Editorial

45th Annual Meeting of the European Pancreatic Club June 26–29, 2013 Zurich, Switzerland

In 2013, the EPC celebrates its 45th anniversary meeting. This very special event will be attended by participants from 40 countries, ample proof that the Club has completed the transition from a closed circle of pancreatic enthusiasts to an international community of leading basic scientists and clinical scholars. The EPC especially welcomes and supports young participants — students and trainees — to sustain the continued efforts toward better understanding pancreatic diseases, hence providing evidence-based rationales for targeted therapies.

The program is in line with the focus of previous meetings. However, two topics have been selected that did not receive attention as independent sessions: Pathology and Transplantation. With the experimental tools using genetically modified animals, mechanistic approaches to diseases have taken a big turn upwards. The down-side, the potential disparities between rodent and human pancreatic pathophysiology have to be critically examined, otherwise, translational approaches will fail.

The second focus, pancreas transplantation, has received little attention in the past. The continuing debate on islet versus whole organ transplantation is testimony to its need for a broad discussion. Hence, this topic is emphasized in the program, albeit, few abstracts have been submitted underlining the limited effort, particularly from the ‘exocrine’ pancreatologists.

Spawned by interesting genetic studies that demonstrated functional relationships with mutant alleles, the question is raised whether all pancreatic diseases may be in part subject to a distinct genetic background. Here, experimental approaches have complemented population studies — an attractive approach since therapeutic concepts can be tested in animal studies without having to rely on heterogeneous patient cohorts.

While keeping the welcoming and approachable atmosphere typical of a club, the meeting has shed its European boundary. This year, scientists from the United States, Asia and the Pacific, account for a remarkable 42% of the total attendees. Reflecting its international nature, the 2013 EPC meeting will also feature a broad spectrum of multidisciplinary topics that fulfill the scientific interests of gastroenterologists (non-interventional, interventional therapies and diagnostic), surgeons (curative and palliative interventions), oncologists (chemotherapy), transplantation surgeons and immunologists (solid organ and islet transplantation, immunosuppression).

This anniversary of the ECP meeting is a fitting tribute to the Club’s mission to provide a unique forum where clinicians and basic scientists can effectively communicate the latest and still unpublished concepts on pancreatic pathophysiology. Special thanks go to the founding fathers of this Club who more than 45 years ago initiated a common interest group that tried to discuss the enigmatic pancreas and its devastating diseases. And of course, we thank all participants who share their insights and ideas making this meeting a platform to foster new approaches and concepts.

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Oral Presentation

0-1 Abstract id: 330.

Preoperative prediction of perioperative risk in pancreaticoduodenectomy by artificial neuronal network analysis


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Introduction: Pancreaticoduodenectomy (PD) has become a standard operation with low mortality, however perioperative morbidity remains substantial. Development of preoperative protective measures is hampered by a lack of strictly preoperative risk stratification. Predictive power of single parameters can be enhanced by optimally weighted combination of risk factors in an artificial neuronal network (ANN).

Aims: prediction of perioperative complication risk by preoperative patient assessment including clinical and radiological parameters

Patients & methods: A panel of clinical and radiological parameters were assessed retrospectively from patients with pancreaticoduodenectomy in our institution and risk factors analysis for the endpoint POPF (clinically relevant Grade B/C of ISGPS definition) were identified. Preoperatively available parameters were used for prediction of a high risk pancreas in an ANN.

Results: A total of 471 patients with PD operated from 2001 to 2012 were included. Out of twelve clinical and radiological risk factors for POPF B/C, the most powerful was a soft pancreas. When an ANN was trained to were included. Out of twelve clinical and radiological risk factors for POPF B/C, the most powerful was a soft pancreas. When an ANN was trained to

0-2 Abstract id: 327.

Perioperative outcome of minimally invasive spleen-preserving distal pancreatectomy: Results of a multicenter survey in Italy


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Introduction: In case of distal pancreatectomy for benign disease, preservation of the spleen may prevent from immunological and haematological disorders; however spleen preservation is technically demanding. As regards minimally invasive spleen-preserving distal pancreatectomy (MISPDP), only data from selected single institutions are available

Aims: To compare the perioperative outcome of MISPDP and minimally invasive distal pancreatectomy with splenectomy (MIDPS) in a multicenter Italian context.

Patients & methods: A survey was conducted among 20 institutions by the Italian Association for Study of Pancreas (AISP). Perioperative data on patients treated with minimally invasive DP in the period 2010-2011 were collected and evaluated by intent-to-treat analysis

Results: Overall 179 patients were treated by minimally invasive technique (148 laparoscopic, 31 robotic). Spleen preservation was attempted in 97 cases (54%) with a success rate of 68% (66 patients). The splenic vessels preservation technique was largely the preferred technique (93%). One of five patients undergoing the Warshaw technique required reoperation for splenectomy. No differences were observed between MISPDP and MIDPS in terms of conversion rate (14% vs 16%, p = 0.8), operative time (234 vs 227min, p = 0.53), blood loss (261 vs 295ml, p = 0.6), pts transfused (27% vs 17%, p = 0.1), morbidity (56% vs 58%, p = 0.9) and postoperative stay (9.5 vs 10.2 d, p = 0.4). Even the subgroup of patients with unplanned splenectomy had no differences in perioperative outcome with respect to patients undergoing MIDPS.

Conclusion: Despite the more demanding technique, MISPDP does not worsen perioperative outcome, even in a multicenter context. With respect to selected single institution reports, a lower success rate of splenic preservation was recorded.

0-3 Abstract id: 88.

Early predictors and outcomes of fluid sequestration in acute pancreatitis: An international multicenter study

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Introduction: The early prediction of fluid sequestration may help to select patients with acute pancreatitis (AP) for more or less aggressive fluid resuscitation.

Aims: 1) To determine early predictors of fluid sequestration in the first 48h (seq48h) after hospital admission. 2) To determine outcome associated with seq48h.

Patients & methods: The prospective AP databases from two tertiary hospitals were evaluated. Adult patients with AP were included. Seq48h was calculated by adding the total amount of fluid administered and subtracting the total amount of fluid lost in the first 48 hours of hospitalization. The predictors of seq48h were obtained in the emergency room.
Results: There were 403 episodes of AP. The median (p25-p75) seq48h was 3.2L (1.4-5.1L). The univariate analysis demonstrated that younger age, alcohol etiology, male sex, SIRS criteria, HCT and creatinine levels were significantly associated with increased seq48h. On multivariate analysis, alcohol etiology, presence of SIRS criteria and HCT were independently associated with increased seq48h. Patients with necrosis vs without necrosis had a median seq48h of 6.4 vs 3L (p<0.001), respectively. Patients with and without acute fluid collections had a median seq48h of 5.3 and 2.5L (p<0.001), respectively. Seventeen patients died (4.2%); median fluid sequestration in the patients who died was 4.2L compared to 3.3L among the patients who survived (p=0.05). Length of hospital stay was associated with Seq48h (p<0.01).

Conclusion: Alcohol etiology, presence of SIRS criteria and hemocencentration in the emergency room were independent predictors of increased seq48h. Patients with increased seq48h are at higher risk of local complications and longer length of stay.

O-4 Abstract id: 183.
Quantitative Endoscopic Ultrasound Elastography (Q-EUS-E) is an accurate method for the differential diagnosis of solid pancreatic masses: A validation study
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Introduction: We previously showed that Q-EUS-E is a useful tool for evaluating solid pancreatic masses.

Aims: Aim of the study was to validate the accuracy of a standardized Q-EUS-E protocol for the differential diagnosis of solid pancreatic masses.

Materials & methods: A prospective observational study of diagnostic accuracy, with consecutive inclusion of patients undergoing EUS for the evaluation of solid pancreatic masses was designed. EUS-elastography was performed with linear Pentax echoendoscope and Hitachi-PREIRUS. Two areas were selected for quantitative elastography: A, representative of the mass and B referring to a soft reference area. The quotient B/A (strain ratio-SR) was considered as the elastographic result. Final diagnosis was based on surgical histopathology and, in non-operated cases, on imaging SR (Karolinska University Hospital, Huddinge). Three cases with unsuccessful pancreatic cannulation were excluded.

Results: SpyGlass investigation was performed to 39 patients (median age 66 years, 38% female) with suspected IPMN (46% incidental findings). The desired part of the pancreatic duct was reached in all cases. Brush cytology was taken in 90% and directed biopsies in 4% (4% and 21% of which showed malignancy, respectively). Of 19 cases consequently operated, the most common diagnoses were IPMN (42%) and IPMC (26%). During follow-up (median 1.9 years), 3 more cases were operated due to radiologic progression after 1-3 years from pancreatoscopy. Endoscopy gave additional information and strongly contributed to clinical decision-making in up to 87% of all cases. The incidence of post-ERCP pancreatitis was 15%.

Conclusion: Peroral pancreatoscopy with directed biopsies seems promising addition to methods in evaluation of IPMN’s extent and main duct involvement. It also contributes to clinical decision-making between follow-up and surgery.

O-6 Abstract id: 54.
Preliminary results of a Swedish, MR based, screening program for individuals at risk for pancreas cancer

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Introduction: Ten % of all pancreatic cancers can be hereditary. A screening program for the individuals at risk (IAR) is recommended, but no defined surveillance modalities are available.

Aims: To analyze the frequency of findings in IAR

Patients & methods: From 2010 to 2013, all the patients with a “genetic risk” to develop pancreas cancer and referred to the Karolinska University Hospital, were included in a MR based surveillance program. All patients were investigated for the most common genetic mutation associated with pancreas cancer.

Results: Forty patients were enrolled. There were 24 female and 16 man. The mean age was 49.9. The mean length of follow-up was 12.9 (+ 11) months. The number of relatives affected by pancreas cancer was 5 in 2 patients (5%), 4 in 5 (12.5%), 3 in 17 (42.5%), 2 in 14 (35%) and 1 in 2 (5%). In 4 patients (10%) a p16 mutation was found, in 3 a BRCA 2 mutation (7.5%), in 1 a BRCA 1 mutation (2.5%). In 16 patients (40%) a suspect lesion was found in the pancreas with MR. Fourteen (35%) had an IPMN and 2 (5%) a pancreas cancer. Three patients (7.5%) required surgery (two for PDCA and one for IPMN) and the remaining 37 continue with the surveillance program.

Conclusion: During a median follow-up of just about a year, we detected pancreatic lesions in about 40% of our patients, of which three underwent surgery. Despite the relatively short time, the surveillance program in IAR seems to be effective.
0-7 Abstract id: 87.

Introduction of an oral feeding strategy after pancreatoduodenectomy enhances recovery without increasing morbidity: A before-after study

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Introduction: Pancreatoduodenectomy is associated with a high incidence of delayed gastric emptying. Data on the optimal routine feeding strategy after pancreatoduodenectomy are lacking.

Aims: To evaluate whether the introduction of an oral feeding strategy after pancreatoduodenectomy improved outcomes as compared to routine nasojejunal tube (NJT) feeding.

Patients & methods: A monocenter before-after study was performed in 102 consecutive patients undergoing pancreatoduodenectomy. In period 1 (June 2010-September 2011, n=51) the routine postoperative feeding strategy was NJT feeding versus oral feeding in period 2 (January-December 2012, n=51). The oral feeding strategy consisted of protocolized resumption of oral intake starting on the day of surgery, a NJT was only placed in case of severe preoperative malnutrition (MUST<2) or when oral intake was insufficient (<50% of daily required caloric/protein intake) on postoperative day 7, supervised by a dietitian. Analysis was by intention-to-treat.

Results: Groups were comparable for baseline characteristics. In period 1 198% received NJT feeding versus 53% in period 2 (because of preoperative malnutrition, n=198) or when oral intake was insufficient (n=7); in period 2 the time to resumption of adequate oral intake (primary outcome) significantly decreased in period 2 (12 vs. 9 days, P=0.01) as well as hospital stay (18 vs. 13 days, P=0.01). There was no difference in the incidence of Clavien-Dindo ≥3 complications, delayed gastric emptying, pancreatic fistula, postoperative haemorrhage and mortality between the groups.

Conclusion: The introduction of an oral feeding strategy after pancreateoduodenectomy reduced the time to resumption of adequate oral intake and length of hospital stay, without negative impact on overall morbidity, delayed gastric emptying or pancreatic fistula.

0-9 Abstract id: 297.

Basic amino acids induce mitochondrial injury in rat pancreatic acinar cells

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Introduction: Acute pancreatitis is the sudden inflammation of the pancreas. Large i.p. doses of basic amino acids induce AP in rodents, although the mechanisms mediating pancreatic toxicity remain unknown. Mitochondrial injury is thought to play a role in the pathomechanism.

Aims: Our aim was to get insight into the mechanisms through which basic amino acids damage the exocrine pancreas.

Materials & methods: Pancreatic acinar cells were isolated from rat pancreas with enzymatic digestion. Isolated cells were treated with different concentrations (20-60 mM) of L-arginine, L-lysine or L-ornithine. The morphology of acinar mitochondria was monitored with electron microscopy. We measured intracellular calcium concentration [Ca2+]i by microspectrofluorometry using the Ca2+-sensitive fluorescent dye FURA-2. AM. The effect of basic amino acids on basal and cerulein-stimulated amylase secretion was tested.

Results: We saw the swelling of mitochondria after incubating the cells for 2 hours with 20-60 mM basic amino acids. However, we did not see any change in the [Ca2+]i of cells, whereas marked Ca2+ signalling was detected in response to 100 μM carbachol. Basal and cerulein stimulated amylase secretion was not influenced by basic amino acids, compared to the control group.

Conclusion: Our data suggest that basic amino acids are unlikely to cause pancreatitis via calcium signalling, they do not alter amylase secretion, but they injure mitochondria. Further experiments are needed to investigate the exact pathomechanism.
**O-11 Abstract id: 281.**

The crucial role of ATP, in the inhibitory effect of ethanol and its non-oxidative metabolites on CFTR in pancreatic ductal cells

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**Introduction:** Excessive alcohol consumption causes acute pancreatitis but the mechanism involved is not well understood. Recent investigations suggest that pancreatic ductal epithelial cells (PDECs) are involved in the pathogenesis of pancreatitis. The cystic fibrosis transmembrane conductance regulator (CFTR) channel plays a major role in pancreatic ductal function both in vitro and in vivo. The localization of CFTR in wild-type and NHERF-1 KO mice was performed by immunohistochemistry. AP was induced by administration of intraperitoneal cerulein or by intraductal sodium-taurocholate. The severity of AP was evaluated by measuring histological and laboratory parameters.

**Aims:** The main aims of this study were to investigate the physiological and pathophysiological relevance of NHERF-1 expression in the pancreas.

**Materials & methods:** We analyzed the effects of NHERF-1 deletion on ductal function both in vitro and in vivo. The localization of CFTR in wild-type and NHERF-1 KO mice was performed by immunohistochemistry. AP was induced by administration of intraperitoneal cerulein or by intraductal sodium-taurocholate. The severity of AP was evaluated by measuring histological and laboratory parameters.

**Results:** NHERF-1 mRNA was markedly expressed in the pancreatic ducts of wild-type mice. We show that NHERF-1 plays a critical role in modulating the apical localization of pancreatic ductal CFTR. The trans-localization of CFTR resulted in significantly lower pancreatic ductal bicarbonate and fluid secretion. NHERF-1 expression also influenced the development of AP in both mouse models; the disease severity, especially the degree of acinar cell death, was higher in NHERF-1 knock-out vs. wild-type mice.

**Conclusion:** Our findings provide evidence for the crucial role of ductal fluid and HCO₃⁻ secretion in the protection of pancreas from acute stressors, which cause AP.

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**O-12 Abstract id: 273.**

Ethanol and fatty acids strongly decrease the activity and the expression of CFTR Cl⁻ channel in pancreatic ductal epithelial cell

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**Introduction:** Excessive ethanol consumption is one of the most common causes of acute pancreatitis. Sarles observed elevated sweat Cl⁻ concentration in alcoholic patients, which suggests decreased function of cystic fibrosis transmembrane conductance regulator (CFTR), however the effect of ethanol on pancreatic bicarbonate secretion was not investigated in details.

**Aims:** Our aim was to evaluate the effects of ethanol and non-oxidative ethanol metabolites on pancreatic ductal epithelial cells (PDEC).

**Materials & methods:** In our experiments Capan-1 cells, guinea pig PDEC and human pancreatic tissue were used. The effects of ethanol, fatty acid ethyl esters and fatty acids on intracellular pH (pHi), Ca²⁺ concentration ([Ca²⁺]i), ATP ([ATP]i) and CFTR Cl⁻ current of PDEC were measured. The expression and localization of CFTR were detected in PDEC and in human pancreatic tissue.

**Results:** The administration of 10mM ethanol stimulated pancreatic HCO₃⁻ secretion via IP₃ mediated [Ca²⁺]i elevation. In contrast, 100mM EtOH and 200µM palmitoleic acid (POA) inhibited the HCO₃⁻ secretion of PDEC and decreased the CFTR Cl⁻ current via sustained [Ca²⁺]i elevation and (ATP) depletion. We also showed that ethanol and POA significantly decreased the expression of CFTR in PDEC after 48h incubation. Moreover, the CFTR expression of intralobular pancreatic ducts was significantly decreased in acute (AP) and chronic pancreatitis (CP) patients.

**Conclusion:** These results suggest that CFTR could play an important role in the pathogenesis of alcohol induced pancreatitis. Restoration of CFTR localization and function may be potential therapeutic possibility in alcohol induced AP and CP.

This work was supported by OTKA, MTA and NFU/TÁMOP.

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**O-13 Best of APA.**

Lessons on aggressive intravenous hydration in acute pancreatitis: A meta-analysis of clinical trials

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Despite limited clinical research in humans, over the past decade, a dozen guidelines from the United States and Europe on the management of acute pancreatitis have put forth aggressive intravenous hydration at the forefront. Largely based on animal studies and indirect evidence in humans, experts have put forth the notion that aggressive intravenous hydration, early in the course, would attenuate the severity of the disease in patients with acute pancreatitis. Recent clinical studies in human subjects evaluating the efficacy of aggressive intravenous hydration have demonstrated conflicting results. The purpose of our study was to systematically review, analyze and combine the different studies in a meta-analysis to determine patterns of efficacy that may exist in order to promote appropriate fluid management in patients with acute pancreatitis.

In order to be included in the analysis, the published study needed to include patients with acute pancreatitis were enrolled in a consecutive, prospective or retrospective fashion. The study needed to provide information regarding the amount of fluid for each group, and outcome,
such as organ failure, necrosis, and mortality. The amount of fluid over the first 24-48 hours needed to be provided. When combining the various studies, the weighted mean of power (sample size) was used to determine the relative value of significance. Sensitivity analysis evaluated sample sizes, timing, type of fluids and severity of patients included.

Ten published studies fulfilled the criteria to be included in the analysis, which included 1495 patients. There were 6 retrospective, 4 prospective studies. While 3 studies concluded that aggressive hydration was beneficial, 7 studies showed no benefit and/or harm. Using a weighted mean analysis, when evaluating the effectiveness of aggressive intravenous hydration beyond 24 hours, there was no significant difference in the development of organ failure, pancreatic necrosis or mortality (OR 1.2, CI 0.4 -1.9). However, in a subgroup analysis excluding patients presenting with severe disease, there was a significant benefit to aggressive intravenous hydration in preventing organ failure and/or pancreatic necrosis (OR 1.8, CI 1.5 –2.8, p = 0.02). Additionally, there was a significant decrease in organ failure and/or pancreatic necrosis if the aggressive intravenous hydration was given early, within the first 24 hours (OR 2.1, CI 1.6 – 2.9, p= 0.03) and 6-12 hours (p = 0.02).

Based on this meta-analysis, aggressive intravenous hydration appears to be most beneficial when applied to patients with acute pancreatitis early in the course of the disease, within the first 6-24 hours, before severe disease develops. In general, there does not appear to be a benefit to aggressive hydration in patients with acute pancreatitis beyond the first 24 hours. Clinicians should recognize the importance of applying the principles of aggressive hydration as early as possible, especially to patients who have mild disease. The benefit of early aggressive hydration appears to be preventing severe disease, organ failure and/or pancreatic necrosis.

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### O-14 Abstract id: 189.

Role of tobacco as compared with alcohol in the activation of pro-inflammatory factors and cytokine release from pancreatic acinar cells

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**Introduction:** Triggering of the inflammatory process through the activation of pro-inflammatory transcription factors, as NFkappaB, and secretion of pro-inflammatory cytokines is a central pathogenic mechanism of chronic pancreatitis (CP). Previous studies suggest a role for alcohol in this inflammatory process, but the effect of tobacco, which is a recognized risk factor for CP, is unknown.

**Aims:** To analyse the effect of tobacco compared with alcohol in the activation of pro-inflammatory factors and cytokine release from pancreatic acinar cells in culture.

**Materials & methods:** Pancreatic acinar cells were isolated from Swiss mouse pancreas by enzymatic (collagenase) and mechanic degradation, filtration and centrifugation. Cells were stimulated over 3 hours with cholecystokinin (CK, positive control), alcohol (at 10,25,50,75,100 mM) and tobacco (at 0.001,0.01,0.1,0.2,0.4 mg/ml). NFkappaB activation (translocation of the subunit p65 into the nucleus) was measured by Western blot. Interleukin-1β secretion was analyzed by ELISA in cellular supernatant. Data are shown as mean and standard error, and analyzed by ANOVA test.

**Results:** Tobacco, but not alcohol, induces activation of NFkappaB (2.69±1.05 fold increase of p65 translocation at 0.1 mg/ml over the negative control). Neither tobacco nor alcohol induces interleukin-1β release, ranging between 141±1.1 pg/ml (negative control) to 201±3.6 pg/ml (tobacco 0.1 mg/ml), and to 23.8±9.2 pg/ml (ethanol 100 mM) (n.s.).

**Conclusion:** Tobacco, but not alcohol, initiates the inflammatory process through the activation of NFkappaB in acinar cells. By this mechanism, tobacco can act as a pathogenic factor in chronic pancreatitis.

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### O-15 Abstract id: 248.

Serotonin mediates pancreatic acinar cell cytoskeletal remodeling in mice

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**Introduction:** Serotonin (5-hydroxytryptamine, 5-HT) is a potent bioactive molecule involved in a variety of physiological processes. In our previous study, we showed that 5-HT is necessary for pancreatic acinar cell secretion in both physiological and pathological conditions.

**Patients & methods:** Biochemical and immunohistochemical methods were used to evaluate cytoskeletal remodeling both in vivo and in vitro. Acute pancreatitis was induced using supramaximal concentrations of cerulein in wild-type (WT) or tryptophan hydroxylase-1 knockout (THP-1/-) mice, which lack peripheral 5-HT. Cell adhesion molecules were analyzed on pancreatic tissue, isolated pancreatic acinar cells, primary rat pancreatic fibroblasts and AR42J acinar cell line.

**Results:** Reduced in vivo availability of 5-HT was associated with altered acinar actin and delayed E-cadherin dynamics under both physiological and pathological conditions. Interestingly, we observed also a re-localization of the small GTPase protein Rac-1, a key regulator of cytoskeletal remodeling. Moreover, in vitro experiments revealed that lack of 5-HT and inhibition of its re-uptake resulted in stronger cell-cell interaction compared with control cell.

**Conclusion:** These data propose that 5-HT regulates cytoskeletal dynamics in both acinar cells and pancreatic fibroblasts. Our current investigations aim to elucidate whether 5-HT, through a process named “serotonylation”, directly binds cytoskeletal components and its regulators and hence modify their activities.

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### O-16 Abstract id: 141.

Nucleotide-binding oligomerization domain protein 2 (NOD2/CARD15) mutation p.R702W predisposes to a fatal outcome of severe acute pancreatitis

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**Introduction:** Acute Pancreatitis is the most common non-malignant gastrointestinal disorder requiring hospital admission in the US and, when severe, burdened with a mortality of up to 20%. Whether genetic factors affect the disease severity is unknown.
Aims: This study investigated whether loss of function mutations in the NOD2/CARD15 gene represent risk factors for pancreatitis and its severity.

Patients & methods: In this prospective study a total of 941 patients with acute pancreatitis (761 Europe, 180 US) and 926 blood donor controls (662 Europe, 264 US) were recruited. Three established loss-of-function mutations in the NOD2/CARD15 gene were genotyped and patients were stratified according to disease severity, complications and survival.

Results: Carrier status for the p.R702W mutation, but not for the p.G908R or the p.L1007fs mutations, conferred an increased risk for severe pancreatitis with fatal outcome (11% vs. 4.5%; p<0.01 on meta-analysis, odds ratio 2.64; CI 1.35-5.05). Among patients who died from severe pancreatitis 40% carried the p.R702W allele and 16.4% the wild type allele with an odds ratio for death of 2.5 (CI 1.25-5.02) for heterozygous carriers and 9 (CI 0.8-100.93) for homozygous p.R702W carriers. Stratification for different complications found a positive association with multiple organ failure (odds ratio 4.25; CI 1.28-14.3; p<0.02), but not for infected necrosis, sepsis or single organ failure.

Conclusion: This study identifies the p.R702W mutation in NOD2/CARD15 as a genetic risk factor for developing organ complications and for mortality related to acute pancreatitis. Patients known to carry this allele may require specific measures to prevent multiple organ failure early in their disease process.

O-17 Abstract id: 201.
Effects of a mitochondria-targeted antioxidant (MitoQ) in murine experimental acute pancreatitis
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Introduction: Oxidative stress has been implicated in the pathogenesis of acute pancreatitis (AP), although recent clinical evidence has found no benefit of antioxidant therapy. This may reflect the ability of general antioxidants, such as N-acetylcysteine, to shift the balance of pancreatic acinar cell death from apoptosis to necrosis. However, the actions of newer mitochondrial-targeted antioxidants in AP remain undetermined

Aim: To evaluate MitoQ and DecylQ (a positive control that does not possess an antioxidant moiety) in a hyperstimulation murine AP model (CER-AP).

Materials & methods: AP was induced in C57BL/6J mice by hourly intraperitoneal injections of caerulein (50μg/kg × 7). MitoQ and DecylQ were administered at the 1st and 4th injections of caerulein and mice were sacrificed at 12 h to assess AP severity.

Results: MitoQ (10mg/kg and 25mg/kg) partially attenuated pancreatic local damage with ~30% reduction of the CER-AP histopathological score; oedema and inflammatory infiltration were reduced by ~40-45% but with no effect on necrosis. Interestingly, similar changes were also observed in the DecylQ-treated group. Confocal microscopy experiments showed that both Mito-Q and DecylQ were able to inhibit H2O2-induced rises of ROS in these cells. In addition, MitoQ did not mitigate serum amylose, pancreatic trypsin and myeloperoxidase activity in CER-AP, with the higher dose (25mg/kg) actually causing a further increase of serum amylose of ~92% above the CER-AP-induced elevation. Furthermore, MitoQ caused ~70% increase of lung myeloperoxidase activity per se.

Conclusion: MitoQ only partially protected against local pancreatic damage in CER-AP, with significant detrimental systemic effects evident that might preclude potential clinical application.

O-18 Abstract id: 204.
L-histidine- but not L-arginine-induced acute pancreatitis in mice involves cyclophilin D-dependent opening of mitochondrial permeability transition pore
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Introduction: Intraportal administration of large doses of L-Arginine, L-Ornithine and L-Lysine has been shown to induce acute pancreatitis (AP) in rodents, but the mechanisms have not been determined.

Aims: To determine the role of cyclophilin D-dependent opening of the mitochondrial permeability transition pore (MPTP) in amino acid-induced AP.

Materials & methods: Freshly isolated murine wild type (wt) or cyclophilin D knockout (Ppif−/−) pancreatic acinar cells were treated with amino acids and confocal cell death assay undertaken using propidium iodide (PI) fluorescence. In vivo, mice received two hourly ip injections of L-Arginine, L-Ornithine, L-Citrulline, or L-Histidine (2.0 or 4.0 g/kg), controls receiving starch solution of identical osmolarity. Mice (6 per group) were sacrificed at 72 h to assess AP severity.

Results: In vitro, 20 mM L-Arginine, L-Citrulline and L-Ornithine induced PI uptake in wt and Ppif−/− cells at similar rates, whereas 20 mM L-Histidine induced less PI uptake in Ppif−/− cells. In vivo, stach or low dose amino acid injections did not induce AP. In wt mice L-Ornithine caused rapid mortality, while L-Citrulline caused only pancreatic oedema; both L-Arginine and L-Histidine caused AP. AP in Ppif−/− mice induced by L-Histidine was significantly reduced compared to wt mice, but not following L-Arginine.

Conclusion: A new model of murine experimental AP was developed by injection of high dose L-Histidine. L-Histidine- but not L-Arginine-induced pancreatic acinar injury in mice involves cyclophilin D-dependent opening of MPTP.

O-19.
Prognostic factors in the assessment of the severity of primary acute pancreatitis
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In a prospective series of 205 patients with primary acute pancreatitis, objective grading of severity of disease has been carried out by assessment of the number of objective prognostic factors present within the first 48 hours of hospitalization. The factors were seven biochemical, one haematological and age over 55 years. The presence of at least three of these nine factors was taken to indicate severe disease. Seventy four patients were found to have severe disease and the mortality rate in this group was 24.3%. The remaining 131 patients were graded to have “mild” disease and the mortality rate in this group was 0.8%, a highly significant difference (p<0.001). The single patient who died in the group with “mild” disease had early severe hypoxaemia, but no other factor present. Mechanical ventilation was necessary in this his third and final attack. All patients who maintained a PaO2>70mmHg survived.

A smaller proportion of patients with an alcohol aetiology met the criteria for severe disease. There was also a greater mortality than in a comparable group of patients with biliary disease aetiology. Future trials of...
specific therapy in this disease must concentrate on the high risk group of patients as defined by objective criteria of severity. (An appraisal of the predictive value of individual prognostic parameters will be presented in respect of the two main aetiologies.)

O-20 Abstract id: 222.
Risk contribution of SNPs rs10273639, rs7057398, and rs12688220 to alcoholic chronic pancreatitis

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Introduction: Several pivotal studies have identified genetic risk loci for chronic pancreatitis (CP). Recently, the first genome wide association study discovered the association of variants located in the CLDN2 (rs7057398, rs12688220) and the PRSS1-PRSS2 loci (rs10273639) that alter the risk for development of sporadic and alcohol-related CP (ACP).

Aims: We aimed to replicate this finding in a large German and European cohort with ACP.

Materials & methods: Melting curve analyses were performed to genotype SNPs (rs7057398, rs12688220, and rs10273639) in 272 German ACP, 277 European ACP, and 415 French patients with idiopathic or familial CP (ICP/FP). In addition, we analysed 1826 German and 1978 European controls. Calculations were conducted using two-tailed Fisher’s Exact test for genotypes (dominant, recessive model) and for allele frequencies.

Results: T-allele of SNP rs10273639 is overrepresented in controls and, hence seems to protect against the development of ACP (OR 0.6-0.7, p-value <0.0001), but not against ICP/FP (OR 0.8, p-value 0.8). We identified that the T-allele of SNP rs12688220, is a risk factor for ACP development in male patients (p<0.001, OR 2.2-2.4, 95% CI 1.6-3.3), while the C-allele of SNP rs7057398 increases the risk in male patients to develop ACP in both cohorts (p<0.001, OR 2.2-3.5, 95% CI 1.5-3.5). These findings were not replicated in ICP/FP patients.

Conclusion: Our study identifies association of SNPs (rs7057398, rs12688220, and rs10273639) with ACP in a large European cohort. On the other hand there was no association with ICP/FP. Our findings underline the value of replication of hypothesis free studies.

O-21 Abstract id: 238.

Is the association of the p.N34S SPINK1 variant explicable by a high risk haplotype rather than the polymorphism?

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Introduction: The p.N34S polymorphism of the SPINK1 gene (PS1) is associated with idiopathic chronic pancreatitis however there is no clear functional effect of the sequence variant. It has been suggested that the polymorphism is associated with a high risk haplotype but this is widely disputed.

Aims: To identify whether a haplotype that distinguishes pancreatitis cases from controls where both cohorts have the p.N34S variant.

Patients & methods: DNA from patients with chronic pancreatitis of no known aetiology (idiopathic) and controls were analysed by pyrosequencing to test for the p.N34S variant. A 2MB region (146Mb and 148Mb of chromosome 5) surrounding the SPINK1 gene was targeted using a
custom designed liquid based capture system (SureSelect, Agilent) and sequenced using next generation sequencing (Illumina GAIIx) in 5 pancreatic disease and 5 control patients, heterozygous for the p.N34S variant. Identified sequence variants were then filtered based on their increased frequency within chronic pancreatitis patients, revealing 7 haplotype segments. Seven variants (Single Nucleotide Polymorphisms), one selected within each haplotype segment, were then screened in 38 pancreatitis patients and 20 controls (both groups heterozygous for p.N34S).

Results: 29 haplotypes were identified; only haplotype 13 was significantly associated with pancreatitis (p = 0.0009, hapscore: -3.31).

Conclusion: It is possible that a high-risk haplotype rather than a simple base variant is responsible for SPINK1 associated pancreatitis.

O-22 Abstract id: 306.
Copy number variants of carboxyl ester lipase – A role in pancreatic disease?
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Introduction: We have previously described a syndrome of exocrine and endocrine pancreatic dysfunction caused by single-base mutations in the highly polymorphic carboxyl ester lipase (CEL) gene. Copy number variations (CNV) of the CEL gene have also been reported.

Aims: We aimed to characterize the structure of CEL CNV alleles and to examine their potential functional properties.

Materials & methods: PCR, fragment analysis and sequencing were performed for genotyping of CEL CNV alleles. For functional analysis, we did transfection of human embryonic kidney (HEK293) and mouse acinar (266-6) cells, protein deglycosylation, Western blotting, pulse-chase analysis, enzyme activity measurements, immunostaining, and confocal microscopy.

Results: We identified and fine-mapped three recombined CEL CNV alleles, two with gene duplication and one with a deletion. These alleles have all probably arisen from non-allelic, homologous recombination events between CEL and the neighbouring CEL pseudogene (CELP). The deletion allele encodes a CEL protein with a truncated C-terminal end. This protein showed reduced glycosylation, secretion and enzyme activity as compared with the CEL wild-type protein. In addition, the truncated protein exhibited a tendency to accumulate inside the cell, and confocal microscopy indicated that it localized to intracellular bodies in HEK293 cells.

Conclusion: We have determined the structure of three recombined CEL alleles. One of them encodes a truncated CEL protein, which showed impaired functional properties in transfected cells. Further investigations are now needed to examine whether this protein variant has a role in pancreatic disease.

O-23 Abstract id: 245.
Clinical, morphological and functional aspects of patients suffering from pancreatitis associated with mutations of CFTR and SPINK1 genes
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Introduction: Sporadic pancreatitis may be associated with mutations of CFTR and SPINK1 genes. Few data are present in literature about clinical, instrumental and functional profiles of pancreatitis associated with CFTR GM compared to SPINK1 GM.

Aims: To evaluate pancreatitis associated with CFTR Vs SPINK1 GM.

Patients & methods: Data from patients suffering from pancreatitis associated with GM were studied. The diagnosis of GM was gathered by investigation on 35 CFTR GM or complete gene sequencing and the 2 main SPINK1 GM (N34S and P55I). Patients were divided in 3 groups: CFTR− (single CFTR GM), CFTR−D (compound CFTR GM) and SPINK1 (single or double SPINK1 GM).

Results: 114 pts (59 M, 45 F) were studied, 72(63.2%) in CFTR-S group(45 M, 27 F, mean age 31.1±14.6 yrs), 23(20.2%) in CFTR-D group(12 M, 11 F, mean age 29.3±16.4 yrs) and 19(16.7%) in SPINK1 group(12 M, 7 F, mean age 30.5±18.3 yrs). 118 CFTR GM were found in 95 pts and 21 N34S SPINK1 GM in 20 pts. 17 pts(15%) suffered from painless pancreatitis. No differences were observed in episodes of pancreatitis, need for an endoscopic approach, evolution toward pancreatic insufficiency among groups. However, a diagnosis of chronic pancreatitis(p<0.05) and onset of calcifications(p<0.01) were more frequently observed in SPINK1 group. 24 pts(21%) underwent surgery, 12 derivative-type and 12 demolitive-type. 6 pts developed a pancreatic neoplasia(4 adenocarcinoma and 2 IPMNs) at a mean age of 58 yrs(range 48–72), and 4 patients died for pancreatic adenocarcinoma.

Conclusion: Pancreatitis associated with SPINK1 gene mutations seems to differ from that associated with CFTR gene mutations.

Epigenetic regulation of autophagosome formation in pancreatic cancer cells by the methyltransferase G9a
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Introduction: Macroautophagy is a highly conserved cellular process involved in the clearance of proteins and organelles, impacting several cellular and developmental functions including cell growth, homeostasis, and immunity. Due to its integral function in these vital processes it is not surprising that macroautophagy has been implicated in diseases such as cancer and neurodegenerative disorders.

Aims: Although the cytoplasmic network leading to macroautophagy induced by starvation, hypoxia, or receptor stimulation is widely studied, and recent publications have identified transcription factors involved in the induction of autophagy, the mechanisms regulating chromatin reorganization that initiate and maintain the macroautophagy process have not been elucidated.

Materials & methods: We performed ChIP, Array, qRT-PCR, WB, and IF in cancer cells, MEFs, and naive human T-cells.

Results: Here we provide experimental evidence that modulation of the chromatin landscape in pancreatic cancer cells facilitated by the methyltransferase G9a regulates the expression of key players in autophagosome formation, a crucial step in the process of macroautophagy. We show that G9a associates with, and epigenetically represses the MAP1LC3B (refers to LC3B), WPI1 and TP53INP2 (refers to Diabetes and Obesity Regulated - DOR) gene promoters through histone methylation under normal conditions, but G9a repressive histone marks are removed during starvation and T-cell stimulation, two processes that induce macroautophagy. Interestingly, pharmacological inhibition or RNA-mediated suppression of G9a induces autophagosome formation, but is not sufficient to complete the autophagic flux, which requires an additional signal following mTOR inhibition.

Conclusion: Together these findings provide evidence that epigenetic control in pancreatic cancer represents an important mechanism during the regulation of macroautophagy.
O-25 Abstract id: 115.

Preoperative characteristics of patients with presumed pancreatic cancer but ultimately benign disease: A multicenter series of 344 pancreatoduodenectomies


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Introduction: Differentiation between malignant and benign pancreatic tumours can be difficult. Consequently, a proportion of patients undergoing pancreatoduodenectomy for suspected malignancy will ultimately have benign disease. A predictive model might prevent unnecessary pancreatoduodenectomies in a subgroup of these patients.

Aims: To compare preoperative clinical and imaging characteristics of patients with unexpected benign pathology after pancreatoduodenectomy with those of patients with confirmed (pre)malignant disease.

Patients & methods: We performed a multicenter retrospective cohort study in 1629 consecutive patients undergoing pancreatoduodenectomy for suspected malignancy between 2003 and 2010. Preoperative characteristics were compared in a 1:3 benign: malignant ratio. Malignant cases were randomly selected from the entire cohort. A multivariable logistic regression prediction model was constructed to predict benign disease.

Results: Out of 340 pancreatic resections performed from 2000 to 2012, twenty-nine patients were identified who underwent a pancreatoduodenectomy with PV-SMV resection with histologically proven venous tumor in- filtration. Postoperative mortality occurred in 3 patients after PV-SMV resection and in 2 patients without venous resection. Postoperative morbidity was 83% and 65%, respectively (p=0.23). Of note, bleeding complications were not
significantly different. Median survival, 1-year survival and 3-year survival was 23 months, 60% and 33% in case of PV-SMV invasion compared to 12 months, 56% and 28% without venous resection (p=0.68).

**Conclusion:** Histologically proven venous invasion in patients with pancreatic adenocarcinoma is not associated with an impaired long-term survival. Portal vein infiltration can probably be considered as late phenomenon, and it is rather associated with local tumor growth than with biologic aggressiveness of pancreatic adenocarcinoma.

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O-28 Abstract id: 171.

Is a watch and wait strategy justified in patients with small non-functional pancreatic neuroendocrine tumors?

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**Introduction:** Management of patients with small (≤ 2 cm) asymptomatic pancreatic neuroendocrine tumors (pNETs) is still controversial. Recent European guidelines suggest that the risk/benefit ratio of surgical resection is questionable and that a “watch and wait” strategy might be justified.

**Aims:** To study natural history of small pNETs

**Patients & methods:** Retrospective study in 2 European Centers including asymptomatic patients with a sporadic non-functioning pNET (pathological confirmation and/or positive somatostatin receptor imaging), ≤ 2 cm, without locoregional or distant involvement. Patients underwent at least annually one imaging procedure.

**Results:** 47 patients (37 female), median age 60 [31-82] years were included. Median lesion size was 12 [5-20] mm. The tumor was located in the pancreatic head, corpus and tail in 47, 36 and 17 %, respectively. EUS-FNB was performed in 40% of the patients, and confirmed grade 1 pNET in all cases. Somatostatin receptor imaging was positive in 75%. After a mean follow-up of 36 [2-118] months, a ≥ 20 % increase in size was observed in 8 pts (17%), 7 of whom underwent surgery. All had grade 1 tumors without locoregional or distant involvement. Post operative morbidity was seen in 3/7 pts (42.8%).

**Conclusion:** After a mean 3-year follow-up, no significant increase in size was observed in 83 % of the patients with small asymptomatic pNETs. Surgical intervention at time of size increase is safe and allows resection of still non aggressive tumors. Watch and wait strategy seems justified in these patients.

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O-29 Abstract id: 184.

Dacarbazine chemotherapy in pancreatic NET

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**Introduction:** Streptozocin based chemotherapies are widely used in well-differentiated pancreatic neuroendocrine tumors (pNET). Dacarbazine (DTIC) can easily be applied in an outpatient setting, but data on efficacy are limited.

**Aims:** Analysis of the efficacy of chemotherapy with DTIC in patients with progressive metastasized neuroendocrine tumors of the pancreas (pNET) and the predictive value of MGMT status.

**Patients & methods:** 51 patients were enrolled in this open trial. 8 courses of DTIC (650mg/m² every 4 weeks) were administered in median (range 1 - 46). For all but 4 pts DTIC was at least second line therapy. The MGMT expression was measured before therapy in 16 pts by immuno-histochemistry using paraffin embedded tissues.

**Results:** A partial regression (PR) could be documented in 16 pts (31%) lasting in median 26 months (range 6 – 96), Stable disease (SD) was observed in 18 pts (35%), it lasted in median 15 months (range 3 - 40).

Further progression occurred in 17 pts. Side effects were common, but were usually mild (grade 1-2). No grade 3 hematotox. was seen. There was no correlation detectable between MGMT expression and the response to DTIC therapy.

**Conclusion:** DTIC demonstrated efficacy in patients with progressive well-differentiated pNET with clinical benefit (PR and SD) in 66%. Side effects were common, but mild. MGMT deficiency was not a reliable predictor of response to DTIC therapy.

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O-30 Abstract id: 89.

Pancreatectomy with major arterial resection

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**Introduction:** Major arterial involvement is considered an absolute contraindication to resection in pancreatic cancer (PDAC).

**Aims:** We herein report our experience with 27 patients undergoing pancreatectomy plus resection of a segment of major peripancreatic arteries.

**Patients & methods:** Between 01/1993-03/2012, 27 patients were selected.

**Results:** 12/27 were males; mean age was 64 years. Two total pancreatectomy were performed, 6 pancreatecoduodenectomy and 19 distal splenopancreatectomy.

Celiac axis (CA) was resected in 14 patients, hepatic artery (HA) in 9, CA+HA in 3, and superior mesenteric artery in 1. Arterial reconstruction was required in 9. In-hospital-mortality was 3.7%, overall-morbidity 54.2%. 2/27 underwent neoadjuvant-chemotherapy and 17 completed the adjuvant-chemotherapy.

Final pathology disclosed PDAC in 18 patients. All resections were R0. Arterial involvement was proven in 10 patients: tumor reached the adventitia in 4, the media in 4, the intima in 2.

After a mean follow-up period of 115months, median overall-survival was 22months (1-232). Survival at 1, 3, 5 years was 66.7%, 29.6%, 10%. All patients died from distant metastasis without local recurrence. 25% of the PDAC-patients was alive at 3 years-after-surgery and one at 5 year (median-survival 22.5months). Median-survival of the 17 without infiltration was 22months as compared with 19.5 in patients with infiltration (p= NS). Equivalent figures for PDAC–patients were 22months vs. 24 (p=NS)

**Conclusion:** Resection remains key to achieve long-term survival. The isolated involvement of CA and/or HA may reflect tumor location rather than tumor biology.

Under this rare circumstances resection may be pursued especially in the modern era of neoadjuvant therapies.

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O-31 Abstract id: 95.

1010 Consecutive cases of pancreaticoduodenectomy

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**Introduction:** Pancreatecoduodenectomy (PD) is one of the most challenging procedures in general surgery. Better outcomes were reported in experienced hands and in high-volume centers.

**Aims:** To investigate short- and long-term outcomes after PD for periampullary lesions in a tertiary teaching hospital in China.

**Patients & methods:** From January 1986 to April 2012, 1010 patients underwent open PD in our hospital, including 711 cases of classic PD and
299 pylorus-preserving PD (PPPD). Thirty-seven cases were combined with resection of additional organs or major vessels. Data were reviewed and analyzed in retrospective way.

**Results:** There were 612 male and 398 female patients in this group, with mean age of 57.3±11.8 year-old. The most common pathological diagnosis were pancreatic adenocarcinomas (392/1010, 38.8%), ampullary adenocarcinomas (262/1010, 25.9%) and duodenal adenocarcinomas (144/1010, 14.3%). Intraoperative data showed a mean operation time of 312±73min and a mean estimated blood loss of 575±307mL. The most frequent postoperative complications were grade B-C delayed gastric emptying (226/1010, 22.4%), hemorrhage (102/1010, 10.1%), pancreatic fistula (101/1010, 10%), chyle fistula (71/1010, 7.0%), and intraabdominal infection (49/1010, 4.9%). Reoperation occurred in 38 patients (38/1010, 3.8%). Thirty-days mortality rate was 0.6% (6/1010). Length of postoperative hospital stay was 19.7±10.5 days.

**Conclusion:** Though its mortality rate dropped to less than 1%, PD or PPPD remains a challenging procedure for surgeons, for its substantial postoperative complication rates. Technique proficiency may improve the outcomes.

