Elastography for detection of cACLD

Over the last two decades, liver elastography has become essential in the work-up of patients with chronic liver diseases. In addition to transient elastography (TE), which has been available for more than two decades, several other modalities have also been developed for liver stiffness measurement, in particular different variants of shear wave elastography (SWE). Numerous clinical studies have validated the use of liver elastography as a rapid an easily available method for assessing stage of liver fibrosis. Most documentation has been achieved with TE, however, increasing documentation is also available for several other methods. Elastography is useful both to rule out and rule in cACLD with high sensitivity and

specificity. Importantly, however, cut off levels for the various stages are not interchangeable between different methods (2, 3).

Detection of clinical significant portal hypertension (CSPH)

While clinical significant portal hypertension (CSPH) is clearly indicated by ascites and gastroesophageal variceal bleeding in patients with chronic liver disease, CSPH may be overlooked before these events occur. Often, CSPH may be diagnosed by various ultrasound findings mentioned above, however, it may also be present in the absence of these findings. In this situation liver elastography may offer additional information as it has been shown that liver stiffness correlates with portal pressure as measured by hepato-venous pressure gradient (HVPG). In clinical practice, presence of gastroesophageal varices can be ruled out when liver stiffness is below 20 kPa (measured by TE) and platelets number is greater than 150 x 10^9/L (1).

Furthermore, elastography can also be applied on the spleen, as spleen stiffness is increased in CSPH (4). The combination of liver and spleen elastography may be of particular interest in patients with non-cirrhotic portal hypertension.

Complication of cirrhosis

Hepatocellular carcinoma (HCC) is a well- known complication of liver cirrhosis. Surveillance with ultrasound every six months is recommended for all cases with cirrhosis that will benefit the detection of HCC. In case of focal lesions, contrast enhanced ultrasound (CEUS) is useful for further characterization together with multiphasic CT scan or MRI.

Portal vein thrombosis is a known complication of liver cirrhosis. Anticoagulation improves the prognosis. The patency of the portal vein should therefore always be assessed when patients are examined with ultrasound as part of HCC surveillance. CEUS can be used for further assessment if a malign thrombus is suspected.

Final comments

For the hepatologist, ultrasound and elastography are highly appreciated supplements in routine clinical practice that undoubtedly increase the quality of care and the job satisfaction for the doctor.

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Notes:

Session 3: Pancreas

Cystic neoplastic lesions of the pancreas - the percutaneous option of ultrasound

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In former time the most cystic pancreatic neoplasms (CPN) were detected in an advanced and symptomatic stage, now a days CPN are mostly diagnosed incidentally by Ultrasound or CT in an asymptomatic stage. With the asymptomatic patients it is most important to ask about a previous pancreatitis, because 90 % of all detected pancreatic cysts are pseudocysts with a previous history of acute or chronic pancreatitis and CPN in those cases is extremely unlikely.
Increasing imaging quality and examination technique of the pancreas lead about since 2000 to rare incidental findings of asymptomatic cystic pancreatic neoplasms (CPN) in our US lab.
At that time the clinical pathway of these mostly elderly patients was mainly unclear due to less experience even in bigger centers. Pancreas surgery became low in complications and therefore - in general - most pancreas surgeons recommended an operation. We had two main problems: how to achieve the most likely final diagnosis and according to prognostic reasons, which patients should be operated and who should have follow up.

The differential diagnosis was based on well known epidemiological data (table1).
Our pragmatic but careful diagnostic approach at that time is demonstrated in table 2.

Cystic Pankreatic Neoplasia: Epidemiology, Malignancy

modif. Brugge et al NEJM 2004; 351 1218

Entitiy	sex	Decade	Frequency	Risk of Malignancy
Serous Cystadenoma (SCA)	female	7	32-39 %	extremely rare
Mucinous Cystadenoma (MCA)	female	5	10-45 %	high
IPMN	m:f=1:1	6/7	21-33 %	high
Solid pseudopapillary N.	female	4	< 10 %	malignant
Cystic endocrine N.	m:f=1:1	5/6	< 10 %	Malignant NET
Ductal Adenoca with cystic degeneration	m > f	6/7	< 1 %	Rare variant of ductal PCa
Acinuscell-Cystadenocarcinoma	m	6/7	< 1 %	Rare entity of PCA

Table 1 Entities in Cystic pancreatic neoplasia modified after Brugge(1)

Pragmatic sonographic and clinical approach in CPN

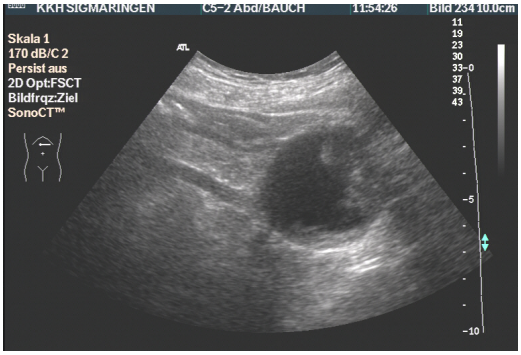
1 Ultrasound: image optimization of pancreatic head and tail by graded compression and translienal views. Imaging of the pancreatic duct
2 description of pancreatic lesions: location, diameter, single or multiple cysts wall thickness, irregularities inside the cysts, description of Wirsung´s duct
3 CEUS of the pancreas: vascularization of the cystic wall and irregularities inside, appearance of other lesions
4 careful „second“ anamnesis regarding abdominal symptoms, missing history of acute/chronic pancreatitis
5 clinical diagnosis and therapeutic option, if necessary additional endoscopy, CT or MRT, EUS (available from 2010)
6 individual follow up to clinical diagnosis and age of the patient

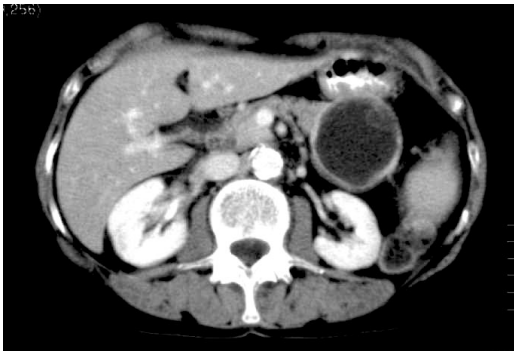
Table 2 Pragmatic approach to CPN with US

Characterization of the 4 most frequent types of CPN

1 Mucinous Cystadenoma (MCA):
Almost only women > 50-70 y.
Macroscopy: one or a few cysts with different thickened wall, cysts mostly >2 cm up to 15cm in diameter. More than 90 % are located in the pancreatic tail.
Cyst fluid: with extremely elevated CEA, which is no sign of malignancy.
Ultrasound: thickened wall, content may be not totally free of echoes.
CEUS: more ore less perfusion of the thickened wall.

Prognosis: increasing malignant degeneration in the long-term course, possibly in especially thick-walled cysts.
Cytology: mucinous cell elements, possibly malignant cells.





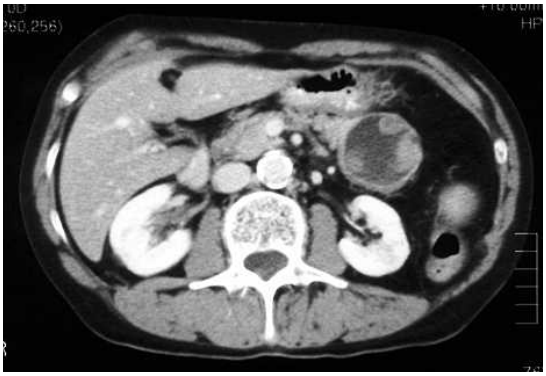


Fig.1 Typical MCA (pTis) in the pancreatic cauda
Left: US-finding in 2004: massive, different wall thickening of an MCA
Right: CT-finding in 2001 misdiagnosed as pancreatic pseudocyst as result of an an ommitted anamnesis!
Below left: CT-finding in 2004, concordant finding to US.
Typical for MCA: slow growth and successful resection

2 Serous Cystadenom (SCA)
Same frequency in pancreatic head, corpus an tail, m : f = 1:3, age: around 60 y Macroscopy: spongelike, multiple cysts < 2cm, thin septa, malignant degeneration extremely rare. **Ultrasound:** lesion with multiple or innumerable tiny cysts. Pinhead sized cysts, which are below sonographical resolution may dominate and produce a hyperechogeneous pattern. Small central calcifications may form a central scar.
CEUS: the septa are extremely thin and more ore less hypervascularized.
Therapy depends on individual situation.

