The 3rd Romanian-German Symposium of Gastroenterology

Al 3-lea Simpozion Româno-German de Gastroenterologie

Timisoara, March 31 – April 1, 2016

Program and Abstracts

Thursday, March 31, 2016, 19.00

Official opening of the Symposium:

Museum of Art, Baroque Hall, 1, Unirii Square, Timisoara

Welcome

Prof. Dr. Monica Acalovschi, Symposium President, University of Medicine and Pharmacy, Cluj-Napoca

Prof. Dr. Ioan Sporea, Symposium President, University of Medicine and Pharmacy Timisoara

Prof. Dr. Markus Lerch, President, German Society of Gastroenterology, Digestive and Metabolic Diseases

Prof. Dr. Marius Raica, Rector, University of Medicine and Pharmacy, Timisoara

Mona Isabela Petzek, Director of the Deutsches Kulturzentrum Temeswar

Lecture

Dr. Ştefan Sorin Mureşan, Würzburg
„Principles and systems of health insurance in the Social Market Economy of Germany"

Piano concert

Visit of the Corneliu Baba Collection, Museum of Art

Welcome Cocktail, Locanda del Corso Restaurant, 10, Marasesti Str., Timisoara

Friday, April 1, 2016

Scientific Program, Senate Hall, University of Medicine and Pharmacy Timisoara

9.00-11.00 Session I. Chair: Prof. Dr. Peter Galle, Prof. Dr. Monica Acalovschi

9.00 – 9.25: *Prof. Dr. Wolfram Zoller, Stuttgart*
Colorectal cancer screening: 14 years experience in Germany (Screeningul cancerului colorectal: experienta de 14 ani din Germania)

9.25 – 9.50: *Prof. Dr. Michael Jung, Mainz*
Serrated colorectal lesions and their malignant potential – Update 2016 (Leziunile colorectale serate si potentialul lor de malignitate – Actualizare 2016)

9.50 – 10.15: *Prof. Dr. Mircea Diculescu, Bucharest*
Optimizing therapy in Inflammatory Bowel Disease (Optimizand terapia bolilor inflamatorii intestinale)

10.15 – 10.35: *Assoc. Prof. Dr. Adrian Goldiş, Timişoara*
Inflammatory bowel disease - phenotypic and regional differences: National and European trends (Boala inflamatorie intestinala – diferente fenotipice si regionale: tendinte nationale si europene)

10.35 – 11.00: *PD Dr. Anca Zimmermann, Mainz*
Check Point Inhibitors in gastro-intestinal tumors and the management of endocrine adverse events (Inhibitori Check Point in tumori gastrointestinale si managementul reactiilor adverse endocrine)

11.00 – 11.30 Coffee Break

11.30-13.30 Session II. Chair: Prof. Dr. Wolfram Zoller, Prof. Dr. Ioan Sporea

11.30 – 11.55: *Prof. Dr. Markus Lerch, Greifswald*
What causes pancreatitis? (Care este cauza pancreatitei?)

11.55 – 12.15: *Assoc. Prof. Dr. Andrada Seicean, Cluj Napoca*
Endoscopic ultrasound guided fine needle aspiration in bilio-pancreatic diseases (Aspiratia cu ac fin ghidata prin eco-endoscopie in leziunile bilio-pancreatice)

12.15 – 12.40: *Assoc. Prof. Dr. Zeno Spârchez, Cluj Napoca*
Interventional ultrasound in hepato-biliary diseases: the value of new US techniques (contrast, navigation, fusion) (Ecografia interventionala in bolile hepato-biliare: valoarea noilor tehnici ultrasonografice - contrast, navigatie, fuziune)

12.40 – 13.05: *Prof. Dr. Michael Sackmann, Bamberg*
Bile duct stenosis: diagnosis and treatment by endoscopy (Stenoza cailor biliare: diagnostic si tratament endoscopic)

13.05 – 13.30: *Prof. Dr. Marcel Tanţău, Cluj Napoca*
Endoscopic treatment of esophageal fistula (Tratamentul endoscopic al fistulelor esofagiene)

13.30 – 14.30 Lunch Break and Poster Viewing

14.30-17.00 Session III. Chair: Prof. Dr. Markus Lerch, Prof. Dr. Mircea Diculescu

14.30 – 14.55: *Prof. Dr. Peter Galle, Mainz*
Management of hepatocellular carcinoma (Managementul carcinomului hepatocelular)

14.55-15.20: *Prof. Dr. Sebastian Mueller, Heidelberg*
A novel concept of liver cirrhosis: the 'sinusoidal pressure hypothesis' (Un nou concept al cirozei hepatice: 'ipoteza presiunii sinusoidale')

15.20 – 15.45: *Prof. Dr. Ioan Sporea, Timișoara*
One or more elastographic methods for liver stiffness evaluation? (Una sau mai multe metode elastografice pentru evaluarea rigiditatii hepatice ?)

15.45–16.10: *PD Dr. Beate Niesler, Heidelberg*
Lessons learned: Resolving the enigma of genetic factors in Irritable Bowel Syndrome (Rezolvand enigma factorilor genetici in sindromul intestinului iritabil)

16.10 – 16.35: *Assoc. Prof. Dr. Paul Jürgen Porr, Sibiu*
Microbiota - friend or foe? (Microbiomul – prieten sau dusman ?)

16.35–17.00: *Prof. Dr. Monica Acalovschi, Cluj-Napoca*
Management of intrahepatic cholangiocarcinoma (Managementul colangiocarcinomului intrahepatic)

17.00: *Prof. Dr Ioan Sporea, Timisoara*
Closing remarks and the best poster award.

18.30 Dinner and wine tasting at Recas Winery (Cramele Recas)
Departure by bus at 18.30 from the Hotel Continental, 5, Revolutiei Bvd., Timisoara

Session I

Colorectal cancer screening: 14-years experience in Germany

Wolfram G. Zoller[1], Wolfram Bohle[1], Jürgen F. Riemann[2]

1) Katharinenhospital, Klinikum Stuttgart; 2) Stiftung Lebensblicke, Ludwigshafen, Germany

Since 2002, a colonoscopy performed every ten years has been an integral part of the colorectal cancer screening program in Germany, offered to all member of statutory health insurance at the age of 55, and covering a population of approximately 16.7 million people. In addition, the screening program includes standardized patient information, performed on 2,240,000 people/year, and fecal guaiac fecal occult blood test (fGOBT), performed in 4,051,000 people annually.

Approximately 395,000 screening colonoscopies were performed annually, and data from more than 1750 participating centers were centrally collected and analyzed. However, only 2 – 2.5% of the entitled members annually participated in colonoscopy. The relative rate of colonoscopy was correlated with the social status. Females participated more often than males. Therefore, from 2003 to 2012, 4,403,030 colonoscopies were performed, with simultaneous polypectomy in 31.8% of the examinations. More than 290,000 advanced adenomas were resected. Colorectal cancer was diagnosed in 42,000 patients, predominantly at a low tumor stage (UICC stage I-II: 69%). The overall complication rate of screening colonoscopy was low, with severe complications (bleeding or perforation) in approximately 0.05 – 0.2%. A Markov Model estimation revealed 180,000 prevented cases of colorectal carcinoma (1/28 of screening colonoscopies), 40,000 carcinomas detected earlier than they would have been diagnosed without screening (1/121 screening colonoscopies), and 4500 cases of over-diagnosis (1/1089 screening colonoscopies).

Epidemiological data reveals a decrease in incidence and mortality due to colorectal cancer from 1999 to 2012. In the future, the next steps will be the establishment of a more individualized screening program according to certain populations at risk for colorectal carcinoma.

Serrated colorectal lesions and their malignant potential - Update 2016

Michael Jung

Klinik für Innere Medizin und Gastroenterologie, Katholisches Klinikum Mainz, Germany

Sessile serrated lesions (adenoma/polyps) are recognized as precursors of colorectal cancer. They develop from aberrant crypt foci and progress from benign hyperplastic lesions to sessile serrated adenoma (SSA) and serrated carcinoma. Hyperplastic polyps follow a more benign course than SSA, but the histologic appearance of both types of polyps is similar. Serrated adenomas are flat with abundant mucus production and are more frequent in the right colon than in other parts of the bowel. Histologically, they show abnormal proliferation and structural dysplasia. The SSAs play a dominant role in the development of right-sided colorectal cancers.

BRAF mutations are frequently found in SSA.

In the left-sided colon, the traditional serrated adenoma (TSA) is present in 1-6% and shows a marked serrated morphology.