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**O-32 Abstract id: 218.**

Pancreatic Exocrine Insufficiency (PEI) in chronic pancreatitis (CP) and cystic fibrosis (CF) patients: Combining clinician insights and existing literature to develop a conceptual model to aid in the identification and management of PEI

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**Introduction:** PEI occurs when pancreatic exocrine secretions are inadequate to maintain normal digestive function, resulting in nutrient malabsorption. PEI is most commonly recognized in adults with CP and children with CF.

**Aims:** To develop a conceptual model capturing the burden of PEI and explore clinicians’ experience of treating PEI.

**Materials & methods:** A PEI conceptual model was developed through a literature search and review of patient-reported outcomes. 10 specialists in France, Germany and England were interviewed with open-ended questions exploring symptoms, diagnosis, treatment and consequences of PEI. Interviews were qualitatively analyzed and concepts were mapped against the conceptual model.

**Results:** The most common diagnostic method used was the faecal elastase test. However, two clinicians stated that diagnostic tests were not always conducted due to costs or patients’ preference. CF patients were often diagnosed and treated immediately upon presenting with PEI symptoms. PEI was thought to be underdiagnosed in CP patients. Clinician reported symptoms were often not conducted due to costs or patients’ preference. CF patients were often diagnosed and treated immediately upon presenting with PEI symptoms. PEI was thought to be underdiagnosed. 

**Conclusion:** Reliance on clinical signs and symptoms for diagnosis of PEI suggests a need for a specific tool to screen for symptoms in a standardized and reliable way. Adherence concerns indicate a need for a tool to aid clinician-patient communication and disease management.

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**O-33 Abstract id: 316.**

Disruption of fractalkine/CX3CR1 signalling attenuates pancreatic pain in experimental chronic pancreatitis

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**Introduction:** Chronic pancreatitis (CP) is a chronic inflammatory condition of the pancreas leading to severe pain and fibrosis. Fractalkine is a chemokine that chemotaxtacts inflammatory cells through its highly selective receptor CX3CR1 and has been suggested to aggravate pancreatic inflammation. Fractalkine is moreover known to be expressed on spinal neurons and sensory afferents where it has shown major pain-modulatory effects in different experimental pain states.

**Aims:** We aimed to investigate the course of experimental chronic pancreatitis in CX3CR1−/− deficient mice and the potential therapeutic implications of a CX3CR1 small molecule inhibitor.

**Materials & methods:** CP was induced in CX3CR1-knockout and wild-type mice by repetitive intraperitoneal cerulein injections. Treatment groups received an orally available small molecule CX3CR1 inhibitor. Hyperalgesia was assessed by systematic behavioural observation, locomotion analysis, and measurement of abdominal mechanical sensitivity. Pancreatic tissue was harvested after sacrifice for further analyses.

**Results:** Both CX3CR1-knockout and CX3CR1-blocking treated mice showed significantly less pain related behaviour (p < 0.0001) and significantly less weight loss (p < 0.01) when compared to their wild-type controls, with a clear dose-response correlation in the treated mice. This reduction in pain related behaviour was confirmed in IHC and WB analysis of pain markers. Unexpectedly, there was no difference in inflammatory cell infiltrations, fibrosis, Amylase/Lipase levels, and Trypsin/MP0 activity.

**Conclusion:** Fractalkine/CX3CR1 signalling seems to be crucial in initiating chronic pancreatic hyperalgesia. It does however not seem to have a direct effect on inflammatory cell infiltration and fibrosis. Nevertheless, these novel findings reveal CX3CR1 as a promising new target for the treatment of chronic pancreatic pain.

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**O-34 Abstract id: 215.**

The development of fibrosis in a novel model of chronic pancreatitis is mediated by complement factor C5

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**Introduction:** Chronic pancreatitis is accompanied with the loss of exocrine function and the development of fibrosis. The presence of complement factor 5 (C5) is a newly established murine model of chronic pancreatitis and compared it to respective caerulein injections.

**Aims:** We investigate the effect of complement factor 5 (C5) in a newly established murine model of chronic pancreatitis and compared it to respective caerulein injections.

**Materials & methods:** Chronic pancreatitis was induced in C5−/− and C5+/+ mice by ligation of the pancreatic duct in the body of the organ (leaving the head unaffected) and a single supramaximal caerulein injection. Animals were sacrificed 21 days after ligation. As a second model we used repetitive supramaximal caerulein stimulation over 10 weeks. We used serum amylase and lipase as markers for pancreatic damage, collagen as a marker for fibrosis and histology for morphological evaluation. Isolated pancreatic stellate cells (PSCs) were stimulated with C5a in vitro.
Results: Pancreatic damage in the initial phase was comparable in both animal strains. In contrast to the early phase, C5−/− mice displayed reduced pancreatic fibrosis in both models. Histology showed decreased collagen I and α smooth muscle actin (αSMA) staining. Also the amount of Ki67 positive cells was decreased in C5-deleted animals. In pancreatic tissue of wild type animals with chronic pancreatitis C5a receptor and αSMA positive PSCs were observed by fluorescence staining. Isolated PSCs could be activated with C5a showing increased αSMA expression and decreased proliferation.

Conclusion: C5 is an important regulator for the development of pancreatic fibrosis during chronic pancreatitis, but does not contribute to the severity of the disease during the acute phase. C5a has direct effects on fibrosis by activating PSCs.

O-35 Best of APA.

Triptolide enriches for CD133+ “stem-like” tumor initiating cells in pancreatic cancer
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Background: Pancreatic Ductal Adenocarcinoma (PDAC) is one of the most devastating human malignancies with patients having a dismal prognosis. Resistance to chemotherapy is thought to be a major cause of treatment failure in PDAC patients. Recent studies suggest that PDAC is driven by a small population of cancer stem cells (CSCs) responsible for tumor initiation and propagation. At present, conventional therapy is directed towards rapidly dividing PDAC cells and thus fails to target CSCs that drive tumorigenesis resulting in poor survival rates. CD133 has been directed towards rapidly dividing PDAC cells and thus fails to target CSCs that drive tumorigenesis resulting in poor survival rates. CD133 has been enriched for CD133 expression in PDAC cells in culture and also promotes tumor initiation and propagation. At present, conventional therapy is driven by a small population of cancer stem cells (CSCs) responsible for tumor initiation and propagation. At present, conventional therapy is driven by a small population of cancer stem cells (CSCs) responsible for tumor initiation and propagation. At present, conventional therapy is driven by a small population of cancer stem cells (CSCs) responsible for tumor initiation and propagation. At present, conventional therapy is driven by a small population of cancer stem cells (CSCs) responsible for tumor initiation and propagation. At present, conventional therapy is driven by a small population of cancer stem cells (CSCs) responsible for tumor initiation and propagation.

Results:
PDAC cells Mia-PACA2, S2VP10 and AsPC1 were treated with low dose (12.5nM) triptolide (12T cells) for 7 days. The surviving cells were recovered briefly in drug-free growth media and then transferred to CSM-CD133+ cells in both CSM and 12T showed greater colony forming and sphere forming ability. Consistent with above observation, when 500 cells were injected subcutaneously in mice, CD133+ cells from CSM or 12T did not form any tumors whereas CD133+ cells from both groups showed tumor formation. Further, 12T-CD133+ cells showed an increased tumor progression compared to CD133- cells from each group, with 12T-CD133+ cells showing higher colony forming ability.

Conclusion: Our results indicated that Triptolide on one hand enhanced the severity of the disease during the acute phase. C5a has direct effects on fibrosis by activating PSCs.

O-37 Abstract id: 232.

Characterization of putative precursor lesions of familial pancreatic cancer
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Introduction: 10% of patients with pancreatic ductal adenocarcinoma (PDAC) show a familial background. Ductal precursor lesions such as PanIN and IPMN are more common in patients with a family history of PDAC (FPC) than in patients with sporadic disease. However, acinar cells might also be involved in PDAC origin, as suggested by genetically engineered mouse models and by the occurrence of atypical flat lesions (ALF), which derive from tubular cell complexes (TC) in areas of acinar-ductal metaplasia (ADM) in FPC patients.

Aims: Aim of this study is to elucidate whether AFL commonly occur in pancreata of FPC individuals and whether they represent a PanIN-independent precursor of PDAC.

Materials & methods: We screened pancreatic specimens from six healthy FPC individuals in order to look for PanIN, IPMN, TC and AFL. Immunostaining for MUC1, MUC2, MUC5, MUC6, p53, SMAD4, Her2neu, p16, Notch1, E-cadherin and K-Ras exon 2 mutation analysis were performed.

Results: In addition to ductal precursor lesions such as multifocal PanIN and multifocal gastric type IPMN, all pancreata showed AFL in ADM areas that displayed a perilesional active stromal reaction. AFL showed a MUC1+, MUC2+, MUC5+, p16+, and Notch1+ phenotype and a focally elevated Ki-67 proliferation index. 69% of PanIN1 and 2 as well as all PanIN and all IPMN proliferation index of Kras mutations. 65% of TC and AFL were KRAS-mutated.

Conclusion: Pancreatic lesions from FPC individuals not only contain PanNs and IPMNs but also AFL. These results suggest a potentially alternative pathway of carcinogenesis in FPC that starts in ADM areas.

O-38 Abstract id: 333.

Analysis of the extracellular matrix protein peristin in early pancreatic carcinogenesis
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Introduction: The stromal activation in pancreatic ductal adenocarcinoma (PDAC) typically starts around preneoplastic lesions such as acinar-to-ductal metaplasia (ADMs) and atypical flat lesions (AFLs). The main cell population contributing to this stromal response are pancreatic stellate cells (PSCs). Periostin, an extracellular matrix protein (ECM), produced by activated PSCs has been shown to play an important role in the early activation of pancreatic stellate cells and in the perpetuation of their activated status.

Aims: To study the role of periostin in early pancreatic tumor events and epithelial cell metaplasia, periostin knock out mice were used in pancreatic regeneration experiments.

Materials & methods: Pancreatic injury was induced by cerulein injections in B6129SF2/J wild type and periostin global knock out mice. Regeneration capacity and immune cell infiltration was assessed at different time points by HE, a-amylose and CD45 staining, respectively. 3D cell culture with wild type acinar cells treated with murine recombinant periostin was performed to assess the influence of periostin on ADM formation.

Results: Regeneration experiments revealed that periostin knockout mice regenerate worse after induction of pancreatitis and show more infiltrated immune cells 21 days after the last cerulein injection. In vitro studies demonstrated that recombinant periostin accelerates the development of ADM in a 3D cell culture model.

Conclusion: The lack of periostin promotes a worse pancreatic regeneration after cerulein induced pancreatic injury. Moreover, periostin affects the development of ADM formation. In further experiments pancreatic tumorigenesis will be studied using oncogenic kras expressing p48Cre1−;LSL-KrasG12D−;Pstn−/− mice.

CUX1 – A marker of invasive phenotype in neuroendocrine tumors of the pancreas

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Introduction: Previously, we identified the transcription factor CUX1 as a mediator of proliferation, resistance to apoptosis, invasiveness and angiogenesis in neuroendocrine tumor cells. However, the molecular signaling pathways driving CUX1 effects in neuroendocrine neoplasias remain to be elucidated.

Aims: Characterization of CUX1-dependent signaling pathways mediating its tumor-promoting effect in vitro and in vivo.

Materials & methods: We performed a RNA profiler comprising genes involved in neoplastic transformation, invasion and angiogenesis. CUX1 effects were evaluated in vivo by xenograft experiments. Furthermore, CUX1 expression was assessed in a tissue microarray of human insulinomas.

Results: Several target genes mediating tumour invasion and metastasis were upregulated by CUX1, among them MMP2, MMP9, TGFß and HIF-1α. In vivo, CUX1 overexpression led to an increased tumour volume accompanied by a higher proliferation index and increased microvessel density. Under hypoxic conditions, CUX1-expressing cells showed increased HIF-1α levels, suggesting a role of CUX1 in mediating HIF-dependent escape mechanisms in tumor hypoxia. Immunohistochemically, malignant insulinomas expressed higher CUX1 levels compared to those with benign behavior.

Conclusion: These data identify CUX1 as important mediator of an invasive proangiogenic phenotype in malignant pancreatic neuroendocrine tumors and suggest a role for CUX1 in mediating HIF-1α-dependent escape mechanisms to antiangiogenic strategies.

O-40 Abstract id: 220.
p21WAF1/Cip1 down-regulation is critical for acinar-to-ductal metaplasia formation during pancreatitis

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Introduction: Transdifferentiation of pancreatic acinar cells into ductal-like lesions, a process defined as acinar-to-ductal metaplasia (ADM), is observed during organ regeneration following pancreatitis. ADM is found in association with pre-malignant PanIN lesions and correlates with an increased risk of pancreatic cancer.

Aims: As the regulatory mechanisms governing ADM are not well understood, we investigated whether this transdifferentiation is modulated by p21WAF1/Cip1, a key regulator of cell cycle progression.

Materials & methods: Pancreatitis was induced in wild type (WT) and p21 deficient (p21−/−) mice by multiple injections of cerulein. Recovery from pancreatitis was analyzed in mice one week after termination of cerulein treatment. The expression of proliferation markers, cell cycle regulators, and the severity of tissue inflammation and fibrosis were analyzed by immunohistochemistry, western blotting and qRT-PCR.

Results: During pancreatitis, we found that p21WAF1/Cip1 was strongly up-regulated in WT acinar cells but absent in cells forming ADM. p21−/− mice showed a significant increase in the number and size of ADM without affecting ADM regression. Surprisingly, the loss of p21WAF1/Cip1 did not increase cell replication rates but resulted in a compensatory activation of positive and negative cell cycle regulators. In addition, the lack of p21WAF1/Cip1 accelerated the expression of progenitor cell markers and the re-localization of β-catenin.

Conclusion: Our findings reveal that p21WAF1/Cip1 is a gate-keeper of acinar cell de-differentiation and formation of metaplastic epithelium. These results suggest an interaction between p21WAF1/Cip1 and β-catenin signalling which is implicated in malignant lesion development.

O-41 Abstract id: 175.
A cell autonomous EGFR-NFATc1 loop promotes acinar to ductal metaplasia in pancreatic carcinogenesis


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Introduction: Recent evidence has shown a crucial role for EGFR activation in KrasG12D-driven pancreatic carcinogenesis. However, the key transcription pathways conferring EGFR signalling in early tumorigenesis are enigmatic.

Aims: To define signaling networks in EGFR driven ADM formation in vitro and in vivo.

Materials & methods: KrasG12D mice strains with pancreas specific differential NFATc1 activation were challenged by chronic pancreatitis. Acinar cells were isolated from KrasG12D or KrasG12D;NFATc1fl/fl mice and treated with EGF (20 ng/ml). Pancreata and acinar cell explants were analyzed by IHC, RT-PCR and WB. ChIP-seq and microarray tools were performed to identify NFATc1 target genes and co-immunoprecipitation was carried out to identify NFATc1 transcription partner.

Results: We identified a cell-autonomous EGFR-NFATc1 loop in ADM formation. Furthermore, genetic depletion of NFATc1 reduced EGFR expression and signaling and thwarted ADM formation in KrasG12D mice, even in context of chronic inflammation. Mechanistically, EGFR induces NFATc1 and c-Jun transduction complex formation on consequent Sox9 promoter induction, a key step in ADM formation.
Conclusion: Our study uncovers an autocrine EGFR-NFATc1 signaling loop which is required for pancreatic cancer initiation.

Introduction: Chronic pancreatitis along with activating mutations of the oncogene Kras is a central risk factor for pancreatic cancer development. Inflammation-induced signaling involves nuclear factor of activated T cells (NFAT) pathways. NFATc1 is overexpressed and activated in Kras-mutated human pancreatic cancers where it mediates cancer growth stimulation.

Aims: This study aims to determine the in vivo role of NFATc1 in KrasG12D-dependent carcinogenesis.

Materials & methods: Transgenic mice expressing KrasG12D and NFATc1 in the pancreas and NFATc1 knockout mice were engineered and analyzed in terms of (inflammation-induced) carcinogenesis. Immuno-histochemistry, Western blot, qPCR analyses, chromatin studies, ChIP-Seq and genome-wide expression profiling were performed to investigate the mechanisms of NFATc1-KrasG12D cooperation in murine and human tissues and tumor cells.

Results: Activation of NFATc1 - upon inflammation and in KrasG12D,NFATc1 mice - dramatically accelerated carcinogenesis and reduced survival. Mechanistically, nuclear NFATc1 activated expression of oncogenic STAT3 transcription factor. Accordingly, high correlative nuclear expression levels of NFATc1 and active STAT3 were detected in the majority of human and murine cancer tissues. In turn, NFATc1/STAT3 complexes, which regulated genome-wide NFATc1 binding to distal chromatin enhancer sites and sub-sequently enforced recruitment of transcriptional co-activators, were identified. Likewise, corresponding enhancer-promoter communications that stimulated NFATc1-dependent transcription of newly-identified target genes were epigenetically promoted. Pharmacologic and genetic depletion of the NFATc1/STAT3-axis significantly arrested carcinogenesis in mouse models and confirmed the requirement of NFATc1 in Kras-driven pancreatic carcinogenesis.

Conclusion: We identified a previously unknown NFATc1-STAT3 complex formation as a driving epigenetic regulatory force in inflammation-linked pancreatic carcinogenesis, which defines this novel pathway a possible point of therapeutic intervention.

Introduction: Pancreatic ductal adenocarcinoma (PDAC) is one of the most stroma-rich cancers. Cancer-associated fibroblasts (CAFs), the most abundant cells in this stroma, orchestrate the secretion of growth factors that engage, in cancer and other stromal cells, survival and angiogenic signals redundant to those targeted by therapies, and of fibrillar components that constitute a barrier to drug delivery.

Aims: Therapeutic pitfalls observed in PDAC may in part be explained by the under-estimation of the influences exerted by the microenvironment on cancer cells. Targeting CAFs may therefore constitute a promising strategy.

Patients & methods: Primary cultures of CAFs have been isolated from human pancreatic tumor resections and used for in vitro and in vivo studies.

Results: Isolated CAFs present, and maintain during the in vitro passages (< 10), an activated phenotype (αSMA-positive). CAFs promote survival, invasion and chemoprotection (against gemicitabine) of pancreatic cancer cells, either in co-cultures or using CAF conditioned media. Interestingly, CAFs present a high intrinsic activation of the PI3K-mTOR pathway. It results in elevated protein synthesis and secretion specifically of pro-tumoral factors and extracellular matrix proteins. Strikingly, drugs that inhibit the PI3K-mTOR pathway abrogate CAF pro-tumoral and chemoprotective effects on cancer cells both in vitro and in vivo, in co-xenografted mice with CAF and pancreatic cancer cells.

Conclusion: Because CAFs are present both in the tumor and in the periphery where drug delivery is still feasible, therapeutic targeting of CAFs using inhibitors of protein synthesis may be of utmost interest for PDAC.

Introduction: Neural invasion in pancreatic cancer is characterized by beta-1-Integrin- and L1-CAM-dependent heterotypic cell adhesion between pancreatic cancer cells and neural Schwann cells.

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Materials & methods: Human SC, PCa cells, human PCA tissue, normal human pancreateas and intrapancreatic nerves were investigated for the expression of the cell adhesion molecules beta-1-Integrin, NCAM, L1-CAM and NrCAM via immunoblotting, QRT-PCR and immunohistochemistry. Heterotypic cell adhesion and mutual migration between SC and PCa cells were quantified via a recently established adhesion assay and 3D migration assay by applying neutralizing antibodies against these adhesion molecules.

Results: Expression of beta1-Integrin and L1-CAM were more prevalent in PCA tissues, human SC, human PCA tissue, normal human pancreas and intrapancreatic nerves were investigated for the expression of the cell adhesion molecules beta-1-Integrin, NCAM, L1-CAM and NrCAM via immunoblotting, QRT-PCR and immunohistochemistry. Heterotypic cell adhesion and mutual migration between SC and PCa cells were quantified via a recently established adhesion assay and 3D migration assay by applying neutralizing antibodies against these adhesion molecules.

Conclusion: Neural invasion harbors heterotypic cell adhesion and mutual migration between SC and PCa cells. Therefore, cell-cell-attachment represents a key pathophysiological mechanism in neural invasion and for the associated local tumor recurrence and neuropathic pain in PCa.
0-45 Abstract id: 242.
Impact of AKT/PI3K signaling pathway in pancreatic cancer and synergistic interaction of the novel Akt inhibitor perifosine with gemicitabine in pancreatic cancer cells
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Introduction: Pancreatic ductal adenocarcinoma (PDAC) is characterized by overexpression of Akt signaling pathway, which has been shown to be associated with aggressive behaviour and chemoresistance.

Aims: The aim of this study was to evaluate the therapeutic potential of perifosine, as a novel Akt inhibitor, in combination with gemcitabine in PDAC.

Materials & methods: In vitro studies were performed in 14 pancreatic-cancer-cells, including seven primary PDAC cultures. Growth inhibitory effects of perifosine and gemcitabine were evaluated in PDAC cells, whereas modulation of Akt and phospho-Akt was investigated by Western-blotting and ELISA. Cell-cycle perturbation, apoptosis induction and anti-migratory behaviors of perifosine were studied by flow-cytometry, AnnexinV, membrane potential, and migration assay, while pharmacological interaction with gemcitabine was determined with combination index (CI) method.

Results: Akt expression was detected by quantitative-RT-PCR in 14 PDAC cells, including 7 primary cell cultures. Perifosine (IC50s, 2-hour-exposure) modulated the expression of Akt, phospho-Akt, mTOR, Bcl-2, Bad and PARP proteins, and synergistically enhanced the antiproliferative activity of gemcitabine, with combination index values of 0.1 (CFPAC-1), 0.45 (PANC-1) and 0.75 (PP109). The drug combination reduced the percentages of cells in G2/M phase (e.g., from 28 to 16% in PANC-1, P<0.05), and significantly increased apoptosis compared to gemcitabine-alone. Moreover, perifosine decreased cell migration, which was additionally reduced by perifosine/gemcitabine combination (e.g., -20% in PP109, after 8hr exposure, P=0.05).

Conclusion: These data show the ability of perifosine to specifically target Akt, interfere with cell-proliferation, induce apoptosis, reduce migration and synergistically interact with gemcitabine, supporting further studies on this novel therapeutic approach for treatment of pancreatic cancer.

0-46 Abstract id: 252.
Minnelide induces cell death in pancreatic cancer through regulation of the transcription factor Sp1
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Introduction: Pancreatic cancer is a devastating disease with an urgent need for more effective therapeutic strategies. Our group has recently synthesized a water-soluble pro-drug of triptolide (a diterpenoid triperoxide), Minnelide that has shown tremendous promise in preclinical studies. However, the mechanism of action of Minnelide is still unclear. In the current study, we show that triptolide induced cell death is mediated by downregulation of prosurvival pathways like HSF1 and NF-kB, which in turn is regulated by the transcription factor Sp1.

Aims: Understanding the mechanism of action of Minnelide in pancreatic cancer.

Materials & methods: Included in results.

Results: Sp1 was 5-15 fold overexpressed in pancreatic cancer cell lines over normal ductal cells. Minnelide induced significant tumor regression by downregulating proteins like HSF1, SP1 and NF-kB. Triptolide also inhibited Sp1 activity in pancreatic cancer cells (80% inhibition). Inhibition of Sp1 resulted in ~70-75% death in pancreatic cancer cells. Additionally, overexpression of Sp1 rescued pancreatic cancer cells from triptolide induced death. Inhibition of Sp1 expression also resulted in downregulation of HSF1 (~60% inhibition) and NF-kB activity (~70% inhibition), similar to that induced with triptolide. Overexpression of Sp1 reverted the inhibition of NF-kB and HSF1 activity, indicating that triptolide or Minnelide induced downregulation of prosurvival pathways leading to cell death was mediated through Sp1.

Conclusion: Our study shows for the first time that triptolide-induced cell death in pancreatic cancer is mediated by downregulation of prosurvival pathways (like HSF1 and NF-kB) controlled by Sp1. This is of great significance as Minnelide goes for clinical trials later this year.

Total pancreactectomy with islet autotransplantation for chronic pancreatitis: The price patients pay for improvements in quality of life
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Introduction: Patients with chronic pancreatitis who have intractable pain that does not respond to standard therapy often seek alternative operative treatment.

Aims: We evaluated the safety and efficacy of total pancreatectomy with islet autotransplantation (TP-IAT) to alleviate the pain and disability of chronic pancreatitis.

Patients & methods: We undertook a retrospective review and analysis of a prospectively collected data base of 102 patients with chronic pancreatitis who underwent TP-IAT. Hospital morbidity and mortality was assessed. The primary outcome measure was improvement in Quality of Life (QOL) measured by the SF-12 at 6 months, 1 year, and 2 years post-op.

Results: The cohort was 79 women and 23 men with a mean age of 42 years. Mean operative time was 236 minutes (75-395), EBL was 621mL (50-7800), and median islet equivalents transplanted was 195,536 (969-1,168,725). Average length of hospitalization was 11 days. Twelve patients required reoperation in the 30-day post-operative period. Postoperative morbidity was 47%. Postoperative mortality was 2%. Seventy-eight patients were available for greater than 6-month follow-up. Five patients (6%) died in the follow-up period. Of the remaining 73 patients, 72%, 74%, and 75% had good physical QOL and 78%, 80%, and 84% had good mental health QOL at 6, 12, and 24 months post-op respectively. New onset diabetes was present in 69%, 69%, and 71% at 6, 12, and 24 months respectively.

Conclusion: Quality of life improves significantly in patients who undergo TP-IAT for chronic pancreatitis. This is achieved with notable post-operative morbidity and mortality and later costs of diabetes and death.

0-48 Abstract id: 194.
Duodenoduodenal anastomosis in pancreas or pancreas and kidney transplantation
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Introduction: Duodenoduodenostomy is a type of exocrine drainage used in pancreas transplantation. It is an alternative method for enteric drainage that may provide some advantages compared to other methods.

Aims: The aim of this study was to summarise experience of our clinic and introduce duodenoduodenostomy as a type of exocrine anastomosis in pancreas transplantation.

Patients & methods: All recipients who underwent deceased donor pancreas or pancreas and kidney transplantation from January 2005 to December 2012 at the Central Clinical Hospital MSW in Warsaw were enrolled in this study.

Results: Medical records of eighty-seven cases of pancreas or pancreas and kidney transplantation including 83 SPK, 1 PAK, 3 PTA performed at our clinic, were analysed. Among these patients 18 had duodenoejunal...
anastomosis and 69 patients had duodenoduodenal anastomosis. Overall patient survival is 85%, 61% of the patients have a good pancreas graft function, 75% present good kidney graft function after 5 years post transplantation. The patients’ demographic data and post-surgical complications were analysed.

Conclusion: In our experience duodenoduodenal anastomosis is a valuable type of exocrine drainage that provides some added advantages compared to enteric drainage. It enables easy and noninvasive endoscopic access to the transplanted duodenum and may be helpful in monitoring the graft survival and preventing some of the possible complications.

O-49 Abstract id: 168.

The CEL-MODY syndrome of diabetes and pancreatic exocrine dysfunction: A frame-shift mutation in the CEL gene causes cellular reuptake of secreted CEL-MUT protein

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Introduction: CEL-MODY is a disease characterized by diabetes, pancreatic lipomatosis and exocrine dysfunction. It is caused by dominant frame-shift mutations (c.1686delT, p.Val563CysfsX111) in the carboxylester lipase gene (CEL), which is highly expressed in pancreatic acinar cells. In a previous study, we have proposed that CEL-MODY is a protein misfolding disease involving a negative gain-of-function effect of the mutant protein.

Aims: We aimed to study the subcellular distribution of the CEL proteins.

Materials & methods: Stably transfected HEK293 cells expressing wild-type (WT) and mutant (MUT) CEL were used as a model system to investigate secretion, degradation and intracellular localization of the proteins by microscopy and biochemical methods

Results: In the present study we have investigated the intracellular distribution of the mutant (CEL-MUT) and wild-type (CEL-WT) CEL proteins in cell line models. By fluorescent immunostaining and confocal microscopy CEL-WT was found to localise typically for secreted proteins in the ER and Golgi, whereas electron microscopy demonstrated the presence of large CEL-MUT aggregates at the plasma membrane and in the lumen of single-membrane vacuoles in the cytoplasm. In a previous study we have proposed that CEL-MODY is a protein misfolding disease involving a negative gain-of-function effect of the mutant protein.

Conclusion: Our results suggest that the aggregated forms of extracellular CEL-MUT can be cleared by cell-mediated uptake and degradation. This might represent a mechanism of preventing cells from the exposure to potentially toxic CEL aggregates that eventually causes exocrine deficiency and diabetes.

O-50 Abstract id: 229.

Deoxysphingolipids, a novel biomarker for type 2 diabetes, are cytotoxic for insulin-producing cells

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Introduction: The prevalence of diabetes mellitus has been rising dramatically worldwide as a consequence of the epidemic spreading of type 2 diabetic patients. Recently, elevated plasma levels of deoxysphingoid bases, including deoxysphinganine (doxSA), have been identified as a novel biomarker for the disease. These atypical sphingolipids lack the C1-hydroxyl group and thus cannot be efficiently catabolized via the canonical degradation pathway.

Aims: In this study, we analyzed whether deoxysphingolipids directly compromise the functionality of pancreatic β-cell.

Patients & methods: The effect of deoxysphingolipids was analyzed in insulin producing INS-1 cells and primary islets isolated from Wistar rats. Cellular viability was analyzed by biochemical and RT-PCR array approaches. Intracellular lipid composition was quantified by mass spectrometry. Cytoskeleton dynamics and phosphorylation of signaling molecules were evaluated by immunostaining and western blotting. β-cell functionality was assessed by quantifying glucose-stimulated insulin secretion.

Results: Treatment with doxSA reduced cellular metabolic activity and insulin secretion in a dose dependent and irreversible manner. DoxSA-induced cytotoxicity had both necrotic and apoptotic characteristics and was accompanied by disassembly of actin cytoskeleton, without alterations in the microtubule pattern. DoxSA incubation increased the cellular levels of deoxyceramides and inhibition of ceramide synthase improved cellular viability. Analyses of signaling pathways identified JNK and p38 MAPK as mediators of cytotoxicity.

Conclusion: Our results revealed that doxSA is a cytotoxic lipid for insulin-producing cells, suggesting that increased levels of this sphingolipid observed in diabetic patients likely contribute to the reduced functionality of β-cells. Thus, targeting deoxysphingolipid synthesis may implement the currently available therapies of diabetes.

O-51 Abstract id: 250.

Autoimmune pancreatitis in Sweden

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Introduction: Autoimmune pancreatitis (AIP) is an enigmatic disease of the pancreas. Recently, a classification and activity scoring system (M-ANNHEIM) and international consensus diagnostic criteria (ICDC) have been described (Schneider et al. 2007; Shimosegawa et al. 2011).

Aims: To classify AIP patients from Sweden according to these two criteria.

Patients & methods: All patients with diagnosis of AIP were enrolled according to the HISORt criteria (i.e. with histology, imaging, serology, other-organ involvement and response to therapy).

Results: To date, 26 patients (15 male, 11 female; median age 62.5 (19-80) years were analyzed). The median follow-up time was 30 months. They presented with pain (n = 20), jaundice (n = 15) or both (n= 11). In one patient with suspected pancreatic cancer the diagnosis was made postoperatively. Upon imaging, 10 presented with swelling of the gland, 1 with focal AIP mimicking pancreatic cancer and 9 with pancreatic atrophy. IgG
and/or IgG4 positive were 20 of 26 patients. Of the AIP type 1 patients, 13 had other-organ involvement, of which the immune-associated cholangitis (IAC) was the most frequent (n = 9), 21/26 patients were classified AIP type 1 (median age: 61 years), whereas 5/26 were classified AIP type 2 (median age: 67 years).

17/26 patients received steroids, 10 patients were only followed, 2 patients were resected. Of the 17 patients who received steroids, 11 relapsed requiring retreatment with steroids or azathioprine/cyclosporine.

Conclusion: The great majority of the Swedish AIP patients are of AIP type 1 with frequent other-organ involvement, most with immune-associated cholangitis. They exhibited a high rate of relapse necessitating retreatment.

O-52 Abstract id: 230.
Distinct pathophysiological profiles for discrimination of autoimmune pancreatitis subtypes

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Introduction: Autoimmune pancreatitis is a newly described form of pancreatitis. Two different subtypes with distinct clinical presentation have been reported including differences in geographic distribution, age of appearance, sex ratio, and histological and immunological features. As both subtypes have been recently individualized, few studies compared both types in term of pathogenic mechanism. Furthermore, diagnosis of AIP remains still a challenge and discrimination between both subtypes is only possible on histological specimen.

Aims: We proposed to evaluate cytokine expression in both, type 1 and type 2 AIP compared to pancreatic cancer and chronic pancreatitis, both difficult differential diagnosis of AIP.

Patients & methods: Seventeen cytokines concentrations have been assessed using the Bio-Plex system in the sera and the pancreatic tissues of our patients. Furthermore, distribution and intensity of 9 cytokines were evaluated using immunohistochemistry.

Results: IL-8, MIP-1b and MCP-1 are significantly more expressed in type 2 AIP than type 1 AIP. These three pro-inflammatory cytokines are significantly more expressed in type 2 than type 1 AIP. These three pro-inflammatory cytokines are produced by macrophages and induce infiltration and activation of leukocytes into the sites of inflammation of pancreas. This results into a continuous activation and amplification of the cytokine cascade that might be the origin of the specific histological characteristic of type 2 AIP that is the granulocytic epithelial lesion.

Conclusion: These three cytokines may help to distinguish both types of AIP. However, further studies are required to explain the role and the origin of this macrophages activation.

In vivo imaging and targeted siRNA delivery using superparamagnetic nanoparticles in pancreatic ductal adenocarcinoma

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Introduction: Pancreatic ductal adenocarcinoma is one of the most aggressive and deadly malignancies. Despite considerable knowledge about the cell biology and the genetic changes of malignant cells, therapeutic options for pancreatic adenocarcinoma remain ineffective. One plausible explanation for the poor tumour response to therapy is an insufficient delivery of anticancer drugs to the tumour site.

Aims: Superparamagnetic nanoparticles, owing to their size and physical properties, could serve a dual purposes: the can delivery anti-proliferative substances to tumour cells and they allow for noninvasive assessment of this delivery by in vivo MRI.

Patients & methods: We synthesized and characterized dual purpose Superparamagnetic nanoparticles for the in vivo application of siRNA with simultaneous imaging of its accumulation in the tumour. Superparamagnetic nanoparticles were designed with a membrane translocation peptide (MPAP-) and with tumour selective peptides (EPPT-) to increase intracellular delivery and tumour specificity, respectively.

Results: In vitro and in vivo experiments using a syngeneic murine orthotopic pancreatic cancer model revealed significant accumulation of Superparamagnetic nanoparticles in pancreatic cancer as well as efficient protein silencing. When we silenced the PLK1, a serine-threonine-kinase, this resulted in a highly significant reduction in tumour size when applied i.v. twice weekly. Significant systemic side effects were not observed.

Conclusion: Superparamagnetic nanoparticles with dual specificity residues for tumour targeting and membrane translocation represent an exciting opportunity for overcoming treatment resistance in pancreatic cancer. Carrying siRNA directed against PLK1 they are well tolerated, can be monitored by MRI, and reduce tumour size.

O-54 Abstract id: 274.
Detection of hypoxic areas in a syngeneic, orthotopic model of pancreatic ductal adenocarcinoma in mouse by in vivo imaging using photoacoustics

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Introduction: In pre-clinical studies, animal models that mimic various human diseases are utilized to evaluate the efficacy of new therapeutics. Non-invasive imaging techniques have been developed to perform longitudinal studies of tumor development and treatment. Recently photoacoustic imaging with inherently co-registered micro-ultrasound has been added developed. This system can make use of endogenous contrast agents such as hemoglobin in order to e.g. determine tissue oxygenation. We used this imaging modality to test the possibility to detect hypoxic/necrotic areas in murine pancreatic cancer.

Aims: The aim of the study was to test if hypoxic/necrotic tumor areas can be identified using photoacoustic.

Patients & methods: 1 Mio. mouse PDAC-Luciferase (KPC-Luc) cells were orthotopically injected under ultrasound-guidance in C57Bl/6j mice using the Vevos®-LAZR integrated micro-ultrasound/photoacoustic system (VisualSonics, Canada). Tumor development was followed by bimodal imaging (3D-ultrasound/IVIS-Spectrum-bioluminescence). Hemoglobin concentration and relative tissue oxygen saturation/distribution were determined with an integrated photoacoustic(20Hz tunable laser 680-970nm)/ultrasound probe (LZ50 at 32 and 40 MHz) in combination with the Vevos®-LAZR software package. 1h before sacrifice, mice were injected with pimonidazole to analyze formalin-fixed, paraffin-embedded tumor sections for hypoxic regions using hypoxiprobe kit.

Results: Tumor development was followed using ultrasound, photoacoustic and bioluminescence imaging. When tumors reached the size of 0.8-1.0cm3 they were excised and analyzed for hypoxic regions by immunohistochemistry (IHC). We were able to associate/match a specific photoacoustic signature with hypoxic/necrotic regions from IHC analysis.

Conclusion: Photoacoustic imaging can be utilized to detect hypoxic/necrotic tumor regions in the mouse and should be useful to assess treatment response in preclinical studies.
Insights into the functional role of tenasin-C in pancreatic carcinogenesis

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Introduction: Pancreatic cancer (PDAC) is characterized by a desmoplastic stroma, which is rich in proteins of the extracellular matrix (ECM). Tenasin-C (TNC), a large ECM glycoprotein, is upregulated in pancreatic cancer and precursor lesions.

Aims: In this study the role of TNC was characterized in PDAC progression in a mouse model.

Patients & methods: Triple mutant mice (KC-TNClco and KC-TNChet) were generated by crossing mice of the LSL-KrasG12D/+/Ptf1a retroviral line (KC), a well characterized mouse model for pancreatic cancer, with TNC knockout mice. The corresponding pancreata of the different genotypes were harvested after different time points (1-15 months). A total of 106 mutant mice were extensively examined by conventional morphology (H&E), as well as by special stains (PASâ€‚ Alcian, Massonâ€‚ Goldner) and immunohistochemistry (Ki67, Caspaseâ€‚ V3, CK19, Claudin-18), focusing on the degree of architectural distortion of the pancreas and on the type and frequency of various precursor lesions and of PDAC.

Results: Three months old TNClco/het mice showed a more pronounced architectural distortion of the pancreas than KC mice with fibrosis, inflammation and acinar-ductal metaplasia (ADM). Precursor lesions were detected in all genotypes at the age of one month, but older KC-TNClco/het mice showed a higher incidence of PanIN3 and PDAC was only observed in KC-TNClco and KC-TNChet mice.

Conclusion: Extensive areas with ADM in KC-TNClco/het mice might be due to a reduced epithelial regeneration of challenged pancreata and a faster progression to invasive carcinoma. This result implicates that TNC might play a critical role in tissue regeneration and stromal homeostasis and possibly in carcinogenesis.

Poster Session I

PI-1 Abstract id: 32.
Experimental acute pancreatitis induces mitochondrial dysfunction in rat pancreas, kidney and lungs but not in liver

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Introduction: Excessive systemic inflammatory response syndrome during severe acute pancreatitis (AP) leads to multiple organ dysfunction syndrome, which is the main cause of death and may be associated with primary mitochondrial disturbances.

Aims: The aim of our study was to evaluate the role of mitochondria during experimental AP in pancreas and vital organs like kidney, lungs and liver within the first 48 hours.

Materials & methods: AP was induced in 35 male Wistar rats by intraductal application of sodium taurocholate (5%, 1.75 ml/kg). Animals were divided into seven groups (control and 1, 3, 6, 12, 24, 48 hours) reflecting the time from induction of the AP till collection of tissues. Mitochondria were isolated by differential centrifugation and mitochondrial respiration rates were measured oxymetrically.

Results: (1) Mitochondria in pancreas are affected within the first 6 hours after onset of AP, (2) kidney mitochondria are affected 24 hours after onset of AP, (3) lungs mitochondria are affected within 48 hours after onset of AP whereas (4) liver mitochondria remain well preserved within the first 48 hours. Severe AP–induced decrease in the oxidative phosphorylation of pancreas, kidney and lungs mitochondria was more pronounced with Complex I–linked (glutamate/malate) than with Complex II–linked (succinate) substrates and was associated with inhibition of Complex I.

Conclusion: Our data show that the disturbances of mitochondrial energy metabolism in pancreas, kidney and lungs may play an important role in the development and progression of AP as a systemic disease.

PI-2 Abstract id: 309.
Inhibition of pancreatitis-associated cell death using a human pancreatic acinar cell model

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Introduction: Inhibition of acute pancreatitis (AP) in rodents as a model for human drug development has largely not been successful. We sought to develop an approach adding selective testing of potential drugs for AP using freshly isolated human PACs.

Aims: To evaluate effects of the cyclophilin inhibitors CyclosporinA (CsA) or Debio-025 on human PACs exposed to tauroliocholate sulphate (TLCS).

Materials & methods: Human PACs were isolated by collagenase digestion, mechanical dispersion and low-speed centrifugation from normal pancreatic tissue gifted by consenting surgical patients. Fluorescent confocal microscopy was used to assess mitochondrial membrane potential (MMP) and cell death profiles of human PACs were similar to published data in rodent PACs.

Results: CsA or Debio-025 preserved MMP (P<0.05) and prevented propidium iodide uptake (P<0.05) compared to control cells in response to 500 μM TLCS. MMP and cell death profiles of human PACs were similar to murine PACs in response to this toxin.

Conclusion: CsA and Debio-025 preserved MMP and reduced necrosis in human PACs following TLCS, likely through inhibition of cyclophilin D. Testing of compounds with human PACs may promote evaluation of potential drugs for AP.

PI-3 Abstract id: 270.
Decrease of bicarbonate dependent pancreatic ductular secretion after cerulein-induced acute pancreatitis in rats

Category: Basic science - acute pancreatitis.

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Introduction: The effect of acute pancreatitis (AP) on ductal cells has not been so extensively studied as in acinar cells. 

Aims: To study the influence of experimental AP on the fluid secretion of pancreatic duct cells.

Patients & methods: AP was induced by cerulein hyperstimulation. Fragments of pancreatic ducts were isolated, cultured for 12±6 hours, and fluid secretion was studied by digital videomicroscopy in sealed ducts.

Results: Cerulein (100 pM or 1 nM) did not stimulate fluid secretion in pancreatic ducts from control rats. In a perfusion solution with HCO3⁻ and Cl⁻, fluid secretion of ducts from pancreatic tissue rats showed a significant reduction (71±10 pL min⁻¹ mm⁻²), compared to ducts from control animals (141±16 pL min⁻¹ mm⁻²), after forskolin stimulation. Chloride secretion, after stimulation with forskolin, showed no differences in control (70±11 pL min⁻¹ mm⁻²) versus pancreatic (48±15 pL min⁻¹ mm⁻²) rats. Similar results were obtained when we analysed HCO3⁻-dependent secretion, driven by NHE, after forskolin stimulation (91±15 vs. 76±13 pL min⁻¹ mm⁻², in control and pancreatic animals, respectively). However, we found a significant decrease in the HCO3⁻-dependent fluid secretion, driven by NBC, in ducts stimulated by forskolin, from pancreatic rats (42±11 pL min⁻¹ mm⁻²) compared to those from control animals (98±18 pL min⁻¹ mm⁻²).

Conclusion: Cerulein induced pancreatitis reduces bicarbonate dependent fluid secretion in pancreatic duct cells, specifically affecting its NBC-driven component.

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PI-4 Abstract id: 202.

Interferon alpha (IFN-α) promotes pancreatitis-associated lung injury in murine experimental acute pancreatitis

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Introduction: Acute pancreatitis (AP) is an inflammatory condition that occurs in ~50 per 100,000 annually. Interferon alpha (IFN-α) or pegylated IFN-α has been associated with drug-induced AP, but mechanisms have not been determined.

Aims: To determine the effect of IFN-α on the severity of experimental AP.

Materials & methods: Murine IFN-α (0.1, 1.0, 3.0 or 10.0 MIU/kg sc) was given on day 1 and 30 min before AP induction in male CD1 mice (six per group) by (i) seven hourly ip caerulein injections (50μg/kg, CER-AP), (ii) retrograde infusion of 150 μL 15 mM taurocholic acid-3-sulfate, TLCS-AP or (iii) two hourly ip injections of palmitoleic acid (150 mg/kg) and ethanol (1.35g/kg FAEE-AP). Blood, pancreas, lung and liver were harvested 12h or 24h after AP induction. IFN-α-induced immune responses were examined by liver mRNA expression of interferon-induced protein with tetratricopeptide repeats (IFIT 1 and 2). The severity of AP was evaluated using standard parameters including blinded assessment of histopathology.

Results: Administration of IFN-α at different doses resulted in higher liver inflammatory gene expression and standard AP parameters than in experimental AP models without IFN-α (p<0.05). Application of IFN-α at 1 or 3 MIU/kg caused marked increases of lung MPO activity in all AP models (80% in CER-AP, 280% in TLCS-AP and 40% in FAEE-AP vs. AP without IFN-α, p<0.001).

Conclusion: This study suggests that IFN-α exacerbates AP through immune responses that contribute to pancreatic and distant organ injury, confirming that distant organ injury is immune-mediated. The mechanism by which IFN-α initiates AP has not been addressed.

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PI-5 Abstract id: 158.

Inhibition of histone deacetylation mediates epigenetic changes and reduces severity in acute pancreatitis

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Introduction: Severe acute pancreatitis (AP) is characterized by pro-inflammatory, inflammation and acute lung injury (ALI). The degree of severity depends on the magnitude of the inflammatory activity. Post-transcriptional modulation of histones can alter the transcriptional pattern in cancer and inflammatory processes.

Aims: Our aim was to analyze the impact of histone deacetylase (HDAC) inhibition in an experimental model of AP.

Materials & methods: Male C57Bl/6 mice were pretreated ip. with the HDAC inhibitor Trichostatin A (TSA, 2mg/kg). AP was induced by retrograde infusion of taurocholic acid (5%) into the pancreatic duct. Animals were sacrificed 24h after onset of AP. Severity was determined by degree of pancreatic tissue injury, levels of S-amylose, pancreatic macrophage inflammatory protein (MIP)-2 and myeloperoxidase (MPO). Lungs were analyzed for MPO and histological signs of inflammation. RT-PCR was used during AP to evaluate gene expression, focusing on a panel of pro-inflammatory genes in the pancreas.