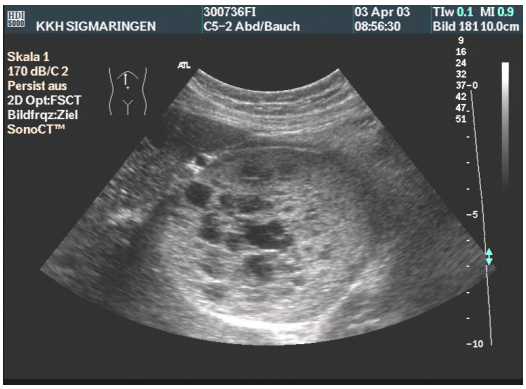


Fig 2 Pancreas corpus, SCA , 5 cm in diameter.

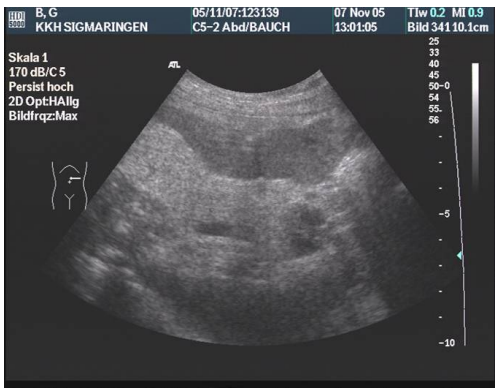


Fig.3 Pancreas cauda, small SCA (2cm)

3 Solid peudopapillary cystic Neoplasia:
Generally women , age 25-40 y
Macroscopy/US: solid tumor with cystic proportions , malignant degeneration 10-15% with good prognosis
Therapy: usually resection

4 Intraductal papillary mucinous neoplasia (IPMN)
Preferred occurrence in the late 7th or 8th decade, both sexes are equally affected.
There are 2 different types, the main duct type (MDT) (fig. 4), and the branch duct type (BDT). The main duct type is connected with the dilated WD (>5mm), the murine production may lead to the fish mouth papilla, which is pathognomonic for IPMN (fig. 5). In 80% the IPMN is situated in the pancreatic head, the branch duct type is often multifocal.
Prognosis: malignant degeneration is found in 30 % and increasing in long-term course. Partly a ductal carcinoma will develop with a 5-year survival rate of 10%, in case of a mucinous carcinoma the 5-year survival rate is much better (50%). The individual prognosis depends on multiple parameters. The branch duct type is predominantly characterized by cystic dilated side branches. „Cystic lesions“ < 3 cm in diameter have a lower risk of malignancy, especially when intracystic nodules are absent.
Ultrasound: Diagnosis of MDT is easy when the DW is wormlike dilated. Sometimes a circumscribed bag like dilatation is present too. The DW wall may be thickened in some cases and low reflectable material inside. In this case the next step is a duodenoscopy to demonstrate the fish mouth papilla (fig.1).
In BDT a sonographic diagnosis is extremely difficult. In most cases there are some smaller cystic elements without detectable connection to the pancreatic duct. Cystic walls may be thickened, the most suspicious finding are intracystic nodules. The proof of diagnosis has to be achieved by MRT and endoscopic Ultrasound (EUS).

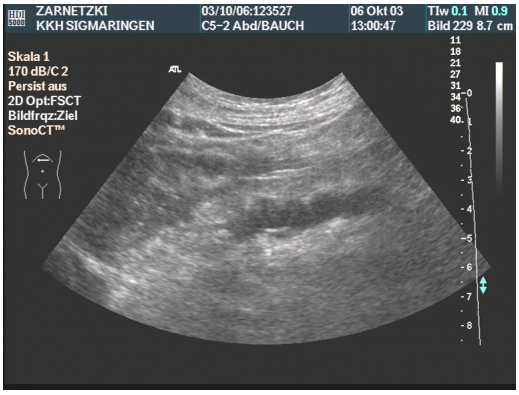


Fig.4 IPMN, main duct type.
Wormlike dilated DW containing echogeneous mucus.

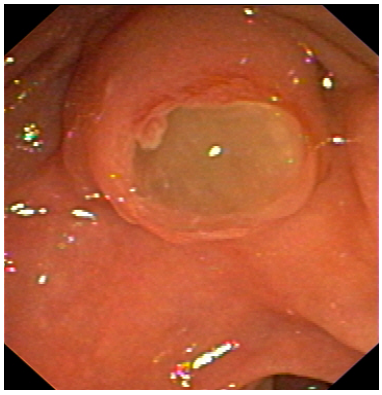


Fig.5 fish mouth papilla
Papilla with oozing mucus

Results and comments

The following tables 3-6 demonstrate detailed information concerning our patients with cystic pancreas lesions without a history of pancreatitis. More than 8O% are incidental findings.

Med. Department District Hospital Sigmaringen
Pancreatic cysts without previous acute/chronic Pancreatitis

2000-2010 **n = 76**
Sex **m:f 27 : 59**
Age **mean 75 y (45 – 87)**
Localization (all lesions)
Caput/Corpus/Cauda **women 1:1:1**
men 3:2:1
incidental findings > 80%
symptoms:
rarely questionable related to CPN (diameter)
some patients with uncharacteristic complaints

Operations **n =15**

Table 3 Patients and clinical data
CPN without previous pancreatitis

Med. Dept. District Hospital Sigmaringen
2000-2010 **CPN** **n=76**

Diagnosis based on clinical data, US, percut. FNAspiration/FNBiopsy: lLab, Cyto-, Histology
If necessary: CEUS, EUS, CT, MRT

Degenerated Cyst	24
SCA	20
MCN	11
IPMN	7
Neuroendocrine CPN	1
Hamartoma	1
„Unclear“	8
Diff.-Diagnosis: deg.C vs SCA, SCA vs MCN, MCN vs. IPMN	3

Table 4 Final clinical diagnosis diagnosis

Med. Dept. District Hospital Sigmaringen
2000-2010
CPN **n=76**

Operation	15
IPMN	5
MCA of which malignant 1 pTis 1	4
SCN	3
Cystic endocrine Neoplasia	2
Hamartoma	1

Table 5 Resection in 15 of 76 Patients with CPN and postoperative diagnosis

Med. Dept. District Hospital Sigmaringen 2000-2010
Natural history of cystic pancreas lesions

CPN (primary operated n =4)	76
Follow up provided Follow up rejected	54 18
Of which operated within 3 months after 1, 10y	9 2
Follow up	45
Follow up time (n=45)	Mean 50,9 m (3-177)
Diameter of solitary cysts (n =37)	Mean 17,8 mm (5-47)
Diameter of lesion with multiple cysts (n=12)	Mean 29,6 mm (12-80)
IPMN (n = 5)	Diameter DW mean 8,7 mm (4-12)
Number of cysts	Same 33 more 8 less 4
Diameter of cysts	Same 20 bigger 16 smaller 9
Cyst growth per year during follow up (n = 45)	mean 1 mm/year
growth in growing cysts (n= 16)	Mean 12,2 mm per 50,9 months Mean 2,8 mm/year

Table 6: Follow up in CPN

In our experience many findings are harmless, especially solitary cysts < 2-3 cm with thin walls, because they are not or extremely slowly growing and without clinical importance. In these cases additional diagnostic effort, like CT, fine- needle aspiration (FNA) or EUS is not necessary.
Of high interest are thick walled cysts; these cysts are suspicious for MCA, development of malignancy is present and an individual diagnostic effort and risk analysis should be done.
Particularly noteworthy is the fact that initial manifestation of IPMN may be mimicked by an acute pancreatitis.

In our limited collective 20% of the patients were operated, some of them during follow-up. Generally indications for operative therapy must be individual. Younger patients should be operated, especially with cystic lesions in the pancreatic cauda. In cases of IPMN the diagnosis is easy in classical MDT but very difficult in BDT and mixed duct type. With its relatively high risk of malignancy the whole diagnostic battery is as well needed as experience of the managing doctors and tertiary should be involved.