The prevalence of SSA in a screening population has been found to be 7-8%, and dysplasias are rare. A polyp size of ≥ 10 mm is regarded as a risk factor for proximal serrated lesions. Further predictors for cytological dysplasia or cancer are the adenomatous tissue (pit pattern III-V) and a sessile or pedunculated component. The time span until malignant progression is longer compared to classic sporadic adenomas (> 10-15 years).

Serrated adenomas are different in frequency and size in the left and the right colon. The SSAs can easily be missed in the right colon because of the flat appearance with mucus

and stool covering. They contribute to a considerable part of interval carcinomas of the colorectum. Serrated polyposis syndrome (SPS) is a rare disease, characterized by more than 20 hyperplastic polyps of any size in the entire colon or more than 5 hyperplastic polyps proximal to the sigmoid. In these cases the risk for colorectal cancer is 5 fold increased.

Guidelines therefore recommend endoscopic polypectomy of all flat lesions ≥ 5 mm in size for the right colon and > 10 mm for the left colon. Smaller SSAs in the right colon may be treated following the "resect and discard" strategy. Follow-up endoscopy after right sided polypectomy or mucosectomy in SSA without or with dysplasia should be performed up to 3 years after therapy.

Optimizing therapy in Inflammatory Bowel Disease

Mircea Diculescu, Alexandru Lupu

Carol Davila University of Medicine, Bucharest, Romania

In the past decade, incidence and prevalence of Inflammatory Bowel Disease (IBD) in Romania have increased 10 fold. The first epidemiological report in 2004 published by Gheorghe et al. estimated about 1,000 patients and actual evaluations are estimating more than 10,000. In particular, areas such as Bucharest and its surrounding county, reported in the IBDPROSPECT study more Crohn's disease cases than ulcerative colitis and also more difficult cases, which require frequently biologic therapy or a complicated surgical approach. A new epidemiological prospective study was initiated in 2014 in Bucharest and Ilfov (its surrounding county) in order to assess the real actual data.

From our previous database at the Fundeni Clinical Institute and from the IBDPROSPECT study we now have data regarding IBD management in Romania, especially in the dedicated centres. In the early 2000s, the use of 5-ASA and corticosteroids was very frequent. In the following years, an increase in the number of the patients treated with immunosuppressive drugs, especially azathioprine was registered. The era of the biological drugs then followed.

Nowadays, the classical Step-Up approach (pre-biological era) of 5-ASA, antibiotics, steroids, immunosuppressive drugs, and biologicals is changing, especially because of the new data available concerning the ratio efficacy / adverse events (mainly corticosteroid use).

Mucosal healing, deep remission, and sustained deep remission are the new targets for treatment. For obtaining better results in Romania, we have to apply more actively the ECCO (European Crohns and Colitis Organization) guidelines concerning both diagnosis and treatment in IBD. Shifting the paradigm of treatment to a good selection of cases that will need Top Down or accelerated Step-Up approach seems to be required nowadays.

Optimizing treatment in Crohn's disease and ulcerative colitis may lead to less unnecessary surgery, and lower the costs of hospitalization and treatment of difficult cases.

In conclusion, optimizing therapy in IBD in Romania is an urgent requirement in view of the increasing incidence and increasing frequency of the difficult cases diagnosed in our country.

Inflammatory bowel disease - phenotypic and regional differences: National and European trends

Adrian Goldis, Daniela Lazar

Department of Gastroenterology and Hepatology, Victor Babes University of Medicine and Pharmacy Timisoara, Romania

Inflammatory bowel diseases (IBD) represent autoimmune conditions with a relatively low incidence, but associated with a marked geographic variation, that has not been yet uniformly explained. In Europe a North-South and East-West gradient of IBD incidence seems to exist.

Starting with 2010, EpiCom, a prospective, population-based inception cohort of newly diagnosed IBD patients was elaborated in 31 European centers (14 Western and 8 Eastern European countries), covering a total background population of approximately 10.1 million. Romania was represented in this study by its western county Timiş, which comprises 664.433 inhabitants. All the patients were introduced into a web-based epidemiological database. The aim of this study was to investigate whether an East-West gradient in the incidence of IBD in Europe exists.

Overall, 1,515 patients were included during 2010, of whom 35% were diagnosed with Crohn's disease (CD), 54% with ulcerative colitis (UC) and 11% with unclassified IBD (IBDU). The median crude annual incidence rates per 100,000 in 2010 for CD were 6.5 in West and 3.1 in East, for UC 10.8 and 4.1, respectively, and for IBDU 1.9 and 0, respectively. The crude annual incidence rate per 100,000 in 2010 for IBD in the Timiş county was 4.1 (1.7 for CD and 2.4 for UC), much higher than that reported in 2004, when the incidence was 0.97/100,000 and 0.50/100,000 for UC and CD, respectively. In 2011, the annual incidence rate of IBD/100,000 in the Timiş County was 5.5.

Another study, comprising 1,085 patients diagnosed with IBD during 2004-2008 in the western part of Romania revealed a mean incidence in the 5 years studied of 3.06/100.000 new cases per year for UC and 1.05/100.000 new cases for CD. Although an increasing incidence since 2004 is observed, Romania has encountered a much lower incidence compared with our Hungarian neighbors (Veszprem province) that presented the highest Eastern European incidence of IBD (23/100,000), comparable with Western European incidence.

Inspired by these intriguing results, we developed a cross-border study (EpiRom Hu-Ro) with the Hungarian Debrecen province, including a similar population with our county. Our aim consists of comparing the incidence and phenotypic and genetic profile of these two populations regarding IBD. Genetic assessment refers to NOD2 and CARD determination for CD and UC, respectively. This is a prospective study and we do not have yet preliminary data, nevertheless interesting data could come to light.

In conclusion, there exists an East-West gradient in IBD incidence in Europe. The overall annual incidence rates in all Western European centers are roughly twice as high as the rates in all Eastern European centers for CD and UC. Although the incidence of IBD in our country has increased over the past few years, Romania still presents a low incidence of IBD, lower when compared with Western European Countries.

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Check Point Inhibitors in gastro-intestinal tumors and the management of endocrine adverse events

Anca Zimmermann

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Cytotoxic T-lymphocyte antigen-4 (CTLA-4) is a key player in the immune checkpoint system. Antibody-mediated blockade of CTLA-4 receptors lead to an increase of antitumoral immunity, through T-cell activation and proliferation. For Ipilimumab there is clinical evidence for survival benefit in melanoma. Preclinical data in murine tumor models for colon cancer showed a synergistic effect of CTLA4 blockade in combination with chemotherapy, in settings where either agent alone was not effective in inducing tumor regression. PD1 inhibitors (anti-programmed death 1 immune checkpoint inhibitors) counteract T-cell apoptosis and augment herewith the immune antitumoral response. For the PD1 inhibitor Pemprolizumab, immune-related objective response rate and immune-related progression-free survival rate in patients with progressive metastatic colon carcinoma were associated with the mismatch repair status. Immune hypophysitis is a common adverse event of the treatment with CTLA4 or PD1-inhibitors. The clinical appearance is often unspecific, with headaches and fatigue, which are often misinterpreted as being due to the underlying disease or the treatment itself.

Standardized diagnostic and therapeutic recommendations are lacking. Based on the available literature data, a summary of screening and diagnostic tools and of therapeutic strategies will be given. The role, screening start and frequency of monitoring the pituitary axis is presented. The relevance of pituitary MRI is discussed. The need for dynamic testing of the corticotrope axis to rule out central adrenal insufficiency is stressed. If confirmed, glucocorticoid substitution is promptly needed. Further directions of screening include hypothyroidism, hypogonadism and somatotrope insufficiency. However, the latter has no substitutive consequence in the context. Diabetes insipidus should be also thought of; if confirmed, treatment strategies are presented. Further treatment options are presented, discussing the pro and cons of pharmacologic versus substitutive glucocorticoid treatment.

Session II

What causes pancreatitis?

Markus M. Lerch

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Pancreatitis has now become the major reason for hospital admission in developed countries and in Germany is burdened with 1500 in-hospital deaths (more than twice the number associated with AIDS). Acute and chronic pancreatitis, of which the latter is characterized by extensive fibrogenesis [1] and distinct complications [2], are now regarded as a continuum of the same disease with different clinical manifestations. Large scale epidemiological studies have recently identified a number of environmental [3] and genetic risk factors [4]. Among them are the immoderate consumption of alcohol (which conveys a surprisingly low pancreatitis risk), as well as tobacco smoke and obesity (now regarded as independent risk factors with greater impact than alcohol). Among the protective habits are the regular consumption of fruits and vegetables, which lower the pancreatitis risk. None of these environmental factors either increases or decreases the relative risk by more than twofold from a population based incidence of ~1/10.000.