Results: Infusion of taurocholate increased s-amylose, MIP-2, MPO, signs of pancreatic tissue injury and ALI. Expression of COX2, MIP-2 and IL-1β were increased more than 10 times compared to controls. The systemic and local inflammation was significantly reduced by pretreatment with TSA and the transcriptional pattern was altered in favour of anti-inflammation.

Conclusion: TSA reduce severity in AP through suppression of pro-inflammatory genes. No significant alterations of non-inflammatory genes were seen in this model. Taken together HDAC inhibition could serve as a novel therapeutic approach in the management of AP.

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PI-6 Abstract id: 323.

L-arginine-induced acute pancreatitis in mice: Revisited

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Introduction: Acute pancreatitis (AP) is a sudden inflammation of the pancreas. The pathogenesis of AP is not well understood and it has no specific therapy. To investigate the pathomechanism of AP, we mainly rely on animal models such as L-arginine-induced AP. The use of L-arginine to induce AP in mice is becoming increasingly popular. However, we found high mortality with the originally published dose (2x4 g/kg) of L-arginine in mice.

Aims: Thus, we aimed to establish a basic amino acid-induced AP model with a lower mortality rate.

Patients & methods: AP was induced with various intraperitoneal (ip.) doses of L-arginine in CFLP or C57Bl/6 mice. Control mice were injected with physiological saline. Laboratory (serum amylose and pancreatic myeloperoxidase activities) and histological (necrosis and inflammatory infiltration) parameters were measured to determine AP severity.

Results: Ip. injection of mice with 2x4 g/kg L-arginine resulted in a 40 % mortality rate in CFLP and 39% in C57Bl/6 mice, which was independent of the disease. Using 3x3 g/kg L-arginine dose, we found significantly lower mortality (15% in CFLP and 19% in C57Bl/6 mice), and similar degree of AP morbidity compared to 2x4 g/kg L-arginine. The pancreatic myeloperoxidase and serum amylose activities and histological parameters were significantly elevated in all L-arginine treated groups compared to control mice.
Conclusion: There is a fine borderline between the effective and lethal dose of L-arginine. All laboratories have to precisely determine the effective dose of L-arginine used for the induction of AIP.

PI-7 Abstract id: 304.
Ameliorating effect of ursodeoxycholate on the toxic effect of chenodeoxycholate on pancreatic ductal epithelia
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Introduction: Introduction: Recent work by our group has shown that chenodeoxycholate (CDC) at high concentration (1 mM) strongly inhibited ion transporters and induced irreversible mitochondrial injury in intact guinea pig pancreatic ducts. Previous studies demonstrated that ursodeoxycholate (UDC) and its conjugated forms have antiapoptotic and cell protective effects

Aims: The aim of this study was to investigate the effect of UDC on cell damage induced by high concentration of CDC.

Patients & methods: Methods: Inta-interlobular ducts were isolated from guinea pig pancreas by enzymatic digestion. Ducts were then pretreated with different concentration of UDC (0.1 and 0.5 mM) for 5 and 24-hours and changes in intracellular Ca²⁺ concentration [Ca²⁺], ATP level [ATP], and pH [pH] were measured by microfluorometry. Morphological changes of mitochondria were studied by transmission electron microscopy.

Results: Results: 5-hour pretreatment with 0.1 or 0.5 mM UDC and 24-hour pretreatment with 0.1 mM UDC did not significantly influence the effect of 1 mM CDC on duct cells. In contrast, 24-hour pretreatment with 0.5 mM UDC significantly decreased the rate of ATP depletion and mitochondrial injury caused by 1 mM CDC. In addition, 0.5 mM UDC prevented the inhibitory effect of CDC on acid-base transporters.

Conclusion: Conclusion: Our results indicate that UDC may represent a novel option against bile acid-induced ductal injury, however further investigations are needed.

This study was supported by OTKA, MTA and NFU/TAMOP.

PI-8 Abstract id: 148.
Defective mRNA splicing caused by exonic CTRC and SPINK1 variants
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Introduction: Loss-of-function mutations in CTRC and SPINK1 are risk factors for chronic pancreatitis. Previous studies demonstrated that the functional deficit is usually caused by impaired activity, proteolytic degradation or misfolding induced secretion defect. Less attention has been paid to mutation-induced disturbances in pre-mRNA splicing, which could lead to significantly reduced mRNA levels and expression.

Aims: In this study we investigated the effect of mutations c.132G>A (p.R65Q) in CTRC and c.194G>A (p.R65Q) in SPINK1, which alter the last nucleotide of the exon, on mRNA splicing and protein expression.

Materials & methods: HEK 293T cells were transiently transfected with expression plasmids carrying either the cDNA sequence or a minigene construct containing the intron following the mutated nucleotide. Protein expression was measured in the conditioned media by functional assays and by SDS-PAGE or western blot. Splicing efficiency was investigated by RT-PCR.

Results: When the mutations were introduced to the cDNA sequence, CTRC c.132G>A had no effect on protein expression, whereas SPINK1 c.194G>A reduced expression by 25%. When tested in the mini-gene construct, the same mutations caused 90% and 75% loss of protein expression, respectively, relative to wild type. RT-PCR showed a significant reduction in the correctly spliced mRNA.

Conclusion: Mutations in CTRC and SPINK1 can increase risk for chronic pancreatitis by altering mRNA splicing and thereby reducing protein expression. Defective splicing can be caused not only by intronic splice site mutations, but also by changes in flanking exonic sequences.

PI-9 Abstract id: 195.
Comparative effectiveness of immune-cell depletion in the treatment of autoimmune pancreatitis
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Introduction: The long-term management of autoimmune pancreatitis (AIP) - a relapsing steroid-responsible disorder - is still elusive. We previously demonstrated that acinar specific lymphotxin expression in mice Tg(Ela1-Lta,b) induces autoimmunity with features reminiscent of human AIP. This includes formation of tertiary lymphoid organs, increased serum IgGs, anti-nuclear antibodies and immune-complex glomerulonephritis. Mice were responsive for corticosteroid treatment but it did not revert the autoimmune repertoire. In contrast, inhibition of Lymphotoxin beta receptor (LTβR) signaling pathway (LTβR-Ig) dampened auto-antibody production, chemokine expression, and renal immune-complex deposition and abrogated AIP.

Aims: To identify the functional role of B- and T-cells in AIP, we applied different treatments to deplete these subsets of immune cells.

Patients & methods: Tg(Ela1-Lta,b) mice with established AIP were treated with anti-CD20 (Rituximab) and anti-CD4 mAb in order to deplete B- and CD4+ T-cells respectively. Histology, autoantibody production, chemokine expression and renal immune-complex formation was tested, and compared to LTβR-Ig treatment.

Results: Rituximab and LTβR-Ig treatment led to significant decrease in autoantibody production and inflammatory cell infiltration. The molecular mechanism of this beneficial effect possibly involves the downregulation of Stat3 activation. In contrast to Rituximab, blocking LTβR-signaling reverted acinar cell proliferation and acinar-to-ductal metaplasia formation and prevented the activation of the non-canonical NF-kβ signaling pathway.

Conclusion: In Tg(Ela1-Lta,b) mice, we demonstrate that therapy with LTβR-Ig is superior to Rituximab and CD4+ T-cell depletion. We reveal novel mechanisms of anti-inflammatory and anti-autoimmune effects by repressing Stat3 activation and the non-canonical NF-kβ pathway upon LTβR-Ig treatment. Therefore, inhibition of LTβR-signaling pathway could become an alternative or supplementary approach for AIP treatment.
**PI-10 Abstract id: 103.**

**Autophagic cell death by SPINK insufficiency induces chronic inflammation in the pancreas**

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**Introduction:** The loss-of-function mutations of SPINK1 gene are associated with various forms of human chronic pancreatitis. We previously showed that deletion of Spink3, the mouse homologue of human SPINK1, causes pancreatic acinar cell death by excessive autophagy. Although autophagic cell death is known by morphological study, the role of it in vivo is not clear.

**Aims:** The aim of this study was to rescue the Spink3−/− phenotype by generating Spink3−/−: mice with SPINK1 expression, and to analyze the role of autophagic cell death in vivo.

**Patients & methods:** We generated the new mouse model which CAG promoter-SPINK1 minigene poly-A (SP1) transgene is inserted into X chromosome. X-inactivation is a process whereby one of the two copies of the X chromosome present in female mammals is inactivated. By utilizing X-inactivation, we were able to create unique mice in which SPINK1 is expressed partially. These mice were crossed to Spink3−/− mice to generate Spink3−/−:SP1 transgenic mice.

**Results:** Female Spink3−/−:SP1 transgenic mice (Spink3−/−:X(−)SP1) in which SP1 transgene is present on only one of the two X chromosomes, contained both normal and degenerated acinar cells with accumulation of autophagic vacuoles at birth. These mice developed pathologic features of chronic pancreatitis, including loss of acinar cells, interstitial fibrosis with activated stellate cells, and inflammatory cell infiltration, and older mice displayed prominent expression of proto-oncogenes Egfr, Her2, and Ras.

**Conclusion:** The results reinforce the role of SPINK1/Spink3 gene deficiency in the development of chronic pancreatitis and indicate that chronic pancreatitis trigger by autophagic cell death.

**PI-11 Abstract id: 283.**

**Cigarette smoke extract inhibits stimulated fluid secretion of isolated guinea pig pancreatic ducts**

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**Introduction:** Smoking represents an independent risk factor for the development of chronic pancreatitis (CP), however, the pathomechanism remains unclear. Pancreatic ductal epithelial cells (PDEC) secrete an alkaline fluid mediated by anion transport, which is responsible for maintaining the integrity of the gland. Cigarette smoke extract (CSE) was found to modulate anion transport mechanism in human airway epithelial cells, however, no information is available whether smoking has such effects on PDEC.

**Aims:** Our aim was to investigate the effects of CSE on pancreatic ductal fluid secretion.

**Patients & methods:** Intra/interlobular pancreatic ducts were isolated from guinea pig pancreas with enzymatic digestion and microdissection. Basal and forskolin-stimulated fluid secretion into the closed luminal space of the ducts was followed with videomicroscopy. Low magnification (4x objective) bright-field images were acquired at 1-min-intervals using a CCD camera. Relative volume was calculated with Scion Image software.

**Results:** Isolated guinea pig pancreatic ducts were capable of secreting fluid in the presence of bicarbonate, the fluid secretion increased up to 1.55±0.12 (n=9). The administration of 5 μM forskolin induced a sustained increase in the relative luminal volume which reached an average value of 1.84±0.12 (n=7). Parallel administration of 40μg/ml CSE blocked the stimulatory effect of forskolin (the relative luminal volume decreased to 1.57±0.11, n=6).

**Conclusion:** CSE inhibits stimulated pancreatic ductal fluid secretion suggesting a deleterious effect of smoking on fluid secretion. This inhibitory effect may contribute to the pathogenesis of CP; however, further experiments to confirm this needed. Supported by TAMOP and OTKA.

**PI-12 Abstract id: 222.**

**Inflammation contributes to the regression of acinar-to-ductal metaplasia during pancreatitis**

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**Introduction:** Acinar-to-ductal metaplasia (ADM) is the de-differentiation of pancreatic acinar cells into progenitor-like cells, a process phenotypically characterised by the formation of tubular complexes expressing ductal cell markers. ADM is transient the regenerative phase after pancreatic injury. However, in the presence of prolonged damage, ADM may progress towards the formation of malignant lesions. The regulation of ADM regression is critical for pancreas homeostasis but still remains unclear.

**Aims:** In this project we aim to investigate the contribution of inflammation to ADM regression.

**Materials & methods:** Pancreatitis was induced by multiple injections of cerulein. The expression of inflammatory markers and immune cells was quantified by immunohistochemistry and qRT-PCR. 60% pancreatotomy was achieved by resecting the pancreatic tail. Recovery from pancreatitis was analysed in mice one week after the termination of cerulein injections in the presence or absence of anti-inflammatory treatment.

**Results:** A higher number of infiltrating leukocytes was observed in ADM areas compared to intact acinar tissue during pancreatitis. A similar level of inflammation was observed in ADM areas after 60% pancreatotomy, while the pancreatic parenchyma remained devoid of inflammatory cells. Further immunohistochemical analyses revealed that the inflammatory response mostly consisted of infiltrating macrophages with a minor proportion of T and B cells. Interestingly, anti-inflammatory treatment administered after ADM establishment prevented ADM dissolution.

**Conclusion:** Our data revealed that ADM is associated with a strong inflammatory response, which is independent from the total level of inflammation in the pancreatic tissue. Notably, the anti-inflammatory treatment suggested that the immunity plays an active role in the regression of ADM.

**PI-13 Abstract id: 213.**

**Characterization of perineural immune cell infiltrates in pancreatic neuritis in chronic pancreatitis and pancreatic adenocarcinoma**

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**Introduction:** Pancreatic neuritis is one of the hallmarks of pancreatic neuropathy in chronic pancreatitis (CP) and pancreatic adenocarcinoma (PCa) and correlates to pain sensation of CP and PCa patients. However, the exact characteristics of this perineural inflammation in CP and PCa are yet unknown.

**Aims:** To investigate the immune cell subtypes that compose pancreatic neuritis in CP and PCa.

**Materials & methods:** Pancreatic tissues from patients with CP (n=20) and PCa (n=20) were immunostained against markers for leukocytes,
macrophages, cytotoxic T-lymphocytes, T-helper cells, B-lymphocytes, plasma cells, neutrophils, eosinophils and mast-cells (MC). The inflammatory cells of pancreatic neuritis were colorimetrically quantified and correlated to pain sensation. Expression of the protease activated receptor type 1 (PAR-1) and 2 (PAR-2) was measured in CP and PCa tissues via QRT-PCR and correlated to pain.

Results: Cytotoxic T-lymphocytes (PCA: 35%, CP: 33%), macrophages (PCA: 39%, CP: 33%) and MC (PCA: 21%, CP: 27%) were the predominant immune cell subtypes in pancreatic neuritis. However, only the amount of activated mast cells (PCA without pain: 14% vs. PCa with pain: 31%; CP without pain: 19% vs. CP with pain: 34%), not other of cell subtypes, was significantly elevated in patients with neuropathic pain. Par-1 and Par-2 expression did not correlate with pain in CP and PCa.

Conclusion: The majority of immune cells in pancreatic neuritis are cytotoxic T-cells, macrophages and mast cells. The particular elevation of MCTC-type mast cells around intrapancreatic nerves suggests that these cells play an important role in pancreatic neuropathic pain.

PI-14 Abstract id: 23.
Endogenous nitrogen losses (precaecal and total) in case of exocrine pancreatic insufficiency (induced by pancreatic duct ligation) in pigs – Used as a model for humans
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Introduction: Exocrine pancreatic insufficiency (EPI) causes a distinct reduction in digestibility and absorption of nutrients but information regarding impact on endogenous losses of protein in those patients is scarce.

Aims: This study aimed to quantify endogenous N losses in pancreatic-duct-ligated (PL) pigs - used as a model for human EPI - and healthy control (C) pigs.

Materials & methods: 8 Göttinger minipigs (4 PL, 4 controls) were fitted with an ileo-caecal re-entrant fistula. The diet fed was almost N-free [crude protein content (cp): 0.3 %], 222 g dry matter (DM) of the diet were given twice a day. Ileal chyme was collected over 12 hours on 7 consecutive days. Feces were collected in a separate study for 10 days.

Results: In PL the amount of chyme was higher (factor 5.5) and DM-content of chyme was markedly higher, while cp-content of chyme was higher in C. Mass of feces did not differ but cp-concentration was higher in PL. Basal ileocaecal cp-flux (g/kg DM intake) was higher in PL (346 ± 7.15) compared to control (125 ± 3.68). Endogenous N losses (g/kg DM intake) via feces were also higher in PL (18.3 ± 6.66) than in controls (7.99 ± 4.36).

Conclusion: In controls endogenous N losses were comparable with those of other studies, while in PL-pigs endogenous N-losses were 2 to 3 times higher. Therefore higher cp-recommendations for maintenance in case of EPI might be reasonable to compensate higher endogenous losses.

Lymphotoxin-associated inflammation as an etiologic factor of pancreatic carcinogenesis
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Introduction: Pancreatic inflammation is a well-known risk factor for pancreatic ductal adenocarcinoma (PDAC) development in humans, and its initiation is linked to activating mutations in KRAS oncogene. Recent studies propose a stepwise process starting from acinar cells undergoing ductal reprogramming (acinar-to-ductal metaplasia, ADM) throughout premalignant PanIN (pancreatic intraepithelial neoplasia) lesions leading to tumor formation.

Aims: To investigate the mechanisms how inflammatory damage promotes ADM and PanIN progression.

Patients & methods: Here we establish a new genetic model by intercrossing the commonly used p48+/Cre;Kras+/-G12D (KP) model for pancreatic tumorigenesis, to a novel transgenic mouse developing spontaneous pancreatic inflammation, due to pancreas specific overexpression of lymphotoxin (LT). Immunohistochemistry along with RT-PCR were used to obtain an inflammatory signature.

Results: Overexpression of lymphotoxin in mice harbouring a constitutively active form of Kras mutation in the pancreas (LTKP) dramatically accelerates the development of premalignant PanIN lesions compared to KP animals. Already at 6 weeks of age we observed highly proliferating cells, development of ADM and PanIN in LTKP mice. This coincided with a significant upregulation of pro-inflammatory cytokines and cell-cycle inhibitors. This type of molecular and phenotypic change was only observed around 16 weeks of age in Kras animals. Similarly, earlier activation of downstream targets of Kras was observed in LTKP mice. Furthermore, in the KP model we detected a significant elevation of ligands and receptors of the LT-R-signaling pathway during PanIN progression.

Conclusion: Our data point towards the involvement of the LT-R-signaling pathway in the initiation of pancreatic cancer, revealing lymphotoxin as a critical component of spontaneous and pancreatitis-accelerated PDAC precursor formation.
activated phenotype in infiltrating macrophages, which is associated with a distinct miRNA profile facilitating tumour progression.

**Introduction:** Pancreatic ductal adenocarcinoma (PDAC) is a tumor with dismal prognosis due to aggressive tumor biology and the lack of effective therapies. Although surgical resection of the primary tumor remains still the only curative treatment, frequent tumor recurrence and ineffective therapies. Although surgical resection of the primary tumor results in a dismal prognosis due to aggressive tumor biology and the lack of effective therapies. Although surgical resection of the primary tumor remains still the only curative treatment, frequent tumor recurrence and outgrowth of metastases are life limiting.

**Aims:** To reflect a clinical relevant situation of PDAC, preclinical resection models are urgently needed for investigations of novel adjuvant therapies.

**Patients & methods:** We established a corresponding endogenously induced, primary PDAC in mice through intrapancreatic injection of Sleeping Beauty-based, oncogenic transposon-plasmids followed by subsequent electroporation. This ensures a locally restricted, resectable primary tumor formation. The transposon-plasmid included the constitutively activated Akt-2- oncogene together with a placid for Cre recombinase and were applied in Kras<sup>G12D</sup>;p53<sup>-/-</sup>/Il-mice to induce the p53-knockout and KRas-activation.

**Results:** Mice developed a single tumor lesion at the electroporated locus. PDAC was verified by histological analysis. Molecular analysis after electroporation provided evidence for acinus cells as origin of PDAC formation. Metastases in the lungs, liver and peritoneum could be detected. After R0-resection of the primary tumor, we were able to prolong median survival with the observation of local disease recurrence, peritoneal carcinomatosis, and metastases in liver and lung. Since, the recurrence patterns of our resection model reflects the clinical situation in humans, it holds promise for preclinical evaluation of novel multimodal and adjuvant therapies in genetically defined pancreatic cancers to prevent recurrence and outgrowth of metastases after R0-resection.

**Conclusion:** In conclusion, we could establish for the first time a murine tumor R0-resection model of an autochthonous developing PDAC

**Materials & methods:** We have developed a unique strategy that combines integrative bioinformatic platforms, versatile mouse models (Pinho et al, Gut 2011; Wauters et al, Cancer Res 2013) and unique human tumor tissue resources ([www.pancreaticcancer.net.au/apgi](http://www.pancreaticcancer.net.au/apgi)) to prioritise those genes and pathways that may have a role in disease onset.

**Results:** At present, we are evaluating a group of genes with high confidence aberrations that catalogue into a novel pathway or biological mechanism, i.e. genes that are typically involved in axon guidance and neural positioning.

**Conclusion:** We present a research strategy that provides new biological insights into pancreatic cancer development, using an approach that integrates finding from next generation sequencing and different (mouse) model systems.

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**Introduction:** Etiology of post-ERCP pancreatitis is multifactorial, involving mechanical injury to papilla and pancreatic duct with impaired drainage of pancreatic juice, chemical and hydrostatic damage by infection, thermal injury due to electro surgical current during biliary and/or pancreatic sphincterotomy. Multifactorial pathomechanism needs combination of measures for prevention. There are 3 established techniques for prevention of post-ERCP pancreatitis: pancreatic stent placement, rectal NSAIDs, and sublingual with/without transdermal NO.

**Aims:** Early jejunal feeding is on the horizon for severe pancreatitis, it is time to use it for prevention of post-ERCP pancreatitis at least in the most fragile cancer cases when diagnostic purposes, intraductal cytology and operative maneuvers are equally important. At the same time jejunal route is the most physiological way of early fluid resuscitation and supplementary enteral feeding can be beneficial preoperatively or at the first period of chemotherapy.

**Patients & methods:** A combination of at least 2 preventive measures were applied: the most frequent technique used was jejunal tube placement at the end of ERCP with rectal NSAID and/or sublingual plus dernal NO.

**Results:** In the last 5 years we have performed 219 ERCPs with intraductal cytology, with/without papillotomy and stenting for biliary and pancreatic cancer. Post-ERCP amylase elevations occurred in 17 pts with 9 mild, 7 moderate, and 1 severe pancreatitis. Death happened in 1 case with COPD.

**Conclusion:** Post-ERCP pancreatitis is less frequent even in the most fragile pancreatic cancer patients if a combined preventive measure is used. A prospective randomised study is needed to select the best combination with the more rational jejunal feeding to prevent definitively post-ERCP pancreatitis in these unfortunate patients.

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**PI-21 Abstract id: 200.**

### The isoforment of PI3K p110alpha is necessary for oncogenic Kras-driven initiation of pancreatic cancerogenesis

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**Introduction:** PI3K signaling is stimulated by four non-redundant isoforrnents of catalytic subunits called p110s and global PI3K activity is increased in PDAC.

**Aims:** Since no genetic data currently support an active role of this crucial signaling pathway in pancreatic cancer, we investigated if one specific PI3K isomorf is involved in vivo.

**Materials & methods:** Using a unique system mimicking a pharmacological intervention, which allows a conditional knock-in of p110alpha coding gene pik3ca, we inactivated pancreatic p110alpha in a model recapitulating the progression of pancreatic cancer induced by Kras mutation in combination to cerulein-induced inflammation.

**Results:** Inactivation of p110alpha in the pancreas did not lead to lethality nor to any modifications in the endocrine compartment regulating glucose metabolism. While all Kras mutated pancreata present cancerous lesions, apparition of all types of pancreatic lesions is blocked by genetic inactivation of p110alpha. No early modification corresponding to the first steps of pancreatic cancerogenesis, ductal-to-acinar differentiation nor any onset of other signaling pathways were ever observed in p110alpha-defective Kras mutated pancreata. Inactivation of p110alpha only blocked synergistic effect of ceruletreatment in Kras-mutated animals.

**Conclusion:** Our genetic evidence provides the rationale for PI3K as a major therapeutic target candidate in this pathology and demonstrate an unsuspected role for the non-mutated form of PI3K p110alpha in PDAC: p110alpha is a master key signaling molecule for the priming step of pancreatic cancerogenesis.

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**PI-22 Abstract id: 133.**

### Fatty pancreas is a risk factor for PanIN lesions

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**Introduction:** Obesity was recently described as a risk factor of pancreatic cancer with a specific link with insulin resistance, glucose intolerance and diabetes.

**Aims:** To characterize the frequency of PanIN in case of fatty pancreas (FP).

**Materials & methods:** Consecutive pancreatic specimens of patients operated on for neuroendocrine tumors (adenocarcinomas and IPMN were excluded)) (2009–2011) were analyzed. Parenchyma was analyzed 2 cm apart from tumor. Fatty infiltration and fibrosis of parenchyma (intra and extra lobular locations) were assessed by two investigators according to specific scores. Dysplastic lesions were described according to the WHO 2010 PanIN classification. Body mass index (BMI), diabetes and tobacco intake were collected.

**Results:** 110 pancreatic specimens (males: 42%) were analyzed (median surface per specimen: 7.5 cm²). Median age at surgery was 53.8 [17–85] years. Arterial hypertension, diabetes, tobacco consumption were found in 13%, 15% and 26%, respectively. Median BMI was 24 [16–37]. PanIN lesions type 1, 2 and 3 were observed in 62, 38 and 1%, respectively. FP was found in 56% [extralobal 30%, intralobal 51%]. Intralobal fibrosis was noticed in 24%. PanIN lesions were correlated to fatty pancreas (extra (<0.005) or intra lobular (0.0001)), intralobal fibrosis (0.002), tobacco intake (0.05) and age at surgery (0.05). FP was associated with age (0.0001), higher BMI (0.05), intralobal fibrosis (0.009), hypertension (<0.001), hyperlipidemia (0.01) and diabetes (0.09). We found no correlation between PanIN lesions and dysmetabolic disorders.

**Conclusion:** FP is an independent risk factor of PanIN lesions, especially in case of intralobal location. Fatty infiltration might play a specific role in pancreatic oncogenesis.

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**PI-23 Abstract id: 137.**

### Mechanisms controlling T cell infiltration in pancreatic cancer – Chemotaxis versus contact-guidance

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**Introduction:** Pancreatic ductal adenocarcinoma (PDAC) is among the most common causes of cancer death worldwide and is mostly advanced at diagnosis, resulting in a poor prognosis with a median survival of less than six months. Despite their strong infiltration, especially by T lymphocytes, PDACs are not eradicated by the immune system. The microenvironment plays an important role in the decision between tumor defense or progression, and chemokines and extracellular matrix (ECM) structure influence migration of T lymphocytes within tumors and thereby anti-tumor immunity.

**Aims:** Our study aimed at analyzing mechanisms controlling T cell infiltration in PDAC with regard to chemotaxis and contact-guidance.

**Materials & methods:** Chemokine concentrations in human PDAC lysates were determined by qRT-PCR and BioPlex and compared to infiltration data obtained by IHC. Migration of T cells was studied in vitro in 2D and 3D migration systems. T cell distribution within tumors and ECM structure were analyzed by IHC/IF.

**Results:** Several T cell-active chemokines were overexpressed in PDAC, however, chemokine levels did not correlate with numbers of tumor-infiltrating cells. Furthermore, in vitro-activated T cells responded to chemokines in a 2D system, but not within 3D collagen matrices and their
migration capacity depended on matrix density. ECM architecture within tumors appeared heterogeneous, including areas of loosely arranged collagen fibers and dense networks, mainly found in close proximity to tumor cell clusters. Accordingly, T lymphocytes were heterogeneously distributed, with their majority residing in tumor cluster-distant areas.

Conclusion: ECM architecture may reduce accessibility of tumor cells, thereby interfering with anti-tumor T cell responses and current immunotherapy protocols.

**PI-24 Abstract id: 120.**

CEACAM6 induces epithelial-mesenchymal transition and mediates invasion and metastasis in pancreatic cancer

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Introduction: Pancreatic cancer is a disease with an extremely poor prognosis. Acquisition of invasion properties in pancreatic cancer is accompanied by the process of epithelial-mesenchymal transition (EMT). Carcinoembryonic antigen-related cell adhesion molecule 6 (CEACAM6) is emerging as an important determinant of the malignant phenotype in a range of cancers, including pancreatic cancer.

Aims: The aim of this study was to evaluate the potential involvement of CEACAM6 in invasion and metastasis of pancreatic cancer cells via EMT regulation.

Materials & methods: First we analyzed the association between CEACAM6 immunohistochemical expression and clinicopathological characteristics of 99 pancreatic cancer patients. Second, after generation of stable CEACAM6-overexpressing and CEACAM6-knockdown pancreatic cancer cell lines, we observed the changes of EMT markers by Q-PCT and western blot, the cell proliferation by MTT assay and migration and invasion by transwell. Last, we used the orthotopic pancreatic tumor xenograft model to assess the metastatic ability.

Results: The results of our study showed a positive association between CEACAM6 expression and pancreatic cancer poor prognosis, differentiation, and lymph node metastasis. In addition, elevated levels of CEACAM6 in pancreatic cancer cells promoted EMT, migration, and invasion in vitro and metastasis in animal models, whereas shRNA-mediated CEACAM6 knockdown had an opposite effect.

Conclusion: Collectively, our findings identified CEACAM6, as an important positive regulator of EMT in pancreatic cancer, and they offer an explanation for how elevated levels of CEACAM6 are likely to contribute to the highly metastatic phenotype of pancreatic cancer.

**PI-25 Abstract id: 67.**

Exosomal lipids impact on Notch signaling to drive differentiated SOJ-6 cells towards apoptosis but promote cell survival by inducing SDF-1 production in cancer stem-like MiaPaCa-2 cells

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Introduction: We showed that exosomes produced by human pancreatic cancer cells induced death of pancreatic cancer cells through apoptosis. Cell death occurred when the Notch pathway was abrogated. As exosomal proteins and sugars were not responsible for cell death, we hypothesized that apoptosis depends on exosomal lipids.

Aims: We intended to prove that only lipids were responsible for the observed effects and confirm that the Notch pathway was perturbed. We also investigated why MiaPaCa-2 cells were resistant.

Materials & methods: We produced Synthetic Exosomes-Like Nanoparticles or SELN which mimicked lipid composition of exosomes. We used electron microscopy to study their size and stability. Western blotting, siRNA transfection, inhibitors and confocal microscopy have helped us to understand the effects they induced on SOJ-6 and MiaPaCa-2 cells.

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Conclusion: We showed for the first time that exosomal lipids depending upon cells can induce cell death or promote cell survival via the CXCR-4 – SDF-1 axis, involved in aggressiveness of “stem-like cancer cells”.

**PI-26 Abstract id: 326.**

Autophagy in BxPC-3 human pancreatic cancer cells is similar to PANC-1 when treated with anticancer drugs and inhibitors of autophagy

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Introduction: Autophagy is a regulated process of degradation and recycling of cellular constituents, participating also in cell-death mechanisms. Previously we have reported autophagy in pancreatic cancer cell line PANC-1 treated with anticancer drugs and inhibitors of autophagy.

Aims: As some controversy exists about the effect of autophagy in pancreatic cancer cell lines, the aim of this study was to investigate the role of autophagy in another human pancreatic cancer cell line, BxPC-3.

Materials & methods: BxPC-3 and PANC-1 were incubated with an autophagy inhibitor (chloroquine), two anticancer drugs (5-FU and gemcitabine) and a combination of both drug types. The autophagy status was examined by Western blot analysis of the autophagic marker LC3-II. The effect of the drugs on cell growth was also assessed.

Results: Western blot analysis of LC3-II showed that autophagy is activated in BxPC-3 and PANC-1 under basal culture conditions. This was suppressed by chloroquine. Both 5-FU and gemcitabine induced autophagy in BxPC-3 and PANC-1. When chloroquine, which is known to inhibit the degradation of autophagosomes, was added on the cells together with these anticancer drugs, stronger LC3-II bands were detected. In cell growth experiments, chloroquine greatly increased the growth inhibiting effects of 5-FU and gemcitabine. Chloroquine alone suppressed cell growth less than in combination with either anticancer drug.

Conclusion: In both BxPC-3 and PANC-1 cells, autophagy contributes to cell growth and has a cytoprotective effect against anticancer drugs (5-FU and gemcitabine). Chloroquine increases the cytotoxicity of 5-FU and gemcitabine by inhibiting autophagy. Possible combination therapy of these anticancer drugs and chloroquine should be further studied.

**PI-27 Abstract id: 275.**

Nuclear UHRF1 is overexpressed in pancreatic cancer and its depletion from PDAC cell lines leads to cell cycle arrest and increased apoptosis

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Introduction: Pancreatic cancer (PDAC) is a devastating disease with < 5 % of patients surviving for 5 years. UHRF1 (Ubiquitin-like with PHD and RING finger domain) is a DNA binding protein, involved in epigenetic
maintenance and cell cycle regulation. UHRF1 expression is deregulated in many cancer types, however, little its status in PDAC is not well known.

Aims: 1. To examine the expression of UHRF1 in pancreatic tumour specimens and cell lines. 2. To explore the role of UHRF1 in regulating cell cycle and the growth of PDAC cells.

Patients & methods: UHRF1 expression was determined by immunohistochemistry in 43 pancreatic cancer patients (on a Tissue Microarray). SIpRNA mediated depletion of UHRF1 Suti2, MiaPaca2 and Panc1 cells was assessed by western blotting. UHRF1 knockdown was combined with cell cycle arrest at late G1 by double thymidine treatment and at G2/M by Thymidine Nocodazole treatment. The arrest was confirmed by FACS analysis.

Results: Nuclear UHRF1 expression in patient tumours was variable. High UHRF1 expression correlated with larger tumours (>20mm diameters; p=0.01) with a trend towards poorer survival (p=0.07). UHRF1 expression levels varied at different stages of the cell cycle, with highest levels observed at G1 and at M phases. UHRF1 depletion decreased cell proliferation, blocked the cell cycle at both G1/S and G2/M and led to an increase in apoptosis.

Conclusion: Our data suggest an important role for UHRF1 in the growth of pancreatic cancer. We are currently investigating the role of UHRF1 in promoter methylation maintenance in this cancer type.

PI-28 Abstract id: 315.

Quantification of pancreatic ductal adenocarcinoma stroma

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Introduction: The presence of dense desmoplastic stroma is a defining characteristic of pancreatic ductal adenocarcinoma (PDAC) and can account for more than 80% of the tumour mass. Currently, there is no effective mechanism to qualitatively assess the nature of the stroma without surgically removing the tumour.

Aims: To devise a method for accurately quantifying PDAC stroma. To investigate the relationship between the composition of PDAC stroma and patient outcome.

To generate a candidate serum biomarker profile relating to the tumour microenvironment.

Patients & methods: A tissue microarray (TMA, N=41 PDAC) was generated and sections analysed by immunohistochemistry using antibodies against cytokeratin, z-SMA, blood vessel and lymphatic endothelium, T-cells and macrophages as measures of stromal content. Survival analysis was performed using Kaplan-Meier. Cytokine analysis was undertaken analysing matching serum samples using a luminex panel for 27 cytokines. Associations between serum protein levels and individual markers of stromal content were determined using Spearman’s rank.

Results: Two major patterns (referred to as type A and type B) of tumour and stroma structure were defined. Patients whose tumour alternated in type had improved prognosis compared to those which did not change (P=0.062). High levels of macrophage infiltration also correlated with stromal type with high levels in the stromal correlating with poor prognosis (P=0.046). Significant correlations were observed between markers of stromal content and serum proteins. Results will be validated with definitions and a subsequent array generated.

Conclusion: We have developed a mechanism for profiling stromal levels and observed associations with serum cytokine levels and patient outcome.

PI-29 Abstract id: 135.

No-touch isolation surgical technique reduces dissemination of circulating tumor cells in patients with pancreatic cancer

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Introduction: Circulating tumor cells (CTCs) disseminate from the primary tumor and travel through the bloodstream. The detection and/or increase in the number of CTCs during a patient’s clinical course may be a harbinger of forthcoming overt metastasis

Aims: We aimed to examine the impact of two different surgical techniques, standard pancreaticoduodenectomy (ST-PD) and “no-touch” isolation pancreaticoduodenectomy (NT-PD) on tumor behaviour and outcome in patients with pancreatic cancer by using portal vein CTCs as biomarkers.

Patients & methods: This study was limited to patients who underwent PD for PDAC between September 2010 and April 2012. Patients were randomized into two groups: ST-PD (group I, n=6) and NT-PD (group II, n=6). Intraoperatively, blood samples were taken from the portal vein (PV) for measurement of CTCs (using the bead-based fluorescence CellSearch system) before and immediately after removal of the tumor.

Results: There was no difference in terms of length of operative time, resection margin status or tumor characteristics. An increase in CTCs was seen in 83% of patients in ST-PD, but none in NT-PD (P=0.003). Median overall survival was 13.0 and 16.7 months respectively (P=0.328).

Conclusion: NT-PD significantly reduced the number of CTCs in the PV with a trend towards better overall survival compared to ST-PD.

PI-30 Abstract id: 212.

Collagen type V supports the malignant phenotype of pancreatic cancer cell lines through the integrin signaling pathway

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Introduction: Collagen type V (ColV) is a protein upregulated in the stroma of malignant tumors.

Aims: In this study the effects of ColV on pancreatic cancer cells (PCC) and pancreatic stellate cells (PSC) are investigated to gain knowledge about the epithelial-stromal interactions in pancreatic cancer.

Materials & methods: The expression of ColV and its cell surface receptor β1-integrin was assessed in pancreatic cancer and PanIN lesions by immunohistochemistry. The role of the β1-integrin signaling pathway was further analyzed by performing functional assays (adhesion, migration and proliferation) after pharmacological and antibody-mediated inhibition in PCC. Immunofluorescence and immunoblotting for GFAP and αSMA were used to investigate the activation status and the phenotype of PSC after a transient ColV knock-down. Moreover, fibroblasts bearing a ColV mutation (obtained from patients affected by the classical Ehlers-Danlos syndrome) were compared to PSC by migration and adhesion assays.

Results: ColV is expressed in the stroma of pancreatic cancer and its precursor lesions. PSC are the main source of ColV. Knocking-down ColV induces a change in the morphology but not in the activation status of PSC. On the other hand, ColV specifically activates the β1-integrin signaling pathway in PCC and induces migration, adhesion and proliferation. ColV-mutated fibroblasts showed reduced migration and adhesion compared to the controls.

Conclusion: ColV is overexpressed in the stroma of pancreatic cancer and influences the malignant phenotype of PCC through activation of the β1-integrin signaling pathway. Fibroblasts with functional defective Col V display reduced proliferation and migration, further underscoring the important role of ColV in these cellular processes.
Pancreatic cancer (PC)-derived soluble mediators induce dendritic cells (DCs) to acquire an immunosuppressive phenotype by downregulating CTLA4

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Introduction: The inhibitory co-stimulatory receptors PDL-1 and CTLA4 might have a role in PC-mediated immune suppression.

Materials & methods: PBMC were cultured in Control and in Capan1, BxPC3 and MiaPaCa2 conditioned media or in the presence of 10 nM pre-treated with EGF for 3 days. Total protein lysates were used for the WB (0.02ng/mL) alone or combined. Cells were both left untreated or were pre-treated with EGF for 3 days. Total protein lysates were used for the WB analysis of: Akt (Ser473,Thr308), mTOR (Ser2448,Ser2481), NF-kB (p-IkB-a), MAPK (p-p38, pErk 1/2).

Results: In BxPC3-SMAD4+, cells, EGF activated, while TGFb1 and S100A8/A9 inhibited Akt and MAPK. In these cells, S100A8/A9 and EGF stimulated, while TGFb1 inhibited NF-kB. SMAD4 deletion did not affect EGF signalling, reverted TGFb1 and S100A8/A9 effects on Akt, and allowed mTOR activation after TGFb1, S100A8/A9 and EGF treatments.

Conclusion: SMAD4 deletion in pancreatic cancer cell and chronic treatment with EGF co-operate in activating pro-proliferative and pro-metastatic pathways when cells are treated with growth factors, inflammatory proteins and TGF-b.

SMAD4 deletion and EGF co-operate in favouring mTOR activation in PDAC cells

Dania Bozzato, Stefania Moz, Eliana Greco, Filippo Navaglia, Andrea Padoan, Mario Plebani, Daniela Basso.

Department of Medicine - DIMED, Italy

Introduction: EGF overexpression occurs early, while loss of SMAD4 occurs in more advanced PDAC. Loss of SMAD4 alters TGFb1 signalling, associates with a reduced stromal and an increased cancer cells expression of S100A8/A9.

Aims: To ascertain whether the effects on NF-kB, Akt, mTOR and MAPK signalling pathways exerted by S100A8/A9, TGFb1 and EGF depend on SMAD4 deletion and whether they are sensitive to EGF chronic exposure.

Materials & methods: BxPC3 (SMAD4 homozygous deletion) and SMAD4 expressing BxPC3 (BxPC3-SMAD4+; plasmid expression vector) were stimulated with EGF (100ng/ml), S100A8/A9 (10nM) and TGF-b1 (0.02ng/ml) alone or combined. Cells were both left untreated or were pre-treated with EGF for 3 days. Total protein lysates were used for the WB

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Results: We observed fast and long-lasting ATP release in Capan-1 cells in response to hypotonic and mechanical stimuli. Exposure to extracellular alkaline pH caused a monophasic sustained increase in extracellular ATP concentrations; acidic pH caused a short release of ATP (n=8.8). ATP release observed with addition of UTP (10 μM) and ionomycin (5 μM) were relatively slow. The bile acid chenodeoxycholate (CDC, 0.1-1 mM) induced high and fast ATP release (max 1.0±0.3 μM/10^6 cells/ml). CDC is most likely acting through GPRAR1 and the receptor is expressed in Capan-1 cells.

Conclusion: Together, our data show that various stimuli release ATP with different kinetics and this may indicate different releasing mechanisms. In low concentrations ATP can stimulate opening of Cl− and K+ channels and potentiate ductal fluid secretion. However, overstimulation may deplete the cells of ATP, partially via ATP release, and thereby contribute to pathological processes in pancreas.

PI-35 Abstract id: 241.
Exocrine pancreas ER stress differentially induced by different fatty acids
Ruth Birk, Hila Danino.
Department of Nutrition, Faculty of Health Science, Ariel University, Israel

Introduction: Exocrine pancreas acinar cells have a highly developed endoplasmic reticulum (ER) system, accommodating their high protein production rate. Enzyme synthesis in acinar cells is highly responsive to environmental regulation, including diet. However, it was recently suggested that environmental factors could also induce ER stress, which plays a role in the etiology of pancreatitis and pancreatic cancer. Dietary fat has been suggested by us and others to induce an acinar lipotoxic effect. The effect of different dietary fatty acids on the ER stress response is unknown.

Aims: Analysis of effects of different fatty acids on ER stress response in pancreatic acinar cells.

Materials & methods: We studied the effect of acute (16hr) challenge with fatty acids (1800μM mono and poly-unsaturated) on fat accumulation, digestive enzyme transcripts and ER stress indicators (XBP splicing, UPR transcripts) in exocrine pancreas acinar (AR42J) cells.

Results: We demonstrate that acute exposure of AR42J cells to different fatty acids results in increased triglycerides accumulation dependent on type of fat, in the following order: oleic<linoleic. Lipid challenge significantly affected the UPR response, as demonstrated by both significantly altered XBP splicing, and significantly elevated depending on the different fatty acids: oleic<linoleic and oleic<linoleic, for PL and colipase respectively.

Conclusion: We demonstrate that different fatty acids affect acinar cell fat accumulation, inducing ER stress and affecting pancreatic enzyme expression. The differential effect of the various fatty acids could have potential nutritional and therapeutic implications.

PI-37 Abstract id: 235.
Plasma enzyme levels after the induction of exocrine pancreatic insufficiency (EPI) and pancreatic enzyme replacement therapy (PERT) in a pig model
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Introduction: The pig is a suitable animal model for the study of EPI as the gut anatomy and physiology is similar to that in humans and that it is relatively easy to induce total EPI in pigs, by pancreatic duct ligation (PDL), without affecting bile secretion.

Aims: This study monitored pancreatic and gut enzymes levels in plasma throughout the progression of EPI, after PDL and after PERT.

Materials & methods: Five 6 week-old pigs (10.9±0.2 kg) underwent PDL, while 6 un-operated were used as controls. Repeated blood samples were taken from a jugular vein catheter, following an overnight fast for determination of plasma levels of immunoreactive cationic trypsinogen (IRCT), amylase, lipase, and diamine oxidase (DAO) activity. 30 days after PDL, PERT (4 Creon® capsules, Solvay) was administered with the morning and evening feeds for 1 week.

Results: A substantial increase in plasma levels of IRCT, amylase and lipase was seen at 3 days following PDL surgery. Afterwards, from day 10 post-PDL, all enzyme levels decreased, with IRCT and amylase levels decreasing to that below the controls. Introduction of PERT increased enzyme levels, for amylase towards normalisation. The marker for small intestinal integrity, DAO, decreased slowly to levels below that of controls, until 26 days post-PDL, where introduction of PERT caused a slight increase.

Conclusion: In summary, after an initial plasma surge of all pancreatic enzymes after PDL, the most pronounced effects of EPI were lowered IRCT and increased lipase levels. Reduced DAO indicated that EPI can also affect gut integrity. PERT introduction normalized the amylase plasma levels.

PI-36 Abstract id: 150.
Evidence for active electrolyte transport of two-dimensional monolayer of human epithelial cells
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1 Department of Oral Biology, Semmelweis University, Budapest, Hungary
2 Faculty of Life Sciences, University of Manchester, United Kingdom

Introduction: Reconstruction of inflamed epithelial glands such the diseased exocrine pancreas and salivary is an unresolved challenge for regenerative medicine. To restore lost salivary epithelial function, acinar cell renewal could be achieved by the remnant ductal cells.

Aims: Our aim was to prepare primary cultures of human submandibular gland and to provide optimal conditions for polarized secretory epithelial monolayers.

Materials & methods: Cell cultures were prepared from surgically dissected human glands (Tissue Eng:14:1915-26,2008). Transepithelial electrolyte transport was estimated by short circuit current (Isc) measurements in Ussing chamber.

Results: Monolayers in HepatoSTIM medium developed high-epithelial electrical resistance and achieved transepithelial electrolyte movement. Isc was partly inhibited by basolateral Cl− and bicarbonate withdrawal indicating the involvement of basolateral-to-apical anion transport, and also by the inhibition of apical eNaC activity by amiloride, indicating the involvement of apical-to-basolateral Na+ transport. An almost complete inhibition was observed in response to simultaneous eNaC block and withdrawal of the two anions. Isc was accelerated by apical ATP or basolateral carbachol application but not by forskolin, indicating the regulatory role of Ca2++-activated, but not cAMP-activated regulatory pathways. Inhibition of basolateral NKCC1 by bumetanide reduced the response to ATP indicating the active involvement of this transporter as well.