The increase of detected cystic pancreatic lesions due to more frequent use of US, CT, MRT and EUS leads to a high eperience level. Meanwhile abundant papers with concordant results and recommendations have been published on this topic, therefore only a few of earlier and actual papers can be included in the literature list (2-13). And - by the way - the role of conventional US is still important, because with a precise examination technique US has the first chance to find pancreatic cystic lesion and we should know how to deal with these findings.

Take home Message

1. Try to see the whole pancreas routinely
2. Conventional US is reliably groundbreaking for diagnosis of PCN
3. Pancreatic pseudocysts make up 90% of cases with cystic pancreatic lesions (ask intensively for previous acute or chronic pancreatitis)
4. Avoid following pitfalls:
   - avoid cyst drainage in huge CPN
   - think of pancreatic cancer with cyst as necrosis
   - think of the rare IPMN manifestation as acute pancreatitis

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Notes:

Therapeutic Endoscopic Ultrasound using Radio-Frequency Ablation (RFA) in pancreatic tumors

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Introduction: Endoscopic Ultrasound for diagnosis and staging

Endoscopic ultrasound (EUS) became available in the 1980-ies and has developed into a sub-specialty of endoscopy, typically performed in referral hospitals and academic hospital units. At Haukeland University Hospital (HUH), the method was introduced in 1987 by Dr. Svein Ødegaard, who had learned to use EUS equipment during his specialization in internal medicine and Gastroenterology in Germany. For an extended period, EUS was used mainly to diagnose subepithelial lesions, lymph nodes, tumours in the stomach and esophagus including local staging and diagnosing microlithiasis or other pathology in the biliary tract.

The subsequent significant development in EUS was the introduction of needles for tissue sampling (1). After the introduction of the fine-needle aspiration technic in early 1990-ies, we have seen several new needle designs improving visibility and manoeuvrability as well as tissue acquisition. This has improved the overall results by shifting the tissue sampling from cytology smears to cell-blocks and cylinder biopsies. Still, no single needle design has proved to be superior to FNA needles and aspiration technique, and post-procedure tissue-sample handling are probably important factors (2). However, this method paved the way for using predominantly linear echo-endoscopes. In many centres, it became routine to biopsy lymph nodes in the mediastinum or retroperitoneum for staging purposes. Also in pancreatic surgery, many centres recommended always performing EUS guided tissue sampling before deciding to undergo surgery or particularly oncologic treatment.

A new era: EUS guided treatment of neoplastic lesions

Radio –Frequency-Ablation (RFA) methods are used to deliver focused tissue heating to a temperature level where the cells are degenerated by dehydration. Long-waved longitudinal waves create an area of local heating around a designated ablation zone of a RFA catheter. The first EUS compatible RFA probe was the “Habib catheter,” a 1.2 mm catheter that could be passed through a 19 G FNA needle into pancreatic neuroendocrine tumours or cystic pancreatic lesions (3-5). This resulted in tumour resolution or size reduction in 7/8 cases. The next improvement was a water-cooling system built into an 18 G in the same needle to control the temperature at the ablation zone and avoid overheating and carbonisation. The EUSRA was made available in 2019 (Starmed/Taewoong, Seoul, South-Korea).

Neuroendocrine tumours in the pancreas (pNETs) represent a minority of neoplasms in the pancreas, most of which are not producing hormones (Non-Functional). However, they are slow-growing, and before they reach a diameter of 2 cm, they are rarely malignant, and

guidelines generally do not recommend surgical treatment (6). Some pNETs are producing hormones (Functional), these tumours are highly differentiated, and the most frequent entity is insulin producing tumours; insulinomas, which are nearly always benign. They are often discovered due to their excessive production of insulin which is not regulated by the patient's blood glucose levels and thus leads to repeated episodes of hypoglycaemia. This can be very troublesome to the patients as the glucose level may drop to levels where conscience is disturbed and may lead to dangerous situations where the patient is not able to take care of him/herself, and imply important limitations to the life of patients, such as losing their driver´s license.

Performing EUS Guided RFA may direct thermal energy to the tumour tissue enough to destroy the cells that represent the idiopathic insulin production in a very detailed manner.

In combination with the use of contrast enhanced EUS, we can get a good representation of the tumour geometry before the delivery of heating. Afterwards, we can repeat the contrast administration to confirm that we have covered the whole volume of the tumour. In order to preserve delicate structures such as the pancreatic duct, we place a 5 F drain inside the pancreatic duct if the ablation zone is closer to the tumour than 2 mm. This is done to order to prevent pancreatitis related to the procedure. The endoscopist needs to have experience and skills to selectively cannulate the pancreatic duct with ERP to do this safely.

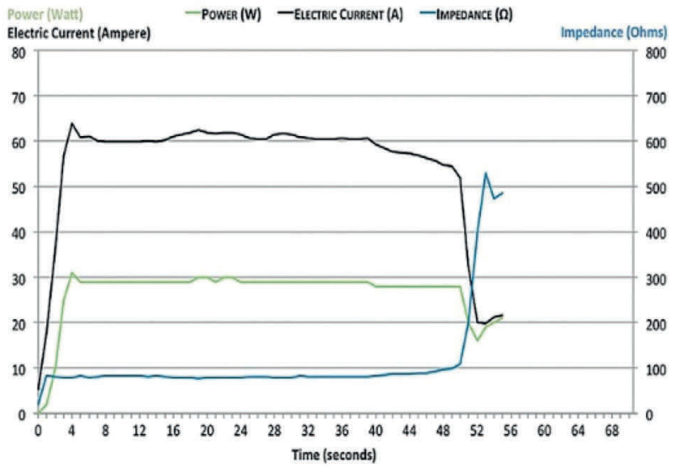

Figure 1: A graph of the RFA power (green, watts), current (black, Ampere) and Impedance (blue) during a session of EUS radio frequency ablation. From: Crino S.F. et al. Radiofrequency Ablation (EUS-RFA) of Solid Pancreatic Neoplasm Using an 18-gauge Needle Electrode: Feasibility, Safety, and Technical Success. JGLD. 31Mar.2018 (7)

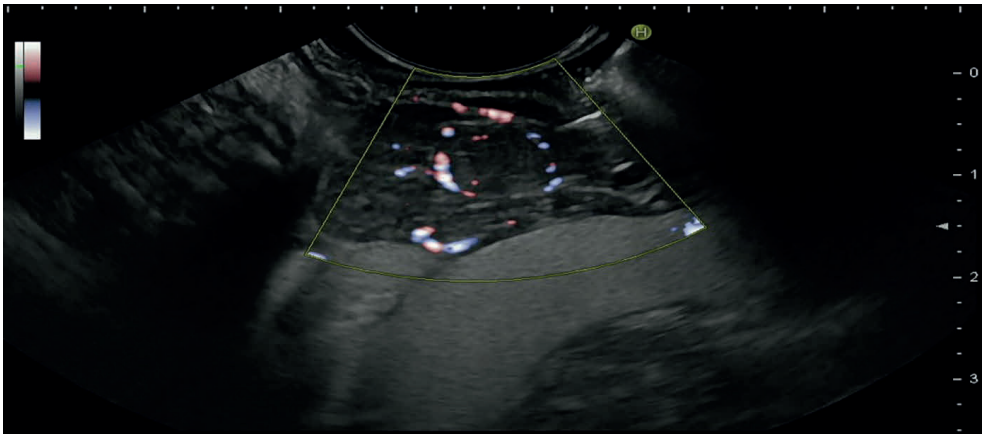

Figure 2: EUS image of isoechoic pancreatic neuroendocrine tumour (insulinoma) with colour Doppler showing increased vascularity surrounding the tumour "basket sign"