Our knowledge regarding the genetic risk factors for pancreatitis is still incomplete. Since the discovery of an association of cationic trypsinogen (*PRSS1*) mutations with the autosomal dominant form of hereditary pancreatitis, the carriers of which develop pancreatitis in 80% [4], a number of mutations in other genes have been discovered which can be regarded as risk factors, rather than directly disease causing, for pancreatitis. These mutations affect the genes of serine protease inhibitor Kazal-type 1 (*SPINK1*), Chymotrpsinogen C, Carboxypeptidase A1 and the Calcium sensing Receptor, the proteins encoded by all of which can play a role in the protease/antiprotease cascade of the pancreas. Four other genes/proteins, namely cystic fibrosis transmembrane conductance regulator (CFTR) [5], bile salt-dependent carboxyl ester lipase (CEL) [6], fucosyltransferase 2 (FUT2) and the ABO blood type B [7], probably confer their increased pancreatitis risk through mechanisms that are unrelated to intracellular proteolytic activity. On the cellular and pathophysiological level four mechanisms have emerged as being critically involved in the disease onset: premature activation of digestive proteases [8], endoplasmic reticulum stress, infiltration and activation of inflammatory cells [9] and the immune mechanisms they trigger, and impairment of secretion from the pancreatic duct [10].

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Endoscopic ultrasound guided fine needle aspiration in bilio-pancreatic diseases

Andrada Seicean

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Endoscopic ultrasound guided fine needle aspiration (EUS-FNA) is indicated in pancreatic diseases for obtaining specimens for cytology and histopathology in order to choose the most appropriate palliative radio-chemotherapy. Another indication is the differential diagnosis of the nodular pancreatic lesions, which can occur in adenocarcinomas, chronic pancreatitis, autoimmune pancreatitis, pancreatic metastases, or neuroendocrine tumors. The main limitations of the procedure are the presence of a duodenal stricture (duodenal ulcer with stenosis, tumor invasion, duodenal stenosis related to chronic pancreatitis), previous surgery (Whipple, Billroth II anastomosis or Roux-en-Y anastomosis) or in cases of coagulation disorders.

The accuracy of the diagnosis obtained by means of EUS-FNA for solid pancreatic lesions is between 85-95%. It depends on several factors, such as the type of needle, the number of passes, the presence of a cytopathologist in the room, the technical quality of processing, and the experience of the pathologist. The quite low negative predictive value (40-80%) can be increased by performing a higher number of passes, by repeating the procedure or by guiding the procedure during a contrast-enhanced EUS. The most difficult region to be reached by the echo-endoscope is the deep part of the uncinate process and it is advisable to target the periphery of the lesion in order to avoid the central necrosis. The presence of the features of chronic pancreatitis or duodenal diverticula may impede the proper visualization of the lesion and the proper position for biopsy. The placement of a plastic biliary stent at least 24 hours before the procedure does not influence the results of the EUS-FNA, but the biopsy may be difficult when a metallic stent is placed in the biliary tree. Complications are rare and rarely severe. Peritoneal seeding has been reported in very few cases.

EUS-FNA of cystic pancreatic lesions should target the cystic wall, for obtaining the best cytology result. There are increased risks of bleeding and of acute pancreatitis when compared to EUS-FNA of solid pancreatic lesions.

EUS-FNA can be easily performed for distal and medial biliary tumors, but it is difficult for proximal tumors. It is recommended to avoid EUS-FNA when the lesion is resectable, as seeding with malignant cells has been reported. Biliary strictures represent another indication for EUS-FNA, especially for distal locations. The sensitivity ofe EUS-FNA for all biliary strictures varies between 43-86%, being lower for proximal strictures.

In conclusion, this procedure is not perfect for performing biliary and pancreatic biopsies, but using contrast substances or new devices, its performance could increase.

Interventional ultrasound in hepato-biliary diseases: the value of new ultrasound techniques (contrast, navigation, fusion)

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Liver biopsy: the value of new US techniques

Ultrasound (US) is mostly used for guidance but with all the advantages offered by this imaging method, the overall sensitivity in the diagnosis of liver tumors remains around 90% [1-2].

Contrast–Enhanced Ultrasound (CEUS) as a guiding method has been shown to increase the accuracy of percutaneous biopsy (PB) in the diagnosis of liver tumors (100% vs. 86.6%, $p< 0.05$) [2]. The increased accuracy was demonstrated for small (<2cm) as well as large lesions (>4 cm) (100% vs. 71.4 % , $p< 0.05$) [2].

The image fusion of US and CT or 18F-FDG-PET/CT with electromagnetic navigation (EN) guidance for biopsy of technically challenging FDG-avid targets has demonstrated its utility for biopsy targets deemed challenging for conventional imaging guidance [3]. Electromagnetic needle tracking (EMT) was also used in US guided percutaneous liver biopsy. EMT significantly reduces needle placement time and the number of needle pullbacks in comparison with conventional methods, and also seems to make the procedure technically easier [4].

Percutaneous treatment of liver abscesses

When compared to conventional US, 95.5% of hepatic abscesses had clearer appearances on CEUS regarding the extent of necrotic or liquefied lesions seen [5]. According to the last reports, administration of US CA into the drainage catheters allows the confirmation of a correct positioning of the needle or catheter, showing possible communication between cavities in complex abscesses, or the presence of fistulas [6, 7].

Percutaneous ablation of liver tumors (RFA/ MWA)

Some liver tumors are clearly visualized on computed tomography (CT), magnetic resonance imaging (MRI), or positron emission tomography (PET) but are completely undetected with US due to their location, small size, or echogenicity [8]. In these circumstances, CEUS guided

ablation has proved to be highly effective. CEUS-guided MWA ablation for HCC inconspicuous on conventional US has an effectiveness rate of 99.05%, with a low local tumour progression rate (1.9%) and no severe complications [9].

CEUS can also be used for the early assessment of HCC after ablation. CEUS sensitivity in early assessment of efficacy is as low as 27-60% and the specificity is not 100% [10]. An early assessment of success after the theoretical end of an ablative treatment is very important since it may allow detection of areas not covered by the treatment, which will need a second insertion. Thus, in patients with a residual tumor, CEUS may facilitate the insertion of the needle in the untreated area and end the ablation at the time of initial therapy. Using this approach, it is possible to decrease the rate of partial necrosis in treated HCCs from 16.1 % to 3.8 % [11]

There are some cases in which even with CEUS the tumor cannot be visualized or its conspicuity is incomplete rendering the target only partially assessable, for example in the case of small HCCs, which often are not sufficiently hypoechoic in the delayed phase of CEUS to enable safe and accurate targeting. In order to overcome these limitations, image fusion techniques have been developed. US-CT/MRI fusion-guided ablation (internally cooled radiofrequency or microwave with standard ablation protocols) was used in 295 tumors detectable on CEUS-CT/MRI, but completely undetectable with unenhanced US and either totally incompletely undetectable with CEUS. A percentage of 95.6 % tumors were correctly targeted with successful ablation achieved in 90.2 % of cases; 5.4 % tumors were correctly targeted, but unsuccessfully ablated and 4.4 % tumors were unsuccessfully ablated due to inaccurate targeting [12].

Even by US fusion with CT/MRI, up to 13.1% of HCCs are invisible [13]. CEUS fusion with CT or MRI is effective for the percutaneous RFA of small HCCs (<2 cm) inconspicuous on fusion imaging with B-mode US. With additional use of CEUS, 83.3% of HCC nodules, initially inconspicuous on fusion imaging with B-mode US became conspicuous and 76.7% of lesions could be treated with percutaneous RFA guided by fusion imaging with CEUS [14].

Percutaneous transhepatic cholangiography and drainage

Percutaneous transhepatic biliary drainage (PTBD) is a widely accepted procedure in biliary obstruction with success rates above 90% [15]. However, when applied to patients with nondilated bile ducts, patients post left hepatic lobe resection or liver transplantation, PTBD may be associated with technical difficulties. Real-time virtual sonography is a diagnostic imaging support system that can synchronize B-mode ultrasound images in conjunction with two-dimensional multiplanar reconstruction (MPR), using a magnetic navigation system. RVS provides the same cross-sectional MPR images of the liver as US images on the same monitor screen in real time using volume data from MDCT or MRI. RVS-assisted PTBD was performed in 30 patients with obstructive jaundice. The interventions were successful in 95% of the procedures. Internal-external drainage was successful in 63% interventions [16].