Conclusion: In conclusion, we successfully developed a human epithelial secretion model, which shows mixed salivary acinar/ductal phenotype. This model may serve to establish the basis for pharmacological or genetic interventions to correct dysfunction not only in salivary glands but in other epithelia such as the exocrine pancreas as well.

Acknowledgement: Supported by OTKA-CK80928, TAMOP-4.2.1/B-09/1/KMR-2010-0001, TAMOP-4.2.2/B-10/1-2010-0013
**PI-38 Abstract id: 342.**

L-glutamate secretion in the pancreatic juice involves transport and metabolism of neutral amino acids in exocrine pancreas

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**Introduction:** The pancreas efficiently absorbs amino acids (AA) for the synthesis of enzymes, but also secretes free AA in the pancreatic juice. Under free protein diet (FPD), the AA release on the pancreatic juice (PJ) may play an important role on the homeostasis maintenance of the small intestine.

**Aims:** The aim of this study was to analyze acinar synthase and secretion of L-glutamate (Glu), the most concentrated AA in PJ.

**Materials & methods:** Expression of enzymes involved in Glu synthesis, AA concentration and protein localization were performed.

**Results:** Two glutaminase isoforms (gls1 and gls2) are expressed in the pancreas, and the mRNA levels of gls2 and of the alanine aminotransferase 1 (gpt) were elevated in animals receiving (FPD). These results suggest Glu may be synthesized in the exocrine pancreas from L-glutamine (Gln) and L-alanine (Ala) and that the dietary protein content can modulate the expression of enzymes involved in the synthesis of Glu. The secretory mechanism of Glu to PJ does not involve zymogen granules vesicles (ZGV). Glu and its precursors were not concentrated in ZGV but were found at high concentrations in the cytoplasmic fraction, suggesting the secretory mechanism does not involve exocytosis. Immunofluorescence of pancreatic tissue suggested that the Naag-dependent Glu transporter EAAT1 (Slc1a3) localizes proximal to the apical membrane of acinar cells and may be involved in the secretion of Glu.

**Conclusion:** These preliminary results suggest a new mechanism for Glu concentration and secretion on the PJ, as well a recycling of neutral AA (Ala, Gln) and Glu between the pancreas and intestine.

**PI-39 Abstract id: 340.**

Characterization of pericytes in adult pancreas tissue sections

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**Introduction:** Pericytes, the mural cells of blood vessels, are key regulators of vascular morphogenesis and play a role in the development pancreas. Apart from their classical role in stabilizing vascular structures, the recent data suggest that a subset of pericytes have the properties of mesenchymal stem or progenitor cells. The existence of such cells in adult pancreas has not yet been defined.

**Aims:** Several molecular markers for pericytes have been identified. However, the specific marker for pericytes remains unknown. The identification of pericytes in tissue sections relies on the combination of different markers.

**Materials & methods:** To define the distribution of pericytes in the adult pancreas, we used the well established pericyte marker NG2 alone and in combination with the endothelial marker CD31 or the mesenchymal stem cell markers CD90, CD105 or CD146.

**Results:** Our data suggest an existence of a distinctive cell pool within the adult pancreas which are double-positive for NG2 and mesenchymal stem cell markers. These data suggest that pericytes may have an additional role other than stabilize the vessels.

**Conclusion:** These descriptive data argue for the heterogeneity of pancreatic pericytes, which may play different roles in pancreatic physiology.

**PI-40 Abstract id: 37.**

Continuous regional arterial infusion of dextran 70 and heparin in the treatment of severe acute pancreatitis: Background and design of cohort interventional study

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**Introduction:** Effects of continuous regional arterial infusion (CRAI) in acute pancreatitis (AP) treatment are reflected in increased tissue concentrations of administered drugs. It was reported a lower mortality rate in severe AP (SAP) when CRAI was applied within 72 hours of disease onset. It is known that hyperosmolar solutions could reduce interstitial and cellular edema, and shown that dextran can improve microcirculatory disorders in SAP. Coagulation disorders, endothelial lesions, vasospasm and the formation of microthrombi in pancreatic microcirculation reduce pancreatic perfusion which is well correlated to the AP severity.

**Aims:**

**Materials & methods:** Study will include all patients with APACHE II score > 10 calculated within the first 48 hours after AP onset. In the next 48 hours, through micro-catheter placed in the celiac artery a CRAI of 500 mL of dextran 70 with 5000 IU of heparin (CRAI-DH) will be infused in a rate of 40 mL/h, in addition to standard therapy. After catheter removal a standard therapy will be continued. Interventional group will be compared with a retrospective control group of 30 patients with SAP treated without CRAI, in regard to the volume of pancreatic necrosis. A total sample size of 17 patients was calculated to demonstrate that CRAI-DH combined with standard therapy for AP can reduce the volume of pancreatic necrosis at least 30% compared to the control group with 80% power at 5% alpha.

**Results:**

**Conclusion:** This study is designed to reveal a reduction of pancreatic necrosis by CRAI-DH combined with standard therapy in comparison with standard therapy alone in patients with SAP.

**PI-41 Abstract id: 269.**

Mean platelet volume (MPV) as prognostic factor in acute pancreatitis (AP)

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**Introduction:** Mean platelet volume (MPV) is a machine-calculated measurement of the average size of platelets and is typically included in blood tests as part of the complete blood count. Vascular thrombosis and systemic hypercoagulable states are well documented complications of acute pancreatitis (AP). Higher values of MPV have been associated with thrombotic disorders. According to the literature, only few studies have investigated the association between AP and MPV.

**Aims:** To determine whether the value of MPV at admission correlates with the occurrence of local and systemic complications of AP; lethal outcomes; and severe form of AP, according to modified Atlanta criteria.

**Patients & methods:** 53 patients (35 male and 18 female) were enrolled in this retrospective study. MPV values were obtained on an automated hematology analyzer (Olympus AU 640, Tokio, Japan). Student’s t-test was used for statistical analysis.

**Results:** There were no statistically significant differences in the average values of MPV regarding local complications (7.51±0.99 vs. 7.91±1.24, p = 0.22), systemic complications (7.60±1.05 vs. 7.72±1.22, p = 0.76), severe form of AP (7.47±0.97 vs. 7.94±1.22, p = 0.13) or lethal outcomes (7.58±1.03 vs. 7.97±1.38, p = 0.41).

**Conclusion:** Our study did not confirm the value of MPV in predicting complications in the course of AP.
Acute pancreatitis in obese patients
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Introduction: Obesity increases severity of acute pancreatitis by unclear mechanisms. Recent clinical studies demonstrate that all major complications are more common and more severe in patients who are obese. Patients with higher body mass index have increased risk of local and systemic complications of acute pancreatitis and patients with android fat distribution and higher waist circumference are at greater risk for developing the severe acute pancreatitis (SAP).

Aims: We investigated the relationship between visceral adipose tissue and acute pancreatitis.

Patients & methods: We examined 13 patients with acute pancreatitis. In 6 patients BMI was more 30. Computed tomography was performed in all patients.

Results: Pancreatitis induces the activation of peritoneal macrophages and a strong inflammatory response in mesenteric sites of adipose tissue. In obese humans, we found that an increase in the volume of intra-pancreatic adipocytes was associated with more extensive pancreatic necrosis during acute pancreatitis and that acute pancreatitis was associated with multisystem organ failure in obese individuals. Patients with SAP had higher BMIs and more intrapancreatic fat than those with mild AP.

Conclusion: The results confirm the involvement of adipose tissue on the progression of systemic inflammatory response during acute pancreatitis. However, there is a considerable diversity in different adipose tissue sites. These differences need to be taken into account in order to understand the progression from local pancreatic damage to systemic inflammation during acute pancreatitis. Therapeutic approaches that target unsaturated fatty acid-mediated lipotoxicity may reduce adverse outcomes in obese patients with critical illnesses such as severe acute pancreatitis.

Extrahepatic ducts neoplasms are correlating with higher incidence of post endoscopic retrograde cholangiopancreatography pancreatitis
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Introduction: Post endoscopic retrograde cholangiopancreatography pancreatitis (PEP) is the most common complication of endoscopic retrograde cholangiopancreatography (ERCP). Causes of PEP are not completely established but there are several risk factors.

Aims: The aim of this study was to investigate correlation between various diagnoses and occurrence of PEP.

Patients & methods: All patients with indication for ERCP at our tertiary care center from January to December 2012 were included. All patients received diclofenac sodium suppositories immediately before procedure. We used Spearman correlation coefficient in order to detect possible significant correlation.

Results: We included total number of 169 patients, 94 males (55%) and 75 females (45%), mean age was 70.58 ± 13.77 years. We observed PEP in 24 out of 169 patients (14%), 13 males (54.2%) and 11 females (45.8%). Mean duration of procedure was 45 ± 26.00 min. Among others, the most common reasons for ERCP were choledocholithiasis (57.6%) and pancreatic carcinoma (12.9%). We found significant correlation of PEP only with extrahepatic ducts neoplasms, r=0.185, p<0.05. There were no correlation among PEP and pancreatic carcinoma, choledocholithiasis, acute or chronic pancreatitis.

Conclusion: Extrahepatic ducts malignancies are correlated with higher incidence of possibly due to difficult cannulation and prolonged procedure.

Acute pancreatitis and the role of BISAP score in the early prediction of severity and mortality in acute pancreatitis
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Introduction: Acute pancreatitis (AP) is a sudden inflammation of the pancreas. A variety of scoring systems are available to evaluate the severity of AP.

Aims: To evaluate the accuracy of bedside index for severity in acute pancreatitis (BISAP) in predicting the severity and prognosis of AP.

Patients & methods: We retrospectively studied 109 cases admitted at the UHC during one year. AP was classified as mild or severe according to the 1992 Atlanta classification. BISAP was calculated using data within the first 24 hours following admission, and the Ranson score was calculated using data from the first 48 hours following admission; CTSI score within 3 days following symptom presentation.

Results: We had 78 males (71.56%) and 31 females (28.44%), mean age 43.74 Std ± 12.05 years. 84 patients (77.06%) had mild AP (MAP), while 22 patients (20.18%) had severe AP (SAP), 3 patients died (2.75%). We found significant correlations between the scores of any two systems. BISAP performed similarly to other scoring systems in predicting SAP, pancreatic necrosis, mortality, and organ failure in SAP patients, in terms of the area under the receiver-operating characteristic curve.

Conclusion: We compared BISAP scores with Ranson, and CTSI scores (when applicable) in predicting the severity and prognoses of AP in our patients. We demonstrated that BISAP has the advantages of simplicity and speed over traditional scoring systems and performed similarly to other scoring systems in predicting SAP and the prognoses of SAP. We confirmed that the BISAP score is an accurate method for risk stratification and prediction of prognosis in patients with AP.

Acute necrotizing pancreatitis model
Viktor Gorsky, Mikhail Agapov, Marina Khoreva, Igor Leonenko.
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Introduction: There is no model that would ideally represent AP in humans. Since “cytokine storm” plays an important role in AP pathogenesis, cytokine hyperproduction should be one of the factors of the experimental model.

Aims: To develop the acute necrotizing pancreatitis model characterized by increased cytokine levels in the peripheral blood.

Patients & methods: 60 male outbred CD rats. Two models (cerulein-, alcohol-induced) were tested with no positive results. We proposed our own mechanical model. The cerulein-induced model included intreperitoneal injection of Nerulein solution. The alcohol-induced AP was obtained by continuous administration of 10% ethyl alcohol solution. The mechanical model constituted a partial stenosis of the common bile duct. 9 rats were given 40 μg/kg cerulein as an additional pancreatitis inducer.

Blood test for amylase, AST, ALT, and cytokines levels; tissue samples histological examination.

Results: Cytokine levels in the intact animals group were used as a reference. No cases of pancreatic necrosis were observed after the cerulein and alcohol administration. These models were not associated with statistically significant increase of cytokine levels.

Increased IL-6 level (224.2±5 pg/ml) was observed only with alcohol–cerulein combination. The mechanical model demonstrated morphological signs of marked inflammatory and necrotic lesions of the pancreatic tissue in all animals. The additional cerulein administration led
to total pancreatic necrosis. The mechanical model enhanced with cerulein administration is characterized by statistically significant increase in cytokine secretion (IL-10 - 72.39 ng/ml). AOPP administration is characterized by statistically significant increase in cytokine secretion (IL-10 - 72.39 ng/ml).

**Conclusion**: The ANP model in rats that includes partial ligation of the biliary duct may be recommended for the efficacy evaluation of the medications with cytokine inhibiting activity.

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**PI-46 Abstract id: 30.**

**Advanced oxidation protein products in acute pancreatitis**

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**Introduction**: In the pathogenesis of acute pancreatitis a key role play oxidative stress. Measurement of oxidation protein products (AOPP) may be used as a reliable marker for assessing oxidative damage to proteins in patients with acute pancreatitis and to predict the potential effectiveness of different therapeutic strategies aimed at reducing oxidative stress.

**Aims**: We studied the role of advanced oxidation protein products in acute pancreatitis.

**Materials & methods**: We examined 53 patients with acute pancreatitis and 14 healthy donors. According to the criteria of Atlanta (1992) in 28 patients diagnosed severe acute pancreatitis, in 25 - mild. AOPP in plasma were determined by using standard commercial kits (Immunodiagnostik AG, Germany). Blood sampling was performed at admission, on the 3rd and 7th day of treatment.

**Results**: In patients with mild acute pancreatitis the level of AOPP does not differ from healthy donors during all periods of examination. At the same time in severe pathological process from the first day AOPP concentration more than three times higher than normal levels. Peak values were observed in the first and third days, but remained high at the end of the first week of stay of patients in the hospital. We are noted a direct correlation in necrotizing pancreatitis between the level of AOPP and glucose and C-reactive protein.

**Conclusion**: In acute pancreatitis patients, especially severe, greatly intensifying the processes of oxidative stress. AOPP is indicated not only as a marker of proteins oxidative damage, but also as an indicator of disease severity, the intensity of inflammation and metabolic changes.

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**PI-47 Abstract id: 63.**

**Natural history of Acute Fluid Collections (AFCs) in acute pancreatitis (AP): A prospective cohort study**

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**Introduction**: Studies of natural history of AFCs in AP > 2 decades old. Improved pathophysiologically-based management of AP may have altered the natural history.

**Aims**: Study natural history of AFCs in AP.

**Patients & methods**: 109/122 patients > 12y, admitted with AP, having baseline abdominal CT within 5-7 days of symptom-onset were eligible. They underwent ultrasound at 4-week intervals for > 6 months, with repeat CT at 8-12 weeks and/or anytime with new/persistent symptoms. Definitions of local and/or systemic complications were according to original Atlanta criteria [Bradley ELArch Surg 1993; 128:586-90]. All patients managed according to standard guidelines. Baseline severity assessed by APACHE II, BISAP and CTSI. Symptomatic pseudocysts and sterile/infected pancreatic necroses (IPNs) were drained. Asymptomatic pseudocysts followed till spontaneous resolution. IEC clearance was obtained. Appropriate statistical analysis done and p-value < 0.05 was significant.

**Results**: 91/109 developed AFCs, 86% being Acute Necrotic Collections (ANCs) by revised Atlanta. 40 (37%) developed into pseudocysts, all WOPNs. 5 (4.6%) died, all with IPNs. 27 (25%) and 7 (6%) had persistent pseudocysts at 3- & 6-months, respectively. 14 (15%) underwent drainage; 5 surgical necrosectomy(3-5wks; 2died) & 9 for symptomatic-pseudocyst after(-median:SD:20±6.7 wks. Univariate predictors for developing AFCs- pseudocysts will be presented. On multivariate analysis, transferred patients(OR 4.2 [95%CI:1.1-15.5]; p=0.03) and longer hospital stay(OR 1.8 [95%CI:1.1-2.8]; p=0.01) were predictors of AFC formation. PCV >44% and/or fluids =6l-first 72h (OR 5.6 [95%CI:1.8-17.3]; p=0.01) and BUN>20mg/dl(OR 8.9 [95%CI:2.9-27.6]; p<0.0001) were independent predictors for pseudocyst. BISAP >3 (OR 3.6 [95%CI:1.5-8.5]; p=0.01), AFC <6cm(OR 12.8 [95%CI:3.8-42.8]; p=0.0001), biliary(OR 2.5 [95%CI:1.1-5.5]; p=0.03) and idiopathic(OR 3.3 [95%CI:1.5-7.5]; p=0.01) etiologies were independently predictors of spontaneous resolution.

**Conclusion**: Markers of hemoconcentration are predictors for AFC/ pseudocyst development. 15% of AFCs require intervention. BISAP-AFC-size and etiology are independent predictors of spontaneous resolution.

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**PI-48 Abstract id: 36.**

**Acute pancreatitis severity evolution in diabetic patients: Relationship or causality?**

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**Introduction**: Diabetes may increase the risk of acute pancreatitis and may also adversely affect the evolution of the AP.

**Aims**: To evaluate if diabetes is associated with higher incidence of severe acute pancreatitis.

**Patients & methods**: Since 1997 to 2012 we treated 276 acute biliary pancreatitis. Severe Acute Pancreatitis (SAP) was 21.7% (60); among SAP were identified 13 (21.6%) critical forms (ESAP). Clinical features and therapeutic choices between SAP (47) and ESAP (13) were compared. We evaluated in each group, AP, SAP, ESAP, the prevalence of patients with diabetes.

**Results**: The comparison between SAP and ESAP shows the following results: impairment degree of pancreas (Balthazar CT score): SAP 2.3 – ESAP 3.85; abdominal compartment syndrome (ACS): ESAP 76% (11/13); MODS: ESAP 46.1% (6/13); simple organ dysfunction: SAP 51% (24/47) – ESAP 53.8% (7/13); hypoxemia: SAP 65.9% (31/47) – ESAP 46.1% (6/13); simple organ dysfunction: SAP 51% (24/47) – ESAP 53.8% (7/13); mortality: SAP 42% (2/47) – ESAP 15.4% (2/13). Among 276 patients with AP, 54 were diabetics and 222 non diabetics. The prevalence of diabetes in AP was 19.5% (54/276). In SAP group the prevalence of diabetes was 31.6% (19/60). About severity criteria diabetic patients had a prevalence of 23.3% (14/60) in single organ dysfunction and the prevalence of 23% (3/13) in MODS and moreover the prevalence of 6.6% (4/60) in septic complications of fluid necrotic collections.

**Conclusion**: The association of AP with the diabetes is in evidence: the risk of acute pancreatitis is raised by diabetes, but also of critical forms.

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**PI-49 Abstract id: 13.**

**Treatment of drug-induced pancreatitis in patients with pulmonary tuberculosis**

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**Introduction**: Treatment of patients with drug-induced pancreatitis is considered to be a difficult task for the doctors.

**Aims**: To evaluate the preparation’s based on bee products efficacy in patients with drug-induced pancreatitis on the background of the chemotheraphy of pulmonary tuberculosis.

**Patients & methods**: We examined 280 patients with pulmonary tuberculosis. Drug-induced pancreatitis was diagnosed in cases of the increase in α-amylase, lipase of blood more than 3 times. Patients abusing alcohol were not included in the study. Drug-induced pancreatitis was
PI-50 Abstract id: 167.
Experimental assessment of the anti-mediator therapy efficacy in severe acute pancreatitis

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Russian Pancreatic Club, Russia

Introduction: Changing concepts on SAP pathogenesis lead to the emergence of anti-cytokine therapy. Majority cytokine inhibiting activity medications did not demonstrate their efficacy due to the pleiotropy of cytokines effects.

Aims: To experimentally support the necessity of anti-cytokine therapy as a part of SAP conservative management.

Materials & methods: 30 male outbred CD rats. The anti-mediator therapy scheme: Lornoxicam or Ketorolac, 3 days, 1.6 mg/kg/day, 1 hour after Cerulein administration.

Blood tests for amylase, AST, ALT, cytokines (IL-10, IL-6, TNF-α); histological examination of tissue samples of pancreas, liver, kidneys, lungs.

Results: A mechanical SAP model was used to assess the efficacy of anti-mediator therapy. A rat was injected IM with a mixture of 5% ketamine and 2% xyflazine for anesthesia. Partial mechanical stenosis of common bile duct was made, resulting in bile passing into pancreatic duct, which, led to SAP. The bile passage was preserved. Cereuline 40 µg/kg was administered 1 hour post-op as an additional pancreatitis inducer.

Cytokine levels of intact animals group were used as a reference. Morphological signs of total necrosis of pancreas was observed in the mechanical model with cereuline administration. This model was characterized by a statistically significant increase in cytokine secretion (IL-10-72.39±11; IL-6 -457.19±25; TNF-α-34.62±9 pg/ml). Administration of both NSAIDs resulted in decreased cytokine levels, however, lornoxicam produced a more significant inhibiting effect (IL-10-47.66±7; IL-6-115.45±4; TNF-α-7.27±4 pg/ml).

Conclusion: NSAIDs can inhibit cytokine synthesis in the experimental SAP model. Lornoxicam caused significantly more pronounced decrease of cytokine secretion as compared to ketorolac. This study may provide rational for clinical trials of NSAIDs for SAP anti-mediator therapy.

PI-52 Abstract id: 311.
Acute pancreatitis: Prognostic value of the retroperitoneal fluid spreading

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Introduction: The present investigation focuses on the prognostic role of the computed tomographic (CT) imaging in severe acute pancreatitis (SAP). We suggest that insufficient attention has been paid to characteristics of the retroperitoneal fluid spreading.

Aims: The aim of study is to evaluate the prognostic usefulness of retroperitoneal inflammatory damage in SAP.

Patients & methods: From 2008 to 2012 CT examinations of 56 patients with SAP were retrospectively reviewed. Overall mortality rate was 33.5% (n=19). We evaluate different CT data in respect of their influence on systemic complications of SAP and mortality.

Results: We observed significant correlation between pancreatic parenchymal nonenhancement (points, according to Balthazar scoring system), number of patients having extended pancreatic necrosis and death (p<0.001; p<0.05, respectively). Surprisingly, there was no correlation between number of fluid collections and mortality rate. However, lateral extension of retroperitoneal fluid beyond the aponeurotic layer was closely associated with organ failure and death, (p<0.01).

Conclusion: Our results highlight the potential prognostic value of lateral exudate spreading in SAP. We consider, inflammatory infiltration of subcutaneous fat should be qualified as radiologic reflection of Grey-Turner sign.

PI-53 Abstract id: 244.
The value of procalcitonin, antithrombin III and BISAP score at predicting the severity of acute pancreatitis

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Introduction: Early recognition of severe acute pancreatitis (AP) would enable the clinician to consider more aggressive interventions within a time frame that could potentially prevent adverse outcomes. Procalcitonin and Antithrombin III have demonstrated, in some studies, to be good

PI-51 Abstract id: 134.
Implementation of percutaneous necrosectomy in infected pancreatic necrosis

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Introduction: Surgical interventions in infected pancreatic necrosis are associated with significant morbidity and mortality.

Aims: To improve the results of treatment of acute necrotizing pancreatitis.

Patients & methods: We have analyzed the results of treatment of 231 patients with ANP, treated in our clinic in the period of 2006-2010 years. Infected necrosis with septic complications was diagnosed in 111 (48,05%) patients. There were 56 (24,24%) female patients and 175 (75,76%) male patients, with an age, ranging from 18 to 79 years. Main group comprised of 14 patients with ANP, mainly with separated necrosis, in which percutaneous necrosectomy was done. In all patients ultrasound- controlled draining of peripancreatic fluid collections was done. Indications for the procedure was insufficient drainage of the peripancreatic fluid collection. In all patients drainages were put in the retroperitoneal space. In 13 patients necrosectomy was done in cases of left peripancreatic fluid collections, in 1 patient – in case of right retroperitoneal abscess. Drainages were taken away after complete stop of fluid output.

Results: Retroperitoneal necrosectomy was successful in 14 patients. In 2 patients reoperation was needed 8 and 12 days after procedure due to the progression of the disease. Drainages were taken away in patients on 5-34 postoperative days. No postoperative mortality and no procedure-dependent complications were observed in this group of patients. In the late postoperative period pancreatic pseudocyst occurred in 1 patient and chronic pancreatic fistula was formed in 1 patient.

Conclusion: In the selected patients percutaneous necrosectomy could be applied with satisfactory nearest results.
predictive serologic markers of AP severity, however, this characteristic remains controversial. BISAP score presents effective predictive value similar to APACHE II.

**Aims:** Determine the value of Procalcitonin, Antithrombin III and BISAP score as prognostic factors in early risk stratification of severe AP.

**Patients & methods:** Prospective study included 81 patients (16% with severe AP). In the first 24h and 48h of admission the procalcitonin, antithrombin III serum concentrations and BISAP score were determined.

**Results:** A total of 81 patients were included (51% males) with a median age of 64.42 years. Etiology: 60.2% biliary, 19.8% alcoholic, 26% post-ERCP, 3.8% toxic, 1.2% autoimmune, 1.2% hereditary, 1.2% anatomic, 1.2% traumatic and 8.7% idiopathic. According to Atlanta Classification 84% were mild and 16% presented severe AP. 96.1% had no complications, there were 4 deaths from serious systemic complications. There was correlation between Procalcitonin and BISAP score and the severity of AP on admission (p=0.008 and p=0.002, respectively). BISAP score correlated with complications of AP (p=0.019 on admission and p=0.001 at 48h). Antithrombin III (p=0.049) and BISAP score (p=0.009) showed correlations with the mortality (serious systemic complications).

**Conclusion:** In our experience, Procalcitonin and BISAP score showed to be good early predictors of severe AP on admission and Antithrombin III in prediction of fatal outcome.

**PI-54 Abstract id: 293.**

Usefulness of serum calprotectin in the determination of the severity of acute pancreatitis

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**Introduction:** Calprotectin (Cal) is a calcium-binding protein secreted predominantly by neutrophils and monocytes. Serum Cal is thought not to be a useful marker for early prediction of severity of pancreatitis.

**Aims:** To evaluate the role of serum Cal in the prediction of infected acute necrotizing pancreatitis.

**Patients & methods:** Between November 2011 and December 2012 patients with acute necrotizing pancreatitis admitted to our clinic were recruited. Additionally positive controls with edematous pancreatitis and healthy negative controls were enrolled into the study. Serum samples were prospectively taken for the measurement of Cal, procalcitonin (PCT), C-reactive protein (CRP) and white blood cell (WBC) count.

**Results:** 13 patients with acute necrotizing pancreatitis were recruited in the study (11 male, 2 female, mean age: 50.3±18.9y). The serum Cal level on the first day of admission differed significantly between the groups of infected necrosis and necrotizing acute pancreatitis (p<0.006) and between the group of infected necrosis and acute edematous pancreatitis (p<0.003); however there was no significant difference between necrotizing acute pancreatitis and edematous acute pancreatitis. Analyzing the time-course changes of the inflammatory parameters, in 70% of the cases Cal was the marker which elevated first. In 86% of the patients Cal elevation was followed by the increase in CRP level, while WBC count and/or PCT were slightly elevated or normal.

**Conclusion:** Serum Cal is elevated in acute pancreatitis, but it is not able to differentiate between edematous and necrotizing pancreatitis. Cal determination may be a useful marker to predict infected necrosis. Further cases are needed to evaluate its role in the diagnosis.

**PI-55 Abstract id: 339.**

Cholestasis is independent risk factor for post endoscopic retrograde cholangiopancreatography pancreatitis?

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**Introduction:** Acute pancreatitis is the most common major complication of endoscopic retrograde cholangiopancreatography (ERCP). Its incidence has substantial variations ranging from 5.1% to more than 25% of all ERCP procedures. In some cases pancreatitis is followed by severe course with pancreatic necrosis and multiorgan failure. Risk factors for post ERCP pancreatitis (PEP) are not well established.

**Aims:** We aimed to correlate influence of cholestatic parameters, eg total bilirubin, gamma-glutamyl transpeptidase (GGT), alkaline phosphatase (AP) and liver transaminases (AST and ALT) on development of PEP.

**Patients & methods:** During 2012 at the setting of tertiary care center, we conducted prospective study that included in-patients scheduled for ERCP. We recorded maximal values of above mentioned laboratory values before procedure and calculated correlation using t-test for independent samples. All patients received diclofenac sodium suppositories immediately before ERCP.

**Results:** We included total number of 169 patients, 94 males (55%) and 75 females (45%), mean age was 70.58±13.77 years. We observed PEP in 24 out of 169 patients (14%), 13 males (54.2%) and 11 females (45.8%). Mean duration of procedure was 45±26.00min. Mean values of bilirubin in the PEP patients was 193±31.22 μmol/l. We found significant positive correlation between level of total bilirubin, t (df=2167; 1.93) p<0.05 and GGT t (df=2167; 2.35) p<0.02 with occurrence of PEP. There is no correlation between AP and incidence of PEP, t (df=2167; -0.106).

**Conclusion:** Higher values of cholestatic markers observed in patients who developed PEP may be independent predictor for development of PEP.
PI-57 Abstract id: 47.

Assessment of the liver state in patients with chronic pancreatitis associated with metabolic syndrome
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Introduction: The major ingredients of the metabolic syndrome (MS) closely connect with functional state of the organs of the digestive system.
Aims: Purpose of investigation was to study some features of metabolic disturbances of the liver in the patients with chronic pancreatitis associated with MS.

Materials & methods: Material and methods: The study was carried out on 52 patients, of them 9 males and 43 females.

Results: The state of dyslipidemia expressed in the majority of patients with associated form of pathology showed formation of the resistance to insulin. The changes revealed in the blood lipid spectrum was accompanied by increase in levels of non-esterified fatty acids, on the average, tree times and indicated about damage of their transfer by blood and absorption by cells. Increase in blood of the levels of free fatty acids was accompanied by the hyperinsulinemia and provided disorder of the function of the receptors to insulin and absorption glucose by cells.

First of all the complex of systemic metabolic changes involves carbohydrate metabolism in the liver hepatocytes and the in the other organs. Under these conditions mitochondria and cellular membranes become insensitive to hormone effect and the pathological syndrome of resistance has been developed to the effect of insulin. The results of blood investigations showed also 2.5-fold higher levels of mitochondrial enzyme malate dehydrogenase (p<0.05).

Conclusion: Thus, in the patients with CP associated with MS there was observed disorders in the glucose-insulin homeostasis related to hormonal disorders and also to change of metabolism in the cells induced by free fatty acids.

PI-58 Abstract id: 12.

Influence of pinaverium bromide on the dynamics of pain intensity and ‘deviation’ of pancreatic enzymes to blood in patients with chronic pancreatitis (CP)
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Introduction: Organic and functional changes of Oddi’s sphincter have great importance in the pathogenesis of CP. Pinaverium bromide has spasmyotical influence on this sphincter.
Aims: To study the efficiency of the pinaverium bromide in the treatment of CP patients.

Patients & methods: We observed 64 patients with CP. 32 of them (main group) received traditional therapy in combination with pinaverium bromide. Other 32 patients (comparison group) received only traditional treatment. We studied the dynamics of pain and activity of blood and urine a-amylase and pancreatic isoamylase (P-isoamylase), level of lipase and pancreatic elastase-1 (18.7%) patients, moderate a<sub>V</sub> in 7 (10.9%) patients, severe a<sub>V</sub> in 5 (7.8%) patients. After treatment there was greater positive dynamics of fecal elastase level in study group versus comparison group. Normal fecal elastase-1 levels were detected in 18 (56.2%) and 20 (62.5%) patients, mild a<sub>V</sub> in 8 (25.0%) and 6 (18.7%) patients, moderate a<sub>V</sub> in 4 (12.5%) and 3 (9.4%) patients, severe a<sub>V</sub> in 2 (6.3%) and 3 (9.4%) patients of study and comparison groups, respectively. After treatment 1 patient of study group who initially had moderate pancreatic insufficiency after treatment had mild one. And 4 patients who initially had mild insufficiency after treatment had normal function. In comparison group patients who initially had moderate and severe pancreatic insufficiency after treatment still had insufficiency of the same degree. Only 1 comparison group patient who initially had mild insufficiency had normal function after treatment.

Conclusion: Addition of magnesium preparation to CP treatment improves exocrine pancreas function.

PI-59 Abstract id: 56.

Dynamics of exocrine pancreatic function in patients with chronic pancreatitis (CP) under the influence of magnesium preparation treatment
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Introduction: CP is an inflammatory disease characterized by impairment of exocrine function.
Aims: To study the effect of the magnesium preparation in CP treatment on exocrine pancreatic function.

Patients & methods: 64 patients with CP were examined. They were divided into 2 groups: 32 patients in each group. Study group patients in addition to conventional therapy received Magnesium preparation (1 ampoule per os tid). Comparison group patients received only conventional treatment. Pancreatic elastase-1 level was examined in stool at admission and after treatment.

Results: Before treatment test results were normal in 38 (59.4%) patients. Mild pancreatic insufficiency was observed in 14 (21.9%) patients, moderate a<sub>V</sub> in 7 (10.9%) patients, severe a<sub>V</sub> in 5 (7.8%) patients. After treatment there was greater positive dynamics of fecal elastase level in study group versus comparison group. Normal fecal elastase-1 levels were detected in 18 (56.2%) and 20 (62.5%) patients, mild a<sub>V</sub> in 8 (25.0%) and 6 (18.7%) patients, moderate a<sub>V</sub> in 4 (12.5%) and 3 (9.4%) patients, severe a<sub>V</sub> in 2 (6.3%) and 3 (9.4%) patients of study and comparison groups, respectively. After treatment 1 patient of study group who initially had moderate pancreatic insufficiency after treatment had mild one. And 4 patients who initially had mild insufficiency after treatment had normal function. In comparison group patients who initially had moderate and severe pancreatic insufficiency after treatment still had insufficiency of the same degree. Only 1 comparison group patient who initially had mild insufficiency had normal function after treatment.

Conclusion: Inclusion of pinaverium bromide into the treatment of CP could be effective.

PI-60 Abstract id: 75.

Famotidine in the treatment of chronic pancreatitis
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Introduction: Famotidine (H2- histamine blockers) firmly holds an appropriate place in the treatment of acid-dependent diseases (which include chronic pancreatitis).
Aims: To study the effect of famotidine (kvamatel) on lipid peroxidation in patients with chronic pancreatitis (CP), combined with coronary heart disease (CHD).

Patients & methods: The research included 51 patients with chronic pancreatitis and 10 healthy volunteers, of which there were 32 men, women - 31. The groups were matched for sex, age, duration of disease. Famotidine (kvamatel) was given by 20 mg at night and 20 mg in the morning 45 minutes after meals for 14 days. Product of lipid peroxidation (LPO) - malondialdehyde (MA) and reduced glutathione (as an enzyme that determines the reaction of antioxidant) in the blood investigated by the method of Y.A. Vladimirov, A.I. Archakova (1972) and modified by I.F. Meschisben (1983).

Results: Analysis of the results showed that lipid parameters significantly (p <0.005) higher in patients with CP combining with coronary disease.
artery disease than in patients only with CP. Famotidine therapy in this group of patients was significantly reduced lipid peroxidation indices (p < 0.05) and significantly improved the indices of reduced glutathione (p = 0.076), indicating drug normalizing effect on antioxidants protection system and improve quality of life of patients after 14 days of treatment.

Conclusion: Famotidine reduces lipid peroxidation and restores glutathione antioxidant link, which can be an indication for use in treatment of CP and CHD.

PI-61 Abstract id: 76.

Chronic pancreatitis: psychophysiological features adaptation of the patient
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Introduction: The mental state of patients with chronic pancreatitis (CP) defines the rate of recovery, quality of life and adaptation to existing conditions.

Aims: To study the psychophysiological adaptation of patients with chronic pancreatitis to determine the significance of psychogenic factors in recurrence disease and clinical prognosis.

Patients & methods: Examined 35 patients with chronic pancreatitis, of which 10 patients CP combined with peptic ulcer, 12 - with chronic cholecystitis men was 21, women - 14. Psychophysiological adaptation strategies examined by the Minnesota multipersonality questionnaire (MMPI) S. R. Hathaway.

Results: Thus, patients with uncompensated course of CP mental changes were detected in 80.2% of patients, and in 44% they were pronounced. Of the patients with uncompensated CP mental disorders were observed in 69.5%, and only 19.5% were severe. In compensation stage of CP psychopath symptoms were observed in 49.2% of cases, in 12.7% - was pronounced. By the nature of psychiatric disorders were the most diverse, but all patients had hypochondriacal disorder. MMPI data confirmed the clinical observations. All groups showed a general rise in the profile of MMPI, and above all - on the scales of the neurotic triad and with the highest peak by hypochondria scale, which indicates considerable fixing rate of attention on his health, the revaluation of the severity of the disease, inner tension, anxiety, depressed mood.

Conclusion: In patients with CP psychiatric disorders depend on the severity of the disease and are accompanied by deep neuroticism, hypochondriasis and depressive triad.

PI-62 Abstract id: 11.

New features in the treatment of patients with chronic pancreatitis on the background of obesity
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Introduction: There is a considerable increase of the frequency of obesity around the world in the last decade. Pancreatitis has more severe course on the background of obesity. In addition, obesity increases the risk of pancreatic cancer. The efficiency of L-carnitine is proved in the treatment of non-alcoholic steatohepatitis (M. Malaquarnera et al., 2010). L-carnitine wasn’t used in chronic steato pancreatitis.

Aims: To examine the effectiveness of L-carnitine in the treatment of chronic non-alcoholic steato pancreatitis in patients with obesity.

Patients & methods: We observed 68 patients with chronic steato pancreatitis on the background of obesity. Patients abusing alcohol were not included in the study. Patients were divided into 2 groups: main (conventional treatment of chronic pancreatitis + L-carnitine, 450 mg 3 times daily for a month) and the comparison group (only traditional treatment of chronic pancreatitis). We also examined 30 healthy persons. The dynamics of clinical manifestations, the activity of pancreatic isomlase of blood, sonographic changes of the pancreas were evaluated.

Results: In patients of main group the abdominal pain decreased or disappeared in 2.3 times more frequent than in the comparison group (p<0.01). The activity of pancreatic blood isomlase in the main group decreased significantly (p<0.01) and normalized. In the comparison group only non-significant trend to decreasing of pancreatic blood isomlase was observed. According to the results of sonography, structural changes of the pancreas after treatment were less marked in the main group.

Conclusion: L-carnitine is effective in the treatment of chronic non-alcoholic steato pancreatitis.

PI-63 Abstract id: 79.

Comprehensive assessment of quality of life in patients with chronic pancreatitis on the background of chronic obstructive pulmonary disease
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Introduction: Assessment of quality of life (QL) of patients in most developed countries has its valid place alongside traditional methods of examination and treatment of patients.

Aims: To study the quality of life of patients with chronic pancreatitis with concomitant COPD with the help of questionnaires: MOS SF-36 (Medical Outcome Study Short Form-36), GSRQ (Gastrointestinal Symptom Rating Scale) and St. George’s Hospital questionnaire (SGRQ).

Patients & methods: The study involved 58 patients, including 28 patients with COPD II-III stages without accompanying pathology, 30 patients with COPD II-III stages with concomitant chronic pancreatitis in unstable remission and 19 healthy individuals.

Results: Analysis of the results of the study showed that COPD patients with concomitant CP decrease physical (38.3 %) and mental (38.3 %) components of health according to MOS SF-36 compared with a group of healthy individuals (p<0.05). Considering the data of the GSRQ questionnaire the prevalence of dyspeptic syndrome in 76.7 % of COPD patients with CP has been revealed. Assessment of respiratory questionnaire of St. George Hospital has established an increase of rate “symptoms” scale (14.5%) in patients with comorbid diseases compared with isolated COPD.

Conclusion: Comprehensive assessment of QL of patients with a combination of pathologies, made it possible to find out the effect on the course of chronic pancreatitis COPD, and vice versa. These relationships between questionnaires revealed their interchangeability that simplifies operation and allows in practice to use one of them to assess the quality of life in patients with COPD with concomitant CP.

PI-64 Abstract id: 77.

Circadian and season features malondialdehyde indicators, reduced glutathione in patients with chronic pancreatitis (CP)
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Introduction: The value of circadian and seasonal rhythms in the course of chronic oxidative stress in patients with CP has been insufficiently studied.

Aims: To study the indicators of malondialdehyde and reduced glutathione in patients with chronic pancreatitis (CP), depending on the daily and seasonal rhythms.

Patients & methods: The study included 31 patients with chronic pancreatitis and 10 healthy volunteers, of which there were 19 men, women - 12. The groups were matched for sex, age, duration of disease.
Product of lipid peroxidation - malondialdehyde (MA) and reduced glutathione (as an enzyme that was determined reaction of antioxidant system) in the blood investigated by the method of Y.A. Vladimirov, A.I. Archakova (1972) modified by I.F. Meschishein (1983).

**Results:** The concentration of MA in the blood of patients with a chronic relapsing pancreatitis and chronic pancreatitis during the day was raised and had a nearly monotonic level. Level of reduced glutathione was decreased and also wore a monotonic nature, but was more stable. Fluctuations relative to seasonal rhythms of MA – the activity rate increases from October to March (which is clinically in 32.3% of patients with chronic pancreatitis was accompanied with exacerbation with varying degrees of severity) with a decrease in the late spring and summer. Indicators level of reduced glutathione in chronic relapsing pancreatitis depends on the degree of activation of lipid peroxidation.

**Conclusion:** Indicators of the level of reduced glutathione and malonic aldehyde have to be considered when we’re planning rehabilitation of patients with chronic pancreatitis, always taking care about particular season of the year.

**PI-65 Abstract id: 217.**

**Cystadenomas of the pancreas – 30 Years of experience**

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**Introduction:** Cystadenomas represent rare pancreatic cystic tumors.

**Aims:** To assess clinical, surgical and pathological features of patients operator for pancreatic cystadenoma.

**Patients & methods:** Over a 30 years period (1983-2013) we operated 62 (49 female and 13 male) patients for cystadenoma of the pancreas. There were 39 mucinous and 23 serous cystadenomas. Eleven patients had tumor in the head, while in 51 tumor involved the body and tail of the pancreas. Average tumor diameter was 67 mm. The leading symptom was epigastric pain in 42 patients (67.7%). Palpable mass was present in 17 (27.4%), weight loss in 16 (25.8%), nausea and vomiting in 17 (27.4%) and chronic diarrhea in 4 (6.4%). Accurate preoperative diagnosis was established in 41 (66.1%).

**Results:** Ideal excision was done in 17 patients (27.4%), with splenectomy in 4 (6.4 %), distal pancreatectomy with splenectomy in 38 (61.2%), with additional anastomosis between pancreatic duct in 1, excision of liver cyst in 1 and Whipple procedure also in 3. Malignant alteration was found in one patient with mucinous cystadenoma. One patient developed perforation of the small intestine and peritonitis, and despite reoperation in one patient with mucinous cystadenoma. One patient developed cyst in 1 and Whipple procedure also in 3. Malignant alteration was found with additional anastomosis between pancreatic duct in 1, excision of liver show an improvement too.

**Conclusion:** The preoperative diagnosis of cystadenoma of the pancreas can be established with high accuracy. A total excision can be carried out.

**PI-66 Abstract id: 6.**

**Peculiarities of manifestations of the chronic pancreatitis (CP) in patients infected with hepatitis B (HBV) and C (HCV) virus**

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**Introduction:** It’s known that HBV and HCV may affect the pancreas, but the peculiarities of course of the CP in this case aren’t studied.

**Aims:** To analyze manifestations of the CP in patients with chronic HBV- and HCV-infection.

**Materials & methods:** Study included 32 patients with CP who were diagnosed to have chronic hepatitis or cirrhosis of the liver caused by HBV or HCV.

**Results:** It was identified that patients had such peculiarities of the CP as: absent or mild pain syndrome; indurative-fibrose (‘pseudotumor-like’) pancreatitis with extrahepatic cholestasis; lack of the clear increase of enzymes in the blood (both of the pancreatic or hepatic origin); possibility of the moderate elevation of α-fliprotein and CA 19–9; start of manifestations from slowly progressing signs of the excretory pancreatic insufficiency; presence of HBV- or HCV-infection markers; association with chronic hepatitis or cirrhosis of the liver with minimal inflammatory-necrotizing activity.

As there was a replication of the viruses in all cases, patients received antiviral therapy (with HBV-infection - PEG-Interferon α2-b + ribavirin; with HCV-infection - PEG-Interferon α2-b). During the treatment 18 (56.3%) patients were noted to have positive dynamics of the indices of pancreatic enzymes in the blood and urine. Results of the sonography of the pancreas showed an improvement too.

**Conclusion:** Clinical and laboratory manifestations of the CP in patients with HBV- and HCV-infection have some peculiarities. CP takes its course as pseudotumor-like one. Antiviral therapy has certain effect in reducing the phenomenon of ‘deviation’ of enzymes in the blood.

**PI-67 Abstract id: 7.**

**Genetic variants of ethanol metabolism in patients with alcoholic chronic pancreatitis (CP) in Ukraine**

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**Introduction:** Pathogenesis of the alcoholic dependence includes a wide range of mechanisms. Genetic predisposition matters a lot among them.

**Aims:** To study the frequency of mutations of various genes of ethanol metabolism upon alcoholic CP in Ukraine.

**Materials & methods:** Examination included 72 patients with CP and 80 healthy persons. Genetic testing was performed to detect different isoforms of alcohol dehydrogenase (ADH) and aldehyde dehydrogenase (ALDH) genes. Variant of the polymorphism of ‘alcoholic cytochrome’ CYP2E1 -1293G/C increased in 1.3 and 3.5 times in comparison with control group.

**Results:** Majority of the patients had a combination of active form of ADH gene (ADH1B*2) and active form of ALDH gene (ALDH2*1) a•• 42 (58.3%) patients. Combination of low-activity form of ADH gene (ADH1B*1) and active form of ALDH gene (ALDH2*1) was detected in 14 (19.4%) patients. Combination of low-activity form of ADH gene (ADH1B*1) and low-activity form of ALDH gene (ALDH2*2) a•• in 11 (15.3%) patients. Combination of active form of ADH gene and low-activity form of ALDH gene was the rarest one (in 5 patients a••• 6.9%). Distribution of ‘alcoholic cytochrome’ genotypes -1293G/C CYP2E1 in patients with a combination of active form of ADH gene (ADH1B*2) and active form of ALDH gene (ALDH2*1) corresponded to: G/G a••• 14.2%, G/C a••• 47.1%, C/C a•• 38.7%. Number of patients with allelic variant of G/C and C/C gene CYP2E1 -1293G/C increased in 1.3 and 3.5 times in comparison with control group.