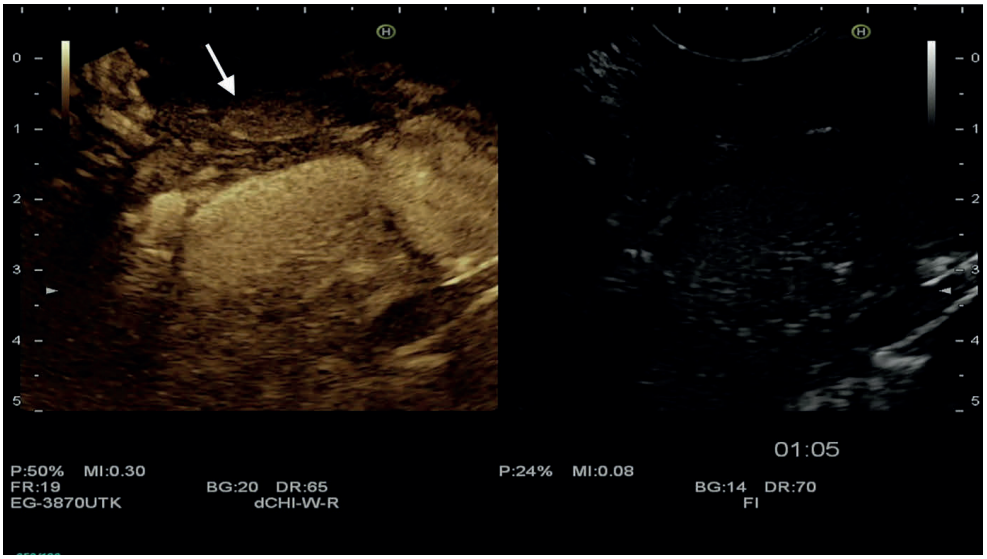

Figure 3: Contrast enhanced EUS with Sonazoid in the venous phase showing an oval pancreatic insulinoma as a hyper enhancing area (arrow).

The first experience

At Haukeland University Hospital, we have had the necessary equipment to perform temperature and impedance controlled EUS guided RFA for the last 18 months and treated six patients with insulinomas with EUS-RFA. The equipment used were standard linear EUS echoendoscopes from Olympus or Pentax, US scanners with Colour Doppler and Contrast

media options, and the EUSRA system from Starmed/Taewoong. The tumours were located in the pancreatic head, body or tail. Two of the patients had < 2 mm distance from the tumour edge to the pancreatic duct, and we placed a 5 F drain in the pancreatic duct with a duodenoscope. Colour Doppler and Sonazoid contrast were applied before and after the ablation to define the outline of the tumour and secure that no tumour tissue was left unablated. An ablation needle with an adequate length of the ablation zone was passed through the working channel of the echo-endoscope and positioned inside the tumour tissue under EUS guidance. The ablation was started and continued until the impedance suddenly increased, indicating that the nearby tissue was dehydrated. This frequently coincided with the development of visible bubbles around the ablation needle. If needed, the position of the ablation needle was moved to cover an unablated volume of the tumour. We performed from 1- 4 repeated ablations during one session.

Patients were observed as in-patients to the next day, and no one experienced excessive pain, bleedings, developed pancreatitis, nor any other adverse event. Patients were followed closely on their glucose level the first 24 hours, and all patients experienced a stable glucose level after the procedure.

Patients were re-examined after three months with EUS, including colour Doppler and CEUS. We did not find remaining tumour tissue, and patients had stopped measuring their glucose levels.

One patient presented a more diffuse uptake of Ga DOTATOC tracer on PET-CT in the pancreatic head. On repeated EUS examinations, a defined tumour could not be positively identified. Still, we finally approached an area in the uncinate process where a “basket sign” had been observed on colour Doppler. Unfortunately, he continued to have hypoglycaemic episodes, even after an attempt to ablate an area in the pancreatic head was performed. No typical tumour entity was discovered in repeated EUS examinations as well as Ga PET-CT.

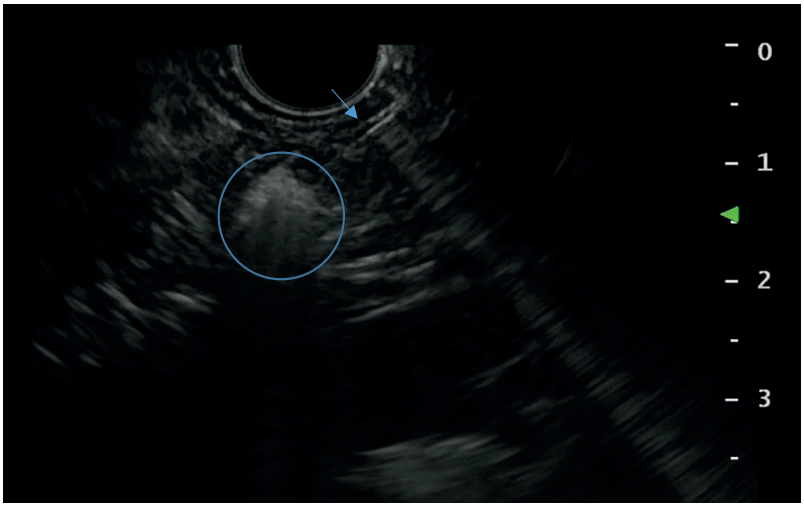

Figure 4: EUS image of EUS guided RFA of a pancreatic insulinoma. EUSRA probe (arrow). A t heating the tumour tissue becomes hyperechoic with a shadow below the hyperechoic signal (circle).

Further studies

We have joined an international multi-centre study (RAPNEN-study, Alberto Larghi, Rome, Italy) and we have included one patient in this study so far. We have also recently established cooperation with the National Centre for Neuroendocrine Tumours at Rikshospitalet for patients with pNETs, where we have a common National protocol for patients with pNETs. We will invite patients with pNETs that fall within the inclusion criteria to join these studies using EUS-RFA as the method of treatment instead of surgery (8).

We would also like to apply this method for more precise ablation of pancreatic adenocarcinomas/plexus neurolysis to reduce pain in pancreatic cancer. Some studies have already combined local treatment of locally advanced adenocarcinoma, but further data is needed to conclude if this has any value for the patient's (4, 7). An exciting feature of heating the tissue may be that the remaining tumour cells become more susceptible to immunogenic response due to increased inflammation in the vicinity of the ablated area. This process may also improve vascularity and availability of chemotherapy and possibly immune-therapy but may also cause side effects (9, 10).

Another promising palliative application is to perform intraductal ablation of cholangiocarcinoma with RFA to keep the biliary ducts open and prevent cholestasis and cholangitis. We already have some experience in this where it seems to increase the period where the patient is available for chemo-therapy and to add both time and quality of life to these patients.

Conclusion

EUS guided RFA represents a minimally invasive method for treating localised tumours in the pancreas with a low rate of adverse events. Nearly all lesions available for EUS directed FNA/biopsies are also available for RFA treatment. The method requires skills and experience in EUS, including Doppler and contrast imaging as well as tissue sampling and ERCP. Based on present limited experience, it is an efficient method to treat insulinomas and possibly other neuroendocrine tumours. It is an intriguing possibility that combination therapy between local tumour ablation may prolong the period where inoperable patients are candidates for chemotherapy, or even increase the tumour´s susceptibility to systemic oncological treatment. This must be addressed in further studies.

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Notes:

Sonoporation in pancreatic cancer (PDAC)

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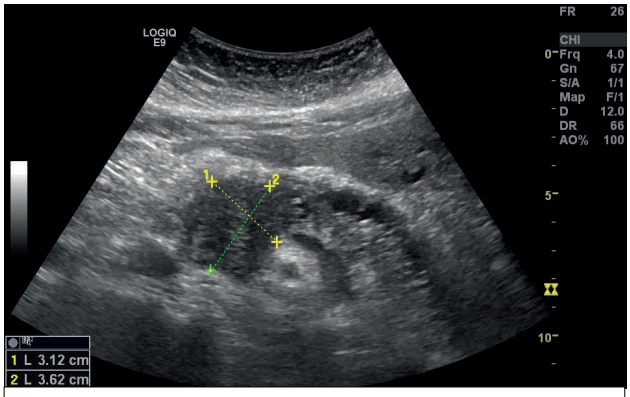

Figure 1: A hypoechogenic and diffusely contoured adenocarcinoma in the pancreatic head, and a dilated main pancreatic duct.

Pancreatic cancer remains one of the most lethal cancers. It is currently the seventh most common cause of cancer death in both men and women worldwide and has a five-year survival rate of only 9% [1,2]. Already at the time of diagnosis, about eighty percent of patients have locally advanced or metastatic disease, excluding surgery as a treatment option.