A major limitation of US guided PTBD is the necessity of fluoroscopic cholangiography (FC) to determine the position of the drainage catheter and evaluate the level and degree of biliary obstruction. Intrabiliary CEUS (iCEUS) might be the potential substitute to FC in the PTBD procedure [17]. Ignee A et al. concluded that iCEUS can confirm whether the needle and catheter have been inserted in the bile ducts, determine the site, degree and cause of obstruction and assess complications. However, iCEUS could not completely replace fluoroscopy for the PTCD procedures in which an internal-external catheter or a metal stent is required [18].

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Bile duct stenosis: diagnosis and management by endoscopy

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Bile duct stenosis may be caused by various malignant or benign diseases. By patient history, laboratory chemistry and ultrasound examination, several diagnoses can be confirmed or be ruled out. Magnetic resonance cholangiography is a very helpful diagnostic tool for biliary stenosis. However, the exact diagnosis remains challenging in many cases, and definite diagnosis can frequently be obtained only by endoscopic retrograde cholangiography (ERC). Furthermore, jaundice can be relieved within the same procedure.

Prior to ERC, a stenosis of the distal bile duct can be specified by endoscopic ultrasonography (EUS). A bile duct stenosis may be further characterized to be benign or malignant by brush cytology, forceps biopsy, cholangioscopy, intraductal ultrasound and confocal endomicroscopy. Analysis of bile proteomics obtained by endoscopic aspiration has yet to be evaluated further.

In most patients, one or more stents are inserted after endoscopic sphincterotomy. In selected patients, dilation of strictures is performed by balloons or bougies. In malignant distal bile duct stenosis, available data favor self-expanding metal stents over plastic stents in terms of stent dysfunction, stent patency, repeated interventions, and even in patient survival. In addition to stenting, hilar or intrahepatic bile duct cancer may be treated by photodynamic therapy or by radiofrequency ablation. In hilar obstruction, most data favor drainage of opacified ducts, but do not support routine bi-hilar stenting. Currently, endoscopic ultrasonography-guided access to the biliary system is being evaluated and might proof helpful in selected cases.

ERCP and EUS might elucidate most causes of bile duct stenoses. Tissue sampling, cholangioscopy, and intraductal ultrasound may be added in selected cases.

Endoscopic therapy for bile duct stenosis primarily consists of stenting. In selected patients with bile duct cancer, tissue ablation by photodynamic therapy or radiofrequency ablation can be applied additionally.

Endoscopy is the essential step in diagnosis and management of bile duct stenosis.

Endoscopic treatment of esophageal fistulae

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Background. The formation of an acquired esophageal fistula (AEF) is a rare but serious complication. The proximity of the esophagus, trachea, upper mediastinal organs and large blood vessels can further complicate surgery and anaesthesia. Therefore, today the preferred treatment is a less-invasive approach, represented by the endoscopic closure of fistulae. The main causes of esophageal fistulae are iatrogenicity, malignancy and trauma, which have now superseded infection, formerly the predominant etiology of AEF.

Methods. We report a series of cases that underwent endoscopic treatment for AEF in one of the four endoscopy units in our institution. The endoscopic procedures used to treat the AEF were: endoscopic stenting with self-expanding metal stents, endoscopic closing of the hole with metal clips and over the tube clips (OVESCO).

Results. During a period of 18 months, between January 2014 and December 2015, we performed over 50 endoscopic procedures for AEF. For most of the patients, more than one procedure was needed, a total of 20 patients being treated. There were 8 cases of malignant fistulae, 4 cases of iatrogenic fistulae and 8 cases of anastomotic leakage after bariatric surgery (all of them larger than 1 cm and situated at the esogastric junction). All of the malignant fistulae were efficiently closed, 2 cases of fistulae after bariatric surgery and 1 case of iatrogenic fistula required surgical intervention.

Conclusions. The most demanding cases were those of esophageal fistulae after bariatric surgery. The most common procedure was endoscopic stenting and the most efficient one (i.e. efficiency/number of procedures) was the endoscopic closure of fistula with OVESCO. Technical and clinical success was higher when the interval between occurrence of fistula and endoscopic treatment was shorter.

Session III

Management of hepatocellular carcinoma

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Hepatocellular carcinoma (HCC) is the third most common cause of cancer-related deaths worldwide. HCC represents more than 90% of primary liver cancers. There is a growing incidence of HCC worldwide. In the Western world, HCC arises in a cirrhotic background in up to 90% of cases, and cirrhosis itself is a progressive disease that affects patient survival. Thus, outcome in patients with HCC and the chances for anti-tumoral treatment and its results are dependent not only on tumor-associated factors but also on liver function.

Assessment of tumor extension is critical for defining staging and treatment strategy and needs to be complemented by an assessment of liver function. The current EASL–EORTC GP guidelines endorse the Barcelona-Clinic Liver Cancer (BCLC) classification. It includes prognostic variables related to tumor status, liver function and health performance status along with treatment-dependent variables.

Early HCC (BCLC stage A) is defined in patients presenting single tumors >2 cm or 3 nodules <3 cm of diameter, ECOG-0 and Child–Pugh class A or B. Median survival of patients with early HCC reaches 50–70% at 5 years after resection, liver transplantation or local ablation in selected candidates.

Intermediate HCC (BCLC stage B): Untreated patients at an intermediate stage – BCLC B class (multinodular asymptomatic tumors without an invasive pattern) present a median survival of 16 months or 49% at 2 year. Chemoembolization extends the survival of these patients to a median of up to 19–20 months.

Advanced HCC (BCLC stage C): Patients with cancer related-symptoms (symptomatic tumors, ECOG 1–2), macrovascular invasion (either segmental or portal invasion) or extrahepatic spread (lymph node involvement or metastases) bear a dismal prognosis, with expected median survival times of 6 months, or 25% at 1 year. This outcome varies according to the liver functional status and other variables. The only available systemic treatment option to date is the tyrosine kinase (TK) inhibitor Sorafenib, which improves overall survival in the Western population by about 3 months.

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A novel concept of liver cirrhosis: the sinusoidal pressure hypothesis (SPH)

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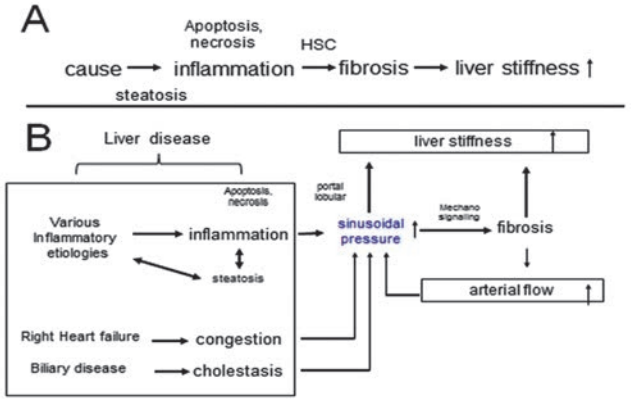
All chronic liver diseases frequently lead to scarring of the liver (cirrhosis), which is associated with progressive loss of organ function and a high mortality due to complications such as cancer or portal hypertension. The underlying molecular mechanisms are poorly understood and, except of liver transplantation, no efficient treatment strategies are available. In addition, present concepts of cirrhosis are not able to explain several key findings in cirrhotic patients e.g. A) typical macroscopic features of cirrhosis such as large fibrous septa spanning through the liver; B) why so diverse etiologies ranging from inflammatory, infectious, biliary, metabolic or even non-inflammatory congestion ultimately

lead to histologically almost identical forms of liver cirrhosis; C) why cirrhosis progresses at some stage despite treatment of the underlying cause (so-called "point of no return") and D) why no segmental cirrhosis exists despite the popular presence of segmental steatosis.

We therefore developed a novel concept over the last five years [sinusoidal pressure hypothesis (SPH)] with sinusoidal pressure (SP) as novel important mechanistic factor that determines the development of liver cirrhosis [1]. The scheme below shows SPH (B) in comparison to the conventional understanding (A).



According to SPH, all potential causes of cirrhosis whether of inflammatory or non-inflammatory origin ultimately lead to an elevated sinusoidal pressure. At the cellular level, SP is the actual driving force for the production of extracellular matrix by stretching of perisinusoidal cells e.g. hepatic stellate cells. Elevated LS is the consequence of both elevated SP and increased matrix deposition. According to SPH, fibrosis progression is determined by the degree and time of elevated SP. Arterialization of the fibrotic liver is the final key event ultimately exposing the low-pressure organ liver to pathologically high pressures.

We postulate that arterialization defines the point of no return for cirrhosis. Major support of SPH has been come from novel clinical and experimental observations using liver stiffness measurements. The presentation aims at introducing to SPH, provides recent clinical and experimental findings in support of the novel hypothesis, highlights the challenges to study pressure-associated pathologies and mechanosignaling, and briefly discusses novel attractive therapeutic strategies to treat cirrhosis.