**Conclusion:** Peculiarities of the combinations of allelic variants of ADH, ALDH and CYP2E1 genes occur upon alcoholic CP.

**PI-68 Abstract id: 78.**

The dependence of triglycerides from the clinical course of chronic pancreatitis

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**Introduction:** Study the state of hypertriglyceridemia and its influence in the development of non-alcoholic fatty disease of the pancreas, chronic pancreatitis in obesity and coronary artery disease is important in explaining the pathogenesis of these diseases and their comorbidity.

**Aims:** To study the numbers of triglycerides in patients with chronic pancreatitis, depending on the duration of disease and age featuring.

**Patients & methods:** Examined 43 patients with chronic pancreatitis, and 12 healthy volunteers, of which there were 27 men, women - 16. The groups were matched for sex, age, duration of disease. Studied the indicators of triglycerides by enzymatic method, using standard diagnostic kits by “Simko Ltd” company (Ukraine).

**Results:** Analysis of the results showed that in healthy volunteers indicators of triglycerides was up to 1.7 mmol / l (1.43±0.04 mmol / l), with disease duration of 5 years (8 patients) showed a tendency to increase (p=0.127), with disease duration of 10 years (23 patients) rates exceed the established threshold and amounted to 2.36±0.08 mmol/l. Increasing rates were observed in 5 patients, predominantly obese 1-2 degrees, older than 42 years. Insulin resistance observed in 11 patients (out of 23 in this group), 2 patients detected type 2 diabetes, comorbidity with coronary heart disease was detected in 7 people.

**Conclusion:** Comorbidity of chronic pancreatitis, obesity and coronary heart disease increases hypertriglyceridemia, which is a risk factor for cardiovascular events in this group of patients and requires preventive measures.

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**PI-69 Abstract id: 334.**

**Autoimmune pancreatitis associated with intraductal papillary musinous neoplasly (IPMN)**

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**Introduction:** Autoimmune pancreatitis is characterised by chronic lymphoplasmocytic infiltration and fibrosis of the pancreas associated by high serum gammaglobulins especially serum IgG4. Autoimmune pancreatitis might lead suspicious pancreatic mass and can mimic pancreatic carcinoma. However there is no report about the association of IPMN and autoimmune pancreatitis.

**Aims:** Here we report a case with autoimmune pancreatitis and IPMN.

**Patients & methods:** Forty seven years old women was admitted to out patient clinic with abdominal pain for a year. Her evaluation showed elevated amylase and enlarged edematous pancreatic head. She was admitted to inpatient clinic with prediagnosis of acute pancreatitis.

**Results:** Radiological evaluation of the patient showed enlarged irregular pancreatic duct all along with enlarged side branches. Pancreatic paracynema was atrophic at tale of the pancreas. ERCP was performed and fish mouth papilla with thick musinous discharge was diagnostic for IPMN. EUS evaluation showed pancreatic IPMN as well as suspicious mass like lesion in the pancreatic head. Patient was operated with prediagnosis of IPMN and whope procedure was performed. Histopathology revealed lymphoplasmocytic sclerosing chronic pancreatitis that is autoimmune pancreatitis and also cystic tumour in the pancreas relevant with IPMN.

**Conclusion:** We reported an IPMN case developed in the background of autoimmune pancreatitis. This is the first case in the literature with autoimmune pancreatitis and associated IPMN. The typical initial findings were suspicious for IPMN however histopathological evaluation showed autoimmune pancreatitis associated with IPMN. This case showed that autoimmune pancreatitis may mimic IPMN and in the background of autoimmune pancreatitis IPMN may develop.

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**PI-70 Abstract id: 140.**

**Organ-preserving surgery in patients with chronic pancreatitis**

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**Introduction:** The use of resection surgery in patients with chronic pancreatitis (operations Beger, Frey pyloruspreserving pancreatoduodenal resection) is substantiates severe local morphological changes in the head of the pancreas.

**Aims:** to prove the same types fibrous changes in the head, body and tail of the pancreas in chronic pancreatitis, which cause to pancreatic ductal hypertension.

**Patients & methods:** In 59 patients with chronic pancreatitis was performed the developed organ-preserving operation. During the operation was carried out intake of the material for morphological studies at the same time from the head, body and tail of the pancreas. Histological and immunohistochemical methods were performed, and US, CT-scan, ERCP, intraoperative US, C-peptid, endogenous insulin, parathyroid hormone, CA - 19-9, Ig G, fecal elastase-1.

**Results:** It was shown the same type of morphological changes in the head, body and tail of the pancreas: a significant in size periductal fibrosis with focal of immune-cells infiltration, formation of connective tissue sheaths around the pancreatic ducts, penetration of a-SMA-positive stel late cells from periductal fibrosis in the area of interlobular stroma with the formation of fibrotic septa.

In the long term (5 years) in patients abdominal pain ceased. The sizes of the pancreas head has turned to normal for 4 – 6 months, and was no worsening of the exocrine and endocrine insufficiency.

**Conclusion:** Fibrous transformation of chronic pancreatitis is morphologically the same in all sections of the pancreas. Patients with chronic pancreatitis required organ-preserving type of operation with complete removal of ductal hypertension.

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**PI-71 Abstract id: 98.**

**The first experience laparoscopic proximal pancreatic resections in patients with chronic pancreatitis**

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**Introduction:** The use of laparoscopic access in treatment of chronic pancreatitis has to be explored.

**Aims:** The first experience laparoscopic proximal pancreatic resections in treatment of chronic pancreatitis was analyzed.

**Patients & methods:** 8 laparoscopic proximal pancreatic resections for chronic pancreatitis and its complications was performed in Vitebsk Regional Clinical Hospital. Women, 2, men 6. Mean age 40 A± 5.

**Results:** Laparoscopic proximal pancreatic resections were performed in 8 cases: the Beger procedure without proximal pancreatoenterostomy (BwPPE) 2 and the Berne modification (BM) 6. Mean operating time was 330±88 minutes. Blood loss was 105A±59 ml. Postoperative hospital stay was 8A±2 days.

**Conclusion:** Clinical experience in the use of laparoscopic procedures in chronic pancreatitis treatment supports the conclusions of other authors concerning the advantages of laparoscopic techniques which are of better tolerance and which shorten hospital stay. The application of minimally invasive surgery techniques may be effective on condition that there is a thorough selection of patients taking into account the anatomic features of the pancreas and its duct system in every individual case.
PI-72 Abstract id: 84.
Exocrine pancreatic insufficiency (EPI) after gastrectomy
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Introduction: Following gastric resections, EPI is a common clinical problem that may reflect a reduced enzyme-release response to endogenous stimulation or to reduced enzyme activation caused by bacterial overgrowth. Pancreatic enzyme replacement therapy (PERT) is indicated in patients who have undergone GI surgery with evident steatorrhea, weight loss or malabsorption. Whether asymptomatic patients with an abnormally high daily faecal fat excretion are candidates for substitution therapy is debatable. However, such patient has been often treated as irritable bowel disease, resulting in insufficient therapy and unsatisifed outcomes.

Aims: The aim of the study is to evaluate the efficacy of PERT for chronic diarrhea in patients with gastric surgery.

Patients & methods: A total of five patients, aged 41-82 years, with a past history of partial gastrectomy attended to our hospital with a chief complaint of diarrhea lasting for more than 3 months. Although they all had been treated with many kinds of drugs, diarrhea had not disappeared.

Results: PERT with pancrelipase was performed the assumption that asynchrony between the gastric emptying of nutrients and bilo-pancreatic secretion as a result of anatomical reconstruction and large and hard-to-digest nutrient particles reaching the jejunal lumen because of resection of the distal stomach might cause EPI. In 3 (60%) subjects, diarrhea was disappeared in 2 weeks after the beginning of PERT.

Conclusion: Exocrine pancreatic insufficiency after partial or total gastrectomy is a main cause of malabsorption and postoperative weight loss and should be treated with adequate PERT. Adequate substitution with pancreatic enzymes prevents malabsorption, improves postoperative nutritional status and may improve non-specific symptoms.

PI-73 Abstract id: 102.
Interconnection of the nervous tissue lesion in the head of the pancreas with the degree of fibrous changes
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Introduction: Nervous tissue lesion in the head of the pancreas.

Aims: To study the interconnection of the nervous tissue lesion in the head of the pancreas with the degree of fibrous changes as well as with the level of pain syndrome and QoL of patients with CP.

Patients & methods: 37 patients with CP were examined. The VAS was used to evaluate the intensiveness of the pain syndrome; the questionnaire SF-36 was applied to study QoL. The area of each nervous structure, the number of nerves and total area of the histological preparations used to evaluate the intensiveness of the pain syndrome; the questionnaire SF-36 was applied to study QoL. The area of the nervous tissue were evaluated at the microscopic research.

Results: While comparing the number of nerves depending on the fibrosis area it was found out that the number of nerves differs significantly at the 1st and 3rd degrees of fibrosis. While comparing the 1st and 2nd as well as the 2nd and 3rd these differences were unreliable. While comparing the area median of one nerve, one revealed no dependence on the fibrous changes. The area of the nervous tissue, numbers of nerves, area median of one nerve don’t correlate with the QoL as well as they don’t depend on the pain syndrome level.

Conclusion: At CP the lesion of the nervous tissue in the pancreas head depends on the degree of the fibrous changes. Proportion increase of the nervous tissue area to the pancreas tissue occurs due to the number of the nervous elements increase. The marked character of the pain syndrome and QoL doesn’t depend on the nervous tissue lesion.

PI-74 Abstract id: 228.
Frey procedure in patients with chronic pancreatitis
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Introduction: The Frey procedure is considered safe and realiable method for treatment of the patients with chronic pancreatitis.

Aims: The analysis of postoperative complications, pain relief and preservation of endocrine and exocrine functions of pancreas.

Patients & methods: From 2007 to 2012, 32 patients with chronic pancreatitis underwent the Frey procedure at First University Surgical Hospital, Clinical Centre of Serbia. Most of patients were male (81%), with mean age of patients about 54.3 years. The alcoholism was the most frequent ethiological factor for chronic pancreatitis (91%), and idiopathic in 3 patients, while the indication for surgery was pain in all of the patients. A scoring system used for assessing the severity of pain consisted of a visual analogue scale, frequency of pain attacks, analgesic requirement and time of disease-related inability for work. An oral glucose tolerance test was used for assessing pancreatic endocrine insufficiency, and the presence of steatorrhea for the estimation of exocrine pancreatic function.

Results: mean follow-up was 18 months. Pancreatic leakage was most frequent postoperative complication and it was present in 5 patients. One patient reccurred reoperation for anastomotic leakage, and one death occured because occurance of pancreatic fistula and consecutive septic condition. In 91% of our patients endocrine function was preserved and exocrine function was not altered in any of patients. Complete pain relief was achieved in 27 patients.

Conclusion: According to our experience, Frey procedure provides a long time pain relief in the majority of patients with chronic pancreatitis and it also enables preservation of endocrine and exocrine function of pancreas.

PI-75 Abstract id: 325.
When in doubt, take it out? Cholestasis and obstructive gastric outlet syndrome in a patient with chronic pancreatitis
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Introduction: In some patients with tumors located in the pancreas or in the periampullary region, the decision to perform a surgical resection is dificult and even more challenging in patients with chronic pancreatitis (CP), since a definitive preoperative differentiation between non-malignant and malignant tumors is often not possible. In rare cases an uncommon non-malignant entity like a periampullary hamartoma may be diagnosed after surgical resection only.

Aims: To present an interesting and informative case report.

Patients & methods: A 52-year old man presented with the diagnosis of CP. During a former hospital stay, abdominal ultrasound revealed a dilated main common bile and a slightly dilated main pancreatic duct and a pancreatic pseudocyst. The origin of CP was linked to alcohol. On abdominal ultrasound, the main common bile duct was dilated to 12 mm and the pancreatic duct was dilated to 6 mm. Endoscopic ultrasound could not be performed, since the duodenum was compressed. A CT scan revealed an isodense tissue alteration with cystic tumor in the region of
The Papilla Vateri with dilatation of the pancreatic and biliary ducts and intrahepatic cholestasis.

**Results:** After extensive discussion the patient underwent pylorus-preserving pancreatectoduodenectomy. Histology revealed congenital cystic lesions consistent with a solid and cystic periampullary hamartoma and no malignancy and no signs of CP.

**Conclusion:** In conclusion, the paradigm “when in doubt, take it out” should not be applied to all patients. Surgery should be recommended for those patients that are symptomatic and if malignancy cannot be ruled out, such as in the patient described in this case report.

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**PI-76 Abstract id: 100.**

The relationship between the quality of life, severity of pain and morphological changes in the pancreas in chronic pancreatitis

Sergey Lyarski.

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**Introduction:** We investigate the relationship between the indicators of QoL, severity of pain and morphological changes in the pancreas in CP.

**Aims:** To investigate the relationship between the indicators of quality of life, severity of pain and morphological changes in the pancreas (P) in chronic pancreatitis (CP).

**Patients & methods:** 51 patients were examined. To evaluate the intensity of pain the visual analogue scale (VAS was used); to examine the quality of life (QoL) questionnaire SF-36 was used. Material for microscopic examination was taken during the resection of the pancreas head.

**Results:** A wide range of fibrotic changes in the pancreas head was revealed. The correlation between the intensity of pain, QoL and an area of fibrosis was not significantly different. When comparing groups of patients with pancreatic head size of less than 40 mm and more than 40 mm, the area of fibrosis was not significantly different. When comparing groups of patients with the width of the main pancreatic duct (MPD) of less than 6 mm and more than 6 mm, the area of fibrosis was not significantly different.

**Conclusion:** QoL and intensity of pain don’t correlate with the degree of fibrotic changes occurring in the pancreas head. Pancreatic head size and width of the main pancreatic duct don’t depend on the degree of fibrotic changes in the pancreas head.

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**PI-77 Abstract id: 3.**

Clinical observation of carcinoid tumor of the pancreas

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**Introduction:** Carcinoid tumors of the pancreas are rare ones. Their frequency is 0.5-1% of all tumors of the organs of abdomen (A. Burgos et al., 1998).

**Aims:** We managed to observe a patient with this pathology.

**Patients & methods:** Patient O., 55-year-old, was delivered to the hospital with complaint about aching pain in the left hypochondrium after eating, thirst, dry mouth, weight loss of 8 kg over period of 6 months.

**Results:** She considers herself to have been ill for 3 years. Ultrasound revealed a hypoechogenic area of a size 7.6 cm in the tail of the pancreas. Cancer of the pancreas was diagnosed, and symptomatic treatment was recommended. However, patient felt satisfactorily and continued working. State of health worsened in 3 years, when the thirst appeared, and she began to lose weight. Diabetes mellitus was diagnosed. Re-CT showed only slight increase in the formation of the pancreas. In view of the long duration of disease the diagnosis of pancreatic cancer was rejected, and patient was delivered to the hospital with a preliminary diagnosis of pseudotumor-like pancreatitis.

**Conclusion:** There’s no anemia. Amylase and lipase in the blood are normal. Fecal elastase-1 is equal to 124 mcg/g. There’s a decrease in the level of C-peptide, hyperglycemia and a small increase in the level of serotonin in the blood.

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**PI-78 Abstract id: 4.**

Clinical observation of 62-year-old patient with pancreas annulare

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**Introduction:** Pancreas annulare is a rare anomaly of the pancreas, which is diagnosed in newborns or in early childhood.

**Aims:** Patient R., 62-year-old, had a complaint on feeling of heaviness in the epigastrum, worsening after eating, hiccups, vomiting with a food eaten more than a day ago, evident general weakness, weight loss. He noted pain in the left hypochondrium. Abdominal distension, liquid stool, presence of the undigested food debris in the feces were disturbing him.

**Patients & methods:** He’s been ill for almost 20 years. Vomiting, which had been lasting for 2-3 weeks, appeared on the background of the pain syndrome. In those periods he noticed remnants of food eaten more than a day ago in vomit mass, he lost up to 10 kg of body weight during that time too. Then vomiting ceased gradually, and patient put on former body weight. During the acute condition of disease patient was diagnosed for several times to have decompensated pyloric stenosis of unknown origin. Mild form of diabetes was revealed 5 years ago.

**Results:** The general state of health is satisfactory, with decreased state of nutrition.

**Conclusion:** Patient was diagnosed to have pancreas annulare, chronic pancreatitis with a pseudocyst in the head of the pancreas. Gastro-enteroanastomosis was performed. Current state of the patient is satisfactory now. He receives enzyme replacement therapy.

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**PI-79 Abstract id: 80.**

Retrospective analysis of risk factors for postoperative pancreatic fistula after distal pancreatectomy

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**Introduction:** Postoperative pancreatic fistula (PF) after distal pancreatectomy (DP) is the most critical complication.

**Aims:** The aim of this study was to determine risk factors associated with the occurrence of clinical PF after DP.

**Patients & methods:** Twenty patients who underwent DP between April 2006 and February2013 were enrolled in this study. The relationship between the incidence of PF and several clinical factors (age, gender, body mass index, serum albumin level, existing of diabetes, intra operative bleeding and operation time) was retrospectively analyzed. PF was defined according to the criteria by the International Study Group on Pancreatic Fistula.
Results: Although 15 patients (75%) had Grade A PF, clinically relevant Grade B PF was found in only 4 patients (20%). Moreover, there were no patients with Grade C PF and/or surgery-related mortality. As for risk factors, univariate analysis revealed that compression thickness of pancreatic stump divided by the stapler alone was a significant risk factor.

Conclusion: The incidence rate of clinically relevant PF after DP is relatively low as previous reports showed. The most important risk factor for PF was considered to be the thickness of the pancreatic stump.

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PI-80 Abstract id: 22.
Solid tumors of the pancreas can put on a mask through cystic change
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Introduction: Solid pancreatic tumors such as pancreatic ductal adenocarcinoma (PDAC), solid pseudopapillary tumor (SPT), and pancreatic endocrine tumor (PET) may occasionally manifest as cystic lesions.

Aims: In this study, we have put together our accumulated experience with cystic manifestations of various solid tumors of the pancreas.

Patients & methods: From 2000 to 2006, 376 patients with pancreatic solid tumor resections were reviewed. Ten (2.66%) of these tumors appeared on radiological imaging studies as cystic lesions. We performed a retrospective review of medical records and pathologic findings of these 10 cases.

Results: Of the ten cases in which solid tumors of the pancreas manifested as cystic lesions, six were PDAC with cystic degeneration, two were SPT undergone complete cystic change, one was cystic PET, and one was a cystic schwannoma. The mean tumor size of the cystic portion in PDAC was 7.3 cm, and three patients were diagnosed as pseudocyst with or without cancer. Two SPT were found incidentally in young women and were diagnosed as other cystic neoplasms. One cystic endocrine tumor was preoperatively suspected as intraductal papillary mucinous neoplasm or mucinous cystic neoplasm.

Conclusion: Cystic changes of pancreas solid tumors are extremely rare. However, the possibility of cystic manifestation of pancreas solid tumors should be kept in mind.

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PI-81 Abstract id: 136.
Was the Wirsung duct discovery facilitated by intemperate alcohol consumption in 17th century Italy?
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Introduction: The story of Johann Georg Wirsung (1589-1643) is very well known. Much has been written about his life. Wirsung discovered the pancreatic duct on March 2nd, 1642 during an autopsy of Zuane Viaro Della Badia, a 30-year-old murderer who had been hanged the day before. Instead of publishing his discovery, he engraved a drawing of the duct on a copper plate, from which he made at least seven imprints. The copies were sent to leading anatomists of Europe to obtain their opinion. Wirsung was shot to death on August 22nd, 1643; conflict over the discovery of the duct was suggested as the most probable reason for the assassination. The story of Wirsung is fascinating in itself. However, other circumstances of the discovery attracted our attention.

Aims: Our main hypothesis is that Zuane Viaro suffered from chronic pancreatitis.

Patients & methods: Several facts support this hypothesis:

Results: - Chronic pancreatitis is a well known entity throughout history.
- Alcohol consumption in 17th Italy century was intemperate; especially wine consumption was higher than nowadays.

Conclusion: In conclusion, possible alcohol abuse and resulting chronic pancreatitis of Zuane Viaro could have enabled Wirsung to discover the pancreatic duct at the autopsy.

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PI-82 Abstract id: 126.
Total gastropancreatectomy with portal vein resection for giant renal-cell cancer metastases into the pancreas: a report of two cases
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Introduction: Renal-cell cancer metastases into the pancreas are relatively common. However, total gastropancreatectomy has not yet been reported in patients with giant renal-cell cancer metastases into the pancreas.

Aims: To present the results of two total gastropancreatectomies for giant renal-cell cancer metastases into the pancreas.

Patients & methods: Both patients were 61 and 64-years old male. Patient one presented 14 years after left nephrectomy for renal-cell cancer with diabetes, anemia and a 17 cm mass, involving entire pancreas, stomach and portal vein with a thrombus. Three small lung lesions were also found. Patient two presented 12 years after right nephrectomy for cancer with a solitary 12 cm pancreatic mass with portal vein, splenic vessels, left gastric artery and colonic mesentery involvement.

Results: Patient one underwent total gastropancreatectomy with portal vein resection, thrombectomy and prosthetic repair and was discharged on post-operative Day 12 to get targeted therapy. Patient two had total gastropancreatectomy, portal vein and colon resection. Colonic anastomotic leak with multi-organ failure developed leading to ileostomy and 70 days of hospital stay. Despite the absence of cancer progression and massive enzyme substitution in both cases severe malnutrition developed necessitating frequent institutionalization. Patient one died from myocardial infarction 9 months after surgery. Patient two is alive 10 months after surgery, however, cachectic and receiving semi-elemental enteral nutrition.

Conclusion: Total gastropancreatectomy with portal vein resection is a technically feasible and might be prognostically favorable procedure in giant renal-cell metastases into the pancreas. However, it leads to severe malnutrition and necessitates intensive follow-up and nutritional support.

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PI-83 Abstract id: 9.
Giardiasis with a lesion of the pancreas
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Introduction: Lamblias may have a direct pancretotoxic effect by the penetrating into the parenchyma of the pancreas and causing the development of pseudotumor-like pancreatitis (I. Nakano et al., 1995). There’s a possible risk of development of the exocrine pancreatic insufficiency and diabetes mellitus (T. Miyahara et al., 1997).

Aims: To evaluate the exocrine pancreatic function in patients with chronic pancreatitis and giardiasis.

Materials & methods: The study included 28 patients with chronic pancreatitis and giardiasis. Diagnosis was confirmed by the presence of antibodies in the blood. Specific antigen GSA 65 was detected in the stool. All patients underwent fecal elastase test (with a lyophilization of feces) and sonography. Two patients with pseudotumor-like pancreatitis underwent percutaneous trepanobiopsy of the pancreas.
Results: Such peculiarities of the chronic clinical pancreatitis in patients with giardiasis as the apparent asthenic syndrome, aching moderate abdominal pain attracted our attention. According to the sonography, pseudotumor-like pancreatitis occurred in 15 (33.6%) patients. Lamblia were detected in the tissue of the pancreas of 2 patients who underwent a biopsy of that organ. In accordance with the results of fecal elastase test, severe pancreatic insufficiency was detected in 5 (17.8%) patients, moderate and mild insufficiency were identified in 7 (25.0%) and 8 (28.6%) patients respectively. Normal levels of fecal elastase-1 were defined in 8 (28.6%) patients.

Conclusion: Patients with giardiasis have pancreatic insufficiency in almost 1/4 of cases, and more than half of them have pseudotumor-like variant of the chronic pancreatitis.

PI-84 Abstract id: 287.
Massive gastrointestinal bleeding in an 82nd day-post-pancreatoduodenectomy patient caused by a portoenteric fistula and complicated by a Meckel’s diverticulum: A case report
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Introduction: Post-PD hemorrhage occurs in 2-15% of all patients.
Aims: We report an unusual cause of gastrointestinal bleeding three months after pancreaticoduodenectomy

Patients & methods: SP, 50/M, underwent PPPD for ampullary adenocarcinoma. Pancreaticejejunostomy was done using duct/mucosa technique. Patient had an unfavorable post-operative course and was discharged on 7th POD.

Results: On 82nd POD, he had episodes of melena/hematochezia. He underwent UGI endoscopy. Scope was inserted 20 cm into efferent limb, 10 cms into afferent limb. No note of any active bleeding nor recent bleed. Colonoscopy revealed blood clots at cecum with no masses, polyps or diverticulum.

At ICU, while awaiting for angiogram, patient had melena/hematochezia with hemodynamic instability. A decision to operate was made. During laparotomy, there was note of Meckels diverticulum 80 cms from IVC. Intraoperative colonoscopy showed clots from rectum to transverse colon without bleeding. Enteroscopy proximal to diverticulum showed visualization of 120 cms of bowel proximal to diverticulum without bleeding. Enterocolonoscopy from diverticulum to ascending colon showed clots without bleeding. Ileal mucosa adjacent to the diverticulum was boggy with superficial erosions. Segmental resection of ileum including the diverticulum with en bloc right hemicolectomy with hand sewn anastomosis was performed. The area of pancreaticoduodenectomy was intact.

Conclusion: On second post-operative day, there was recurrence of hematochezia with hypotension. Repeat laparotomy showed blood-filled small bowels and stomach. Entotomy of afferent limb showed a connection between the jejunum and portal vein. All anastomoses were intact. There were no signs of inflammation. The patient went into CP arrest during exploration and was not revived.

PI-85 Abstract id: 51.
Pancreaticobiliary ductal anatomy in normal population
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Introduction: The complex anatomy of the pancreaticobiliary duct was crucial in management of pancreatic disease.
Aims: To demonstrate the basic data of pancreaticobiliary ductal anatomy.

Patients & methods: Fresh specimens of the pancreas were obtained en bloc from the autopsies of 150 patients who had no pancreatic disease. Methylene blue infusion via the pancreatic duct cannulation and careful dissection was performed.

Results: Ninety-three male and 67 female patients were included (age 15-78 years). The mean length of the pancreas was 16.2±1.7 cm (9.8-20) cm. The intrapancreatic portion of the common bile duct showed patterns of three types; most common 85.30% was type A, in which the anterior surface of the common bile duct was totally covered, while its posterior surface was partially covered, by the pancreatic parenchyma. On dissection of the accessory duct of Santorini, the accessory duct was traceable to the duodenal wall in 67.56%. The anatomy of the Wirsung-choledochus confluence was grouped into five different types. The common channel (junction of the common bile duct and pancreatic duct) was found in 75.60% of specimens and its length varied from just a common junction (so-called “V-type” anatomy) to 15 mm (Y-type-b). Separate papillae (ill-type) were found in 15.72% of specimens. Separate openings in the same papilla (U-type) were found in 13.54% of specimens. The Wirsung duct at the pancreatic neck was most often located posterior and superior in relation to the surface of pancreas.

Conclusion: Several important points regarding the anatomy of the pancreaticobiliary junction and pancreatic ductal system were illustrated in this study.

PI-86 Abstract id: 124.
Exocrine pancreatic insufficiency in patients with celiac disease
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Introduction: The association between celiac disease (CD) and exocrine pancreatic insufficiency (EPI) was a topic of many researches in which different diagnostic methods were used.
Aims: To determine whether exocrine pancreatic function is impaired in patients with CD in our population. We are presenting preliminary results.

Patients & methods: Pancreatic exocrine function was determined by the fecal elastase-1 concentration (FEC). Patients were divided into three groups: A - newly diagnosed CD; B - known CD patients on a gluten-free diet (GFD) and C - patients with known CD on a normal diet (those who refused medical advice).

Results: There are currently 46 patients included in the study, 34 (73.9%) female and 12 (26.1%) male, mean age 44.4±7.0 years (range 20-76). Mean duration of CD was 5.8±7.8 years. There were 13 (28.3%) patients with Marsh 3 CD; 9 (19.5%) patients with Marsh 2 CD; 8 (17.4%) patients with Marsh 1CD and 16 (34.8%) Marsh non-classified patients (no histology data in medical records). The majority of patients had known CD on GFD (n=37; 80.4%) followed by newly diagnosed CD (n=5; 10.9%) and known CD without GFD (n=4; 8.7%). FEC was reduced in 2 (4.35%) patients: moderately reduced (FEC 131 µg/g) in 69– year-old male with newly diagnosed CD Marsh 1 and severely reduced (FEC 63 µg/g) in 24-year-old female with known CD Marsh 3 on GFD.

Conclusion: EPI occurred much less frequently than in previous studies. However, these results may have an impact on the daily work of the clinician. Follow-up of patients with CD should include evaluation of EPI.

Results: In accordance with the results of fecal elastase test, severe pancreatic insufficiency was detected in 5 (17.8%) patients, moderate and mild insufficiency were identified in 7 (25.0%) and 8 (28.6%) patients respectively. Normal levels of fecal elastase-1 were defined in 8 (28.6%) patients.

Conclusion: Patients with giardiasis have pancreatic insufficiency in almost 1/4 of cases, and more than half of them have pseudotumor-like variant of the chronic pancreatitis.
PI-87 Abstract id: 14.
Non-alcoholic fatty disease of the liver and pancreas: Frequency of combination
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2 Lviv National Medical University n. a. D. Galitsky, Ukraine

Introduction: Problem of Absorption of such an independent nosological form as non-alcoholic fatty disease of the pancreas has been widely debated in the past few years (M. M. Smits, 2011).

Aims: To study the frequency of combination of non-alcoholic fatty disease of the liver and pancreas according to the results of computed tomography.

Patients & methods: 180 patients with obesity were examined. All patients underwent computed tomography with an assessment of the organs’ density pursuant to the Hounsfield scale. Presence of fatty infiltration of both organs was determined upon the identification of hypodensia. Other computer-tomographic signs of steatosis of the liver and pancreas were also taken into consideration, particularly, steatosis of the pancreas was accompanied by a lobulation and certain lack of clarity of its structure. Density of the pancreas in the regions of its head, body and tail was determined.

Results: Combination of steatosis of the liver and pancreas was detected in 126 (70.0%) patients. Steatosis of the pancreas in conjunction with a normal density of the liver was detected in 45 (25.0%) patients according to the results of computed tomography. The rarest variant that presupposed steatosis of the liver upon the absence of fatty infiltration of the pancreas was diagnosed in 9 (5.0%) patients.

Significant differences of the densitometric density of the pancreas in its head, body and tail were not found.

Conclusion: In the majority of cases, both steatosis of the liver and steatosis of the pancreas are developing in patients with metabolic syndrome.

PI-88 Abstract id: 321.
Ectopic pancreas in the gastric antrum: A spectrum of imaging findings
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Introduction: EP has been associated with inflammation, bleeding, intussusceptions and even adenocarcinoma. Surgical resection is indicated when it is symptomatic, but whether to remove suspected EP that is found incidentally remains controversial.

Aims: To describe egds, rx and eus findings of suspected EP in the gastric antrum in order to identify features useful for a correct diagnosis and for an appropriate and safe management.

Patients & methods: From October 2011 to January 2013 barium contrast upper gastrointestinal series, CT scans and EUS were performed in 7p. With suspected localization of EP in the gastric antrum.

Results: In 5 p. EGDS and rx, suspected EP presented similar features (nodular masses < 1 cm with central umbilication in the gastric antrum on the greater curvature). One p.showed at rx study the presence of a thin blind-fistula. The CT confirmed no connection with the adjacent organs. The echo pattern was heterogeneous: hypechoic images with internal small hyperechoic areas. Tissue was located in the II and in the III layers. In these p. treatment was conservative and endoscopic follow up at 6 months reveal no changes. In 2 patients suspected EP presented with nodular mass > 2 cm. P1:EMR was performed because of the increasing mass, the EUS marked heterogeneity and severe and frequent pain. Histologic findings reveal EPP2.25 mm mass, antrectomy was performed because the IV layer was involved at EUS. Histologic reveal GIST.

Conclusion: These case reports confirm that the gastric EP diagnosis requires further investigations in order to obtain a better characterization of each lesion and to perform an individual and safe management.

PI-89 Abstract id: 205.
Evaluation of the emergency department applications in patients with pancreatic cancer
Hacettepe University School of Medicine, Emergency Department, Turkey

Introduction: Pancreatic cancer is progressive disease leading to various clinical and oncological emergencies with poor prognosis and high rate of mortality.

Aims: Emergency applications of pancreatic cancer are available in only form of case reports in English Literature.

Patients & methods: Between the dates of 01/01/2005 and 12/31/2012, records of patients over 18 years of age with pancreatic cancer admitted to Emergency Department of Hacettepe University were retrospectively reviewed.

Results: 87 patients (59 M) with 114 applications were enrolled in the study. The mean age was 61 (22-93) years. The thirteen patients (15%) were newly diagnosed as pancreatic cancer in the emergency department. Most common complaints were thrombembolic events in 18 patients, and abdominal pain, distention and flatus in 18 patients, which were followed by sepsis in 15, vomiting and diarrhea in 15, fleus in 11 respectively. Tumor grades were as follows, stage 1 in 19; stage 2 in 15; stage 3 in 2; stage 4 in 51 patients respectively. 31 patients underwent pancreatic resections (23 Whipple, 5 distal pancreatectomies and 3 total pancreatectomies). A total of 17 (15%) patients died.

Conclusion: Patients with pancreatic cancer might be admitted to emergency department due to various reasons including exocrine pancreatic insufficiency (EPI) at different stages of the disease. Although emergency physician should treat the cause of the complaint selectively, EPI should be also kept in mind in all patients as it could be treated with simple enzyme replacement therapy.

PI-90 Abstract id: 93.
Pylorus-preserving pancreaticoduodenectomy with technique modifications
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Introduction: Pylorus-preserving pancreaticoduodenectomy (PPPD) is a technique-demanding procedure with high complication rates.

Aims: To share our experience of PPPD in a high-volume center for pancreatic surgery in China.

Patients & methods: PPPDs in our center are performed with modifications: 1. Pancreaticojunostomy (P-J): P-J is typically performed in end-to-side invagination fashion. The posterior inner row of anastomosis is first placed with interrupted stitches, taking bites of parenchyma on pancreatic side and full thickness bites of bowel wall on jejunal side. The anterior inner row is subsequently finished in the same fashion. After inner layer accomplished, posterior and anterior outer rows are performed with
interrupted suture sequentially, which approximate jejunal serosa to pancreatic capsule, thus allowing invagination of pancreatic stump into jejunal. 2. Omental patch: A strip of omentum is prepared and patched surrounding P-J, isolating this anastomosis from free abdominal cavity, and especially important vessels. 3. Duodenojejunosotomy (D-J): Before anastomosis, clamped duodenal resection margin is first cauterized for hemostasis and sealing the wall into one layer. Then inner layer of anastomosis with running suture is placed, taking bites of the single layer on duodenal side and full thickness bites of bowel wall on jejunal side. Outer layer is performed with continuous Lembert sutures. 4. Intraluminal anastomosis with running suture is placed, taking bites of the single layer mostasis and sealing the wall into one layer. Then inner layer of anastomosis, clamped duodenal resection margin is surrounded P-J, isolating this anastomosis from free abdominal cavity, and jejunum. 2. Omental patch: A strip of omentum is prepared and patched pancreatic capsule, thus allowing invagination of pancreatic stump into periampullary tumors. This procedure carry a significant risk and mortality. No one of our patient developed pancreatic leak, acute pancreatitis, 5% were having intra-abdominal collection, 15% were having wound dehiscence, 15% of the patients developed biliary leak, 10% experienced delayed gastric emptying, 5% were having intra-abdominal collection, 15% were having wound infection, 5% developed wound dehiscence, 15% of the patients developed atelectasis, 5% diagnosed with DVT and 10% with PE, 10% of the patient were died due to intraoperative hemorrhage as a result of porta hepatis injury. No one of our patient developed pancreatic leak, acute pancreatitis nor cholangitis. PI-91 Abstract id: 21.

Is pancreaticogastrostomy a safe procedure?
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Introduction: Pancreaticoduodenectomy is treatment of choice for periampullary tumors. This procedure carry a significant risk and morbidities. Most of them are related to pancreatic anastomotic failure. For that many techniques has been established to decrease the morbidity rate, pancreaticogastrostomy is one of those techniques.

Aims: evaluate the pancreaticogastrostomy procedure after pancreaticoduodenectomy

Patients & methods: Design: Retrospective review was done for all patient who diagnosed with periampullary tumor between 2008 to 2012. Setting: king Faisal Specialist Hospital & Research Center- Jeddah, Saudi Arabia. Outcome Measures: Indication for surgery, intra-operative and post operative variables, operative technique and post-operative complications.

Results: In group of patient who underwent pancreaticogastrostomy (n=20) including 10 males and 10 females, the mean age was 56.2 years. The histopathology post operatively showed 4 benign tumors and 16 malignant tumors, with mean size of tumor 3.39 cm in diameter. The median hospital stay was 10.8 days with median survival months were 13.05 months. The complications from pancreaticogastrostomy following pancreaticoduodenectomy has been calculated as following 5% of the patients developed biliary leak, 10% experienced delayed gastric emptying, 5% were having intra-abdominal collection, 15% were having wound infection, 5% developed wound dehiscence, 15% of the patients developed atelectasis, 5% diagnosed with DVT and 10% with PE, 10% of the patient were died due to intraoperative hemorrhage as a result of porta hepatis injury. No one of our patient developed pancreatic leak, acute pancreatitis nor cholangitis.

Conclusion: Pancreaticogastrostomy is a safe procedure with a relatively low mortality and morbidity rate. It should be considered as a suitable choice after pancreaticoduodenectomy.

PI-92 Abstract id: 199.
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Introduction: Current strategy for local advanced pancreatic adenocarcinoma (LAPC), based on chemotherapy and radiation therapy, shows poor outcome. A novel form of tissue ablation has been proposed in the treatment of solid tumors with promising results: irreversible electroporation (IRE). The technique uses high voltage pulses applied to the target tissue to induce cells’ apoptosis.

Aims: We aim to show the efficacy and safety of IRE as a palliative treatment on clinical outcome of LAPC.

Patients & methods: A 59-year-old caucasian man diagnosed in January 2012 with a stage III (T4N1M0) LAPC of the body-tail (60x30mm) encasing the superior mesenteric vessels and the small gastric curve underwent a 6 months neo-adjuvant gemcitabine-based chemotherapy and was planned for Whipple procedure. Since the tumor was still unresectable, US-guided IRE using the NanoKnife System by Angiodynamics has been performed.

Results: Postoperative course was uneventful and the patient was discharged six days after the treatment. The follow up at one month, 3 and 6 months showed a CT-scan-documented reduction of the primitive mass (40x22mm VS 60x30mm). CA 19.9 levels’ trend showed also a decrease. After 15 months from the diagnosis the patient is still alive in a state of mental and physical wellbeing.

Conclusion: IRE promises encouraging results in local control of LAPC. The technique has shown to improve both the overall survival and the quality of life compared with previous palliative strategies. Further studies are needed to elucidate the real advantages of this innovative technique and its future application even in the management of resectable pancreatic adencarcinomas instead of conventional surgery.

PI-93 Abstract id: 145.
Characteristics of patients with chronic pancreatitis and pancreatic cancer
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Introduction: Chronic pancreatitis is a chronic inflammatory disease of the pancreas leading to exocrine and endocrine pancreatic insufficiency. Pancreatic cancer is a malignant neoplasm of the exocrine pancreas in which the mortality rate is almost equal incidence of disease. The disease is diagnosed at a late stage and the surgical treatment possible in only 10-15% of patients. Chronic pancreatitis and pancreatic cancer have complex and unclear etiology and pathogenesis.

Aims: The aim of this study was to determine which characteristics of patients- age, gender, fat intake, smoking, alcohol consumption have the greatest importance in the development of chronic pancreatitis and pancreatic cancer.

Patients & methods: The study included 55 patients with chronic pancreatitis, 45 patients with pancreatic cancer and 70 healthy controls. Multivariate regression analysis was used to identify predictive risk factors for pancreatic diseases.

Results: Results of our study showed that male, sex, older age, smoking, fatty diet were significantly higher in patients with pancreatic cancer. Women have five times lower risk for the occurrence of chronic pancreatitis and about four times lower risk for pancreatic cancer. With each year of life the risk of pancreatic cancer is increased by 5%. Smokers were under 3.5 times higher risk for pancreatic cancer.

Conclusion: In conclusion, these results suggest that pancreatic cancer occurs more frequently in older males and smoking is predictive risk factor for pancreatic cancer.
Early ligation of inferior pancreaticoduodenal artery does not decrease blood loss during pancreaticoduodenal resection

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Introduction: One of the factors that influence early and late post-operative results of pancreaticoduodenal resection is intraoperative blood loss.

Techniques of early ligation of the inferior pancreaticoduodenal artery (IPDA) were proposed to improve blood loss rate.

Aims: To decrease blood loss after pancreaticoduodenectomy.

Patients & methods: We have analyzed the results of 95 pancreaticoduodenectomies in our clinic in the period of 2011 year. Among them in 23 cases early ligation of IPDA was done. It was a non-randomized trial.

Simultaneous vascular resections were done in 3 (13,0%) patients of early IPDA ligation group, including 2 vein and 1 artery resection. In the standard procedure group simultaneous vein resection was done in 10 (23,6%) patients of standard group (p<0.05).

Two patients died: 1 (4,3%) in early IPDA group and 1 (1,4%) in standard procedure group. The median age was 63.7 years. Pancreaticojejunostomy was identified with P-J stricture. Laparotomy was carried out and P-J was partially re-did to restore patency of the anastomosis.

Results: Postoperative complications developed in 7 (30,4%) patients of early IPDA group and in 17 (23,6%) patients of standard group (p<0.05). Two patients died: 1 (4,3%) in early IPDA group and 1 (1,4%) in standard (p<0.05). Mean blood loss was 504,3±259,6 ml in early IPDA ligation group and 622,7±320,1 ml in standard. The difference was not significant (Mann-Whitney U test was 649,5, p=0.2).

Mean duration of the operation was 383,0±58,3 minutes in early IPDA ligation group and 429,1±94,8 minutes in standard. The difference was not significant (Mann-Whitney U test was 598,5, p=0.08).

Conclusion: Early ligation of IPDA could potentially decrease intraoperative blood loss, still other surgical techniques, such as careful haemostasis, have more significant influence on the intraoperative blood loss.

Squamous cyst of pancreatic ducts

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Introduction: In the last years, cystic pancreatic lesions are detected often when clinically silent, because of the wider use of diagnostic imaging techniques. First described by Othman in 2007, “squamous cyst of pancreatic ducts” (SCPD) represents a cystic dilation of ducts, lined by non-keratinized squamous epithelium.

Aims: To report the first case of SCPD in Italy.

Patients & methods: A 68-year-old woman presented a cystic lesion (4 cm) of the pancreatic tail as incidental finding at MRI. It had a thickened wall, no internal septa. No communication with the Wirsung duct was evident. A CT scan showed a lamellar calcification on its posterior wall. A 18FDG-PET was negative. Blood tests were normal, including CEA and CA19-9. We performed a spleen-preserving distal pancreatectomy.

Results: Histology showed a unicollicular cyst, with serous fluid and a fibrous wall, with multilayered epithelium without cytological atypias. Immunohistochemistry was positive for CK7 and negative for CK5. The patient is still alive and without disease after 32 months of follow up.

Conclusion: In the English literature only seven resected cases for this condition were reported. No preoperative test can achieve a definitive diagnosis, so surgical resection remains the treatment of choice in order to exclude a malignancy.

Pancreatic fistula after PD – Single institution experience

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Introduction: Pancreatic fistula (PF) is one of the most common postoperative complications of pancreaticoduodenectomy. Although PF is generally treated conservatively, some cases may require interventional procedures or may be life-threatening and necessitate emergency reoperation.

Aims: The aim of our retrospective study was to evaluate the incidence of postoperative PF after PD and to assess the prognosis and risk factors for this condition.

Patients & methods: We retrospectively analysed 106 patients between 2009–2011. Perioperative risk factors associated with PF and associations with morbidity and mortality were assessed. Morbidity and PF were graded according to ISGPF and the Dindo-Clavien classification. Factors included in occurrence of pancreatic fistula (consistency of pancreas, diameter of pancreatic duct and type of reconstruction) were included in multivariate analysis.

Results: The median age was 63.7 years. Pancreaticojejunostomy was performed in 86 patients, and pancreaticogastrostomy in 20 patients. Overall mortality was 1.8%. Overall pancreatic fistula rate was 32%
(observed in 34 patients), reinterventions in 3 patients, because of bleeding, and 2 of those patients died. PF occurred was observed at 28 patients with PJ, and at 6 patients with PG. Using multivariate analysis significant risk factors were small pancreatic duct, soft pancreatic parenchyma and PJ. Severe complications (graded with Dindo–Clavien) occurred more often with PJ, but not statistically significant. Overall mortality and reoperations were more often with PG.

Conclusion: Combination of soft pancreatic parenchyma, small of pancreatic duct (under 3mm) and PJ can be considered as risk factors for PF after PD. We did not determine significantly higher incidence and clinical severity of PF between PJ and PG.

PI-98 Abstract id: 86.
Angiosarcoma of the pancreas mimicking severe acute pancreatitis – Report of a case
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Introduction: Angiosarcoma of the pancreas is a rare neoplasm. Sarcomas in the pancreas are often mimicking signs of acute pancreatitis.

Aims: Authors report a case of a primary angiosarcoma found in the pancreatic tail in a patient admitted for severe acute pancreatitis.

Patients & methods: A 58-year-old man presented at the hospital with two weeks history of abdominal pain after excessive food intake and GI tract bleeding. Laboratory results were significant for CRP (87 mg/L), haemoglobin level was 10.6 g/dL, PCT was not elevated. Endoscopy failed to reveal the origin of bleeding. US and CT scan showed acute haemorrhagic, necrotizing pancreatitis involving the pancreatic tail, splenic hilum and small bowels. CT-guided drainage of intrabdominal and peripancreatic fluid was performed and parenteral feeding through a nasojejunal tube was strated. After 13 days, the amount of drained fluid persisted, the patient had fever, and a palpable mass in the left upper quadrant of the abdomen developed. Laparotomy was indicated. A large, haemorrhagic mass was found at the pancreatic tail, necrosectomy and drainage was performed.