When treating patients with inoperable pancreatic cancer, the tumor's response to chemotherapy is notoriously low. This is because of a dense desmoplastic stroma and poor blood supply in and around the tumor [3, 4], albeit, perfusion is sufficient to observe substantial signals in contrast-enhanced ultrasound (Fig. 2). For patients with non-resectable pancreatic cancer, there are currently two major chemotherapeutic regimens available: FOLFIRINOX (Oxaliplatin, Irinotecan, Fluorouracil, and Leucovorin), considered the first line treatment, or a combination of Gemcitabine with a nanoparticle formulation of Paclitaxel (Nab-Paclitaxel), the second line treatment. Though both regimens are aggressive, the overall survival for patients with pancreatic cancer has barely changed over the past decades [5]. For this reason, there is a need for innovative strategies to improve drug delivery and clinical outcome for these patients.

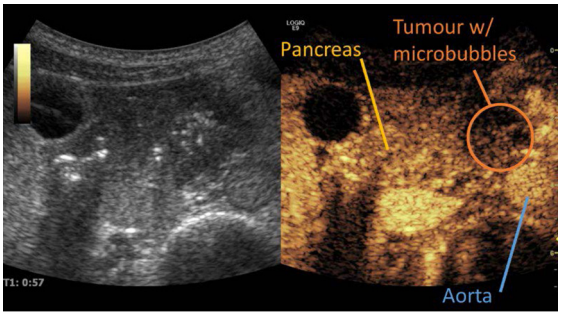

Figure 2: Contrast-enhanced ultrasound image showing the tumor of a patient treated in the research group's previous sonoporation trial [11]. Though the blood supply to the tumor was poor, it was sufficient to observe substantial signals in contrast-enhanced ultrasound

Though most commonly used in diagnostic settings, potential therapeutic applications for ultrasound are being explored. One such applications is sonoporation, where ultrasound and focused ultrasound contrast agents (microbubbles) are combined with the aim of enhancing the therapeutic efficacy of a given drug. When exposed to ultrasound, the microbubbles volumetrically oscillate due to the changes in pressure (Fig. 3). When the oscillating microbubbles come into contact with biological barriers such as cell membranes or

vascular walls, the microbubble pulsation creates pores and gaps in these barriers [6-10]. These pores increase the permeability of the barriers, thus allowing the chemotherapeutic drugs to pass from the vasculature into the tumor in increased concentrations. Sonoporation only occurs in the area targeted by ultrasound, so the increased permeability only occurs in the areas where it is needed: in and around the tumor.

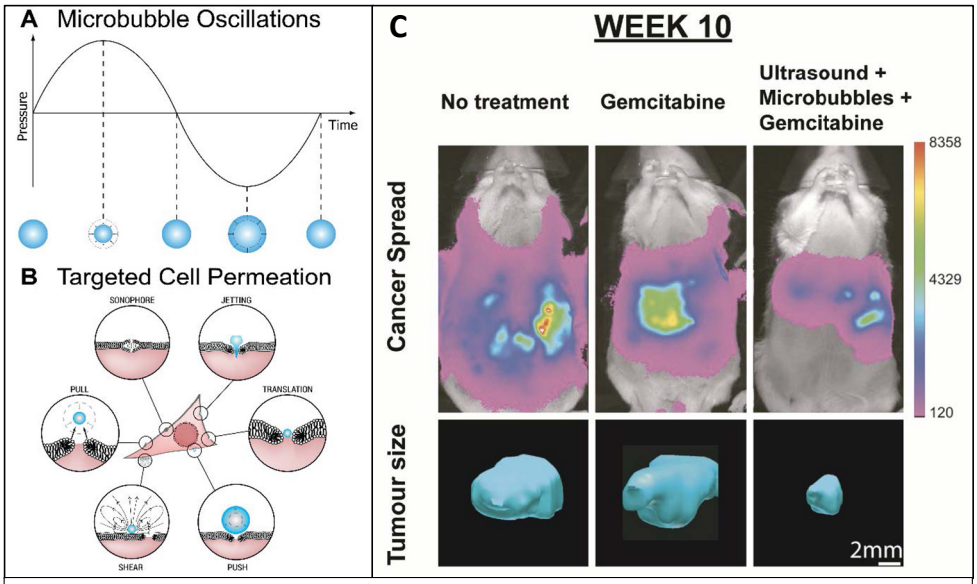

Figure 3: The mechanisms and results of sonoporation. Panel A: Microbubbles oscillating due to changes in pressure. Panel B: Mechanisms of sonoporation. Microbubbles form pores in cells when ultrasound is present. Panel C: Tumor growth and metastatic spread is inhibited.

Taking into account that a major drawback to traditional chemotherapy is the systemic toxic side effects, especially when used in high therapeutic concentrations, sonoporation may provide an effective solution. This scenario results in greater treatment efficacy, improving quality of life and, theoretically, survival. As the chemotherapy remains systemic, it will still abate metastatic development.

In our group's previous phase I clinical trial [11, 12], 10 patients with inoperable pancreatic cancer were treated with Gemcitabine, microbubbles (Sonovue) and ultrasound. Among the patients treated with sonoporation, 50% showed tumor size reduction, and compared to historical controls, the median survival significantly increased from 8.9 months to 17.6 months. Moreover, patients tolerated an increased amount of treatment cycles suggesting a prolonged period of high quality of life. No additional toxicity or increased frequency of side effects were registered in the patients treated with sonoporation. Thus, sonoporation may have the potential to safely improve the outcome of patients with pancreatic cancer.

In our upcoming phase II randomized clinical trial, we will combine microbubbles (Sonazoid) and focused ultrasound with today's standard of care chemotherapy: FOLFIRINOX and Gemcitabine/Nab-Paclitaxel. A total of 120 patients with inoperable pancreatic ductal adenocarcinoma will be included at the two sites; Haukeland University Hospital (Norway) and Thomas Jefferson University (USA). We aim to establish a safe, efficient and optimized

therapeutic method for sonoporation-enhanced chemotherapy in patients with pancreatic cancer. The primary outcome is progression-free survival, and secondary outcomes include overall survival and changes in tumor size. Moreover, the trial will apply shear wave elastography (SWE) measures and state-of-the-art contrast-enhanced ultrasound imaging techniques such as subharmonic imaging (SHI) and subharmonic-aided pressure estimation (SHAPE) to characterize the pancreatic tumors.

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Notes:

Session 4: GI tract

Bowel wall ultrasound -from Bench to Bedside

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2) Department of Clinical Medicine, University of Bergen, Norway

The beginning of bowel ultrasound

Even though the images from ultrasound scanners were of a much lower quality in the early years of ultrasound pioneers, studies using transabdominal ultrasound for the detection of intestinal disease started appearing as early as the late seventies (1-2). By the mid 80-ties, the use of high frequency ultrasound in endoscopic ultrasound paved the way for the characterisation of bowel wall layers. An entire supplement was published in Scandinavian journal of Gastroenterology in 1986 dedicated to endoscopic ultrasound of the GI tract (3-5). In the 90-ties the transabdominal scanners caught up somewhat and more clinical papers started appearing.

Bowel ultrasound and histology

Comparison with histological specimens revealed that the different ultrasound layers seen in the GI tract with high frequency ultrasound corresponded closely, but not perfectly to the histological layers. There was a discussion whether or not the muscularis mucosa could be identified or not which was particularly important for deciding the invasive depth of cancer in the oesophagus (3-4). Our very own Svein Ødegaard found using an elaborate experimental set up that pressure affected the number of layers that could be seen and that the normal Muscularis mucosa could in fact not be clearly distinguished in most cases unless thickened or using very high ultrasound frequencies (6-7). Our group's previous experience with experimental set ups and Trygve Hausken's particular interest in IBD patients was the foundation for my entry into the wonderful world of bowel ultrasound. With a wide-open aim we set out to compare operation specimens with ultrasound to see if we could find features particularly related to fibrosis development.