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One or more elastographic methods for liver stiffness evaluation for daily practice

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Many years ago, tissue elastography started to be used in clinical practice as a method that could help clinicians to evaluate the severity of some diseases. Strain elastography and shear wave elastography are the two techniques used to interrogate tissues in regard to their elasticity (stiffness).

Strain elastography was used especially for breast nodules evaluation (and maybe for thyroid nodules), while shear wave elastography (SWE) mainly for the liver. Transient Elastography (TE), using a FibroScan device (EchoSens, Paris, France) became a clinical method more than 10 years ago and now it is a validated method for liver stiffness evaluation. Thousand of scientific papers have evaluated this method, showing its accuracy compared with liver biopsy in patients with chronic viral hepatitis, with NAFLD, ASH or other hepatopathies. EASL guidelines on non-invasive evaluation of fibrosis severity in chronic hepatopathies and EASL guidelines 2015 on HCV infection recommend the use of this method of evaluation. But TE is quite difficult to perform in obese patients, it is not feasible in patients with ascites and the maintenance costs are still high.

Latterly, other SWE systems have appeared on the market: point SWE and 2D SWE. All these systems are integrated into standard ultrasound machines able to perform other explorations (such as standard ultrasound, Doppler evaluation or Contrast Enhanced Ultrasound). Also, these systems can perform elastography in patients with ascites, having good feasibility and low maintenance costs.

Thus, the question arises whether it is practical to use only one or more elastographic methods for liver stiffness evaluation in daily practice?

Meta-analyses and large multicenter studies have demonstrated the non-inferiority of point SWE or 2D SWE for Radiation Force Impulse (ARFI) technology fibrosis assessment in chronic hepatopathies. Two meta-analyses regarding Virtual Touch Quantification (VTQ) using Acoustic, while for 2D SWE, a large individual patient data based meta-analysis including more than 1300 patients have been published as well as other numerous papers are appearing continuously for other systems.

Considering all of the above, we believe that this is the time to validate the other elastographic methods for liver stiffness evaluation, so that TE, point SWE or 2D SWE could be used in daily practice.

Lessons learned: Irritable Bowel Syndrome resolving the enigma of genetic factors in

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Irritable bowel syndrome (IBS) is a complex disorder of multifactorial origin but largely unknown pathogenesis. The roles of environmental, dietary and physiological factors in the patho-etiology of IBS are well established. However, despite a known and significant role of genetic components in the manifestation of IBS, the particular contribution of genetics to the development of IBS is largely unsolved [1, 2]. Genetic studies carried out in the IBS field range from family and twin studies to candidate gene approaches and, more recently, genome-wide association studies [1, 3, 4]. However, despite the use of enlarged sample sizes, increased statistical power and meta-analyses, genetics data are still scarce and/or have not been replicated in independent cohorts [1]. To date, genes involved in the serotonergic system (e.g. SLC6A4, HTR2A, HTR3A and HTR3E, as well as HTR4 encoding the serotonin transporter and the serotonin receptor genes 2A, 3A, 3E and 4), the immune system (e.g. IL-6, IL-10, TNFA and TNFSF15) and neuronal signal transduction (e.g. voltage-gated sodium channel SCN5A) have been replicated in independent studies [1, 2, 5-7]. This underscores the urgent need for replication studies in additional case-control cohorts. Epigenetic and pharmacogenetic approaches are still in their infancy: to date, only a few microRNA studies have been performed, and DNA methylation and histone modification are yet to be addressed.

The IBS genetics field currently faces a lack of large homogenised case-control cohorts recruited according to standardised and harmonised criteria. In order to address this major problem, the COST (COoperation in Science and Technology) Action BM1106 GENIEUR (GENes in Irritable Bowel Syndrome Research Network EURope) [8] was established to overcome these obstacles and to take advantage of synergies between genetics and epigenetics studies.

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Microbiota – friend or foe?

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Intestinal flora (microbiota, microbiome) is formed at birth, and develops under food influence, genetic factors, different environmental factors and becomes nearly specific for each individual. The microbial density rises from the jejunum to the colon, as does the microbial diversity, forming a perfect symbiosis with our organism. The microbiota has important metabolic, protective and structural functions.

Normally, a equilibrium exists between the different types of bacteria, a situation called eubiosis, but in different situations an irregularity of their composition can occur, which is called dysbiosis. This is the cause of acute or chronic infections of the bowel. Dysbiosis is treated by antibiotics and/or pro- pre- or sinbiotics.

A special case is the more and more frequent occurrence of a pseudomembranous colitis caused by *Clostridium difficile*, with more and more resistant bacteria. In these cases a very efficient therapy is faecal microbiota transplantation.

But microbiota has an important pathogenetic role in other diseases as well. In IBS, a different microbiota has been demonstrated as compared to that in healthy individuals, with repercussions on the reaction to stress, anxiety, behavior, memory and intestinal function.

A decreased diversity, stability and an altered composition of microbiota with more proinflammatory than immunoregulatory properties has been described also in IBD.

The implication of microbiota in carcinogenesis was also demonstrated, not only in colorectal cancer, but also in gastric and liver cancer.

There exists also a correlation between changes in microbiota and obesity; probably it is a reciprocal interrelation. Changes in microbiota influence also atherogenesis, with all its cardiovascular consequences. Microbiota influences the insulin resistance by producing butirate, especially in pregnancy diabetes so that pre- and probiotics can even be considered as potential therapeutic tools to improve gut integrity in type 1 diabetes mellitus.

The influence of microbiota on allergy occurrence has been also discussed. The hygiene theory is explained by the microbiota influence. For example, it was found that prebiotics administrated to newborns reduce atopic dermatitis by 50%. Also in rheumatoid arthritis microbiota has a pathogenetic role.

In conclusion, microbiota has multiple effects, even in some diseases which apparently have no relation to the intestinal flora. The pathological effects appear because of dysbiosis, often of iatrogenic origin. Restoration of eubiosis in these cases is essential. This can be obtained by, at least, adjuvant pre-, pro- or synbiotic therapy.

In conclusion, answering the title question, one can say that microbiota is one of our best friends: without the symbiosis between microbiota and our organism, our life would be not possible. However, in some conditions, this friend can become dangerous, influencing the local and the general immune system, with many consequences. Often this change into foe is induced by oral antibiotic therapy.

Current management of intrahepatic cholangiocarcinoma

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Cholangiocarcinoma (CCA) is the most common biliary malignancy and the second most common hepatic malignancy after hepatocellular carcinoma (HCC). Intrahepatic cholangiocarcinomas (iCCAs) are located within the hepatic parenchyma, arising from small intrahepatic bile ducts. The second order bile ducts serve as the point of separation between iCCAs and perihilar CCAs (pCCAs). The cystic duct anatomically delineates pCCAs from distal CCAs (dCCAs). The three entities are increasingly regarded as each having a distinct epidemiology, pathogenesis and management.

Incidence rates for iCCA have risen steadily across the world over the past few decades for a still not entirely elucidated reason. Intrahepatic CCA is a histologically diverse hepatobiliary malignancy, considered to develop from the malignant transformation of the cholangiocytes, and in a subset of cases from hepatic progenitor cells. A mixed HCC-iCCA tumor is increasingly recognized.

The different distribution of the risk factors at the global level is mainly responsible for the large geographic variations in the incidence rates of CCA. Presence of chronic biliary inflammation is a unifying feature for most risk factors for CCA.

In the Western world, primary sclerosing cholangitis (PSC) is the most common predisposing factor for CCA. In patients with PSC, the annual risk of development of CCA is 0.5–1.5%, and the lifetime prevalence is of 5–10%. In Southeast Asia, infection with the hepatobiliary flukes Opisthorchis viverrini and Clonorchis sinensis is the most common cause. Hepatolithiasis, frequently occurring in Asian countries, is a further risk factor for iCCA, due to secondary chronic biliary tract inflammation and to the often associated hepatobiliary flukes.

Intrahepatic CCA has also risk factors similar to HCC, including cirrhosis, chronic viral hepatitis, alcohol excess, diabetes, and obesity, and suggesting common pathogenetic pathways to all primary liver parenchymal tumors [1]. Hepatitis B virus (HBV) and hepatitis C virus (HCV) infection have been identified as potential etiologies of iCCA. HCV is a strong risk factor for HCC. As hepatocytes and cholangiocytes have the same progenitor cell, it could be postulated that HCV could induce carcinogenesis in both cell types by the same mechanism. HCV seems to be associated with iCCA in regions with relatively low prevalence of HBV infection (USA, Italy, Japan), while HBV infection is significantly associated with iCCA in China.