Results: Histology revealed angiosarcoma. On the third postoperative day the patient was reoperated because of abdominal compartment syndrome. Large amount of haemorrhagic ascites and paralytic ileus was found. Two days later the patient died of MOF, sepsis.

Conclusion: Angiosarcoma of the pancreas is a rare entity and not well described. If the patient has fever without elevated PCT levels, the presence of a malignant tumor in the pancreas should be considered.

Enucleation of three branch duct IPMN cysts in a patient with a family history of pancreatic cancer
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Introduction: IPMN might be a phenotypic expression of familial pancreatic cancer. However, no data are available in literature regarding the natural history of IPMN in high-risk individuals and no treatment consensus exists.

Aims: Description of a clinical case.

Patients & methods: A 75-year-old woman, treated 25 years earlier for rectal cancer, was recruited to a screening program for surveillance of patients at risk for pancreas cancer at Karolinska University Hospital due to family history.

Results: Two of patient’s brothers died with pancreas cancer at 60 years of age. The first MRI showed a multifocal branch duct IPMN (BD-IPMN) of the pancreas with 3 major cystic lesions: a 23 mm in the head, a 15 mm in the body and a 20 mm in the tail of the pancreas. None of the lesions had radiological signs of malignancy, but due to the family history and symptoms (significant weight loss) the patient was considered for surgery. A total pancreatectomy was considered initially, but due to patient’s age and the absence of radiological signs of malignancy, this was regarded as overtreatment. Therefore, enucleation of the three major cysts was performed with the double aim to confirm the diagnosis and potentially to treat the bigger lesions. The post-operative course was uneventful. The histology showed mild dysplasia IPMN in all the cysts.

Conclusion: This case report shows that enucleation of BD-IPMN can be a useful diagnostic method and at the same time to treat patients with BD-IPMN who are at increased risk for pancreas cancer development.

PI-100 Abstract id: 262.
A case of microglandular pancreatic carcinoma
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Introduction: Microadenocarcinoma (MA) of the pancreas is rare. Cubilla and Fitzgerald in 1975 proposed this term for a subtype of pancreatic carcinoma, based on morphological features (small crowded microglandular structures forming a cribriform pattern and sometimes solid sheets).

Aims: To present a case of microglandular carcinoma of the pancreatic head observed in our Unit.

Patients & methods: A 77-year-old man presented with dyspepsia and weight loss. Abdominal US showed a pancreatic head mass (5 x 5.5 cm), confirmed by CT scan and MRI. CA 19-9 was 46.3 kU/L. A 18FDG-PET showed an increased tracer uptake (SUV max 3.0). We performed a pancreaticoduodenectomy.

Results: Histology: microglandular carcinoma of the pancreatic head (size 6.5 cm), with ductal and acinar differentiation. Immunohistochimeristy: CAM 5.2 positive, neuroendocrine-related markers negative, Ki-67 = 70%. The patient died for disease progression 55 months after surgery and chemotherapy with Gemcitabine.

Conclusion: The status of microadenocarcinoma as an independent tumor entity is still a matter of controversy. It is important to recognize this rare variant of pancreatic carcinoma in order to avoid misdiagnosis with other primary and metastatic neuroendocrine neoplasms. Immunohistochemical studies are useful in such cases for differential diagnosis.

PI-101 Abstract id: 279.
Postoperative pancreatic fistula after pancreaticoduodenectomy with pancreaticogastrostomy – Initial experience
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Introduction: Despite advances in pancreatic surgery, postoperative pancreatic fistula remains the most important postoperative complication after cephalic pancreaticoduodenectomy. Pancreaticogastrostomy (PG) is an alternative method to pancreaticojejunostomy(PJ) that has been reported to be safer in terms of preventing postoperative fistula formation.

Aims: We present our initial experiences with pancreaticogastrostomy after pancreaticoduodenectomy in terms of preventing postoperative pancreatic fistula.

Patients & methods: A total of 20 patients underwent pancreaticoduodenectomy for carcinoma of the head of the pancreas,
ampullary carcinoma or carcinoma of the distal common bile duct from January 2011 to June 2012. End-to-side pancreaticogastrostomy was performed with insertion of pancreatic remnant through posterior gastric wall. Pancreatic remnant was fixed using single-layer purse string suture and additional sutures between pancreatic capsule and stomach wall. In all cases pancreatic remnant was soft with diameter of pancreatic duct up to 3mm.

**Results:** Among 20 patients who underwent PD overall morbidity rate was 35%, mortality rate was 0%, with pancreatic fistula in 30% of patients (Grade A and B - 20%; Grade C - 10%) according to the International study group for pancreatic fistula classification.

**Conclusion:** Pancreaticojejunostomy is still widely used method of reconstruction after pancreaticoduodenectomy, and pancreaticogastrostomy is yet to prove itself to be a valid alternative. Our initial experiences shows that PGA is safe and easy to perform, but further analysis and larger group of patients are needed in order to establish difference in postoperative pancreatic fistula formation between PG and PJ. Also, further randomized controlled studies are necessary in order to determine the best pancreaticoenteric anastomosis after pancreaticoduodenectomy.

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**PI-102 Abstract id: 45.**

Pancreatojejunostomy with purse-string suture

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**Introduction:** During the last decades operative mortality following pancreatic resections has considerably decreased. However pancreatic fistula is still one of the leading surgical complications, especially in case of pancreaticojejunal anastomoses made with fragile pancreatic remnant.

**Aims:** The authors investigated a modification of pancreatojejunostomy created with purse-string suture. The rationale of this method is to avoid extraluminal stitches put into the pancreas, which could be the possible origin of leakage of pancreatic juice.

**Patients & methods:** The technique was applied at 8 patients, who were operated on radically for malignant pancreatic head or periampullary tumours. Pylorus-preserving Whipple procedure was preferred. End-to-side pancreaticojejunal anastomoses were performed with a single 3/0 PDS purse-string suture and with 4-5 additional fixation stitches. None of the latter ones were put into the external surface of the pancreatic parenchyma. Stenting of the main pancreatic duct was also applied in case of narrow duct and friable pancreas.

**Results:** In the postoperative period one wound infection and one gastrointestinal bleeding from duodenojjejunal anastomotic ulcer occurred. However the rate of pancreatic fistula-related morbidity was advantageous, compared to the previously used technique.

**Conclusion:** Though this series is small, first experiences are encouraging. The method seems to be safe, easy to perform and it spares suture material.
**Introduction:** Laparoscopic pancreaticoduodenectomy (LPDE) is an alternative to traditional surgery for patients with tumor of the head of pancreas and periampullary area. 

**Aims:** To show our experience in treatment of 46 patients with tumor of the head of the pancreas and peripancreatic area by using a total laparoscopic approach.

**Patients & methods:** From January 2007 to January 2013 46 out of 54 patients underwent total laparoscopic pancreaticoduodenectomy (TLPDR) in our clinic. There were 29(63%) females and 17(37%) males, average age was 59.4(range, 45-76) years. In retrospective study we analyzed the main outcome measures: conversion rate, blood loss, operative time, length of hospital stay, postoperative morbidity and mortality.

**Results:** For 8 patients procedure was palliative or converted because of the spread of the tumor infiltration at the mesenteric vessels or serious adhesive process in parapancreatic area. Median blood loss was 425 ml (range, 100-2100). The median operative time was 458±101,1 min. Tumor localizations were: the head of pancreas(n-25), papilla(n-13); distal part of extrahepatic bile duct(n-4); duadenum(n-2) and chronic pancreatitis(n-2). The complication rate was 21(45,6%). CLAVEN-DINDO-STRASBERG classification: I, II(n-7); IIIA(n-7); IIIB(n-4);IV(n-1);V(n-2). R1(n-1).

**Conclusion:** Laparoscopic resection for treating the patients with cancer of biliopancreatodudal area is a feasible and effective procedure. After passing the initial learning curve (about 30 cases), laparoscopic approach permits to make shorter an operative time, that comparable with traditional approach with the same early postoperative results. Randomized controlled study are still necessary.

**PI-107 Abstract id: 267.**
**The failure of pancreas function: How non-specific gastrointestinal symptoms can hide the metastatic involvement of pancreas in advanced malignancies. A case report**

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**Introduction:** Metastatic involvement of pancreas is uncommon and accounts for approximately 2% of pancreatic malignancies. Generally, metastatic blood dissemination from breast cancer causes frequent involvement of lung, bone, liver and brain. The detection of synchronous pancreatic metastases arising from a primitive breast carcinoma is infrequent. We present the case of a misdiagnosed secondary pancreatic involvement in advanced breast cancer.

**Aims:** The aim of the study is to focus on the importance of imaging in order to obtain the right diagnosis and plan the best treatment in pancreatic malignancies.

**Patients & methods:** A 68-years-old woman complaining general fatigue, lethargy, asthenia and jaundice presented with endocrine pancreas failure. Abdominal US showed an ampulla of Vater's papilla. After mammary US and FNAC, due to the increase in CA 15.3, a breast cancer in the left breast involving the ipsilateral axillary lymph stations was also diagnosed. She underwent surgery for both breast cancer and ampulla of Vater's papilla. Whipple's procedure was performed during pancreatic time, while the breast time consisted in Patey's mastectomy.

**Results:** Pathological examination of pancreatic specimen did not confirm primary carcinoma of the duodenal papilla neither adenocarcinoma but showed a synchronous metastatic involvement of pancreas from a lobular breast cancer.

**Conclusion:** This is one of the few reported cases in literature of an isolated pancreatic metastasis spread from breast cancer, in which the definitive diagnosis was obtained only after surgery. It is important to remember that nonspecific gastrointestinal symptoms in women in menoopause can hide a secondary involvement of the gastrointestinal tract arising from the breast.

**PI-106 Abstract id: 92.**
**Middle-segment preserving subtotal pancreatocotomy for treating multifocal lesions in pancreas**

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**Introduction:** Middle-segment preserving subtotal pancreatocotomy (MPSTP) was regarded as a reasonable choice for treating multifocal body-sparing lesions of the pancreas in benign or low-grade malignant disease.

**Aims:** To investigate the short-term outcomes, especially its effect on endocrine function of pancreas after this organ-preserving procedure.

**Patients & methods:** From September 2011 to May 2012, five patients underwent MPSTP in our institution, a high-volume center in China. Perioperative data were retrospectively analyzed.

**Results:** Patients were 3 women and 2 men, with a median age of 50 year-old (37-81 year-old). One patient had past history of diabetes. Preoperative CT examinations revealed multicentric lesions located in head and tail of the pancreas. Four patients underwent pylorus-preserving pancreaticoduodenectomy with distal pancreatocotomy (DP), including two with spleen additionally reserved. The other patient underwent Beger’s procedure and spleen-preserving DP. Median operation time and estimated intraoperative blood loss were 330min (250-600min) and 800ml (400-5500ml), respectively. Pathologic examination demonstrated three cases of metastatic lesions (renal clear cell carcinoma, dermatofibrosarcoma protubersans, and malignant pheochromocytoma) to the pancreas, one chronic pancreatitis and one neuroendocrine tumor. Postoperative complications included two cases of pancreatic fistula, three delayed gastric emptying, one abdominal fluid collection and one pleural effusion. Follow-up studies revealed deteriorated diabetic status in one patient, and the rest four kept well-controlled serum glucose level without any medication. No symptoms of hypoglycemia was identified.

**Conclusion:** MPSTP is a safe and feasible procedure for benign or low-grade malignant multifocal lesions in pancreas, while for most important, patients seem to have a more stable serum glucose level after surgery.

**PI-108 Abstract id: 261.**
**A case of intraductal variant of acinar cell carcinoma**

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**Introduction:** Pancreatic intraductal neoplasms in the past few years had increasing importance, as the incidence of Intraductal Papillary Mucinous Neoplasms (IPMNs) have grown. Acinar cell carcinomas (ACCs) are typically solid tumors; however, a few cases of ACCs with intraductal growth pattern have been described.

**Aims:** To report a case of an acinar cell carcinoma of the pancreatic head with a polypoid intraductal growth observed in our Unit.

**Patients & methods:** A 42-year-old woman had recurrent epigastric pain, a mild increase of serum amylose and negative serum tumor markers. US detected a hypoechoic area in the pancreatic head (diameter 1.5 cm), confirmed by CT scan, which also showed a dilated Wirsung duct. At 18F-FDG-PET the mass had an increased tracer uptake (SUV max 7.5). In the suspicion of a malignant IPMN, we performed a pancreaticctoduodenectomy.

**Results:** Histology showed an acinar cell carcinoma of the pancreatic head with polypoid intraductal growth (T2 N0 M0). Immunohistochemistry: trypsin positive, mucin negative. The patient is still alive without disease 68 months after surgery and chemotherapy with Gemicitabine.

**Conclusion:** A few cases of ACCs with intraductal growth pattern have been described in the literature and they can be easily mistaken for IPMNs. The behaviour of this variant is difficult to know; however, in the few cases reported, metastases at presentation are less common than typically seen in ACCs.
**PI-109 Abstract id: 170.**

The pathological features of FDG-PET negativity in patients with pancreatic ductal carcinoma

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**Introduction:** Usefulness of FDG-PET in pancreatic cancer various studies have been carried out.

**Aims:** In this study, we clarified the pathological features of pancreatic ductal carcinoma with negative positron emission tomography (PET) findings and determined the factors that might affect fluorodeoxyglucose (FDG) accumulation by the pancreatic ductal carcinoma.

**Patients & methods:** Eighteen patients with pancreatic ductal carcinoma and negative findings on PET preoperatively enrolled. Pathological findings (proliferation type and extent of fibrosis) and reproducibility were examined. Proliferation was classified into 3 types: equal, extended, and collective. Reproductive activity was assessed using the Ki-67 index; the Ki-67 indexes for 11 patients with positive PET findings were used as controls.

**Results:** There were 10, 3, and 5 patients with equal, extended, and collective proliferation, respectively. Patients with equal and extended proliferation generally had massive fibrosis. The difference in proliferation type could not be determined by the Ki-67 index, which ranged from 2.7 to 12.6 (average: 6.8). The average Ki-67 index of patients with PET positivity was 26.1 (p < 0.01).

**Conclusion:** PET negativity can be defined by proliferation type; patients with equal and extended proliferation accounted for 72% (13/18) of the patients. These results suggest that low cell density, fibrosis, and extension cancer gland indicate a decrease in the amount of localized cancer cells. The decrease in the number cancer cells caused a reduction in FDG accumulation, which possibly lead to PET negativity. Patients with PET negativity had a lower rate of Ki-67 positivity than patients with PET positivity. It was hypothesized that the reproductive activity of the cancer cells also contributes to PET negativity.

**PI-110 Abstract id: 178.**

Laparoscopic distal pancreatectomy – “The new gold standard”

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**Introduction:** Recent achievements in minimal invasive surgery allowed to perform laparoscopic distal pancreatectomy, with benefit for the patients with both benign and small malignant tumors.

**Aims:** The aim of the present study was to compare the short-term clinical outcomes of patients who underwent laparoscopic and open distal pancreatectomy.

**Patients & methods:** In the period 2009-2013 we performed 110 distal pancreatectomies. The methods were retrospective analysis of patients who underwent laparoscopic (51) and open (59) distal pancreatectomies. Analyzed factors include age and sex of the patients, duration of the operation and hospital stay, spleen preservation and histopathological diagnosis.

**Results:** A total of 110 cases (51 laparoscopic resections, including 11 which required conversions from laparoscopic to open pancreatectomy, and 59 open resections) were analyzed. There were no significant differences in the age of patients in ethier group, duration of the operations and rates of complications. We noticed significant differences in favor of the laparoscopic distal pancreatectomy in hospital stays, and the rate of spleen preservation. The making of the groups were similar except for a predominance of females in the laparoscopic group.

**Conclusion:** Laparoscopic distal pancreatectomy is a relatively safe procedure, which has similar rates of complications, shorter hospital stays, and a much higher rate of spleen preservation. This technique is a good alternative to open pancreatectomy and should be performed in both benign and small malignant tumors.

**PI-111 Abstract id: 127.**

Efficacy of continuous suction drainage tubes on drainage efficiency in patients with pancreatic fistula after pancreaticoduodenectomy

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**Introduction:** The major treatment of postoperative pancreatic fistula (POPF) after pancreaticoduodenectomy (PD) is adequate drainage of amylase-rich fluid leaking from pancreaticojjunostomy (PJ). However, it is still controversial what kind of drainage tube should be used or where drainage tubes should be placed, in order to achieve this goal.

**Aims:** We examined efficacy of continuous suction drainage tubes we placed during the procedure on drainage efficiency in patients with POPF.

**Patients & methods:** This is a retrospective review of 30 patients who underwent PD for periampullary cancer. The remnant pancreas showed a soft texture in all cases. Reconstruction was done by modified Child procedure with PJ using duct-to-mucosa anastomosis. POPF was assessed according to the definition by the International Study Group for Pancreatic Fistula. All patients were divided into 2 groups. Group A (n = 14): patients having drainage tubes behind the foramen of Winslow and in the dorsal space of PJ. Group B (n = 16): patients having an additional tube in the ventral space of PJ. We compared POPF severity, additional treatment and mortality between these groups.

**Results:** The incidence rate of grade B & POPF in group A and group B was 50% and 45%, respectively. Four of 7 patients in group A required ultrasonic-guided percutaneous drainage for intraabdominal abscess in the ventral space. All patients with POPF in group B were successfully managed without additional drainage.

**Conclusion:** To place adequate drainage tubes around PJ seems to be very important in terms of the proper management of POPF after PD.

**PI-112 Abstract id: 265.**

Mixed endocrine-exocrine tumors of the pancreas

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**Introduction:** Mixed pancreatic tumors are very rare. They are characterized by the association of exocrine (ductal or acinar) and endocrine components, and positivity for neuroendocrine (NE) markers in >30% of cells.

**Aims:** To evaluate clinical presentation, surgery, histology, outcome and follow up (FU).

**Patients & methods:** From 2002 to 2011, 133 NE pancreatic tumors were observed in our Department: 6 (4.5%) were mixed tumors. Follow up to December 2012.

**Results:** Out of six patients enrolled (3 F/3 M – averaging 67.5 yrs), 2 were asymptomatic, 3 had jaundice, 1 hypoglicaeisma. Five tumor were located in the pancreatic head, 1 in the whole pancreas (2/6 had liver and peritoneal metastases). Primary tumor size range: 1.4-10.0 cm. Tumor markers expression: 3 cases had high exocrine serum tumor markers expression (CA19-9, aFP, CEA, CA125). Resective surgery was performed in 3 cases (2 pancreaticoduodenectomy, 1 enucleation), 1 bypass surgery, 2 pancreatic/liver biopsy. Post-operative mortality was nil and morbidity 2/4 (1 abdominal fluid collection, 1 pseudocyst). Histology showed 2 acinar cell carcinoma with NE component, 2 ductal adenocarcinoma with NE component, 2 NE tumors with ductal carcinoma component. FU range 12-123 mo. In 3 cases resected DFS was 12, 26 and 123 months. In 2 cases with peritoneal metastases survival was 3 and 6 months.

**Conclusion:** Prognosis of mixed exocrine-endocrine pancreatic tumors is strongly related to the behaviour of the exocrine component. In most cases the diagnosis of Mixed Exocrine/Endocrine tumor is known only postoperatively. Therapeutic approach is not changed by the final diagnosis.
PI-113 Abstract id: 59.
The outpatient activity of a Macmillan pancreatic clinical nurse specialist in a tertiary pancreatic unit

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Introduction: The Clinical Nurse Specialist (CNS) plays a major role in the management of pancreatic cancer patients at all stages during their cancer journey. Since 2010 the CNS has had their own outpatient clinic template for the review of patients.

Aims: To evaluate the outpatient activity of the Macmillan Pancreatic CNS in a tertiary Pancreatic Unit over a 6 month period.

Patients & methods: An audit was undertaken of all patients reviewed in clinic by the CNS. Outcome data included demographics, tumour type, type of consultation, time of consultation, medications prescribed, referrals made, written information provided and tests ordered.

Data was collected prospectively and analysed using EXCEL.

Results: A total of 206 patients (61% male, median time of review 35 minutes, range 10 – 90 minutes) were seen in 42 outpatient clinics between March and August 2012.

155 patients (75%) were seen alone by the CNS. 95 (67%) of these patients were post-operative follow ups. The remaining 60 patients were inoperable, receiving palliative treatment and supportive care. 15 patients had a new inoperable cancer or diagnoses of recurrence. 80 patients (52%) required referrals to other services, 92 (59%) required medication changes and 110 (71%) required further investigations all of which were instigated by the CNS.

51 (25%) patients were seen after a clinician. The majority (72%) being new surgical patients.

Conclusion: The CNS has been found to take on increased responsibilities for post-operative surgical patients and patients undergoing palliative treatment and supportive care allowing the surgeon to better utilise their own clinic time.

PI-114 Abstract id: 33.
Significance of aggressive surgery for invasive carcinoma derived from intraductal papillary mucinous neoplasm

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Introduction: Although intraductal papillary mucinous neoplasm (IPMN) has a good prognosis, biological malignancy of invasive carcinoma derived from intraductal tumor (IC-IDT) is often reported to be similar to that of invasive ductal carcinoma (IDC).

Aims: We discussed significance of surgical treatment from a viewpoint of the outcome.

Patients & methods: We retrospectively studied 7 patients with IC-IDT. Several factors were reviewed: clinical presentation, preoperative imaging, variation of serum CA19-9, peroperative factors, pathological findings, adjuvant chemotherapy and outcome.

Results: The mean age was 67 years. Two were men and 5 were women. The mean follow-up period was 40.1 months. Serum level of CA19-9 was elevated in only 2 cases (29%) and showed a rapid decline after surgery. Five lesions were located in the head and 2 in the body. The mean tumor diameter was 38 mm. Accordind to preoperative imaging, all cases had a borderline resectable cancer. Pancreaticoduodenectomy was performed in 5 patients, distal pancreatectomy in 2. Two patients required vascular resection. The mean operative time was 408min and mean blood loss was 1574ml. Four patients received gemcitabine chemotherapy.

Pathologically, five cases was classified as intestinal type and 2 as gastric type. The major component in the invasive area was tubular adenocarcinoma in 5, mucinous carcinoma in 2. All cases achieved R0 resection. There were no complications. The 3-year survival rate was 100%.

Conclusion: Aggressive curative surgery for IC-IDT could contribute to a good outcome which is superior to that in patients with IDC.

PI-115 Abstract id: 211.
Risk factors, clinical features and outcome of early onset pancreatic cancer patients compared to older patients

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Introduction: The median pancreatic adenocarcinoma (PDAC) onset age is ~65 years, but some 10% are diagnosed 10 years before, and defined as early onset pancreatic cancer (EOPC). Specific features of EOPC have poorly been investigated.

Aims: We aim to analyze the prevalence of EOPC (patients aged <55), risk factors for EOPC occurrence, their clinical and histological features, and outcome compared with “normal onset” (NOPC)

Patients & methods: Prospective cohort of incident PDAC patients. Familial, medical, environmental risk factors and clinical presentation registered through a specific questionnaire. Tumor features and patients’ survival recorded.

Results: Amongst 291 consecutive PDAC patients, 38 were EOPC (13%). There were no differences between EOPC and NOPC for sex distribution, and risk factors, including PDAC family history. The rate of ever smokers was similar (68.4% vs 60.8% p=0.29), but EOPC subjects were more frequently current (50% vs 22.1% p=0.01) smokers, with a slightly higher rate of heavy smokers (47.4% vs 38.1% p=0.28). Previous diabetes was less frequent in EOPC (p=0.003). PDAC presentation symptoms, and diagnostic delay (4.2 months vs 3.5) were similar in the two groups. EOPC patients had more frequently a G3 tumour (62.5% vs 7.6%;p=0.005) and advanced disease at diagnosis (78.9% EOPC vs 67.2%;p=0.18). Median survival estimates were similar (11 months vs 9;p=0.36).

Conclusion: Thirteen percent of PDAC patients have an early onset. Active smoking might play a role in anticipation of PDAC onset. In EOPC patients the neoplasm shows aggressive features (undifferentiated histology and advanced stage), however median survival is not worse, likely due thanks to less comorbidities.

PI-116 Abstract id: 53.
CT-based diagnostics might be insufficient in the determination of pancreatic cancer unresectability

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Introduction: The salient indication of pancreatic cancer (PC) unresectability is superior mesenteric artery (SMA) and celiac artery (CA) encasement, indicating arterial invasion. Computed tomography (CT) is the gold standard for the evaluation of PC resectability.

Aims: To compare CT, intraoperative and survival data of patients with borderline-resectable and unresectable PC
patients & methods: Radiology data were compared with the findings from 51 standard, 58 extended and 17 total pancreaticoduodenectomies; 9 distal resections with CA excision; and 28 palliations for PC. The survival of 11 patients with controversial CT and EUS data with regard to arterial invasion, after R0/R1 procedures (false-positive CT results, Group A), was compared to survival after eight R2 resections (false-negative CT results, Group B) and after 12 bypass procedures for locally advanced cancer (true-positive CT results, Group C).

Results: In all of the cases in group A, operative exploration revealed no arterial invasion, as predicted by CT. The one-year survival in Group A was 88.8%, and the two-year survival was 26.7%, with a median follow-up of 22 months. One-year survival was not attained in groups B and C, with a significant difference in survival (Pa-b = 0.0029, Pb-c = 0.003).

Conclusion: In all of the cases in group A, operative exploration revealed no arterial invasion, as predicted by CT. The one-year survival in Group A was 88.8%, and the two-year survival was 26.7%, with a median follow-up of 22 months. One-year survival was not attained in groups B and C, with a significant difference in survival (Pa-b = 0.0029, Pb-c = 0.003).

PI-117 Abstract id: 299.
Laparoscopic enucleation of benign and borderline pancreatic neoplasms
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Introduction: Minimally invasive enucleation of pancreatic neoplasms is a very uncommon procedure.
Aims: Here we describe the short- and long-term results of laparoscopic enucleations performed at our institution for benign to borderline lesions of the pancreas.

Patients & methods: Patients scheduled for a laparoscopic enucleation between March 2006 and January 2012 were included in the study. The decision on whether to choose the laparoscopic approach was taken at the surgeon’s discretion in patients with small lesions presumed to be benign or borderline. Demographic, surgical, pathological and follow-up details were recorded.

Results: The procedure was attempted in 14 patients, but two patients ultimately underwent totally laparoscopic middle pancreatectomy because of intraoperative damage to the pancreatic duct or close distance between the lesion and the duct itself. In the remaining 12 patients the planned operation was performed. Of these, only one developed an indolent pancreatic fistula, no other morbidity was observed. The mean hospital stay was 6.3 days. Histological examination showed seven insulinomas, four non-functional neuroendocrine neoplasms and one undetermined cystic neoplasm. At a median follow-up of 39 months, no patient exhibited endocrine or exocrine pancreatic insufficiency, tumor recurrence or port site hernia.

Conclusion: When feasible, laparoscopic enucleation of pancreatic benign to borderline neoplasms can be carried out with excellent short- and long-term results in well-selected cases.

PI-118 Abstract id: 196.
A phase II trial of second-line therapy with trabectedin in metastatic pancreatic adenocarcinoma (mPA)
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Introduction: No standard 2nd-line chemotherapy exists for mPA albeit a randomized trial suggested that salvag chemotherapy may improve OS compared to best supportive care.
Aims: This study evaluates the activity and safety of trabectedin as 2nd-line therapy in mPA.

Patients & methods: Patients (pts) with mPA progressing after gemcitabine-based chemotherapy were treated with i.v. trabectedin at 1.3 mg/m2 every 3 weeks. The primary endpoint was the PFS-6 months. Twenty-five pts were required (α = 0.025, 1-failed). If at least 5 pts were PFS-6, the treatment was considered of interest.

Results: Between February 2011 and February 2012, 25 pts with mPA, median age 58 yr (range 48–73); median KPS 90 (range 80–100) received trabectedin. Prior therapy consisted of adjuvant gemcitabine (N = 3); adjuvant PEXG (cisplatin, epirubicin, capetebinate, gemcitabine; N = 2); PEXG (N = 19) or gemcitabine (N = 1) for mPA. Median prior PFS was 9 months; maximum response to prior chemotherapy in 20 mPA pts was PR in 14 (70%) and SD in 6 (30%). Only 1 pt completed all the planned 9 cycles; 23 interrupted trabectedin due to PD, and 1 due to toxicity. Only 2 pts (8%) were PFS-5. Median PFS was 1.9 months (range 0.7–7.4). Median OS was 4.7 months (range 1.1–13.9) and 1-yr OS was 24%. No PR and 6 SD (24%) were observed. Grade 3–4 toxicity consisted of neutropenia (44%); fatigue (16%); anemia; thrombocytopenia and transaminitis (8% each); febrile neutropenia (4%).

Conclusion: This study showed that trabectedin has a limited activity compared to other drugs used as salvage therapy in mPA.

PI-119 Abstract id: 46.
Pancreaticeojunostomy with duct-to-mucosa improves the incidence of over grade B pancreatic fistula in patients with soft pancreas compared with total diversion
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Introduction: Pancreatic fistula (PF) is the most critical complication after pancreaticoduodenectomy (PD). Although pancreateojunostomy with total diversion (PJ-TD) is technically easy, this reconstruction method often results in high incidence of PF. On the other hand, pancreateojunostomy with duct-to-mucosa anastomosis (PJ-DM) has been recently established as the standard procedure despite technical difficulty.

Aims: The aim is to compare clinical outcomes after the procedure between cases receiving PJ-DM and PJ-TD, especially focusing on the incidence of PF.

Patients & methods: Thirty two patients with periampullary cancer underwent PD. Remnant pancreas in all cases showed soft texture. Patients were divided into two groups: receiving PJ-TD (n = 15) and PJ-DM (n = 17). We compared patient backgrounds, perioperative factors, and postoperative complications between both groups. PF was assessed according to the definition of PF by International Study Group of Pancreatic Fistula.

Results: There were no differences in patient backgrounds and perioperative factors. The incidence rate of all grades PF was relatively high, 41% in the PJ-DM group and 67% in the PJ-TD group. However, PF with over grade B were detected in only 1 patient (6%) of the PJ-DM group while 6 patients (40%) of the PJ-TD showed grade B&C PF. There was no surgery-related death in both groups.

Conclusion: The PJ-DM procedure seems to be superior to the PJ-TD method in terms of decrease in the incidence rate of PF.
Cyst fluid neutrophil gelatinase-associated lipocalin (NGAL) concentration in the differential diagnosis of pancreatic cystic lesions: a new factor enters the scene

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Introduction: NGAL - 25 kDa peptide - is at present one of the most fascinating and unrecognized proteins implicated in the process of tumor development.

Aims: The purpose of the study was to determine the utility of NGAL concentration in cyst fluid obtained by Endoscopic ultrasound (EUS) with EUS-guided fine needle aspiration (EUS-FNA) to distinguish neoplastic pancreatic cysts from pseudocysts.

Patients & methods: Twenty two patients underwent EUS and FNA of a pancreatic cystic lesion; 9 of these patients underwent surgical resection, providing a histologic diagnosis of the cystic lesion. Furthermore the final diagnosis was based on cyst fluid cytology, cyst fluid tumor markers (CEA, CA 72-4, CA 19-9) and medical history. Patients were divided in two groups: cystic neoplasms and inflammatory cysts (pseudocysts). Value of cyst fluid NGAL was correlated to corresponding cytopathologic examination, surgical histopathology (when available) and levels of tumor markers in cystic fluid.

Results: Final diagnosis was pseudocyst in 7 patients, serous cystadenoma in four, mucinous cystadenoma in three, intraductal papillary mucinous neoplasms in 6 patients and cystic form of pancreatic adenocarcinoma in two. Cyst fluid analysis of these patients showed that median cyst fluid NGAL for the cystic neoplasm group (211 ng/mL; n=15) was significantly lower (p=0.02) than the inflammatory cystic group (4689 ng/mL; n=7). Correlation analysis showed that only fluid CA 72.4 was positively related to NGAL (r=0.8, p<0.01).

Conclusion: In this single center study, pancreatic cyst fluid NGAL concentration appeared to be useful in distinguishing neoplastic pancreatic cysts from pseudocysts. Larger studies are recommended to evaluate this role further.
evaluated by western blot and immunohistochemistry. Collagen-I was measured by western blot and Masson trichrome.

Results: Tobacco alone (x-SMA 1.83±0.3; p=0.003 versus negative control) or in combination with 50 mM ethanol (x-SMA 1.53±0.2; p=0.04 versus negative control) induced PSC activation in early culture. Tobacco in combination with 50 mM ethanol increased the expression of collagen-I (3.9±1.2; p<0.001 versus negative control) and FNT-1 (3.6±0.3; p<0.001 versus negative control and ethanol alone). Tobacco also increased the expression of FNT-1 in combination of 10mM alcohol (2.23±0.1; p=0.007 versus negative control).

Conclusion: Tobacco alone or in combination with alcohol induces the early activation of PSC. Tobacco associated with alcohol increases the expression of extracellular matrix proteins. These results support for the first time the synergistic effect of alcohol and tobacco in the pathogenesis of chronic pancreatitis.

Poster Session II

PII-1 Abstract id: 156.

P8 deficiency increases mitochondrial ROS formation and induces HO-1

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Introduction: The gene p8 is rapidly and strongly upregulated in pancreatic acinar cells during the onset of acute pancreatitis. It encodes for a small cytoprotective protein that has been proposed to act as a transcription co-factor. Recent data shows that suppression of p8 gene transcription using siRNA leads to induction of heme oxygenase (HO)-1 in mouse embryonic fibroblasts.

Materials & methods: Semi-quantitative RT-PCR and Western Blot in p8 wild-type (p8+/+) and knock-out (p8-/-) mouse embryonic fibroblasts (MEF). Cell cycle arrest using nocodazole. Measurement of general cellular ROS content using CM-H2DCFDA in MEF and MiaPaCa-2 cells and measurement of mitochondrial ROS using MitoSOX™ in MEF.

Results: We show that p8-/- MEF have increased amounts of HO-1 under basal and stimulated conditions. This was independent of the cell-cycle. In addition, we found that p8-/- MEF have increased amounts of overall reactive oxygen species (ROS) and identified the mitochondria as the source of increased ROS. This was not restricted to MEF as also p8 suppression in MiaPaCa-2 cells lead to an increase of intracellular ROS.

Conclusion: Our data suggests that the presence of p8 inhibits mitochondrial ROS production. Absence of p8 leads to an increase of HO-1 expression. We speculate that the worse course of acute pancreatitis in p8-/- mice is caused by an impaired anti-oxidative capacity of the organ.

PII-2 Abstract id: 305.

Extracts from Da-Cheng-Qi decoction protect against pancreatic damage in murine acute pancreatitis

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Introduction: Da-Cheng-Qi decoction (DCQD) is widely used in China for acute pancreatitis (AP) and protects against experimental AP. Circulating compounds of DCQD treatment include rhein, naringenin and honokiol, but active components and their mechanisms have yet to be identified.

Aims: To determine whether fractions or single ingredients from DCQD protect against experimental AP.

Materials & methods: Seven separate fractions of DCQD were extracted using methanol and reverse-phase chromatography or chloroform after acetone precipitation and centrifugation. Murine AP was induced by 50 g/kg caerulein (hourly x 7 ip) and DCQD or each separate fraction (equivalent to 20 g/kg DCQD by gavage) or ingredient (20 mg/kg rhein or 25 mg/kg naringenin ip) was administered 2 hourly with the 3rd, 5th and 7th caerulein injection. Honokiol (5 mg/kg hourly x 7 ip) was given after the 3rd caerulein injection. Mice (6 per group) were sacrificed 12 h after the first injection of caerulein and severity of AP assessed using biochemical markers and blinded histopathology.

Results: DCQD reduced serum amylose, pancreatic myeloperoxidase and histopathology scores significantly (P<0.05) but not trypsin or serum IL6, whereas each separate fraction or ingredient had minimal and/or inconsistent effect; an aqueous fraction had a significant effect on histopathology (P<0.05).

Conclusion: These data suggest that more than one ingredient is responsible for the action of DCQD, possibly synergistically, in keeping with the tenets of traditional Chinese medicine. Further work is required to identify the mechanism of action of DCQD.

PII-3 Abstract id: 338.

Acute pancreatitis causes induction of receptor interacting proteins (RIP)

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Introduction: Cell death is an important event during acute pancreatitis and signaling events regulating cell death are incompletely understood. Recent research identified the family of Receptor Interacting Proteins (RIP) as molecular signaling events leading to programmed cellular necrosis so called necroptosis.

Aims: Our aim was to investigate whether acute pancreatitis leads to induction of RIP.

Patients & methods: Experimental pancreatitis was induced in C57BL/6 mice by secretagogue hyperstimulation and followed by analysis of RIP expression in pancreatic tissue by PCR and Western blot using standard procedures.

Results: RIP 1 expression was found to be expressed in unstimulated controls and no induction following caerulein pancreatitis was observed. In contrast RIP3 expression was scarce in unstimulated controls but found to be induced following caerulein pancreatitis.

Conclusion: The discovery of receptor interacting proteins (RIP) recently offered new insight into our understanding of cell death. We now found that there is abundant basal expression of RIP1 as well as inducible expression of RIP3 following induction of experimental pancreatitis. These findings suggest that RIP specific therapies could help to limit cell death during acute pancreatitis and therefore improve outcome.
PII-4 Abstract id: 105.
Beneficial effects of L-tryptophan metabolite kynurenine on acute pancreatitis in the rats. Involvement of heat shock protein
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Introduction: Melatonin precursor: L-tryptophan protects the pancreas against acute pancreatitis. L-kynurenine (KYN) is the product of L-tryptophan metabolism, but the effect of KYN on acute pancreatitis is unknown. Heat shock proteins (HSP’s) are known as chaperons, saving from harm intracellular compartment.

Aims: To assess the effects of KYN on caerulein-induced pancreatitis (AP) in the rats and on HSP60 production in AR42J pancreatic acinar cells.

Patients & methods: AP was induced by subcutaneous caerulein infusion (25 microg/kg). KYN (25, 50 or 100 mg(k) was given intraperitoneally to the rats 30 min prior to the induction of AP. Lipid peroxidation products (MDA-4HNE) and the activity of an antioxidant enzyme; glutation peroxidase (GPx) were measured in pancreatic tissue. Blood samples were taken for evaluation of amylase and TNF alpha concentration.

Results: AP was confirmed by histological examination and by the increases of amylase and TNF alpha blood levels (by 800% and 300%, respectively). Pancreatic MDA-4HNE was increased by 300%, whereas GPx activity was reduced by 50% in AP rats. KYN significantly diminished histological manifestations of AP, decreased amylase and TNF alpha blood levels, reduced MDA-4HNE and augmented GPx in the pancreas of AP rats. In AR42J cells KYN alone or combined with caerulein markedly increased HSP60 protein signal.

Conclusion: L-kynurenine significantly attenuated acute pancreatitis. This could be related to antioxidative effect of this substance and possibly, to the stimulation of HSP60 by L-kynurenine.

PII-5 Abstract id: 240.
The frequency of SPINK 1, PRSS 1 and CFTR mutations in acute pancreatitis
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Introduction: The leading causes of acute pancreatitis (AP) are cholelithiasis and alcohol. Multiple gallstone attacks in patients, and alcohol in others do not lead to AP.

Aims: The aim of work was the assessment of the frequency of the prevalence of SPINK 1, CFTR and PRSS 1 mutations in patients with AP in comparison with 31 healthy volunteers.

Materials & methods: 72 patients treated due to AP, from whom peripheral blood was drawn and DNA was separated, were included in the research. TETRA-PCR method was used for analyzing mutation p.N34S (c.101A>G) in the SPINK1gene. However, mutations in the genes: CFTR exon10 (defe6508_CTT) and PRSS1 in exon2 (A16V, N29I) and exon3 (p.R116C, p.R112C) were genotyped using a direct sequencing method.

Results: The total frequency of the SPINK 1 mutation in the study sample was 8.3% (6/72), 3.2% (1/31) in the control group of healthy subjects. The mutation was diagnosed in 3.4% (1/29) of the group of patients with mild acute pancreatitis, and in 11.6% (5/43) of the group with SAP; but the statistical significance was not shown. The statistically significant connection of the disease intensification with the presence of SPINK 1 mutation was not shown. There was not found anything to confirm the presence of the PRSS 1 mutation either in the study sample or the control group. The CFTR mutation was found in one patient with biliary SAP.

Conclusion: The presence of the SPINK 1 mutation which was found in the research, may predispose to the severe course of AP but the problem requires further study.

PII-6 Abstract id: 81.
Endotoksemia in the early period of life promotes apoptosis in pancreatic acinar cells via toll-like receptor 4
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Introduction: Lipopolyascharid endotoxin (LPS) is responsible for septic shock and multiorgan failure, however pretreatment of the rats with low doses of LPS has beneficial effect on acute pancreatitis (AP).

Aims: We investigated the effects of the endotoxiaemia induced in the early period of life on toll-like receptor 4 (TLR4), heat shock protein 60 (HSP60) and proapoptotic Bax, caspase-9 and -3 or antiapoptotic Bcl-2 protein expression in the pancreatic acinar cells of adult animals.

Materials & methods: Newborn rats (25g) were injected with endotoxin from Escherichia coli, for 5 consecutive days. Two months later, pancreatic acinar cells were isolated from all groups of animals and subjected to caerulein stimulation (10-8M). Western blot was employed to detect protein expression of TLR4, HSP60, Bax, Bcl-2 and caspases in the acinar cells, whereas DNA fragmentation ladder assay was used to assess apoptosis.

Results: Pretreatment of newborn rats with LPS resulted in the significant increases of TLR4, caspase-9 and -3 levels, but failed to affect basal expression of HSP60, Bax, and Bcl-2. Caerulein stimulation increased TLR4, Bcl-2, and caspases, but diminished HSP60 and Bax proteins in pancreatic acinar cells. Endotoxiaemia dose-dependently increased TLR4, Bax, HSP60, and both caspases protein signals in the pancreatic acini, and inhibited antiapoptotic Bcl-2.

Conclusion: Endotoxiaemia promoted the induction of HSP60 via TLR4 in the infant rats and could be implicated in the LPS-induced pancreatic tissue protection against acute damage.

PII-7 Abstract ID: 164.
Chitosan nanoparticles loaded with glutathione improve intestinal barrier during severe acute pancreatitis
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Introduction: Septic complications of severe acute pancreatitis (SAP) occur due to bacterial translocation (BT) through impaired intestine. Oxidant injury of intestinal epithelia is most important mechanism of it development. Thus local delivery of antioxidants like reduced glutathione (GTH) to intestinal mucosa may have positive effect.

Aims: To investigate effects of local delivery of GTH to intestinal mucosa by chitosan nanoparticles (CNP) on its barrier function.

Patients & methods: SAP was induced in 100 Wistar rats by L-arginine method. To animals of 1 group 50 mg/kg of GTH solution was infused to duodenum through the catheter every 12 h after SAP induction, 2 group – CNP loaded with GTH in the same dose, control group (CG) – same amount of normal saline. CNP loaded with GTH were prepared by inotropic gelation method. Changes of pro- and antioxidative status in small intestine and BT to internal organs have been investigated during first 48 hours of SAP.
Results: In CG animals during 12-48 h level of GTH in intestinal tissue was 40-55% lower (p<0.05) normal values, malone dialdehyde increased twice (p<0.05), BT was observed in 100% cases. GTH infusion (1 group) increased its concentration on 18-23% in comparison with CG, but it remained 1.5 time (p<0.05) lesser than in healthy animals, BT occurred in 65-85% after 24 h. In 2 group level of GTH and malon dialdehyde were not significantly differ from preoperative values, BT was diagnosed in 35-55% cases.

Conclusion: Local delivery of GTH to intestinal mucosa by CNp can improve gut barrier function during SAP.

P11-11 Abstract id: 25.
Effects of exocrine pancreatic insufficiency (EPI) and pancreatic enzyme substitution on bone mineral content of growing pigs ae“ used as a model for children

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Introduction: The pancreatic duct ligated (PL) minipig is an established model for studying effects of exocrine pancreatic insufficiency (EPI) in adults, but studies in juveniles are rare.

Aims: This study aimed to test the effects of EPI on bone density in growing pigs.

Materials & methods: In 8 pigs aged 8 weeks EPI was induced surgically (PL), another 4 pigs served as controls (C). Beginning from 3 weeks post OP 4 PL-pigs received Kreon® (=6300 Ph.Eur.E lipase/g dietary fat,(PL-0)) while 4 PL-pigs received no enzyme substitution therapy (PL-0). Diet contained (per kg DM) 85 g crude fat; 10.5 g Ca, 5.68 g P and 1875 IU vitamin D. Every 2nd week all animals received parenteral vitamin supply. 11 weeks post OP all animals were slaughtered and left ribia was taken and analysed by peripheral quantitative computer tomography for total bone mineral content (BMC) and cortex mineral content (CMC).

Results: BMC and CMC were significantly reduced in PL-0-pigs compared to C-pigs while in PL-0 intermediate values not differing from C at large were observed at distal end of ribia: (mg/cm): C: 482±±40.2a PL-295A±35.6b, PL-0: 390A±70.8ab]

Conclusion: Even all animals received a complete diet and were supplemented parenterally with high dosed vitamins there was an impaired bone mineralization in PL-0 ae“ despite lack of clinical symptoms. Enzyme supplementation improved (but didn’t normalize) bone mineralization presumably due to an improved total tract digestibility of fat (% Control: 80.9; PL-0: 75.5; PL-0: 52.0) ae“ supposed to cause an increase of the absorption of vitamin D and calcium.

P11-2 Abstract id: 310.
Tributaryliths as a reason of peripheral ductal hypertension in chronic pancreatitis

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Introduction: Masses in the head of the pancreas due to neuroimmune inflammation and hypertension in Wirsung duct are two known reasons of severe abdominalgia in chronic pancreatitis (CP). Other reasons of a pain is a controversial.

Aims: Demonstrate that so called «calcinites» into the parenchyma of the pancreas is really a stones in the tributary ducts. They cause a peripheral ductal hypertension.