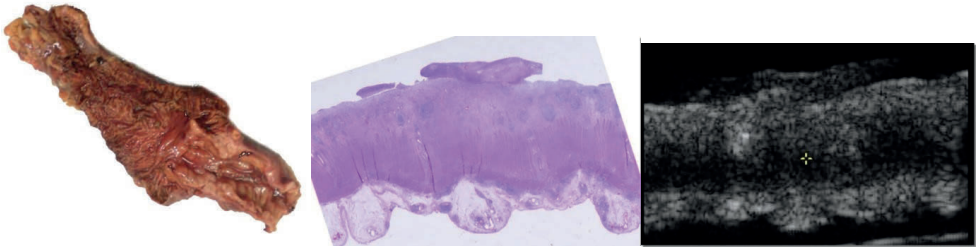

Figure 1: In the left panel an operation specimen with a stenosis consisting of the colon and neoterminal ileum is shown cut open. In the middle panel a histological section through and ulcerated area of the bowel are is shown with the corresponding ultrasound image in the right panel. In the ultrasound image there are changes in the echogenicity of the submucosa and proper muscle as well was hypoechoic elements at the outer border corresponding to lymphocytic aggregates.

We found that fibrosis caused changes in the echogenicity in both the proper muscle and submucosa and that typical features of Crohn's disease such as a thickened muscularis mucosae and Crohn's rosary could be detected. However, these findings are not specific of fibrosis and the problem of differentiating inflammation and fibrosis remains unsolved (8).

Bowel ultrasound and perfusion

Contrast-enhanced ultrasound was emerging as a rather new technique as we were starting our studies on Crohn's and fibrosis. Although, Crohn's disease causes changes in the microvasculature and perfusion (9-10) it became apparent that using ultrasound contrast was not as straight forward as we would have liked. Not only is the technique difficult to standardise, but it is may not be straight forward how the perfusion changes in Crohn's disease. To improve standardisation we investigated new perfusion models (11-13) and several strategies for solving issues with scaling and motion correction (14-17). Currently, the transference from experimental studies to clinical application is lacking.

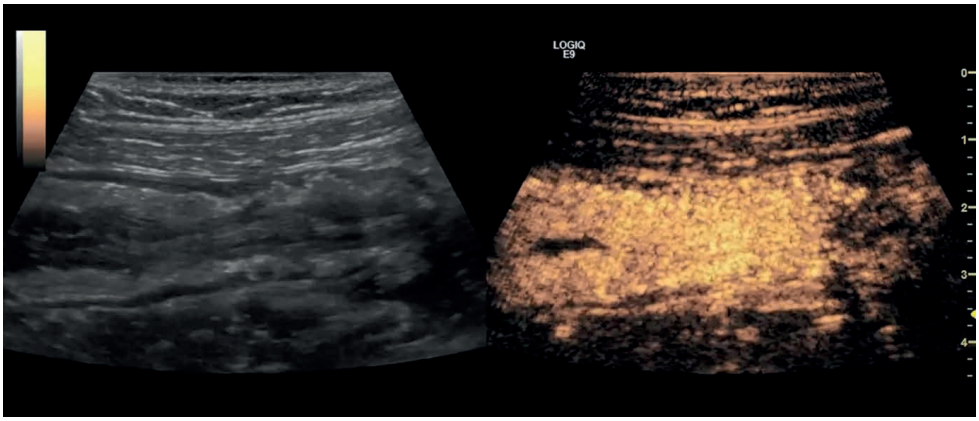

Figure 2: In the left panel the thickened terminal ileum from a patient with Crohn's disease is seen. In the right panel the corresponding contrast enhanced image is shown. There is obvious enhancement in the gastrointestinal wall when compared to the surrounding structures, but it is difficult to standardise between patients and ultrasound machines, and the post-examination analysis is time-consuming.

Bowel ultrasound and patients

Bowel wall thickness is the most important parameter used when examining the bowel. There is a variability in the measurements and how the bowel presents even in the healthy, however. Although pathological wall thickening typically was defined from 3-4 mm it was not clear what was normal and how different patient factors such as fasting, weight and age affected the measurements. Frequently, we also reported "a marked bowel wall" when the bowel as between 2-3 mm and did not quite fulfil the criteria for pathology. In 2009 the studies investigating BWT were mostly older than 10 years or derived from small case-control groups.

After examining approximately 120 healthy volunteers of all ages it became clear that the bowel wall of the entire tract is less than 2 mm except in the antrum, duodenum and rectum. Also, fasting state, age or size did not really influence results significantly (18).
This did not solve the issue of the patients in limbo, however. It was particularly problematic in ulcerative colitis where we frequently felt that we underestimated mild inflammation on ultrasound. In a recent study by Bots et al no cut off was defined for bowel wall thickness, and we found that bowel wall thickness is related to degree of inflammation, but that previous assumptions about pathology was inaccurate. Patients with mild inflammation on endoscopy corresponding to Mayo 1 had a bowel wall thickness over 2.1 mm. Furthermore, Mayo 2 had a bowel wall thickness over 3.2 mm and Mayo 3 over 3.9 mm. These are very interesting data that need to be confirmed in studies (19).

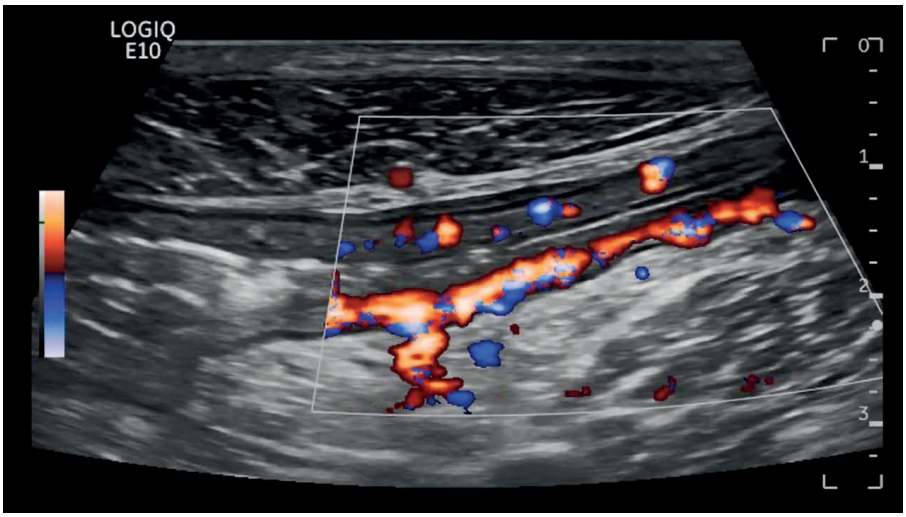

Figure 3: In patients with ulcerative colitis, there is oedema of the bowel wall causing thickening and the intramural vessels dilate to such a degree that they can be seen with colour Doppler. When the inflammation is chronic there us typically loss of haustrations as in this case.

Also, in Crohn's disease work has shifted towards clinical implementation of GIUS. The last few years we have worked with confirming the accuracy of GIUS in inflammatory bowel disease with comparing it with ileocolonoscopy as the reference standard. We have both found an excellent accuracy for detecting disease activity in Crohn's disease and developed an ultrasound score (20-22).

Bowel ultrasound and the future

In many ways, the use of ileocolonoscopy as a reference standard in Crohn's disease is a false assumption, as the luminal disease is not accessible in proximal disease. There is also the transmural nature of the disease and disease complications that requires cross sectional imaging. Recently, studies seem to suggest that normalisation of the bowel wall on ultrasound or so-called transmural healing is a better predictor for remission and a favourable outcome than endoscopic healing (23). Thus, GIUS may become even more important as a diagnostic tool in the future management of IBD patients.

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Notes:

New ultrasound index in Crohn's disease

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Background: Crohn's disease is a chronic inflammatory disorder in the gastrointestinal tract, characterized by alternating periods of remission and disease flare-ups. Thus, subsequent adjustments of medical therapy are required (1). Patients' symptoms do not reliably mirror the inflammatory activity and management should be based on objective evaluations (1, 2). Ileocolonoscopy is the established reference standard method, and ideally, it should be performed regularly for optimal monitoring of disease activity (1). However, the modality holds several limitations restricting repeated use. Gastrointestinal ultrasound seems well suited for systematic activity monitoring of patients with Crohn's disease, as it is rapid, non-invasive, well-tolerated by patients and feasible in the out-patient clinic (3, 4). A standardised ultrasound activity index may simplify the interpretation of sonographic findings, allowing for easier comparison between different examinations during follow up. Thus, several ultrasound activity indices have been developed, but most with inadequate methodology (5). The study aimed to construct, validate and assess interobserver reliability of a new simple ultrasonographic activity index for Crohn's disease.