Intrahepatic CCA is a very aggressive tumor, with reduced overall survival. Staging systems are numerous but have not yet demonstrated a satisfactory stratification for all of the different stages [2]. Radical therapy is surgical resection, unfortunately only a minority of patients are in an operable stage at diagnosis. Adjuvant therapy is under evaluation in randomized trials. Liver transplantation is generally not recommended for iCCA or mixed HCC-iCCA, because of the poor results [1].

The expanding knowledge in the molecular classification of iCCA is currently applied in drug development for CCA. So far, iCCA is considered an orphan cancer with no established first-line treatment option. Hopefully, the latest technological advancements will improve our understanding of the main drivers of this neoplasm and favor development of more efficacious therapies [3], which could improve the dismal prognosis of iCCA.

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What are the cut-off values of liver stiffness measurements assessed by 2D-SWE.GE for predicting significant fibrosis and liver cirrhosis?

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Aim: The aim of this study was to identify reliable cut-off values of liver stiffness (LS) assessed by 2D-SWE.GE for predicting significant fibrosis (F≥2) and liver cirrhosis (F = 4), considering Transient Elastography (TE) as the reference method.

Material and Methods: Our study included 161 consecutive subjects with or without chronic hepatophaties (HBV, HCV), in whom liver stiffness (LS) was evaluated in the same session by means of two elastographic methods: Transient Elastography (TE)- FibroScan, EchoSens (M and XL probes) and the Logiq E9 system from General Electric (2D-SWE.GE). Reliable LS measurements were defined as follows: for TE – the median value of 10 measurements with a success rate of ≥60% and an interquartile range <30% and for 2D-SWE.GE - the median value of 10 measurements acquired in a homogeneous area and an interquartile range < 30%. For differentiating the stages of LF with TE we used the following cut-off values: F1 – 6, F2 – 7.2, F3 – 9.6 and F4 – 14.5 kPa [1].

Results: Reliable LS measurements by TE were obtained in 154 subjects (95.6%), and in 155 subjects (96.3%) by 2D-SWE.GE. Reliable LS measurements by both elastographic methods were obtained in 148 subjects (92%). The distribution of liver fibrosis in this cohort of patients, using TE prespecified cut-off values were: F0 - 25.6%, F1 - 4%, F2 - 5,4%, F3 - 14%, F4 - 51%. In our cohort, the 2D-SWE.GE values ranged from 3.69 to 20.48 kPa (median, 10.6 kPa). The best 2D-SWE.GE cut-off value for predicting significant fibrosis was 7.9 kPa (AUROC = 0.977 with 92.31% sensitivity and 88.64% specificity), while the best 2D-SWE.GE cut-off value for predicting liver cirrhosis was 10.7 kPa (AUROC = 0.956 with 85.53% sensitivity and 91.67% specificity).

Conclusions: The best 2D-SWE.GE cut-off values for predicting significant fibrosis (F≥2) and cirrhosis were 7.9 kPa and 10.7 kPa, respectively.

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Effect of rifaximin in chemotherapy induced gastrointestinal mucositis in rats

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Background & Aim: Oral and gastrointestinal chemotherapy-induced mucositis represents a common challenge for the oncologist, as this complication frequently requires reduction of chemotherapy doses and subsequently decreases the efficacy. The interplay between the gut tissues,

the immune system and microbiota is profoundly unbalanced by the chemotherapy, which acts on all of these components. This study assessed the protective potential of rifaximin in 5 fluoro-uracil (5-FU) induced gastrointestinal mucositis in the Wistar rats intestine.

Methods: Twenty nine adult Wistar rats were divided into 4 interventional groups of 6 animals each (A, B, C and F) and one control group (M) comprising 5 Wistar rats. Groups A, B and C received three days consecutively rifaximin by oral administration: 50 mg/kg in group A, 100 mg/kg in group B and 200 mg/kg in group C. Group F and M received only the vehicle. On the fourth day, 500mg/kg of 5-FU was administered intraperitoneally to the rats of groups A, B, C and F. A semi-quantitative histological assessment for each region of the intestine (duodenum, jejunum and colon) was obtained by rating each of the 11 histological characteristics of mucositis from 0 (normal) to 3 (severe). Semi-quantitative grades were used to measure the TLR4 immunopositivity. Statistical comparison used the Mann Whitney test, with a Bonferroni correction for alpha ($p \leq 0.016$).

Results: In rats of the group F, the most affected areas were the jejunum and the duodenum with a medium score of histological lesions of 25 (range 23-28) for jejunum and 22 for duodenum (range 21-24). The assessment of duodenal histological lesions revealed no significant difference between groups F and A (U=10, p=0.188), a significant difference between groups F and B (U=1.5, p=0.007) and F and C (U=0, p=0.003). The statistical analysis of graded microscopic degenerative lesions on the jejunum found no significant difference between groups F and A (U=10, p=0.191) and F and B (U=4.5, p=0.027), but a significant difference between F and C groups (U=0, p=0.004). Graded TLR 4 immunopositivity in the jejunum surface epithelium was significantly different between groups F and C (U=2.5, p=0.006). On the colonic mucosa, a significant difference was noted regarding microscopic degenerative lesions between groups F and A (U=0, p=0.004) and F and C (U=0, p=0.004).

Conclusion: The most severe histological lesions induced by 5-FU were observed in the jejunum and duodenum. Pretreatment with 100mg/kg or 200mg/kg rifaximin daily for three consecutive days proved efficient in preventing the mucosal degenerative lesions induced by 5-FU in the duodenum and jejunum.

Endoscopic submucosal dissection (ESD) for early gastric cancer – our first two cases

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Background. Endoscopic submucosal dissection (ESD) is an alternative for surgical "wedge resection" of early neoplastic gastric lesions. Following our training in animal *in vitro* and *in vivo* models [1-4], we started ESD for early gastric lesions.

Methods. We treated patients with early epithelial neoplastic gastric lesions with ESD. The procedure was performed under general anesthesia with a surgical team backup. We used Dual Knife (KD-650L, Olympus, Temco Romania) and an electrosurgical generator (ICC 200, ERBE, Elmed Romania) for peripheral marking, circumferential incision and dissection. Voluven (Fresenius Kabi, Romania) with adrenalin and methylene blue were used for submucosal dissection. We did not use CO2 for insufflation.

Results. Two patients were included, one with a Paris 0-Is 4cm antral lesion and another one with a Paris 0-IIac 1.5cm lesion located at the gastric angulus. Both were carcinomas in situ, R0 resections. The first patient is alive and well at 14 months after ESD, the second one is alive and well at one month.

Conclusion. Endoscopic submucosal dissection is safe and feasible in selected cases of early epithelial neoplastic lesions of the stomach.

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Contribution of contrast-enhanced ultrasound in the diagnosis and characterization of liver metastases

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Aim: The aim of this paper is to evaluate the usefulness of contrast enhanced ultrasound (CEUS) in the diagnosis and characterization of liver metastases.

Material and Method: We analyzed 423 patients with liver metastases evaluated by CEUS during 2010-2015 admitted to

the Department of Gastroenterology and Hepatology of the Emergency County Hospital of Timisoara. CEUS evaluation started from the suspicion of liver metastasis in the context of a neoplasia with single or multiple liver lesions or from the suspicion of liver metastasis during standard ultrasound. We analyzed the cause of liver metastases, their appearance in CEUS (hypo- or hypervascular) and the relationship between the primary tumor and its behavior in CEUS.

Results: The most common cause of liver metastasis was colon cancer (in 133, 31.4% of cases), followed by pancreatic cancer (56 cases, 13.2%) and gastric cancer (48 cases, 11.3%). Other causes of liver metastasis were: breast cancer (29 cases, 6.9%), oesophageal cancer (14 cases, 3.3%), ovary, uterus, pharynx, small intestine, kidney, prostate, melanoma, etc (17.3%). In 16.6% of the cases of liver metastasis, the primary tumor was not identified. In 53.4% of the cases, the appearance of metastasis in CEUS was hypervascular and 46.6% of the metastases were hypovascular. A statistically significant correlation was found only between gastric cancer and the hypervascular appearance: 29/48 hypervascular vs. 19/48 hypovascular metastases ($p = 0.0426$). A higher frequency of hypervascular metastases was associated with lung cancer: 75% vs. 25 % hypovascular ($p = 0.0554$). No relationship between the location of the tumor and the vascularity in CEUS of the liver metastases was found: metastases of colon cancer were hypovascular in 63/133 and hypervascular in 70/133 cases ($p = 0.3973$). Regarding pancreatic cancer, there were no differences in the vascularization: 28 hypervascular metastases (50%) and 28 hypovascular metastasis (50%).