Patients & methods: During 2010–2012 yrs we operated on 96 patients with CP by modern Frey (9 cases); Izbicki (n=2) and Berne’s modification of Beger procedure (n=85). From 2010 yr for the first time in the world we carried out 13 antegrade double balloon enteroscopy (DBE) investigations of pancreaticojunaoanastomoses (PJA) lumen after elective surgery of CP.

Results: Estimation of the results of the laser lithotripsy and cavitation during resection of pancreatic tissue (n=35), morphology of latter and DBE data of PJA lumen examination (n=13) allowed us to receive six evidences of the role of tributaries in the creation of peripheral ductal hypertension (PDH). This new reason of abdominal pain in CP was explained earlier as «peripheral parenchymal pressure». We proposed and introduced longitudinal pancreaticotomy and laser cylinder wirsungectomy (n=8) for elimination of PDH with restoration free outflow of pancreatic juice from tributary ducts.

Conclusion: Detected by MRI, CT or US stones in parenchyma of the pancreas body («calcinites» earlier) are the indication for elimination of the PDH and abdominal pain. For the primary surgery of CP most effective was cylindrical wirsungectomy.Izbicki. After Pargningtong–Rochelle or classical Frey procedures indicated V-shaped resection of pancreas by Izbicki.


Interferon gamma and transforming growth factor 1 beta levels in chronic pancreatitis patients with and without cholelithiasis


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Introduction: Transforming growth factor beta 1 (TGF-beta1) plays a key role in promoting fl-brosis by stimulation the expression and deposition of extracellular matrix and inhibition its degradation. Proinflammatory effect of interferon-gamma (IFN-gamma) proved an enhancement of its activity cells, mediated by the action of TGF-beta 1). The ELISA method validated at the Institute of Nutrition RAMS. ADH1B gene polymorphism indicating portions and frequency of consumption over the past 3 months, means of frequency questionnaire in 121 CPP, including product names, consumption patterns in CPP.

Aims: To determine the IFN-gamma and TGF-beta 1 levels in the blood serum of CP (patients) with or without cholelithiasis (CL).

Materials & methods: 85 CPP were examined (including those without CL - 51, with CL - 34 people). The groups were comparable in age and sex. IFN-gamma, TGF-beta 1 levels in the blood serum were determined by the ELISA method.

Results: Mean concentrations of IFN-gamma in serum in CPP with CL were higher (4.8±1.6 pg/ml) than in CPP without CL (1.8±0.3 pg/ml, p<0.05), and TGF-beta 1 in CPP with CL were lower (45.2±7.0 pg/ml) than in CPP without CL (67.2±6.7 pg/ml, p<0.05).

Conclusion: The identified opposite changes in immunological status can probably be explained by the combination of the two pathologies, CP and CL, which leads to a more pronounced (increasing concentrations of IFN-gamma) and long-term inflammation (reduced of collagen-producing activity cells, mediated by the action of TGF-beta 1).

PIL-14 Abstract id: 129.

The influence of hereditary factors in the development of chronic pancreatitis

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Introduction: The influence of hereditary factors in the formation of chronic pancreatitis (CP) is known. The strength of influence depends on the type of CP.

Aims: Identify the prevalence of mutation in genes CFTR, SPINK1 or PRSS1 in patients with CP.

Patients & methods: 150 patients with diseases of the pancreas were examined. All patients had a severe course of disease: acute pancreatitis in anamnesis, calcifications, cysts and other diseases of pancreas. Were presented 41 patients with idiopathic, 75 alcoholic, 17 biliary, 15 other (cancer and cystadenoma), 2 autoimmune. Patients were conducted to identify mutations in genes CFTR, SPINK1 or PRSS1 by PCR.

Results: Mutation in CFTR gene was detected in 3 patients. Mutation PRSK1 was detected in 13 patients, PRSS1- 27 patients. Both mutations were simultaneously detected in 5 patients. PRSS1 mutation was detected in 13 patients with alcoholic pancreatitis, SPINK 1 in 3 patients, both mutations in 3 patients. In patients with idiopathic pancreatitis PRSS1 mutation was detected in 7 patients, SPINK1 N345 in 4 patients, both mutations in 2 patients. In patients with biliary pancreatitis PRSS1 mutation was detected in 3 patients, SPINK1 in 3 patients, both mutations no detected. In this group there are 8 patients with mucinosis cystadenoma. In this group of patients, the mutation SPINK1 detected in 1 case and PRSS1 mutations in 3 cases. Among 7 patients with pancreatic cancer in 3 three identified mutations.

Conclusion: Hereditary CP diagnosed in 32.0% of cases. Patients with mutations in gene PRSS1, SPINK1, CFTR have a high risk of pancreatic cancer.

PIL-15 Abstract id: 106.

ADH2 gene polymorphism and alcohol consumption style in chronic pancreatitis


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Introduction: Alcohol dehydrogenase 1B*2 allele (ADH1B*2) is characterized by high catalytic ability. In ADH1B*2 alcohol abusers is rapidly developing somatic alcohol pathology, but it protect against alcoholism. Studies of ADH1 polymorphism in chronic pancreatitis patients (CPP) from Russian ethnous not performed.

Aims: To study the ADH1B gene polymorphism and alcohol consumption patterns in CPP.

Materials & methods: Alcohol and dietary intake was studied by means of frequency questionnaires in 121 CPP, including product names, indicating portions and frequency of consumption over the past 3 months, validated at the Institute of Nutrition RAMS. ADH1B gene polymorphism studied by PCR.

Results: frequency of ADH1B gene genotypes and alleles in CPP: 1* 1 - 0%, 1* 2 – 19.2%, 2* 2 – 80.8%; 1* 2 – 9.6%, 2 – 90.4%. Alcohol consumption was not significantly different in CPP with ADH1B*1*2 and 2*2 genotypes, respectively: wine 84.0±7.4, 47.8±26.6 ml/day, beer 469,5±169.1 and 443,5±112.2 ml/day, vermouth 10,0±0.1 and 13.2±2.4 ml/day, liquor 5,0±0.1 and 5,5±0.5 ml/day, vodka 15.3±4.7 and 25.7±7.0 ml/day (p>0.05 in all cases).

Conclusion: Among the surveyed CPP did not found ADH1B*1 homozygote. We found no significant differences in the dose of alcohol consumed by CPP in different ADH1B genotypes, but it should be noted that CPP with 2*2 genotype use higher doses of liquor and vodka, compared to those with 1*2 genotype.

PIL-16 Abstract id: 329.

Loss of Ppar-gamma promotes KrasG12D-driven pancreatic ductal adenocarcinoma formation by inhibiting p53 function

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Introduction: The crosstalk between oncogenic Kras (e.g. KrasG12D) and inflammatory pathways (e.g. NF-kB) is crucial in promoting the
development of pancreatic ductal adenocarcinoma (PDAC). Importantly, p53 which is mutated in nearly 50% of human PDACs widely interacts with inflammatory pathways. Recently, it has been shown that the activation of peroxisome proliferator-activated receptor gamma (Pparg) signaling effectively prevents the malignant transformation of pancreatic epithelial cells by inhibiting KrasG12D-mediated activation of NF-kB signaling.

Aims: Pparg activates the p53 pathway in a variety of tumor entities therefore we hypothesize that the tumor suppressor function of Pparg in PDAC derives from its crosstalk with p53 function.

Materials & methods: Functional analysis of an inflammation-accelerated carcinogenesis model by caerulein application in in a mouse model of pancreatic cancer (p48Cre/LSL-KrasG12D) with an additionally combined haploinsufficiency of Pparg and p53. Furthermore, in vitro treatment with a Pparg agonist and antagonist were performed to determine p53 activation status.

Results: The haploinsufficiency of Pparg and p53 significantly accelerated PDAC formation. In addition we observed/confirmed that Pparg haploinsufficiency promotes the inflammatory response after tissue injury; however, the activation of p53 function is impaired in this context. Accordingly, treatment with a Pparg agonist activates p53 whereas a Pparg antagonist inhibits p53.

Conclusion: Therefore, the inflammation-Pparg-p53 axis constitutes a novel tumor suppressor barrier in preventing PDMC progression after the acquisition of an oncogenic Kras mutation.

PII-17 Abstract id: 319.

Involvement of the RNA-binding proteins Sam68 and PTB in the acquisition of the resistance to gemcitabine in pancreatic adenocarcinoma cells

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Introduction: The limited effect of conventional chemotheraphy in pancreatic adenocarcinoma (PDAC) urges for novel therapies, targeting more directly the molecular aberrations of this disease. The molecular characterization of the drug resistant phenotype of PDAC cells remain unexplored, even though some evidence suggests a correlation with the expression of mesenchymal markers. Notably, the epithelial-to-mesenchymal transition (EMT) is promoted by finely-tuned changes in gene expression, at both transcriptional and splicing levels. In this regard, recent observations have shown the requirement for select splicing factors during EMT.

Aims: Characterization of the molecular events that lead to chemotherapeutic resistance in PDAC cells.

Materials & methods: Chronic exposure to gemcitabine to select a drug-resistant PDAC subpopulation. Western blot analyses for the expression of cancer related proteins, RNA-interference of selected genes to investigate their function. MTS assay and clonogenic assay to analyze cell survival.

Results: The chronic exposure of PDAC cells to gemcitabine selected a subpopulation of cells that display a mesenchymal phenotype and are less sensitive to drug-induced cell death. These cells express higher levels of Sam68 and PTB, two oncogenic splicing factors. Depletion of Sam68 and PTB expression caused a partial recovery of drug sensitivity, suggesting that they contribute to the acquisition of the resistance to the drug.

Conclusion: Our data indicate that Sam68 and PTB may represent suitable molecular targets for overcome drug resistance of PDAC.

PII-19 Abstract id: 341.

Xenografting pancreatic cancer: Impact on histology and RNA expression profiles

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Introduction: Recently some groups have established panels of pancreatic cancer xenografts. Those models might be more close to the clinic than cell lines which have undergone multiple passages. However it is not completely understood how xenografting alters tumour properties.

Aims: Aim of this study was to compare histology of primary and xenografted tumours and evaluate changes in RNA expression during passages.

Materials & methods: Tumour tissue was xenografted subcutaneously in immunodeficient nude mice and passed until stable growth was achieved. H/E stained sections of 23 tumours and associated xenografts were evaluated concerning histological morphology and amount of stromal tissue. RNA expression profiles from patient tumour and xenograft passages 1 to 3 were evaluated for 4 tumours using chip technology.

Results: Five histologies were identified: intestinal, ductal, papillary, cribiform and solid. In 17 cases congruent growth patterns were seen. In four cases the primary tumours showed a combination of two growth patterns and the derived xenografts only one of those two. In 2 cases growth
pattern were different. Lesser stroma was seen in the xenografts. A subset of genes with different expression in patient tumour and xenograft was identified. Those were mainly stroma and blood cell related genes. There was no significant change in expression profiles between xenograft passages.

**Conclusion:** Xenografts maintain histological characteristics of primary tumours. They have less stromal tissue, probably due to the fact, that the stromal tissue is provided by the host (mouse). RNA expression analysis also shows the loss of human stromal tissue but shows no further changes between xenograft passages.

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**PII-20 Abstract id: 119.**

Impact of deregulation of the gene expression of hedgehog signaling pathway in resectable pancreatic cancer

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**Introduction:** The hedgehog signaling pathway (SHH) was reported to enhance proliferation and invasiveness and to block apoptosis in pancreatic tumor cells.

**Aims:** The aim of the present study was to investigate prognostic significance of SHH in pancreatic cancer patients who underwent a radical resection in association with clinical and pathological characteristics.

**Patients & methods:** Tumors and adjacent non-neoplastic pancreatic tissues were obtained from 45 patients with histologically verified ductal pancreatic adenocarcinoma (PDAC). The transcript profile of 34 hedgehog signaling pathway genes was assessed using quantitative real-time polymerase chain reaction with a relative standard curve.

**Results:** Most of investigated SHH genes were deregulated in PDAC when compared with adjacent nonmalignant pancreatic tissue and 7 genes were associated with pathological characteristics with a borderline statistical significance. KIF3A was significantly up-regulated in moderately differentiated tumors when compared to high grade tumors (P = 0.009). High expression of PRKACA was associated with a shorter OS of resectable pancreatic cancer patients (P = 0.018) and high level of DHH was associated with a shorter OS in chemotherapy-treated subgroup of the patients (P = 0.038).

**Conclusion:** Despite the fact that expression of majority of SHH genes was strongly deregulated in PDAC it seems to have no striking effect on the prognosis of patients with the resectable stage of the disease.

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**PII-21 Abstract id: 192.**

Clinical impact of MiR-101, MiR-155 and MiR-21 in pancreatic intra-ductal papillary mucinous neoplasms (IPMNs)

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**Introduction:** The Intraductal Papillary Mucinos Neoplasm (IPMNs) show a wide spectrum of histological presentations ranging from adenoma to adenocarcinoma.

**Aims:** The goal of this multicenter study was to identify microRNAs (miRNAs) as potential prognostic biomarkers in patients affected by IPMNs of the pancreas.

**Patients & methods:** The expression of three candidate miRNAs (miR-21, miR-155 and miR-101) was quantified by quantitative RT-PCR in 86 laser-microdissected (LMD) formalin-fixed paraffin embedded (FFPE) specimens, including 65 invasive IPMNs, 16 non-invasive IPMNs and 5 normal pancreatic ductal tissues. Univariate and multivariate analyses compared miRNAs and clinical parameters with overall and disease-free survival (OS, DFS) using log-rank test and Cox’s proportional hazards model.

**Results:** MiR-21 and miR-155 were significantly upregulated in invasive IPMN compared to non-invasive IPMN, as well as in non-invasive IPMN compared to normal ductal tissues. Conversely, miR-101 levels were significantly higher in non-invasive IPMN and normal tissues versus invasive IPMN. Kaplan-Meier survival analysis revealed that high levels of miR-21 expression were closely associated with worse OS (hazard ratio [HR] 2.47, P = 0.0047). Patients with high miR-21 expression also had a significantly shorter median DFS (10.9 vs. 29.9 months, log-rank P = 0.01). Multivariate analysis confirmed miR-21 as independently prognostic for both mortality and disease progression (death-risk, HR = 3.3, P = 0.02; progression-risk, HR = 2.3, P = 0.02), as well as positive lymph-node status (death-risk, HR = 2.6, P = 0.03; progression-risk, HR = 2.2, P = 0.04).

**Conclusion:** The miRNAs evaluated in the present study showed significant differences in invasive versus non-invasive IPMN, and miR-21 expression emerged as an independent prognostic biomarker in patients affected by invasive IPMN, offering innovative tools for the optimal management of these tumors.

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**PII-22 Abstract id: 153.**

The role of the Eps8 binding partners Sos1 and Abi1 in pancreatic cancer

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**Introduction:** Pancreatic cancer (PC) is characterised by marked local invasion, which requires actin cytoskeletal remodelling. EGF receptor pathway substrate 8 (Eps8) is an actin-binding protein with multiple binding partners including Abi1, Sos1, and certain β integrin subunits. αvβ6 integrin is overexpressed in ~70% of PC and enhances invasion.

**Aims:** To examine the role of Abi1 and Sos1 in αvβ6-dependent PC invasion.

**Materials & methods:** We used immunohistochemistry to examine expression of Eps8, Abi1 and Sos1 in normal pancreas and PC. A retrospective patient database was generated of those treated surgically for PC (2000-2008) and used to identify 38 short (< 2 year) and 19 long (> 4 years) survivors. Resection tissue was then stained for Eps8/Abi1/Sos1/αvβ6. We identified three PC cell lines that showed αvβ6-dependent motility in vitro, and performed Transwell® assays to study the functional roles of Abi1 and Sos1.

**Results:** Eps8, Sos1 and Abi1 were upregulated in PC compared with normal tissue. Expression of these proteins in long and short survivors is currently being examined. Eps8, Sos1, Abi1 and αvβ6 expression was confirmed in all three PC cell lines tested. Knock-down of Eps8, Sos1 or Abi1 significantly suppressed αvβ6-dependent migration and invasion.

**Conclusion:** Eps8, Sos1 and Abi1 are upregulated in PC and appear to be critical to αvβ6-dependent PC motility. Interestingly, Sos1 expression was previously shown to fall in response to gemcitabine, the current gold standard chemotherapeutic agent for the treatment of PC. Sos1 therefore requires further investigation as a potential molecular target in the treatment of PC.

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**PII-23 Abstract id: 139.**

Associations of gene expression of major drug transporters with the prognosis of pancreatic cancer

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**Introduction:** The goal of this multicenter study was to identify microRNAs (miRNAs) as potential prognostic biomarkers in patients affected by IPMNs of the pancreas.
**Introduction:** Several lines of evidence indicate that expression profile of drug-associated transporters may contribute to the low response rate to systemic treatment in patients with pancreatic ductal adenocarcinoma (PDAC).

**Aims:** The present study investigated prognostic significance of ATP-binding cassette (ABC) and solute carrier (SLC) transporters in radically resected PDAC patients.

**Patients & methods:** Transcript profile of 49 ABC and 13 SLC transporter genes was followed by qPCR in tumors and adjacent non-neoplastic pancreatic tissues from 32 patients with histology-verified PDAC. Association of expression of individual genes and gene-gene combinations with clinical characteristics and overall survival (OS) of patients was evaluated.

**Results:** High levels of ABCC1 and SLCA2A1 significantly associated with longer OS in all patients (n=32, P=0.005 and P=0.028, respectively). In contrast, high levels of ABC2C2 and ABCC4 associated with shorter OS (P=0.029 and P=0.032, respectively). In a subgroup of chemotherapy-treated patients (n=19), levels of ABC transporters did not associate with OS at all but high level of SLCA2A3 significantly associated with longer OS (P=0.029). Most interestingly, patients with low expression of SLCA2A3 and simultaneously high expression of ABC2C2 had significantly shorter OS in comparison with the rest of chemotherapy-treated patients (P<0.001).

**Conclusion:** Our results further support the concept that drug transporters modify the prognosis of patients with PDAC. The biological mechanism of this association however, does not seem to be straightforward and should be intensively studied. Supported by Czech Science Foundation grant No. P301/12/1734 and project ED/2.1.00/03.0076 from European Regional Development Fund.
**Introduction:** Multicentric studies have been of the utmost importance to identify genetic factors involved in neoplastic diseases.

**Aims:** We have established the PANcreatic Disease ReseArch (PANDoRA) consortium to join the efforts of different research groups and create a large bio- and databank aimed at uncovering new genetic factors for pancreatic cancer risk and survival.

**Patients & methods:** So far, 2220 PDAC cases were retrospectively recruited and collected at the German Cancer Research Center (Heidelberg, Germany), where the DNA bank and the central database were established.

We also collected samples of 114 cases of rarer exocrine pancreatic cancer types, 125 cases of pancreatic endocrine tumours (PETs), 98 Intraductal Papillary Mucinous Neoplasms (IPMNs), 272 cases of chronic pancreatitis and more than 3500 healthy controls.

**Results:** We performed several association studies. In particular we studied all the PDAC risk SNPs from the three published genome-wide association studies (GWAS), performed in a Caucasian, a Chinese and a Japanese populations. We confirmed the majority of the associations found in the Caucasian and none found in the Asian populations, highlighting the importance of the genetic background in the etiology of pancreatic cancer in different ethnicities.

**Conclusion:** We will study additional SNPs from ongoing GWAS, as well as SNPs of key genes involved in the pathogenesis of pancreatic diseases. Additionally, we are measuring telomere length and mitochondrial copy number. We will investigate the role of all these factors in relation to PDAC risk and prognosis. The collection of cases is currently on-going in every participating centre.

**PII-26 Abstract id: 154.**

Aneuploidy levels and mitotic checkpoint proteins in pancreatic intraepithelial neoplasia

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**Introduction:** Pancreatic carcinogenesis involves a wide range of genetic anomalies among which aneuploidy (abnormal chromosome number) and abnormal secretion of mitotic checkpoint proteins like Mad2 and BubR1.

**Aims:** 1. Investigate the aneuploidy and Mad2 and BubR1 levels displayed in premalignant stages
2. Investigate potential correlations and their relevance to progress and survival

**Materials & methods:** We investigated the aneuploidy levels for chromosomes 1, 6, 9 and 18 using fluorescence in situ hybridization (FISH) on stored resection specimens that included premalignant stages of pancreatic intraepithelial neoplasia (PanIN 1 - 3). Immunohistochemistry (IHC) was used to assess the levels of Mad2 and BubR1 in the same histological stages.

**Results:** 68 different histological stages were included: male:female ratio 1:0.42, median age 67.1 and average tumour size 3.7 cm.

Amplifications were the most significant molecular event for all the chromosomes investigated. Significant differences were seen in the average between the normal pancreatic ducts and the advanced tumour (p<0.001) and between the ducts with PanIN 1 and the advanced tumour (p<0.002). The levels of overall aneuploidy increased from PanIN 1 to PanIN 3.

The levels of Mad2 and BubR1 were not directly correlated with the levels of aneuploidy but BubR1 displayed a similar increasing trend towards the PanIN 3 stage, suggesting a potential link to chromosomal instability resulting in aneuploidy.

**Conclusion:** The aneuploidy displayed by chromosomes 1, 6, 9 and 18 in pancreatic intraepithelial neoplasia appears to be related to chromosomal instability generated by abnormal expression of the mitotic checkpoint proteins Mad2 and BubR1.

**PII-27 Abstract id: 335.**

Characterization of gemcitabine resistant Capan-1 cells and the effect of Oct-4 on chemoresistance

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**Introduction:** Pancreatic cancer is characterized by chemoresistance, which is in part mediated by the reactivation of early developmental and stem cell associated pathways. Previous studies have shown that in vitro treatment of pancreatic cancer cells leads to reactivation/seletion of cells expressing stem cell genes.

**Aims:** We generated and characterized Capan-1 cells resistant to gemcitabine and analyzed Oct-4, Abcg2 and Pdx-1 downregulation with respect to gemcitabine resistance.

**Materials & methods:** Capan-1 cells adapted to 10μM gemcitabine were characterized for proliferation, migration, invasion, cell cycle distribution, genomic alterations, expression of stem cell- and chemoresistance-associated genes, and side-population distribution. Using siRNA assays, the effects on chemoresistance of Oct-4, Abcg2 and Pdx-1 downregulation were assessed.

**Results:** IC50 of resistant cells was 80 μM (vs 15 nM in non-resistant cells), they proliferated/migrated faster, while being comparable at cell cycle distribution and invasion. Mutations were observed in several signaling pathways, e.g., in the hedgehog pathway. Pancreatic cancer stem cell signature CD44+CD133+EpCAM+ was increased in the resistant (35.4% positive) vs. the non-resistant cells (23.7%). Side population was 6.9% in resistant cells (vs 3.9% in non-resistant cells). Within the side-population, Abcg2 was upregulated 10.8x, Oct-4 3.3x and Pdx-1 4.4x relative to side-population cells of non-resistant counterparts. Gene knockdown using siOct-4 reduced IC50 of resistant cells to 1.3 μM, siPdx-1 to 14 μM and siAbcg2 to 48 μM.

**Conclusion:** Oct-4 downregulation was able to reduce IC50 to 1.3 μM, indicating an important role of this regulator of stem cell differentiation, warranting further studies. Resistant Capan-1 cells offer a new platform for investigations on chemoresistance.

**PII-28 Abstract id: 34.**

Effects of carbon ion beam in combination with gemcitabine on pancreatic cancer stem-like cells in vitro and in vivo

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**Introduction:** The prognosis of patients with advanced pancreatic cancer is dismal.

**Aims:** The aim of this study is to investigate whether a carbon ion beams alone or in combination with gemcitabine has beneficial effects compared to X-ray by targeting putative human pancreatic cancer stem cells (CSCs).

**Materials & methods:** Human pancreatic CSCs sorted from PANCI, MiaPaca2, BxPc3, and PK45 cells were treated with carbon ion or X-ray alone or in combination with gemcitabine, and then colony, spheroid and tumor formation assays, immunofluorescence γH2AX foci assay as well as in vivo tumor control analysis were performed.

**Results:** The colony, spheroid formation as well as tumorigenicity assays confirmed that CD44+/CD24+ and CD44+/ESA+ cells exactly have
CSC properties compared to CD44+/CD24- and CD44+/ESA- cells. CSCs were more highly enriched after X-ray or gemcitabine compared to carbon ion beam. The relative biological effectiveness (RBE) values for the carbon ion beam relative to X-ray at the D10 levels for CSCs were 2.0-2.19. Immuno-fluorescence assay showed that not only the number but also the size of 

### Conclusion:
Carbon ion beam has superior potential to kill pancreatic CSCs, produced unreparable severe DNA damage, and can achieve high curability when combined with gemcitabine at relatively lower doses compared to carbon ion alone.

### PII-29 Abstract id: 163.
**Phospholipase Cγ-1 regulates cell migration in pancreatic cancer cells**

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**Introduction:** Signalling via growth factor receptors results in the activation of Phospholipase Cγ-1 (PLCγ-1) and phosphatidylinositol (PI) 3-kinase. PLCγ-1 is an intracellular enzyme regulating many biological processes, including transcription factors, proteins mediating cytoskeleton and membrane trafficking, tumor development and progression. Recent evidence suggests the implication of PLCγ-1 in the development of human metastasis.

**Aims:** We designed this study to investigate the expression and the activity of PLCγ-1 in pancreatic cancer.

**Materials & methods:** We analyze PLCγ-1 expression using immunohistochemistry and Western Blotting assays. The intracellular activity was studied using the pharmacological knockdown of PLCγ-1 inhibitors in BxPC-3 cancer cell line. Cell proliferation was measured by MTT assay. In addition, cell motility was analyzed by wound healing assay at regular intervals during cell migration.

**Results:** PLCγ-1 is expressed in BxPC-3 and in human pancreatic cancer specimens showing a cytoplasmic distribution. Knockdown of PLCγ-1 strongly inhibits BxPC3 cell migration in different experimental conditions. Interestingly, PLCγ-1 inhibition did not affect pancreatic cancer growth.

**Conclusion:** Our preliminary data show for the first time the critical role of PLCγ-1 in controlling migration of pancreatic cancer cells and indicate its potential therapeutic role in pancreatic tumor progression and in the development of metastasis.

### PII-30 Abstract id: 294.
**Cellular effects of MEK inhibition in pancreatic cancer cell lines are not correlated with classical predictive markers of response to MEK inhibitors (MEKi)**

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**Introduction:** MEKi are currently tested in PAC. K-RAS and B-RAF mutations, EMT, PI3K-Akt-mTOR pathway activation, and pErk inhibition under treatment may predict response to MEKi in various cancers, but remain unvalidated in PAC.

**Aims:** To compare effects of MEKi in 4 PAC cell lines, according to their status for these predictive markers.

**Patients & methods:** UO126, AZD6244, AS703026 and GSK1120212 are allosteric non-ATP competitive MEKi. Proliferation: MTT assay. Cell cycle modifications: flow cytometry. Protein expression: Western blot. Combinations analysis: Chou-Talalay method.

**Results:** All cell lines except BxPC-3 were K-RAS mutated, and none were B-RAF mutated. MIAPaCa-2 and PAN-1 were mesenchymal, Capan-1 and BxPC-3 were epithelial. PAN-1 exhibited high basal levels of Akt, pAkt, p70S6K and pS6. UO126 and AZD6244 had low cytotoxic activity (72h-IC50 = 5.0-26.0μM) compared to AS703026 and GSK1120212 (72h-IC50 = 0.009-0.65μM). Although both K-RAS mutated and mesenchymal, MIAPaCa-2 was the most sensitive (72h-IC50 = 0.009-13.7μM) and PAN-1 the most resistant (72h-IC50 = 33-61.3μM). Exposure to UO126 and GSK1120212 induced an increase in G0/G1 and decrease in S-phase in both cell lines. An increase in subG1-phase (>30%) was observed after GSK1120212 exposure in MIAPaCa-2 but not PAN-1. Apoptosis induction was confirmed by PARP cleavage. Similar pErk inhibition profile was observed with UO126 (<5h) and GSK1120212 (>72h), and pAkt was increased by MEKi in both cell lines. MEKi and everolimus combination was synergistic in MIAPaCa-2 but not PAN-1.

**Conclusion:** MEKi were active regardless K-RAS mutation and EMT status. There was no correlation between cellular effects and pErk inhibition. MEKi activated the Akt pathway. MEK-1/mTOR inhibition was synergistic in MIAPaCa-2 sensitive cells but not PAN-1.

### PII-31 Abstract id: 66.
**Macrophages enhance invasiveness of pancreatic cancer**

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**Introduction:** Pancreatic cancer remains the most aggressive malignancy of all human cancers. Many years of research have not improved neither treatment nor diagnosis of this devastating disease. Infiltrating inflammatory cells might be part of antitumor response but also they may take part in supporting tumor invasion. In particular macrophages and neutrophils were shown to present pro-tumor phenotype.

**Aims:** To evaluate influence of infiltrating immune cells on pancreatic cancer invasiveness.

**Materials & methods:** Tumor tissue samples were obtained from 36 patients, who underwent macroscopically curative resection. Patients had not received any preoperative treatment. Tissue specimens were analyzed with immunohistochemistry using antibodies against CD3, CD68, elastase, CD56. Zymography in situ was used for evaluation of MMP2 and MMP9 activity.

**Results:** Immunostaining showed numerous macrophages and lymphocyte infiltrates around cancer nests and also in surrounding tissue. Number of macrophages present in tumor tissue was significantly higher in groups with lymph node metastases and also in tumors with perineural invasion. In situ analysis confirmed that infiltrating immune cells are source of active metalloproteinases. Appearance of CD3+ cells was associated with lack of neural and vascular invasion.

**Conclusion:** There is no doubt that infiltrating tumor cells are pivotal element of this microenvironment. Particularly macrophages take part in tumor progression and enable creating metastases. Investigating infiltrating macrophages might be useful in evaluating possibility of metastases incidence.
PIL-32 Abstract id: 44.

Serum MALDI profiling for pancreatic ductal adenocarcinoma biomarkers discovery: A pilot study

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Introduction: The available biomarkers for diagnosing pancreatic ductal adenocarcinoma (ADK) lack in sensitivity and specificity and advances in quantitative proteomics have stimulated its clinical applications founded on the serum analysis.

Aims: To evaluate small proteins and peptides which could discriminate ADK from healthy controls (HC) by MALDI Profiling

Patients & methods: Ten sera from proven ADK patients and 10 from HC were analyzed. The high abundant serum protein components were removed and the MALDI Profiling was adopted for the detection of differentially changed species possibly related to the tumor onset. After acquisition, spectra were processed by ClinProTools for statistics (Wilcoxon test, p < 0.05, PCA analysis and AUC > 0.800).

Results: MALDI Profiling allowed to detect 82 peaks in the acquisition range of 1.5-35 kDa and 35 significantly changed peaks were detected (10 over and 25 underexpressed in cancer) with AUC not lower than 0.872.

Conclusion: These preliminary results suggest the potentiality of this approach to discriminate ADK and HC.

PIL-33 Abstract id: 107.

Kynuramines upregulate HSP27, HSP70 and HSP90 in pancreatic carcinoma cells via 5-HT and MEL A/B-1 receptors

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Introduction: Kynuramines, metabolites of L-tryptophan and melatonin, are synthesized endogenously by oxygenases or by interaction with free radicals. Previously we have reported that melatonin stimulated expression and phosphorylation of HSP27, production of HSP70 and HSP90α/β in PANC-1 cells. Based on above results, we hypothesized that above process could be involved in the mechanism of intrinsic apoptotic pathway interruption.

Aims: Here in, we would like to present that L-kynurenine (L-KYN) and N1-acetyl-N2-formyl-5-methoxykynuramine (AFMK) lead to the overexpression of HSPs synthesis and that this process is partially abolished by 5-HT3 or Mel A/B-1 receptors antagonists.

Materials & methods: PANC-1 cells in culture were treated with L-kynurenine or AFMK, Mel A/B-1 receptors antagonist; luzindole, 5-HT3 receptor antagonists; ketanserin, MDL72222, or combination of above. After incubation, cells had been harvested, the cytoplasmic and nuclear proteins fractions were isolated for immunoblotting or/and immunoprecipitation analysis of HSP27, HSP70 and HSP90α/β.

Results: Our studies have shown that both L-kynurenine and AFMK significantly decreased cytoplasmic HSP27 content, presumably due to increase of its phosphorylation and consequent translocation, confirmed by immunoprecipitation analysis of phosphorylated HSP27. These changes were accompanied by slight augmentation of HSP70 and HSP90 abundance in cytosolic fraction. Pretreatment of the cell cultures with luzindole or MDL72222 followed by the addition of kynuramines reversed the stimulatory effects of L-KYN or AFMK on HSPs expression in PANC-1 cells, whereas ketanserin failed to affect analyzed protein signal.

Conclusion: We conclude that L-kynurenine or AFMK could stimulate phosphorylated HSP27, HSP70 and HSP90α/β production in PANC-1 cells through interaction with the Mel A/B-1 or/and 5-HT3 receptors.

PIL-34 Abstract id: 28.

The diagnosis of genetic predisposition in familial pancreatic cancer

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Introduction: Pancreatic cancer is relatively rare but has very grim prognosis. The incidence/death ratio is almost 0.99. The overall 5 years survival rate, of all stages combined together, is one of the lowest amongst all cancers. It is about 5% in Europe and the United States making it very worrisome in terms of public health. Screening for the early diagnosis of Pancreatic cancer, and thus increasing the chances of cure does not yet established. Pancreatic cancer is often sporadic, however, familial aggregation of this malignancy can occur in many circumstances and is responsible for about 10% of cases.

Aims: This review focuses on pancreatic cancer occurring in a familial context. Many cases of familial pancreatic cancer could have been early discovered and treated if a genetic, clinical test... are available.

Patients & methods: A careful reviewing and detailed analysis of the scientific literatures show that this is indeed possible.

Results: Routine exploration of genes BRCA2, PALB2, CDKN2A, listed in order of involvement, is an important initial step towards establishment of a diagnosis of genetic predisposition to pancreatic cancer.

Conclusion: Routine exploration of genes such as BRCA2, PALB2, CDKN2A, listed in order of involvement, is an important initial step towards establishment of a diagnosis of genetic predisposition to pancreatic cancer.

PIL-35 Abstract id: 18.

Measuring islet cell apoptosis during isolation and transplantation: Advancing a potential cure for diabetes

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Introduction: During islet cell isolation as a precursor to islet cell transplantation, a significant number of islet cells undergo programmed cell death or apoptosis. Due to shortage of pancreatic organ donors, it is crucial that islet cell isolation techniques preserve the integrity of cells to provide maximum yield.

Aims: To identify a cell dissociation enzyme that resulted in the lowest apoptosis rate and the highest yield of viable islets.

Materials & methods: Three active enzymes namely Trypsin, Accumax and Accutase were used for separation of individual islet cells from clumps of islets of langerhan isolated recently from pancreatic donors. Solutions containing islet cells were stained with annexin to identify apoptotic cells, 7-AAD to identify dead cells and also dual staining was done to identify a combination of both. Flow cytometry was used for analysis. 22 parallel assays were run on a single population of islets over six weeks. Data was analyzed by ANOVA testing the Null hypothesis that the dissociation enzymes function equivalently.

Results: Trypsin resulted in a significantly lower percentage of dead and apoptotic cells (p < 0.05) in all three groups (7-AAD, annexin and dual staining) compared to accutase and accumax. Additionally accumax had a significantly lower percentage of dead cells (p < 0.05).

Conclusion: Preliminary results indicate that trypsin method may provide higher viable islet cell yield. However differences in cell counts for
the test cohorts and lack of a standard reference method, more studies are needed to conclude that the trypsin method is superior. We are developing a reference method using confocal microscopy.

P11-36 Abstract id: 17.
Effect of osteocalcin on human beta cell proliferation and function and its role on insulin secretion
Anita Kaw, Daniel Fraga, Craig Fischer.

Introduction: Osteocalcin, a hormone produced by bone cells, has been found to increase insulin production, enhance insulin sensitivity, and promote β-cell proliferation in mouse models, however mouse studies do not reliably affect humans in the same manner.

Aims: This study sought to confirm the effect of osteocalcin on human β-cell proliferation and function and its role, if any, on insulin secretion.

Materials & methods: Three variants of osteocalcin extracted and purified from bovine tibial cortical bone were investigated: osteocalcin (OC), decarboxylated osteocalcin (D-OC), and osteocalcin hexapeptide (H-OC) were utilized in conjunction with a well-established islet model. Protocol included human pancreatic islet isolation from brain dead donors, (OC), decarboxylated osteocalcin (D-OC), and osteocalcin hexapeptide (H-OC) were utilized in conjunction with a well-established islet model. Protocol included human pancreatic islet isolation from brain dead donors.

Results: Our results indicate that after 7 days in culture all three types of osteocalcin improved insulin-content and β-cell proliferation of glucose-stimulated islets, with D-OC showing the most significant and dose-dependent effect. The greatest effect on insulin enhancement was noted at the earliest time point (7 days), and this effect progressively deteriorated at later time points, reflecting perhaps senescence in our culture while apoptosis was not impacted by either osteocalcin or time in culture.

Conclusion: Our findings indicate that osteocalcin or one of its variants may be utilized in patients whose disease conditions show a progressive loss of β-cell mass and function namely type 2 and, in some cases type 1 diabetes.

P11-37 Abstract id: 226.
Impact of pancreatic enzymes on blood glucose and insulin release in a porcine model
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Introduction: Exocrine pancreatic insufficiency (EPI) induced in young pigs by pancreatic duct ligation (PDL) results in growth arrest and a decreased ability to retain/assimilate nutrients.

Aims: The aim of the study was to explore the effects of pancreatic enzyme replacement therapy (PERT) on glucose utilization and insulin secretion in this model.

Materials & methods: Five EPI pigs and six control pigs were studied and meal (MGT), oral (OGTT), and i.v. glucose tolerance tests (IVGTT) were performed, either with or without PERT (Creon® 10,000). Blood glucose was measured with a glucose-meter and plasma insulin levels with an ELISA kit.

Results: The MGT resulted in increased plasma glucose levels similar to that in the controls, but only a negligible increase in insulin levels. The MGT following PERT, resulted in a prolonged increase in blood glucose (above those in controls) and insulin (below that in controls) levels. The OGTT, both with and without PERT, caused a prolonged increase in blood glucose levels compared to controls. A parallel increase in insulin levels was observed, however the increase was smaller in comparison to the controls. PERT before IVGTT, accelerated the elimination of glucose and at the same time lowered the insulin levels, with a shift in the curve peak towards that observed in the controls.

Conclusion: In conclusion, the data indicates that pancreatic enzymes not only affect the availability of glucose from the food, but also affect the post-prandial insulin response - in line with the incretin concept - and thus suggests a factor released in response to PERT which affects glucose utilization.

P11-38 Abstract id: 177.
Pancreatic and pancreatic-like enzymes decrease insulin secretion together with an enhanced insulin efficiency or provoke insulin-independent glucose utilisation
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Introduction: The role of the exocrine pancreas in food digestion is well-studied but its’ possible (para-digestive) effects on insulin release and glucose tolerance has received less attention.

Aims: We aimed to study the effects of pancreatic enzyme supplementation on blood glucose and plasma insulin in normal pigs.

Materials & methods: Twelve pigs, 2.5 months old, were fasted overnight and then administered either porcine enzymes (Creon 10 000) or a mixture of pancreatic-like enzymes of microbial origin (PLEM), or empty capsules as a placebo. After 1h an intravenous glucose tolerance test (IVGTT) was performed (by infusion of 1g glucose/kg, using 50% solution). Repeated blood samples were taken and blood glucose was measured with a glucose-meter and plasma insulin levels with an ELISA-kit.

Results: Blood glucose decreased 1h after enzyme administration (12.8% for Creon, 15.5% for PLEM, p<0.05), while placebo had no influence. Surprisingly, after enzyme feeding insulin levels also decreased to 3-times less than the baseline. The IVGTT showed a similar slope of glucose elimination/utilization in enzyme-supplemented and control pigs, while insulin levels were significantly lower in enzyme-fed pigs as seen after 15 and 30 min after i.v. glucose infusion.

Conclusion: The data indicate that administration of pancreatic and pancreatic-like enzymes reduce insulin release and enhance the glucose tolerance. The results suggest also a para-digestive, insulin-like anabolic action on glucose utilisation via unidentified factor(s) released in response to the enzymes supplementation. The findings might have impact on to-days increased obesity problem related to an enhanced exocrine secretion due to increased carbohydrate consumption.

Modulation of pancreatic amylase secretion by tryptophan metabolite
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Introduction: The kynurenines, products of tryptophan metabolism, are involved in many physiological processes as well as in regulation of the immune response of the organism. These products have been detected within gastrointestinal system, but their effects on pancreatic amylase secretion have not been investigated yet.

Aims: To assess the effects of intraduodenal (i.d.) infusion of L-kynurenine on pancreatic amylase outputs under basal conditions and following the stimulation of pancreatic secretion with diversion of pancreatic-biliary juice (DPB) and the role of CCK in that process.
Materials & methods: The study was performed on Wistar rats weighing 350g. Under pentobarbital anesthesia the animals were surgically equipped with silicone catheters, inserted into pancreatic-biliary duct, and into duodenum. L-kynurenine (50 or 250 mg/kg i.d.) was given under basal conditions or following stimulation of pancreatic secretion with DPBJ. In the part of the study the lorglumide, the CCK1 receptor blocker completely abolished the secretory effects of L-kynurenine on pancreatic exocrine function.

Conclusion: CCK is involved in the stimulatory effects of tryptophan metabolite, L-kynurenine, on exocrine pancreatic secretion in the rats.

PIL-40 Abstract id: 72.
Transplantation of allogeneic mesenchymal bone marrow stem cells in experimental acute and chronic pancreatitis in rats
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Introduction: Transplantation of allogeneic mesenchymal bone marrow stem cells studied not enough.
Aims: Under the experimental conditions to establish safe doses and optimal timing of stem cell transplantation.
Materials & methods: 30 white rats, an experimental model of acute and chronic pancreatitis. Allogeneic stem cells transplantation: a dose 5N...106, a single intraperitoneal injection of 2 ml of saline; 2x106 in 2 ml of saline once or double injection. Animals are parted in 5 the groups: first group - reproduction of an experimental pancreatitis on the third day 5x106; the second group - acute pancreatitis on injection a single dose the 5x106 cells on the 10th day. 4th and 5th groups - the introduction of cells or solution saline. Autopsy of the animals on day 16 after pancreatitis.
Results: First group - the place of introduction of damaging agent in the pancreatic tissue necrotic, the interstitial abscesses. Second group of double injection in doses 5x106 cells of the pancreas edematous, necrotic, the all pancreas were "shrouded" fatty tissue. 3rd group of data are similar to data obtained in the second group. When the audit abdominal necrotic tissue overlay on the pancreas, adhesions, separation of the pancreas injures the surrounding tissues. 4th and 5th groups - the introduction of cells or solution saline. Autopsy of the animals on day 16 after pancreatitis.
Conclusion: After transplantation allogeneic mesenchymal stem cells decreasing inflammatory reaction.

PIL-41 Abstract id: 123.
Exocrine and endocrine pancreatic insufficiency after acute pancreatitis
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Introduction: Incidence and clinical significance of exocrine pancreatic insufficiency (EPI) and type 3c diabetes mellitus (T3cDM) after acute pancreatitis (AP) remains controversial. We are presenting preliminary results of our study.
Aims: To determine whether exocrine and endocrine pancreatic function are impaired in patients after AP and to evaluate its relationship to etiology and severity of AP.
Patients & methods: There are currently included 55 patients; 36 (65.5%) men and 19 (34.5%) women, mean age 56.3±13.4 years. EPI was determined by the fecal elastase-1 concentration (FEC). T3cDM was determined by WHO criteria.
Results: Most common etiologies of AP were alcohol (n=22; 40%) and gallstones (n=22; 40%), followed by unexplained (n=6; 10.9%), hypertriglyceridemia (n=3; 5.5%) and drug-induced (n=2; 3.6%). Mean follow-up was 2.8±4.9 years. EIP was present in 9 patients: in 2 after severe; in 3 after moderately severe and in 4 after mild AP. T3cDM was present in 7 patients (12.7%): in 2 after severe; in 1 after moderately severe and in 4 after mild AP. EPI was more common in patients with alcoholic etiology (7 out of 9) followed by gallstone etiology (2 out of 9). T3cDM was present in 3 patients with gallstone, 2 patients with alcohol and 2 patients with hyperlipemic etiology.
Conclusion: EPI and T3cDM occurred much less frequently than in previous studies. EPI is more common in patients with alcoholic etiology of AP. T3cDM is not related to specific etiology of AP. So far we have not found an association between severity of AP, EIP and T3cDM.

Elevated intra-abdominal pressure correlates with frequency of organ failure and outcome in severe acute pancreatitis
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Introduction: Elevated intra-abdominal pressure (IAP) may contribute organ failure (OF) and increase mortality in patients with severe acute pancreatitis (SAP).
Aims: To assess the correlation between maximal noted IAP (maxIAP) during hospitalization, frequency of OF, and mortality in patients with SAP.
Patients & methods: Study included 44 patients with SAP. SAP was classified retrospectively according to revision of the Atlanta 2012. OF included respiratory, renal and cardiovascular according to Atlanta revision, but liver dysfunction and coagulopathy were included also. IAP was measured daily and maxIAP was included in the study.
Results: Incidence of OF was respiratory in 37(84.1%), renal in 33(75%), cardiovascular in 15(34.1%), liver dysfunction in 21(47.7%) and coagulopathy in 7(15.9%) patients. Six (13.6%) patients had single-OF and maxIAP of 13 mmHg (11-17), 12(27.3%) patients had two-OF and maxIAP of 17 mmHg (14-23), 21(47.7%) patients had three-OF and maxIAP of 21 mmHg (14-26), 5(11.4%) patients had four-OF and maxIAP of 22 mmHg (15-24). Significant correlation between maxIAP and frequency of OF was found (r=0.581, p<0.001). Mortality rate was 11.8% in patients with maxIAP between 11-15 mmHg, 11.8% in patients with maxIAP between 16-20 mmHg, 76.5% in patients with maxIAP between 21-25 mmHg, and 0% in patients with maxIAP ≥26 mmHg (z=-2.774, p=0.006). Overall mortality rate was 38.6%.
0% in patients with single-OF, 11.8% in patients with two-OF, 58.8% in patients with three-OF and 29.4% in patients with four-OF (z = -3.688, p < 0.001).