Methods: In the development phase, 40 patients were prospectively examined with ultrasound and ileocolonoscopy. Endoscopic activity was calculated using the Simple Endoscopic Score for Crohn's Disease (SES-CD) (6). Seven ultrasound variables (bowel wall thickness, length, colour Doppler, stenosis, stratification, fistula, and fatty wrapping) were initially included and severity weighted after current knowledge (Table 1) (7).

	Scores			
Variables	**0**	**1**	**2**	**3**
Bowel wall thickness	< 3.0 mm	3.0-4.9 mm, or 4.0-4.9 mm (rectum)	5.0-7.9 mm	≥ 8.0 mm
Stenosis	No stenosis	Suspected (Thickened wall with narrow lumen)	Suspected several per segment	Suspected with pre-stenotic dilatation (> 2.5 cm)
Length of affected segment	No affection	<5 cm	5-10 cm	>10 cm
Colour Doppler score	No or single vessel	2-5 vessels per cm^2	> 5 vessels per cm^2	
Stratification	Normal	Focal loss	Diffuse loss	
Fatty wrapping	Absent	Present		
Fistula	Absent	Present		

Table 1: Definition and score characteristics for the ultrasound variables that were eligible for inclusion in the ultrasound index. Each variable was calculated in five ileocolonic segments (ileum, right colon, transverse colon, left colon and rectum).

The scores of the included variables were calculated in five ileocolonic segments (ileum, right colon, transverse colon, left colon and rectum), equivalent to the SES-CD. Multiple linear regression was used to select the variables that should be included in the final score, using the SES-CD as the dependent variable. In a second phase, the ultrasound data from each patient were re-examined for interobserver assessment using a dedicated software. Evaluation of interobserver agreement was performed using weighted kappa (wκ) for each ultrasound variable and for the calculated score. Additionally, intra-class correlation (ICC) was used for interobserver assessment for the calculated score as well. In the validation phase, ileocolonoscopy and ultrasound were performed in a new cohort of 124 patients for validation of the activity index. Spearman's rho was used to test the correlation between the ultrasound score and the SES-CD score, and wκ and ICC were performed to assess inter-rater agreement.

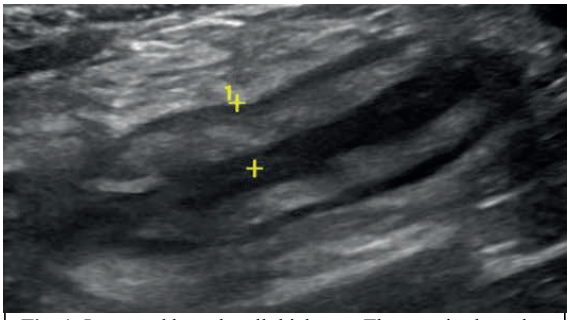

Fig. 1: Increased bowel wall thickness. The anterior bowel wall is delineated between the yellow callipers

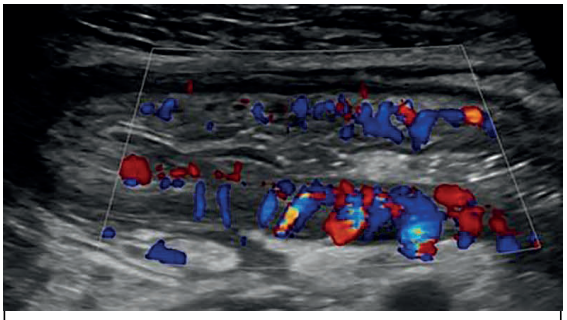

Fig. 2: Increased colour Doppler signals in the bowel wall in longitudinal section.

Results: There were no cases of fistula, and the variable was thus excluded. Furthermore, we found a high intercorrelation between bowel wall thickness and length, and the latter variable was thus excluded. The combination of the remaining variables provided a multiple correlation coefficient of r = 0.78, but the predictive value of the score was not reduced after excluding stenosis. We found a high correlation between the ultrasound score and the SES-CD (rho = 0.88). By re-examining the development cohort using dedicated software, a similar correlation was revealed (rho = 0.85). Furthermore, we found good inter-rater agreement for the constructed ultrasound index (wκ = 0.82, ICC = 0.95), as well as for bowel wall thickness (wκ = 0.81) and colour Doppler (wκ = 0.93). There was, however, poorer agreement for stratification (wκ = 0.46) and fatty wrapping (wκ = 0.51) and these variables were thus excluded. The simplified score (Table 2) consisting of bowel wall thickness (Fig. 1) and colour doppler (Fig. 2) correlated well with SES-CD in both patient cohorts (development cohort: rho = 0.83, $p < 0.001$, validation cohort: rho = 0.78, $p < 0.001$, entire cohort: rho = 0.80, $p < 0.001$ (Fig.3)). Finally, we found good inter-rater agreement in the validation phase (Ultrasound score: wκ = 0.84, ICC = 0.90. Bowel wall thickness: wκ = 0.84. Colour Doppler: 0.86).

Variables	Ileum	Right colon	Transverse colon	Left colon	Rectum	Total
Bowel wall thickness (0-3)						
Colour Doppler score (0-2)						
					Score	

Table 2: Scoring chart for calculation of the simplified ultrasound score. The severity of the variables (defined in Table 1) is summed in each segment. The sum of the scores represents the degree of disease activity. Colour Doppler was not registered in the rectum due to reduced sensitivity at increased depths.

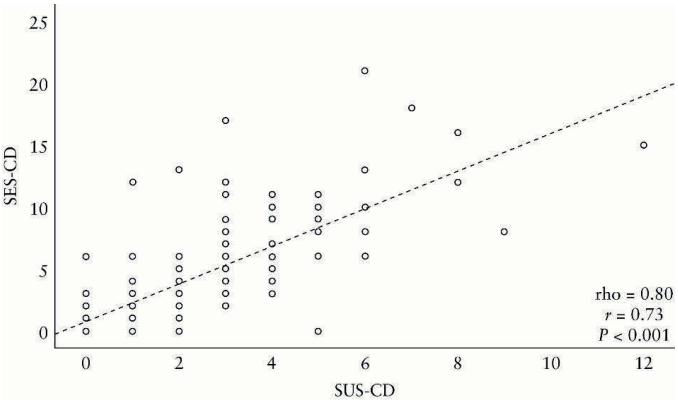

Fig 3.: Correlation between the ultrasound score and the SES-CD for the entire cohort.

Conclusion: We developed and validated a simple and reproducible ultrasound score for Crohn's disease. The ultrasound score correlated well with endoscopic disease activity and may thus be a surrogate of endoscopic activity. Implementation of the activity score may aid the monitoring and management of patients with Crohn's disease and might potentially reduce the need for endoscopic examinations.

The study was published in *Journal of Crohn's and Colitis* and is available (open access) at https://academic.oup.com/ecco-jcc/article/15/1/115/5854303

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Notes:

Gastric Ultrasound in Functional Gastrointestinal disorders

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Functional gastrointestinal disorders are common conditions affecting as many as 20% of the adult western population. It is an important cause for reduced quality of life and absence from work, and the most common conditions are irritable bowel syndrome (IBS) and functional dyspepsia (FD). They are both symptom-based diagnoses, a common denominator being that regular examinations are normal, but increasing evidence point toward disturbances in the gut-brain-communication as an important cause of the conditions.

Functional dyspepsia is characterized by upper abdominal discomfort related to meal intake, early satiety or epigastric pain of a chronic character, not explained by physical examinations[1]. The condition is associated with upper gastrointestinal dysmotility factors such as impaired gastric accommodation, delayed gastric emptying and antral distention and hypomotility[2]. There are several methods for demonstrating these disturbances, but ultrasound has proven an excellent option. In 1993, Hausken and co-workers demonstrated for the first time by ultrasound that patients with FD had antral distention and hypomotility[3]. Furthermore, by using Duplex ultrasound, it was possible to assess the transpyloric flow[4]. In 1996, Gilja et al demonstrated that patients with FD had impaired gastric accommodation by serving a liquid meal and studying the proximal stomach by 3D and 2D ultrasound[5-7]. Several studies using liquid meals to assess gastric function followed, culminating in a pragmatic and efficient ultrasound protocol called “The ultrasound meal accommodation test” (UMAT)[8]. In this protocol, the patient is examined in a fasting state in a seated position, leaning slightly backwards. After measuring a cross-sectional area of the antrum, the patient ingests 500 mL of a low-calorie soup, whereupon measurements are obtained at 1, 10 and 20 min postprandially. In addition, the patient registers his/her symptoms on a visual analogue scale at the same time points. The stomach is measured in three standardized sections:

1. Cross-sectional area of the antrum: Slightly right from the midline in a sagittal section, using the left liver lobe, the abdominal aorta and the superior mesenteric vein as landmarks, the area is calculated tracing the proper muscular layer of the antrum (Fig.1).