Conclusions: Contrast enhanced ultrasound (CEUS) is a good diagnostic tool for liver metastases, allowing their characterization and classification according to vascularization In our study, we found no significant correlation between the primary tumor and a certain type of liver metastasis, hypo- or hypervascular, apart from gastric cancer, which more frequently correlated with hypervascular metastasis.

EUS evaluation of the severity of chronic pancreatitis: Cambridge versus Rosemont classification

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Background and Aim: Selection of chronic pancreatitis patients in a severity class for appropriate management is still under debate. The nine criteria of the Cambridge classification are widely used in ultrasound endoscopy for their ease of use. In the meantime, the new Rosemont classification, with more strict criteria, is considered to increase the inter-observer agreement of final diagnosis, but its role is still under evaluation. Our aim was to evaluate the severity of chronic pancreatitis using both the Cambridge and the Rosemont classification and comparatively assess the results.

Material and Method: For this retrospective cohort study, the endoscopy registries of the Regional Institute of Gastroenterology and Hepatology Cluj-Napoca were searched for patients suspected of chronic pancreatitis sent for endoscopic ultrasound evaluation between August 2014 and July 2015. According to the Cambridge classification, with 5 parenchymal criteria and 4 ductal criteria, a severe chronic pancreatitis was considered in cases with at least 5 positive criteria, and an incipient form in the presence of 1 or 2 criteria. The Rosemont classification uses major and minor criteria for establishing the final diagnosis of chronic pancreatitis: consistent, suggestive and indeterminate. We analyzed the correlation between the two classifications in diagnosing the severity of chronic pancreatitis. Data was analyzed using a significance level of 0.05.

Results: Eighty-four patients were recorded, with a mean age of 52.6 years (25-82 years), men/women ratio of 7/1 (22/3). Alcoholic aetiology was present in 42% of cases. Pan-pancreatic modifications were seen in 54% of the patients, while only 8% had cephalic changes. Using the Cambridge classification, 50% of the patients were considered as having severe pancreatitis, 35% as mild and 15% as having an incipient form. The Rosemont classification permitted the selection of 50% of the patients as consistent with the diagnosis of chronic pancreatitis, 26% as suggestive and 14% of patients as indeterminate. The correlation between Cambridge severe chronic pancreatitis and Rosemont consistent with chronic pancreatitis was strong (OR= 13.44, $p<0.01$, 95%CI 4.74-38.12, Spearman's Rho = 0.57, $p<0.01$), while the correlation between mild-incipient and suggestive-indeterminate status was less strong (OR= 3.17, $p=0.02$, 95%CI 1.24-8.06, Spearman's Rho =0.27, $p=0.01$).

Conclusion: For severe chronic pancreatitis (at least 5 Cambrige criteria present), the Rosemont classification allows an equivalent diagnosis. For the incipient and moderate forms of chronic pancreatitis (less than 5 Cambrige criteria present), the Rosemont clasification appears to be superior by selecting suggestive and indeterminate cases.

Special features of the hepatic abscess – a case report and a systematic review of the literature

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Aim: We aimed to highlight the difficulties of the differential diagnosis of focal liver lesions (FLL) by using different diagnostic procedures.

Methods: The patient, a 47-year old patient, who was admitted with nonspecific upper abdominal pain, weight loss and fever was investigated by: clinical examination, laboratory analysis, color Doppler ultrasound (US), CT, 99mTc-Fyton-

SPECT and 99mTc-in vivo-labeled-erythrocyte SPECT, liver angioscintigraphy (LAS), and histology. A systematic literature search of electronic databases was also performed, using MeSH headings as: "hepatic abscess and SPECT"; abstracts in English, with data regarding the scintigraphic aspects in liver abscess were included in the analysis (10 articles).

Results: The clinical and biochemical findings in our patient were: hepatomegaly, hepatocytolysis, cholestasis, a normal value of α-fetoprotein (3.3ng/ml), high serum creatinine level. The US showed a hypoechoic, inhomogeneous, well-defined, 7cm large FLL in the left lobe of the liver with an anechoic center and perigastric lymph nodes, suspected of malignancy; scintigraphy showed a hypocaptant area in the left lobe of the liver expanding towards the 5th and 8th segments, with irregular shape (99mTc-Fyton-SPECT), moderate intake of red blood cells in the 1st, 3rd and 5th segments (99mTc-in vivo-labeled-erythrocyte SPECT) and arterialization of the perfusion of the left lobe with the hepatic perfusion index of 80% (the rest of the liver had a normal index, 40%). A native CT suggested a necrotic FLL, and detected multiple retroperitoneal lymph nodes. As imaging methods could not rule out malignancy, a histologic examination was required. Surgery was limited at a diagnostic laparotomy due to the FLL location in the liver, which was a 5x3 cm large, white, hard, well-delimited tumor in the 1st segment with expansion to the 8th segment. Histopathology of the resected tumor revealed an old abscess without malignant aspects. The postoperative course was good, with remission of inflammation and the disappearance of the FLL after 3 months, a decrease of perfusion at LAS but with persistent (though decreasing) hypocaptant area at 99mTc-Fyton-SPECT even after 2 years. The final diagnosis was of a liver abscess. The peculiarity of this case was the persistence of a hypocaptant area (possibly after destruction with slow restoration of the phagocytic ability of Kupffer cells), in spite of the fact the FLL was no more visible at the US control after 3 months (drainage of purulent content after the biopsy) and no primary source of infection was found.

Conclusion: Atypical aspects of FLL occurring in the absence of a chronic liver disease, and obtained by using various imaging procedures may cause major problems of differential diagnosis and therapeutic approach.

Long term anti TNF maintenance therapy in IBD - results of a monocenter study

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Background: The management strategy for inflammatory bowel diseases (IBD) should take into account the extension, severity and behaviour of the disease [1]. There are good clinical and endoscopic results after short-term use of anti TNF in patients with IBD: up to 58% obtained clinical response after a single administration of anti TNF (ACCENT 1, 2) [2], clinical remission after one year with Adalimumab (ADA) for Crohn's disease (CD) was reached in up to 83% [3]. Medium term data showed that only 17% of patients with ulcerative colitis (UC) treated with Infliximab (IFX) came to colectomy after a median follow-up of 33 months [4].

Methods: We analyzed the medical files of 31 patients that were on biologic therapy from December 2009 to March 2016. There were 7 patients (22.6%) that received anti TNF therapy for longer than 5 years. In the final analysis we selected the files of 12 patients that were treated with anti TNF for longer or equal to 4 years.

Results: The median follow up was 60.3 months with a maximum of 87 months. Four patients had UC with extensive involvement (pancolitis) and 8 had CD (3 had stricturing pattern, 2 fistulising and 3 non-stricturing non-penetrating). The average age was 35 years.

All the patients with UC were treated with IFX (three were naive to biologics); azathioprine (AZA) was associated in three patients. Two patients (50%) had clinical and endoscopic remission for the entire follow up, two had loss of response (one with high level of antibodies to IFX). No serious adverse events were reported.

Six patients with CD were treated with IFX (50% remained in clinical and endoscopic remission for the entire follow-up) and four with ADA (66.7% had sustained remission), two switched IFX-ADA for serious allergic reactions (8.3%) or drug-induced lupus erythematous (TAILS) (8.3%). In one patient, IFX was stopped for sustained remission with disease reccurence after 6 months.

Conclusion: Anti TNF therapy maintained long term clinical and endoscopic remission in 66.7% of our patients with one case of serious allergic reaction and one case of TAILS.

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Prospective comparison of noninvasive techniques for the assessment of liver stiffness in a cohort of compensated HCV liver cirrhosis

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Background & Aim: Liver biopsy is the gold standard for diagnosing liver fibrosis, but fibrosis also can be diagnosed by means of noninvasive techniques, either biological tests (FibroTest, FibroMax, ELF, etc.) or ultrasound based elastographic techniques. It is important to accurately diagnose the severity of liver fibrosis in HCV patients, for taking a decision regarding therapy (IFN free regimens), since patients with compensated cirrhosis should be treated as soon as possible. The aim of this study was to compare the performance of five ultrasound elastographic techniques and FibroTest in diagnosing compensated HCV liver cirrhosis.

Material and Method: We performed a prospective study, including 54 consecutive patients diagnosed with HCV liver cirrhosis by means of Transient Elastography (TE)>12 kPa (1), or by clinical, biologic, ultrasonographic and endoscopic criteria. All patients had compensated cirrhosis, and none had co-infection with HBV or HIV. All patients were evaluated by five elastographic techniques in the same session, while FibroTest was performed within the same month with elastographic methods. Liver stiffness (LS) as a marker for fibrosis was assessed by: Transient Elastography [(TE)-FibroScan, EchoSens], by two Point Shear Wave elastography techniques: Virtual Touch Quantification [(VTQ)-Acuson S2000, Siemens] and ElastPQ technique-(Affinity, Philips), by 2D Shear Waves Elastography-[Aixplorer, Supersonic Imagine (SSI)] and the LOGIC E9 [General Electric (2D-SWE GE)]. In each patient we performed 10 valid measurements (VM) for TE, VTQ, ElastPQ and 2D-SWE GE, and 3 valid measurements for SSI. For each elastographic technique the median value of VM were calculated. The following published cut-offs were used to diagnose cirrhosis: TE-12 kPa [1]; VTQ-1.81 m/s [2]; ElastPQ-12 kPa [3];SSI-13.5 kPa [4]; 2D-SWE.GE-11.9 kPa [5].

Results: Our cohort included 54 subjects (34 women and 20 men), mean age 59.9±7.9 years, BMI 25.1±3.9. Reliable LS measurements by means of VTQ, ElastPQ, 2D-SWE.GE were obtained in 54/54 subjects, by means of TE were obtain in 51/54 subjects (94.4%) and by means of SSI were obtained in 49/54 subjects (90.7%), so the final analysis included 46/54 subjects (85.2%)- with all five elastographic methods valid and with FibroTest valid.

TE elastography had 95.6 % accuracy, VTQ-89.1%, ElastPQ-82.6%, 2D-SWE.GE-78.2%, SSI-86.9%, and FibroTest-82.6%. There were no significant statistical differences between FibroTest - TE (82.6% vs 95.6%, p=0.25), FibroTest-VTQ (82.6% vs 89.1%, p=0.55), FibroTest-ElastPQ (82.6% vs 82.6%, p=0.95), FibroTest-SSI (82.6% vs 86.9%, p=0.77), FibroTest- 2D-SWE.GE (82.6% vs 78.2%, p=0.78) respectively. Neither between TE-VTQ (95.6% vs 89.1%, p=0.43), TE-ElastPQ (95.6% vs 82.6%, p=0.25), TE-SSI (95.6% vs 86.9%, p=0.26), VTQ-ElastPQ (89.1% vs 82.6%, p=0.55), VTQ-SSI (89.1% vs 86.9%, p=0.99), VTQ-2D-SWE.GE (89.1% vs 78.2%, p=0.23), ElastPQ-SSI (82.6% vs 86.9%, p=0.77), ElastPQ-2D-SWE.GE (82.6% vs 78.2%, p=0.78), SSI-2D-SWE.GE (86.9% vs 78.2%, p=0.40). Significant statistical differences were found only between TE and 2D-SWE.GE (95.6% vs 78.2%, p=0.03).

Conclusion: In this preliminary study, all ultrasound-based elastographic methods had a good performance for the diagnosis of compensated liver cirrhosis and this appears to be similar with that of FibroTest.

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The value of ELASTPQ for the evaluation of liver fibrosis in patients with B and C chronic hepatopathies

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The **Aim** of this study was to evaluate the diagnostic performance of point shear wave elastography using ARFI technique-ElastPQ, in patients with viral B and viral C chronic hepatopathies, using Transient Elastography (TE) as the reference method, since it is a validated method for liver fibrosis assessment.

Material and Methods: The study included 228 consecutive subjects with chronic liver diseases (26% HBV, 74% HCV etiology), out of whom 51% had liver cirrhosis. Liver stiffness (LS) was evaluated in the same session by means of two elastographic methods: TE (Fibroscan, Echosens) and ElastPQ (Philips, Affinity) techniques. Reliable LS measurements were defined as follows: for TE – the median value of 10 LS measurements with a success rate ≥60% and an interquartile range <30%. For ElastPQ - the median value of 10 LS measurements in the liver parenchyma, at least 1 cm below the capsule, avoiding large vessels. For TE, M and XL probes were used. For differentiating between stages of liver fibrosis we used the following cut-off values for TE – mild fibrosis (F1) - 6.1

kPa, moderate fibrosis (F2) - 7.2 kPa, severe fibrosis (F3) - 9.6 kPa and for liver cirrhosis (F4) -14.5kPa [1].

Results: Reliable liver stiffness measurements were obtained in 90.7% of the patients (207/228) by means of TE and in 98.7% (225/228) with ElastPQ. In the final analysis 206 patients were included.The ElastPQ values ranged from 2.32 to 44.07 kPa (median=10.42 kPa). Based on TE cut-off values we divided our cohort into four groups: F1: 62/206 (30.1%); F2: 14/206 (6.8%) F3: 32/206(15.5%); F=4: 98/206 (47.6%). The areas under the receiver operating characteristic curve were: 0.904 ± 0.02 for patients with mild fibrosis (F1), 0.953 ±0.01 for moderate fibrosis (F2), 0.967±0.01 for severe fibrosis (F3) and 0.952±0.01 for cirrhosis. The best cut-off values for discriminating mild, moderate, severe fibrosis and cirrhosis were 6.4, 7.2, 8.5 and 10.1 kPa, respectively. In our cohort, there was a moderate correlation between measurements obtained by Transient Elastography and ElastPQ (r=0.73, p<0.001).

Conclusions: ElastPQ is a method that seems to be reliable for the diagnosis of all stages of liver fibrosis with good diagnostic accuracy.

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A single endoscopist experience in training in ERCP from a tertiary clinic in Romania

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Background & Aim: The process of training in endoscopic retrograde cholangio-pancreatography (ERCP) requires the attainment of some mandatory stages that are time consuming, and presumes a steep learning curve. The use of endoscopy simulators in this situation is seldom necessary or useful. We are presenting the 5-year experience in training in ERCP of a single endoscopist from a Romanian tertiary hospital.

Methods: We retrospectively analyzed the 942 ERCP procedures performed from January 2011 until December 2014. We divided the four-year training period in two stages: Stage I, 2011 to 2013 (458 cases) and Stage II, 2014 (484 cases) and then compared them. We examined the differences between the two stages regarding: the indication, the elderly patients rate (> 80 years old), the rate of un-intended opacification of the Wirsung duct, and the rate of early reinterventions (<14 days).

Results: From the total of 942 procedures performed, 660 (56%) had choledocholithiasis as indication, 62% during Stage I and 56% for Stage II. Only 9 cases (0.8%) were performed for pancreatic duct therapeutic procedures. The medium age of the patients was 62 years: the youngest patient was 18 year-old and the oldest one 98. Females represented 55% and men 45% of the patients. The rate of un-intended opacification of the Wirsung duct was 53%. There was a highly significant difference between the rate of Wirsung duct opacification in Stage I (74%) compared to Stage II patients (39%) ($p < 0.0001$). We noticed a significant decrease for early reinterventions after 200 ERCPs performed.

Conclusion: Learning ERCP is a long and challenging process. Reaching an optimal quality level requires a larger number of interventions than that proposed by the different endoscopy societies. The risk of postERCP pancreatitis is still increased, compared to experts, even after 400 procedures. The rate of early reinterventions decreases significantly after 200 procedures.

The genetic background in Irritable Bowel Syndrome

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Background: Irritable bowel syndrome (IBS) is a functional disorder which affects about 20% of the population and is the result of interaction between a genetic predisposition and environmental factors. The aim of this study was to evaluate the most common studied genetic polymorphisms that may have an etiological role in IBS.

Methods: PubMed was searched for studies analyzing the association between gene polymorphisms and IBS. The studies were systematized according to the gene polymorphisms detected in IBS.

Results: Taking into account the above mentioned criteria, this search resulted in a review of 12 polymorphisms, residing in 10 genes reported to be associated with the pathogenesis and the pathophysiology of IBS. Thirty-one articles published between 2002 and 2015 were included in the review. Out of these 31 articles, 16 articles (51.6%) analyzed the serotonin transporter gene while (SLC6A4), 7 articles (22.5%) analyzed the GNbeta3-C825T genotype, 3 articles (9.6%) analyzed TNFSF15 gene, while 5 articles (16.1%) evaluated genetic polymorphisms with limited evidence.

Conclusions: SLC6A4 polymorphism is the most frequently studied genetic polymorphism. Furthermore, the genetic polymorphisms of tumor necrosis factor super family gene member TL1A gene (TNFSF15), which also predispose to Crohn's disease, suggest a possible common underlying pathogenesis. Studies on functional gastrointestinal disorders and genetic polymorphisms analyzing the same genetic variants in comparably characterized case-control cohorts are also very few.