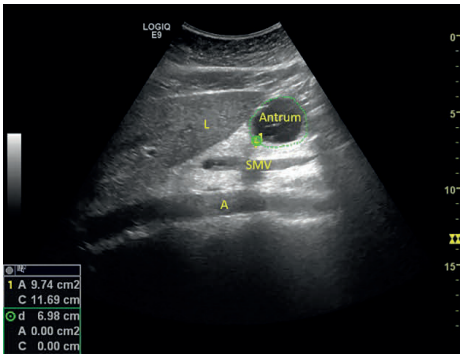

Figure 1 – Ultrasound image of the antrum after a liquid meal. In this sagittal section, we find the antrum in close relation to the left liver lobe (L) and the aorta (A) and superior mesenteric vein (SMV) which are visible posterior to the antrum serving as internal landmarks.

2. Proximal area of the stomach: In a sagittal section left of the midline, using the left liver lobe and hemidiaphragm as landmarks, the fundus of the stomach is visualized. First, a perpendicular line of 7 cm from the proximal fundus is marked, followed by a trace along the margins of the proximal stomach (Fig.2)

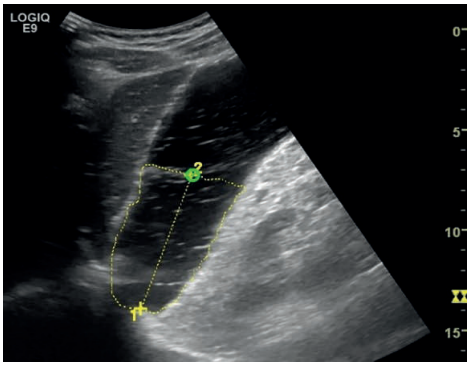

Figure 1 – Ultrasound image of the proximal stomach after a liquid meal, tracing along the upper 7 cm of the stomach.

3. Proximal diameter of the stomach: keeping the same position as in the section 2, the probe is rotated counterclockwise, and the greatest diameter of the proximal stomach is measured.

These three repeated measurements provide information on several aspects of upper GI motility: Section 1 provides information on antral size and emptying. In conditions with delayed gastric emptying, the antral area can be increased, even in a fasting state. By observing the antrum over time, antral contractions and transpyloric flow may be assessed. In gastroparesis, antral contractions may be incomplete or even absent.

Sections 2 and 3 provide information about the proximal stomach. Gastric accommodation is a reflex, occurring within minutes after ingestion. In functional dyspepsia, a typical finding is a lower proximal area and diameter compared to healthy individuals, at 1 and 10 min.

A total assessment of the ultrasound measurements over the 20 min observation time can give further insight to the physician. In a paper published in 2021, we found that patients with diabetic gastroparesis had a larger antral area in both a fasting and postprandial state, and furthermore that the proximal stomach size was affected by delayed gastric emptying). The gastroparesis patients had a slower decrease in proximal stomach size during 20 minutes after the liquid meal compared to healthy controls ($P<0.01$), and proximal stomach size at 20 minutes was correlated to scintigraphy ($r=0.510$, $P=0.001$)[9].

While upper GI motility has been extensively studied in functional dyspepsia, little has been known about gastric motility in irritable bowel syndrome. IBS is a condition with symptoms mainly arising from the colon, characterized by abdominal pain associated with bowel movements, as well as constipation, diarrhea or a mix of both. In a recent paper published by our group, we aimed to investigate upper GI motility in this patient group. We were curious if IBS patients had impaired accommodation, as the condition is closely related to functional dyspepsia. However, our findings suggest that IBS patients in general have normal gastric accommodation. The antral area, particularly in a fasting state, was however enlarged similarly to patients with functional dyspepsia[2].

In conclusion, ultrasound can be used to assess several pathophysiological mechanisms of functional gastrointestinal disorders and contributes to generation of new knowledge about this heterogenous patient group.

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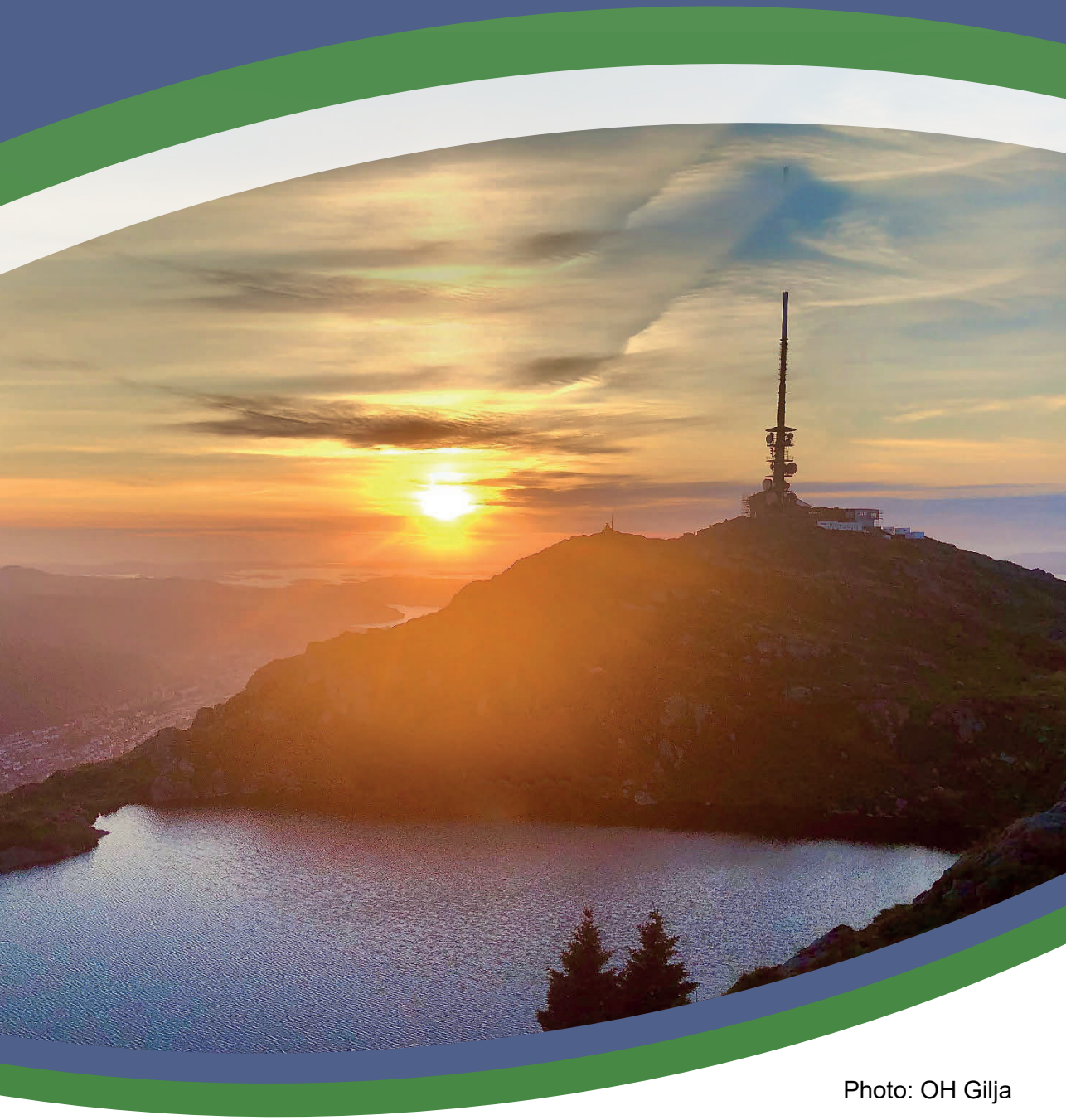

Photo: OH Gilja

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