Conclusion: Elevation of IAP correlates with frequency of OF in patients with SAP. Mortality rate is higher in patients with multi-OF and higher IAP during SAP.

PIL-43 Abstract id: 91.
Plasma citrulline in diagnosing of acute intestinal failure in patients with severe acute pancreatitis
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Introduction: Acute intestinal failure in patients with severe acute pancreatitis (SAP) is common and associated with a poor prognosis. However, a validated it’s definition is lacking. Plasma citrulline, an amino acid produced exclusively by enterocytes, might be a candidate.

Aims: To assess ability of plasma citrulline in diagnosing acute intestinal failure in patients with SAP.

Patients & methods: This prospective study included 86 adult patients consecutively admitted to intensive care unit due to SAP. Clinical and laboratory variables as well as plasma citrulline concentrations were studied. Diagnosis of acute intestinal failure was confirmed by clinical and instrumental investigations. 10 healthy persons represented control group.

Results: In control persons plasma citrulline concentration was 36.8 ± 0.86 μmol/l, but in patients with SAP it decreased to 16.86 ± 0.44 μmol/l (Ne < 0.02) at admission. Among them those with citrulline concentration during first 24–48 h above 20.0 μmol/l were presented with APACHE II score 7±1.4 and minimal symptoms of gut insufficiency. Moderately stable patients (APACHE II score 14±2.9) had citrulline concentration 16.6±0.48 μmol/l and intestinal disorders were determined in 44% cases. Intestinal failure was diagnosed in 83% of persons with citrulline concentration less than 12 μmol/l together with worsening general status (APACHE II score more than 26), increasing frequency of septic complications on 34% (p < 0.05) and decreasing survival more than 50% (p < 0.05).

Conclusion: Plasma citrulline concentration is simple and readily accessible clinical marker for diagnosing and monitoring acute intestinal failure in patients with SAP. Decreasing it level less than 12 μmol/l may be independent mortality factor in such patients.

PIL-44 Abstract id: 251.
Fluid resuscitation in acute pancreatitis: Normal saline or Ringer’s lactate - does it really make a difference?
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Introduction: Crystalloids are currently recommended as initial resuscitation i-vuids in the patients with severe pancreatitis (AP). Nevertheless, the optimal type of fluid therapy remains unclear.

Aims: The aim of this study was to investigate whether administered Ringer’s lactate (RL) could have an impact on the outcome in AP.

Patients & methods: We conducted a retrospective study on 103 patients with a diagnosis of AP. The severity of AP was determined according to the Determinant-based Classification of AP. Patients were stratified into 2 groups on the basis of type of fluid resuscitation; 1–RL group with standard fluid resuscitation with RL 1000 ml solution, or 2–NS group with standard fluid resuscitation with 1000 ml normal saline. All patients from both groups received additional 5% Glucose Solution and Multiple Electrolytes Solution.

Results: We noted 63 (61.1%) patients with mild, 24 (23.3%) moderate, 14 (13.6%) severe, and 2 (1.9%) critical AP. No significant difference in distribution of severity of AP between two groups was found. In 1-RL group we identified 21 (52.5%), 11 (27.5%), 6 (15.0%), 2 (5%) patients comparing to 42 (66.7%), 13 (20.6%), 8 (12.7%) and 0 respectively in group 2-NS; p = 0.230.

No significant differences between 1-RL and 2-NS groups were found in terms of confirmed pancreatic necrosis (10 patients(25%) vs. 12 patients(19%), respectively); p = 0.637.

There were no significant differences between 1-RL and 2-NS groups in mortality and duration of stay in the hospital.

Conclusion: Our study did not confirm the favorable action of RL in the first days of AP.

PIL-45 Abstract id: 237.
A comparative analysis of the selected scales for the assessment of prognosis in acute pancreatitis
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Introduction: The goal of the research conducted was to assess the usefulness of the selected prognostic scales for both the assessment of the severity and risk of death in patients suffered from acute pancreatitis (AP).

Aims: Analysis of the selected scales for the prognosis in AP.

Patients & methods: 1014 patients on 16 surgical wards of the Świętokrzyskie Province in Poland were admitted to hospital due to AP during one year. BISAP, Panc 3 score, Ranson scales were calculated on the basis of the data obtained during the first 24-hours of their stay on a ward.

Results: Based on the modified Atlanta criteria, SAP was diagnosed in 6.9%, moderate pancreatitis in 12.0%, mild pancreatitis in 81.1% of the patients. The death rate due to AP was 3.9%, and in the severe form 52.9% and was significantly higher (p < 0.05) than the death rate in the moderate form (no deaths) and the mild one (0.2%). Area under the receiver-operating curve (AUC) for BISAP, Ranson’s, APACHE-II, and CTSI in predicting SAP are 0.61 (confidence interval CI 0.56 – 0.65), 0.53 (CI 0.49 – 0.58), 0.65 (CI 0.60 – 0.70), and 0.75 (CI 0.70 – 0.79), respectively. AUCs for BISAP, Ranson’s, APACHE-II, and CTSI in predicting death are 0.71 (CI 0.62 – 0.80), 0.68 (CI 0.59 – 0.77), 0.73 (CI 0.62 – 0.83), and 0.49 (CI 0.37 – 0.59), respectively.

Conclusion: The Balthazar grading system and CTSI demonstrated the highest accuracy among the CT scoring systems for predicting severity, but for predicting mortality was greatest predictive value APACHE II scale.

PIL-46 Abstract id: 131.
Is bile microscopy reliable for diagnosis of microlithiasis in acute idiopathic pancreatitis?
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Introduction: Biliary microlithiasis has been suspected as one of the frequent etiologies of acute idiopathic pancreatitis. Polarized microscopic
examination with bile from biliary tract or duodenum has been useful for the diagnosis of microlithiasis.

**Aims:** We evaluated the reliability of bile samples collected directly from the biliary tract during ERCP for polarized microscopic examination.

**Patients & methods:** From April 2012 to December 2012, pure bile was collected from biliary tract just before contrast injection in 91 patients who underwent therapeutic ERCP for the first time. The collected bile samples were analyzed for the presence of microlith by polarized microscopy.

**Results:** In patients with CBD stones or sludge, positive results of bile polarized microscopy were 36 and negative results were 16. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) in bile polarized microscopy were 69.2%, 66.7%, and 61.9%, respectively. In patients with only GB stone or GB sludge, positive results were 8 and negative results were 14. Sensitivity, specificity, PPV, and NPV in bile polarized microscopy were 36.3%, 70.6%, 61.5%, and 46.2%, respectively. In overall patients, Positive results were 44 and negative results were 30. Sensitivity, specificity, PPV, and NPV were 59.5%, 70.6%, 89.8%, and 28.6%, respectively in bile polarized microscopy.

**Conclusion:** Polarized microscopic examination of bile aspirated from CBD showed moderate diagnostic accuracy. Bile polarized microscopic result may not be considered as a reliable diagnostic test for the causative decision of acute idiopathic pancreatitis.

**PIL-47 Abstract id: 291.**

**Effect of necrosis status at the time of intervention on the outcome of severe acute pancreatitis**

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**Introduction:** Although it is known that pancreatic and peripancreatic necrosis may remain solid or liquefy, there are few available data about liquefaction timing and progression.

**Aims:** To assess the effect of necrosis status at the time of intervention on acute pancreatitis outcome; to identify factors favoring necrosis liquefaction.

**Patients & methods:** Fifty-eight patients managed by a step-up approach or open necrosectomy in a tertiary referral center (2008 – 2012) were assigned to 3 groups, according to necrosis status at the intervention time: G1 – 26patients with solid necrosis; G2 – 28patients - semisolid walled-off necrosis (WOPN); G3 – 4patients - liquefied WOPN. Groups outcome were compared. Logistic regression was used to identify factors favoring necrosis liquefaction.

**Results:** Median timing of intervention was 27days (G1=21, G2=31, G3=37days). Twenty patients died (34.4%): G1=53.8%, G2=21.4% and G3=0%. Open necrosectomy was performed in all G1 patients. Percutaneous catheter drainage (PCD) was primarily used in G2 and G3, with 41% and 100% success. When PCD failed, VARD or open necrosectomy followed. Mean hospital stay was G1=89days, G2=77days and G3=51days. Factors favoring necrosis liquefactions were: time from pancreatitis onset, age > 55 years, hypertriglyceridemic etiology, high amylase content, antibiotic prophylaxis > 2 weeks.

**Conclusion:** Interventional debridement should be postponed in solid necrosis, where enzymatic debridement may be tried as suggested by one of the found factors (high amylase content). Antibiotic prophylaxis > 2 weeks favors liquefaction only by postponing necrosectomy. Time is the strongest factor favoring necrosis evolution to semisolid and liquefied WOPN status, when a step-up approach offers better survival and shorter hospital stay.

**PIL-48 Abstract id: 161.**

**Predictive markers for severe acute pancreatitis: A comparative prospective study within a representative cohort**

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**Introduction:** In order to predict severity of Acute Pancreatitis (AP) a large number of biomarkers have been studied retrospectively and in different cohorts.

**Aims:** In this study promising biomarkers will be studied prospectively in a representative cohort of patients with AP aiming to enable comparisons of their predictive capacity in a clinical setting.

**Patients & methods:** Patients with AP admitted to the Malmö University Hospital were consecutively included in the study. Blood samples were obtained on admission and daily up to 72 hours. Socioeconomic factors and information of importance for etiology and severity of AP were recorded in a database. Cut off values were set by reviewing the literature for the predefined biomarkers.

**Results:** 202 patients with AP, 111 men and 91 women, with a median age of 66 years (19-97) were included in the study. 13.4% of the patients had severe AP according to the Atlanta -92 criteria while the corresponding figures for the Revised Atlanta-12 were 5.4%, 15, 3% were classified as Moderately Severe AP. Etiology was biliary in 51.5%, alcohol in 15.8%, unknown in 23.3% and of other origin in 9.4 %. CRP on Day 3 had a median value of 377 mg/l in patients with SAP and 111 mg/l in patients with mild AP.

**Conclusion:** The clinical data shows that the cohort has a representative composition in order to obtain reliable results concerning patients with AP. Preliminary data shows a significant difference in IL-6 and IL-8 between mild AP and severe AP. Further blood samples will be analysed during the first half of 2013.

**PIL-49 Abstract id: 68.**

**New classifications of severity of acute pancreatitis: Validation of determinist-based and revision of the Atlanta classification**

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**Introduction:** The Atlanta classification was published in 1993; definitions were given regarding local and systemic complications, as well as severity of acute pancreatitis (AP). After 2 decades we have learned new concepts about the natural history of AP that have prompted a revision of the Atlanta classification. Two new classifications have been proposed.

**Aims:** Our aim was to validate both new classifications.

**Patients & methods:** We analyzed a prospective database which included every adult patient with AP admitted to a third level hospital between December 2007 and January 2013. Every CT scan was retrospectively reviewed according to new definitions. The classifications were validated in terms of outcomes: length of hospital stay, need for ICU admission, nutritional support, invasive treatment and mortality.

**Results:** We analyzed 543 episodes of AP. The most frequent etiology was gallstones (59.5%), followed by alcohol (13.6%). Pancreatic necrosis was present in 66 (12.2%) of the patients, peripancreatic fat necrosis in 109 (20.1%), acute necrotic collections in 106 (19.5%), walled-off necrosis in 61 (11.2%), peripancreatic fluid collections in 98 (18%) and pseudocysts in 19 (3.5%). Transient organ failure was present in 31 patients (5.7%) and persistent organ failure in 21 (3.9%). Sixteen (2.9%) patients died. Determinant-based and Revised Atlanta classifications were associated to statistically and clinically relevant differences in length of hospital stay, need
for ICU admission, nutritional support, invasive treatment and mortality, classifying subgroups of patients with different natural history.

**Conclusion:** Both classifications, based in current literature and the opinion of experts, describes accurately different subgroups of patients with AP.

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**PIL-50 Abstract id: 337.**

**Preliminary data of a clinical survey on acute pancreatitis based on the Hungarian national registry**

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**Introduction:** The Hungarian Pancreatic Registry was established in 2012.

**Aims:** To investigate the etiological factors, clinical severity and outcome of acute pancreatitis (AP) in our recently established multicentric Hungarian Pancreatic Registry.

**Patients & methods:** Retrospective analysis of 189 AP patients admitted to gastroenterology wards, ICUs and surgery wards between 2008 and 2013 focused on the etiology and clinical outcome.

**Results:** Out of the 189 AP patients, 88 were females and 101 were males, the mean age at admission was 58.7±2.2 and 54.5±1.5 years, respectively. Regular alcohol consumption and smoking was present in 51% and 30% of males, whereas in only 4.6% and 5.8% in female patients, respectively. The most common cause of AP in females was biliary disease (52.3%), whereas in men, it was alcohol (32.7%). AP was idiopathic in 24.4% respectively. The most common cause of AP in females was biliary disease (52.3%) and 30% of males, whereas in only 4.6% and 5.8% in female patients, respectively. Regular alcohol consumption and smoking was present in 51% and 30% of males, whereas in only 4.6% and 5.8% in female patients, respectively. The most common cause of AP in females was biliary disease (52.3%), whereas in men, it was alcohol (32.7%). AP was idiopathic in 24.4% respectively.

**Conclusion:** Our study indicates that the revised Atlanta Classification is suitable for clinical practice, since it differentiates between the mortality rates of moderately severe and severe AP. Furthermore, registry provides a foundation for prospective clinical investigations of AP.

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**PIL-51 Abstract id: 203.**

**Early short-term continuous high-volume haemofiltration improves clinical outcomes of severe acute pancreatitis**

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**Introduction:** Haemofiltration was introduced to treat severe acute pancreatitis (SAP) with early short-term continuous high-volume haemofiltration (HVHF) reported to be the most effective modality, although this has not been tested in randomised clinical trials (RCTs).

**Aims:** To conduct a single centre prospective trial of short-term continuous HVHF in patients with SAP.

**Patients & methods:** Consenting SAP patients with APACHE II scores > 15 on admission to West China Hospital between January 2008 and December 2010 were allocated to receive either optimal standard therapy or 72 h of continuous HVHF on an alternate basis, beginning as soon as possible after admission. Biomarkers and clinical outcomes were compared between the two groups.

**Results:** A total of 61 patients received either conventional therapy (n = 29) or HVHF (n = 32). HVHF treatment was associated with a significant reduction in the incidence of renal failure (P = 0.013), infected pancreatic necrosis (P = 0.048), length of hospitalisation (P = 0.005), mortality (P = 0.033), as well as duration of renal (P < 0.001), respiratory (P = 0.002) and hepatic failure (P = 0.001). APACHE II score, C-reactive protein and interleukin-6 were significantly reduced after the start of HVHF on days 1, 3 and 7 (all P < 0.05).

**Conclusion:** This prospective study suggests that HVHF reduces the incidence and duration of organ failure, complications, and mortality in SAP patients with APACHE II score > 15, although high quality, large RCTs are required to confirm this effect.

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**PIL-52 Abstract id: 162.**

**Raised intestinal fatty acid binding protein correlates to severe acute pancreatitis**

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**Introduction:** Early fluid resuscitation in order to maintain sufficient circulation to vital tissues is essential in the management of Acute Pancreatitis (AP). Intestinal Fatty Acid Binding Protein (IFABp) is released due to intestinal ischemia. S-IFABp was analyzed to evaluate the efficacy of fluid resuscitation up to 3 days after admission in patients with AP.

**Aims:** Our aim was to analyze the relationship between early fluid resuscitation, levels of s-IFABp and severity during the first 3 days of acute pancreatitis.

**Materials & methods:** The study was designed as part of the Pancreas2000 educational program. Patients with AP were consecutively included at 4 centers. Hydration status was assessed 0-3, ranging from 10% to 49.5% of female and male patients, respectively. According to the revised Atlanta Classification, AP was mild in 88.3% and 73.3%, moderately severe in 5.8% and 10.9%, severe in 5.8% and 15.8% of female and male patients, respectively. 1 female (1.2%) and 7 males (6.9%) died among AP patients. Only severe AP resulted in death with a total mortality rate of 38.1%.

**Conclusion:** Our study indicates that the revised Atlanta Classification is suitable for clinical practice, since it differentiates between the mortality rates of moderately severe and severe AP. Furthermore, registry provides a foundation for prospective clinical investigations of AP.

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PIL-53 Abstract id: 280.

Angiopoietin-2 as a predictor of fluid sequestration in acute pancreatitis
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Introduction: Angiopoietin-2 (Ang-2) is a vascular mediator associated with increased endothelial permeability. It has been described that Ang-2 levels are associated with severity of acute pancreatitis (AP). We hypothesize that Ang-2 may be associated with fluid sequestration (FS), thus it may be an early marker of increased fluid requirements.

Aims: Our main aim was to investigate the association between serum Ang-2 levels and FS. Our secondary aim was to investigate the relationship between serum Ang-2 levels and outcome.

Patients & methods: Retrospective analysis of a prospective clinical database and banked serum (obtained in the first 24h of admission) of consecutive patients admitted with AP. Ang-2 levels were measured by enzyme-linked immunosorbent assay. FS was categorized according to percentiles of FS (water balance) in Group A: <p25 (<0.4L), Group B p25-p75 (0.4-3.8L), Group C: >p75 (>3.8L).

Results: We included 123 episodes of AP, 52.8% females, 63.4% gallstone AP. Median (p25-p75) Ang-2 levels (pg/mL) were 3752 (2486-4384) in group A, 4685 (3459-6057) in group B and 4928 (3071-6119) in group C, p < 0.05. Ang-2 levels (pg/mL) were significantly associated with pancreatic necrosis (Ang-2 levels 5031 (4024-8085) vs 4531 (3071-5886)), persistent organ failure (8083 (5027-16132) vs 4387 (3075-5884)) and severity according to the Atlanta classification [5031 (4024-8085) vs 4531 (3074-5922)].

Conclusion: Early serum Ang-2 levels are associated with fluid sequestration and outcome of acute pancreatitis.

PIL-54 Abstract id: 308.

Natural history following a single episode of acute pancreatitis
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Introduction: Acute pancreatitis (AP) is a characterized by multifactorial pathogenesis, primarily associated with biliary lithiasis. Data on natural history following a sentinel attack of AP are limited.

Aims: The aim of the present study was to determine the risk of chronic pancreatitis (CP) diagnosis after the first episode of AP.

Patients & methods: From 2000 to 2011, in a tertiary referral center we prospectively enrolled 145 Italian patients (79 M; 66 F) with single episode of AP. Admission diagnosis and AP etiology were based on typical clinical features, elevated serum amylase and lipase and positive findings on abdominal computerized tomography scan (CT). Acute recurrent pancreatitis (ARP) diagnosis was an exclusion criteria. Every year, we followed each AP patient with physical examination, blood tests, US and MR. Each patient was followed for 8.3±1.6 years. We performed a descriptive statistical analysis.

Results: According to Atlanta criteria, thirty-eight patients (26.2%) had severe pancreatitis: 76.4% had biliary etiology and 23.6% were idiopathic. During follow-up period, chronic pancreatitis (CP) after an AP single episode was diagnosed in twelve patients (8.3%). Four patients (2.8%) died due to severe biliary AP. One-hundred and eight (74.5%) AP was due to biliary etiology, five patients (3.4%) had post-ERCP AP, two (1.4%) AP was due to drugs intake, one (0.7%) AP was due to infections and twenty-nine (20.7%) patients had idiopathic AP.

Conclusion: AP infrequently progressed to CP: a small percentage (8.3%) of severe AP with main pancreatic duct involvement progressed to CP. AP single episode is not a risk factor in the development of CP.

PIL-55 Abstract id: 146.

Organ failure on day 1 of hospitalization predicts development of pancreatic necrosis in patients with acute pancreatitis
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Introduction: Prior studies have evaluated laboratory markers on admission as predictors of necrotizing pancreatitis (NP). However, they did not account for possibility that some might have NP on admission or those with interstitial pancreatitis (IP) on admission may develop NP later during hospitalization.

Aims: To evaluate early predictors of NP in patients who underwent a contrast-enhanced CT (CECT) during first 24 hours and >72 hours after admission.

Patients & methods: Adults (>18 years old) presenting with AP to JHH between 2003-2011 were evaluated. Only patients with CECT in first 24 hours and >72 hours after admission included. Transfer patients excluded. Demographic, clinical, and laboratory variables on admission were evaluated. NP was defined by the CECT >72 hours after admission. Organ failure (OF) defined by revised Atlanta classification.

Results: There were 1504 patients with AP; 99 (4.38%) met inclusion. 29 (29.3%) developed NP. Of the 70 with IP at admission, none developed NP. There were no statistically significant differences between the NP and IP in age, gender, prior AP admissions, etiology, and comorbidity. HCT <44% was found in 12 (41.4%) NP and 12 (17.1%) IP patients (p=0.01). NP patients had higher rates of SIRS (48.3% vs. 22.9%, p=0.01) and OF (70.6% vs. 12.9%, p=0.002) compared with IP. BISAP scores ≥3, BUN>25, and symptoms duration prior to admission were not significantly different between two groups. Only OF (OR= 5.36, 95% CI 1.67-17.14) was significant independent predictor of NP on multivariable analysis.

Conclusion: OF on day 1 is strong predictor for development of NP in patients with ≥2 CECTs during hospitalization.

PIL-56 Abstract id: 112.

 Extracorporeal shock wave lithotripsy of pancreatic stones in children with chronic pancreatitis
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Introduction: Extracorporeal shock wave lithotripsy (ESWL) of pancreatic stones is a treatment option for patients with chronic pancreatitis (CP), when pancreatic stones can not be removed by endoscopic procedures during endoscopic retrograde cholangiopancreatography (ERCP).

Aims: The aim of the study was to elaborate efficiency of ESWL in treating children with chronic pancreatitis with pancreatic stones.

Patients & methods: 12 children (7 girls and 5 boys; mean age 12 years, range: 5.5 to 17 years) with severe CP, hospitalized since 1998 to 2012, were treated by ESWL for endoscopically irretrievable obstructive stones. The medical records of these patients were reviewed for data on the presentation, diagnostic findings, ESWL and endoscopic treatment.
ESWL was performed with an electromagnetic lithotripter. The etiology of chronic calcifying pancreatitis were gene mutations (PRSS1, CFTR, SPINK1) in 9 patients.

**Results:** 12 patients had 15 endoscopic-ESWL sessions. ESWL was administered twice in 3 children. Pancreatic stones fragmentation was achieved in all patients. The procedures were well tolerated by all children. There were no complications related to ESWL. Early pain relief occurred in all cases. Acute episodes of CP after endoscopic-ESWL treatment were observed in 3 patients (25%). Recurrence of endoscopically irretrievable pancreatic stones was revealed in 4 cases.

**Conclusion:** 1. ESWL is a safe and effective therapy in treating children with chronic pancreatitis and irreversible pancreatic stones.

2. ESWL should be considered complementary and not alternative therapy to endoscopic drainage.

**PIL-57 Abstract id: 110.**

**Efficiency of pancreatic duct stenting therapy in children with chronic pancreatitis**

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**Introduction:** Chronic pancreatitis (CP) is a rare disease in childhood. Although Endoscopic Retrograde Cholangiopancreatography (ERCP) is commonly performed in children, effect of pancreatic duct stenting therapy in children with CP is unknown.

**Aims:** The aim of the study was to elaborate efficiency of pancreatic duct stenting in children with chronic pancreatitis.

**Patients & methods:** 208 children with CP hospitalized since 1988 to 2012 were enrolled into the study. ERCP was performed in 157 patients (75.5%). In 86 cases (55.5%) ERCP was done at least 2 times (2 to 21 examinations). Results of endoscopic therapy were documented. Number of pancreatitis episodes/year before and after treatment was analyzed.

**Results:** A total of 481 ERCP were performed. ERCP was successful in 475 cases (98.7%) with a complication rate 1.9% (9/475 procedures). ERCP showed mean 1.68 Cambridge grade. The total number of 223 pancreatic duct stenting procedures were performed in 72 children (34.6%). In 26 cases (11.6%) 2 stents at the same time were inserted. Median number of stent replacement was 3. Median interval between stent replacement was 4.5 months (1-24 months).

We observed statistically significant decrease in the number of pancreatitis episodes/year before 1.75/year to 0.23/year after endoscopic treatment (p<0.05).

Pancreatic duct stenting was performed more frequently in patients with hereditary pancreatitis (61.5%; p<0.05) and with CP and anatomic anomalies of pancreatic duct (65%; p<0.05).

**Conclusion:** Pancreatic duct stenting therapy is a safe and effective procedure in children with CP.

This therapy should be recommended for children with hereditary pancreatitis and patients with anatomic anomalies of pancreatic duct.

**PIL-58 Abstract id: 143.**

**Importance of small intestinal bacterial overgrowth in chronic pancreatitis**

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**Introduction:** Chronic pancreatitis (CP) is one of disorders predisposes patients to the small intestinal bacterial overgrowth (SIBO). SIBO related to exocrine pancreatic dysfunction and stagnation or dysmotility of small intestinal.

**Aims:** evaluation of clinical characteristics of chronic pancreatitis complicated by small intestinal bacterial overgrowth.

**Patients & methods:** 52 patients with CP have been involved in study (22 m & 30 f), mean age 56.6 ± 11.9 years. Pancreatic surgery had been performed in 14 (26.9%) patients: partial pancreatecduodenectomy in 5 cases, pancreatic drainage surgery in 9. Exocrine pancreatic function was assessed by faecal elastase test. SIBO was detected clinically (bloating, abdominal dyscomft, diarrhea), by hydrogen breath test with lactulose, and by faecal content and spectrum of short-chain fatty acids (SCFA).

**Results:** Clinical stigmas of SIBO were found in 34 (65.4%) cases, however hydrogen breath test was positive in 19 (36.5%) and significant increase of common level of SCFA was found in 17 (32.7%) patients. The level of SCFA in patients with uncomplicated CP was 7.2±3.1 mg/g, after pancreatic surgery – 10.5±7.6 mg/g (p=0.02). The most pronounced increase of common level of SCFA was observed in patients after resection surgery (13.0±4.4 mg/g) and with decreased exocrine pancreatic function (12.2±2.6 mg/g).

**Conclusion:** Factors predisposing patients with chronic pancreatitis to SIBO development are exocrine pancreatic insufficiency and pancreato-duodenal resection.

**PIL-59 Abstract id: 10.**

**Reasons for the lack of effectiveness of substitution enzyme therapy in chronic pancreatitis (CP)**

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**Introduction:** Substitution therapy of exocrine pancreatic insufficiency is not always successful in spite of its modern possibilities.

**Aims:** To analyze the reasons for the lack of effectiveness of substitution enzyme therapy in CP.

**Patients & methods:** The study included 564 patients with CP, who had the exocrine pancreatic insufficiency that was confirmed by the fecal elastase test. All patients received minimicrospherical variant of pancreatin in a dose corresponding to the stage of pancreatic insufficiency. Patients with impaired trophological status received 25-40 thousands FIP units of lipase for the main meal and 10-25 thousands FIP units of lipase for the intermediate meal.

**Results:** Effect of substitution therapy was inadequate one in 102 (18.1%) patients. Upon analyzing the reasons for the lack of treatment's effect it turned out that 21 (20.6%) patients didn’t perform doctor’s prescriptions accurately, 26 (25.5%) patients took animal fat in great quantities, 8 (7.8%) patients had insufficient pancreatic dose, 15 (14.7%) patients were diagnosed as those having giardiasis, syndrome of bacterial overgrowth in the small intestine was revealed in 28 (27.5%) patients, and 4 (3.9%) patients had celiac disease.

**Conclusion:** Syndrome of bacterial overgrowth in the small intestine appears to be one of the most common reasons for the lack of effectiveness of substitution enzyme therapy in CP. Attention should also be paid to the amount of consumed fat (there’s a need of nutritionist’s consultation), it’s necessary to exclude giardiasis, celiac disease, to seek for the compliance with patients regarding the implementation of recommendations for the treatment.

**PIL-60 Abstract id: 60.**

**Management of biliary and duodenal complications of chronic pancreatitis: A prospective non-randomised study**

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1 Data Analysis and Interpretation, Drafting of the manuscript, Belarus
2 Critical Revision of the Manuscript, Belarus
3 Data Analysis and Interpretation, Belarus
**PII-61 Abstract id: 52.**

Success of pancreas-preserving duodenal resections proves duodenal origin of "groove pancreatitis"

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Introduction: The term “paraduodenal pancreatitis” was proposed as an umbrella for cystic dystrophy in heterotopic pancreas (DD), paraduodenal cyst and groove pancreatitis, by reasoning that these conditions mimic pancreatic head tumors and share certain histological evidences. It is still unclear what organ “paraduodenal pancreatitis” originates of.

Aims: To assess the results of different types of surgery for “paraduodenal pancreatitis”.

Patients & methods: 1. Prospective analysis of 61 cases of DD (2004-2012), comparing preoperative and histopathological findings in 38 surgical specimens; 2. Assessment of clinical presentation and the results of DD treatment. Groove pancreatitis and duodenal dystrophy were considered as synonyms.

Results: Correct diagnosis was made in all the cases except one suspected cystic tumor of the pancreatic head (1,9%). Patients presented with abdominal pain (100%), weight loss (76%), vomiting (30%) and jaundice (18%). CT, MRI and endoUS were the most useful diagnostic modalities. Patients underwent 22 pancreaticoduodenectomies (PD), pancreatico- and cystoenterostomies (7). Nakao procedures (4), duodenum-preserving pancreatic head (DPPH) resections (4), partial gastrectomy (1) and 8 pancreas-preserving duodenal resections (PPDR). No mortality. Full pain control was achieved after PPRDs in 83%, PDs in 85%, and after PPWH resections and draining procedures in 18% of cases. Diabetes mellitus developed thrice after PD.

Conclusion: The diagnosis of DD can be confidently determined by modern methods prior to surgery. 2. The effectiveness of PPDR provides compelling proof that “groove pancreatitis” is an entity of duodenal origin distinct from tumors and orthotopic pancreatitis. 3. Duodenal origin of the disease motivates the abandonment of the term “paraduodenal pancreatitis.”
Results: In 12 (9/3 male/female) patients, mean age:43.7(19-70)ys with diagnosis of mild to moderate chronic or relapsing pancreatitis, verified by different imaging methods were followed with repeated starch tolerance tests. In 6 pts the pancreatic function became normal or significantly improved in 1-6 years with morphological recovery. In 6 cases the repeated tests demonstrated stable or slightly progressive PEI which was significantly improved(2 pts)or normalized(4 pts) with 10000(2 pts) or 25000(4 pts) IU lipase containing pancreatin preparation. Basal Av correlated with need of pancreatin for normalizing PEI. Body weight increases and clinical improvements followed functional amiliations several months later.

Conclusion: The simple starch tolerance test, easily available in every outpatient laboratories, can demonstrate PEI even in mild to moderate cases and the repeated tests with increasing doses of pancreatin can indicate individual needs of patients for optimal PERT.

Use of hydrogen exhalation test to estimate effects of exocrine pancreatic insufficiency on fermentation of carbohydrates – Results of a study performed in healthy pigs and pancreatic duct ligated pigs – Used as a model for humans

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Introduction: Even reduction of fat digestibility is the main symptom of EPI the enzymatic digestion of carbohydrates is reduced as well and worth mentioning.

Aims: Aim of this study was to test, whether H2-exhalation test is useful to evaluate carbohydrate fermentation in pancreatic-duet-ligated (PL) pigs.

Materials & methods: 15 cross bred pigs were used – 5 shame operated animals served as controls (C) while in 7 animals the pancreatic-duet was ligated at the age of 7 weeks (PLwk7) while 3 pigs underwent surgery at an age of 16 weeks (PLwk16). Animals were fed a complete diet based on wheat and barley. PL-pigs did not receive enzymes. Every 2nd week the animals were sedated for other reasons and breath samples were taken using EC60 gastrolyzer® and a face mask designed for children.

Results: As early as 2 weeks post induction of EPI H2-concentration in exhalate was higher (50 ppm; p<0.03) in PLwk7 in comparison to C (21 ppm). In the PLwk16 pigs H2-concentration rose numerically by the factor three within one week and increased (>160 ppm) within three weeks (p=0.0007), indicating a fast increase of intestinal fermentation. In controls there was no significant rise of H2-exhalation within the observed period of 10 weeks (always <42 ppm).

Conclusion: H2-exhalation was determined for the first time in EPI-pigs and seems to be a useful indirect marker for intestinal fermentation of carbohydrates. This study underlines the very fast increase of intestinal fermentation in case of EPI and emphasis that EPI does not only affect lipid digestion.
with AIP and 55 with alcoholic CP. The serum levels of IgG, IgG4 and CAII parameters.

Introduction: We conducted a survey to clarify the clinical features of chronic pancreatitis (CP) patients in Hungary, based on a multicentric national registry.

Aims: Here we demonstrate the initial results.

Patients & methods: Data on 84 treated and newly diagnosed CP patients were collected retrospectively. Clinico-pathological information on individual patients including symptoms, etiology, diagnostic criteria, treatment and complications were collected from medical records and questionnaires completed by the patients.

Results: There were 66 male and 18 female patients with a mean ±SD age of onset of 47.5±11.0 and 45.4±13.0. Patients were classified by alcoholic 53.3% and non-alcoholic 46.4% etiology. Alcoholic CP affected more males than females accounting for 59.0% and 33.3% respectively. Investigated for p.G60G, 1/18 heterozygous for p.G214R variant of PRSS1 gene was found; 1/18 was trans-heterozygous for p.G208A and 1/18 homozygous for p.G208A and 1/18 heterozygous for p.G214R variant of PRSS1 gene.

Conclusion: While in adults the major etiologic factor of chronic pancreatitis (CP) is excessive alcohol consumption, among children in addition to anatomical anomalies of pancreas and biliary tract, genetic factors seem to be crucial. Mutations in PRSS1 gene cause hereditary pancreatitis, while mutations in SPINK1, CTRC and CFTR genes can predispose patients to develop CP.

Aims: To characterize the frequency of mutations of genes associated with the development of CP in children with idiopathic/hereditary CP and determine the genotype-phenotype correlation in these patients.

Patients & methods: 18 children with idiopathic/hereditary CP diagnosed from 2008 to 2012 at the 2nd Department of Pediatrics, University Children's Hospital, Bratislava were enrolled. Direct sequencing of PRSS1, SPINK1 genes and exons 2,3,7 of CTRC gene was performed.

Results: Median age of symptom onset was 9.1 years (range 2.5–17 years) and the most common presenting symptoms were abdominal pain and vomiting. Family history was positive in 6 cases. In 2/18 patients the p.R122H mutation of PRSS1 gene was found; 1/18 was trans-heterozygous carrier of p.G208A (PRSS1) and p.G60G (CTR) variants. The p.N34S mutation of SPINK1 gene was seen in 5/18 patient (1 homozygous and 4 heterozygous), among them 2 were trans-heterozygotes with p.G60G (CTR) variant. 1/18 patient was homozygous for p.G60G, 1/18 heterozygous for p.R254W and 1/18 heterozygous for p.G214R variant of CTRC gene.

Conclusion: In a group of 18 pediatric patients with idiopathic/hereditary CP we found a high prevalence of pathogenic mutations associated with the development of the disease. These results confirm the importance of genetic testing in children with idiopathic CP.
**Results:** Preliminary results of 66 patients (72.7% M, mean 50yrs) that completed the follow-up (mean 11.7 yrs; SD±4.9 years) are reported. Follow-up is ongoing. Alcohol consumers were 51.5% and 68.1% smokers. In 91% stones were cecalopancreatic. Type IV CP had 75.7% and pancreas divisum 10% of patients. Stone fragmentation/MPD drainage was obtained in all patients with mean 5 (SD±3.9) ERCP and 2 (SD±1.4) ESWL/patient. Mean follow-up was 11.7 yrs (SD±4.9). Complete pain relief had 65.2%, while recurrent pain had 34.8% (12.1% needed narcotics). Surgery was done in 10.6%. During follow-up 21 patients died (pancreatic cancer 23.8%). According to Kaplan-Meier analysis, mortality is increased in females, in case of relapsing pain and alcohol abuse.

**Conclusion:** Combination of ESWL+ERCP for CCP provides long-term complete pain relief in 2/3 of patients. This approach should be first line treatment for painful-CCP. It is repeatable and do not preclude surgery.

**PIL-72 Abstract id: 207.**

**Small intestine bacterial overgrowth in patients with chronic pancreatitis**

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**Introduction:** Small intestine bacterial overgrowth (SIBO) is a factor possibly worsening the course of chronic pancreatitis (CP). However, few studies evaluated the rate of SIBO in CP patients with non-standardized procedures and inconclusive results, also enrolling CP patients with previous resective surgery, which is a cause of SIBO per se.

**Aims:** To assess SIBO prevalence in CP patients without previous surgery as compared with controls, and to analyze factors related with SIBO in CP.

**Patients & methods:** CP patients and controls had SIBO evaluated by H2 glucose breath test (GBT) with a standard protocol according to Rome consensus conference. Positivity rate, basal, peak over basal (HOB) and H2 values at 120 minutes were evaluated. For CP patients, relation between BT results, symptoms, nutritional and clinical variables was analyzed.

**Results:** 35 patients and 36 controls enrolled. Of the 35 CP patients, 15 had PEL, 5 advanced CP. GBT positivity rate was higher, albeit not significantly, in CP (17% vs 8% controls p=0.3). However, the mean H2 excretion basal (6.8 ppm vs 1.9 ppm; p=0.014) and at 120 minutes (4.1 in CP vs 1.4 in controls; p=0.034) were significantly higher in CP. SIBO in the CP group was not correlated with presence of PEI, severity of disease, symptoms, pancreatic enzymes or proton pump inhibitors therapy, nor with nutritional status.

**Conclusion:** Our findings suggest that SIBO is not uncommon in a population of uncomplicated CP patients, who also have higher values of H2 excretion, both basal and after 120 minutes. SIBO in CP patients was not related with clinical features.

**PIL-73 Abstract id: 62.**

**The Frey procedure for the treatment of chronic pancreatitis associated with common bile duct stricture: be aware of duct reinsertion into the resection cavity or choledochoduodenostomy**

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**Introduction:** The Frey procedure (FP) is the treatment of choice for symptomatic, chronic pancreatitis (CP). In cases of biliary stricture, biliary derivation can be performed.

**Aims:** The objective of this study was to evaluate the outcomes associated with different types of biliary derivation.

**Patients & methods:** We retrospectively analyzed demographic, surgical and follow-up data for patients having undergone FP with biliary derivation between 2004 and 2012. Primary endpoint was rate of CBD stricture recurrence. Secondary endpoints were surgical parameters, postoperative complications, follow-up and presence of risk factors for secondary CBD stricture.

**Results:** Eighty patients underwent surgery for CP during the study period. Fifteen received biliary derivations with the FP. Eight of the FP were combined with choledochoduodenostomy, 4 with choledochojjunostomy and 3 with reinsertion of the CBD into the resection cavity. Eleven complications were recorded, including one major that necessitated radiologically-guided drainage of an abdominal collection. The median length of stay was 17 days and the median follow-up time was 35.2 months. Two patients presented stricture after CBD reinsertion into the resection cavity; one was treated with radiologically-guided dilatation and the other underwent revisional Roux-en-Y choledochojejunostomy. Three patients presented alkaline reflux gastritis (37.5%), one (12.5%) presented cholangitis and one presented CBD stricture after FP with choledochoduodenostomy. No risk factors for secondary CBD stricture were identified.

**Conclusion:** As part of a biliary derivation, FP gave good results. CBD reinsertion into the resection cavity appeared to be associated with higher stricture recurrence rate. In our experience, choledochojejunostomy remains the “gold standard”.

**PIL-74 Abstract id: 307.**

**Multivariable logistic regression analysis of alcohol consumption, cigarette smoking and pancreas divisum in the risk of recurrent acute and chronic pancreatitis**

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**Introduction:** Pathophysiology of acute recurrent pancreatitis (ARP) and its progression through chronic pancreatitis (CP) is still debate and not completely elucidated. Moreover, clinical differences between CP and ARP are controversial too.

**Aims:** The aim of the present study was to evaluate the association of alcohol intake, smoking habits and pancreas divisum with ARP and CP.

**Patients & methods:** ARP patients were classified on the basis of recurrence of acute pancreatitis in the absence of radiological findings of CP (ductal dilatation/alteration and/or pancreatic calcifications). Pancreas divisum was diagnosed by means of secretin-enhanced magnetic resonance (sMR) and/or endoscopic retrograde cholangiopancreatography (ERCP). 174 patients with CP and 77 patients with ARP were evaluated. Patients were classified by drinking status: abstainers (<2 Alcoholic Unit per day), moderate drinkers (2 Alcohol Unit per day), heavy drinkers (>2 Alcoholic Unit per day). Similarly, smoking status was classified as abstainers (<3 packs/years), moderate smokers (from 3 to 10 packs/years), heavy smokers (>10 packs/years). Multivariable logistic regression analysis was performed by means of multivariable logistic regression.

**Results:** a) When compared with abstainers, cigarette smoking is a risk factor for CP (respectively moderate smoker p=0.000; OR=0.98 and heavy smoker p=0.023; OR=0.209)

**References:**

b) When compared with abstainers, heavy drinker intake is a risk factor to develop CP ($p=0.038$; $OR=2.583$)

c) Pancreas divisum is a risk factor to develop ARP ($p=0.000$; $OR=10.533$) but not CP.

d) Moderate alcohol intake is not statistically significant in both ARP and CP.

**Conclusion:** Heavy alcohol consumption and smoking habits are independent risks for CP. Pancreas divisum is a risk factor to develop ARP.

**PII-75 Abstract id:** 197.

**Covered self-expanding metal stents (CSEMS) may offer improved clinical success compared to multiple plastic stents (PS) in strictures secondary to chronic pancreatitis: A systematic review and meta-analysis**

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**Introduction:** CSEMS are being increasingly used in the endoscopic treatment of benign biliary strictures (BBS). Despite promising results, there is not yet solid evidence to support their routine use.

**Aims:** To evaluate feasibility of CSEMS compared to PS in BBS in terms of clinical success and complications.

**Materials & methods:** A systematic search of Medline, Scopus and Embase database for studies published 2000-2012 combined to hand-search of reference lists resulted 4977 articles. Out of 99 potentially relevant studies selected for full-text review, 12 CSEMS (376 patients) and 13 PS studies (570 patients) met the final inclusion criteria. A systematic review was made using proportion meta-analysis.

**Results:** A tendency to successful use of CSEMS in strictures related to chronic pancreatitis (CP) was shown: clinical success of 77% and 33% (95% CI 61-94% vs. 4-63%, $p<0.001$). A direct linear correlation was found between the SR and the probability of PEI (from 4.2% in patients with SR $<2.5$ to 92.8% in patients with SR $>5.5$).

**Conclusion:** The degree of pancreatic fibrosis as measured by EUS-guided elastography allows quantifying the probability of PEI, and thus the need for oral pancreatic enzyme therapy, in patients with CP.

**PII-77 Abstract id:** 296.

**Morphological features of pancreatic cystic lesions in endoscopic ultrasonography (EUS) examination – A single-center experience**

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**Introduction:** EUS became a useful tool in assessing cystic pancreatic lesions.

**Aims:** A retrospective analysis of morphological features of cystic pancreatic lesions detected in EUS examinations.

**Materials & methods:** EUS examinations were performed in a group of 4982 patients from 2004 to 2012. Cystic lesions were detected in 401 cases. Unilocular cystic lesions were found in 64.3% of the patients, whereas multilocular ones in 30.5%. In 21 cases (5.2%) worrisome intraductal papillary mucinous neoplasms (IPMN) branch-side duct type (mean diameter 14 mm), with a multifocal localization.

**Results:** In 7 patients non-enhancing mural nodules were assessed in the EUS examination before surgery. After surgery the diagnosis of IPMN was confirmed in all cases, one of which was an intraductal papillary carcinoma, and one a microinvasive intraductal papillary mucinous adenocarcinoma. Cytology and fluid CEA analysis was found to be inconclusive in terms of the preoperative diagnostic accuracy.

Serous cystic neoplasms with a characteristic honeycomb appearance were found in 16 cases. Of these, 50% were located in the pancreatic head, 44% in the body, and 6% in the tail.

**Conclusion:** A honeycomb appearance could be diagnosed in experienced Centers by endoscopic ultrasonography.

In our experience morphological features of pancreatic side-branch IPMN seem to play the most important diagnostic role in the pre-operative assessment, whereas cytology and fluid CEA analysis was found to be inconclusive.

**PII-78 Abstract id:** 253.

**Reactive C Protein (RCP) and white blood cells (WBC) as early predictors of postoperative inflammatory complications (PICs) in pancreatic surgery**

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Introduction: Pancreatic surgery is associated with high morbidity; this is probably the reason why surgeons are still reluctant in applying fast-track recovery programs. Identification of diagnostic criteria to early predict PICs development could be useful in tailoring perioperative management to patient personal risk.

Aims: Assessment of diagnostic accuracy of RCP and WBC as early predictors of PICs in pancreatic surgery.

Patients & methods: Between Jan-2010 and Feb-2013 we performed 319 pancreatic resections, of which 187 pancreaticoduodenectomies (PD). RCP (detected with a high-sensitivity method) and WBC from POD1 to POD7 were analyzed searching for association with PICs (anastomotic leakage, sepsis, airways, urinary tract and wound infection, abdominal collection); using receiver-operating-characteristic method (ROC), diagnostic accuracy was evaluated by area-under-the-curve (AUC) analysis.

Results: PICs incidence was 41.8% (PD: 46.7%). Cancer diagnosis, chemotheraphy, age, ASA, blood-loss didn’t influence PIC rates, contrary to increasing BMI (p < 0.001). Mean RCP levels were higher in all patients who developed PIC each day from POD1 to POD7 (p < 0.001), regardless of surgical procedure, while mean WBC levels were higher in this group only from POD4 to POD7 (p < 0.001). The highest diagnostic accuracy was observed in PD for RCP levels on POD4 (AUC = 0.835; 95%CI); a 14.70 mg/L cut-off revealed 83% sensitivity and 81% specificity for PICs. RCP from POD1 to POD7 associated with high grade PICs (Clavien-Dindo Grade II-IV; p < 0.001).

Conclusion: POD4 RCP level appears predictor for PICs in pancreatic surgery and could guide patient’s management (fast track recovery programs or diagnostic research for septic processes); WBC, more influenced by physiological postoperative inflammatory response, fail in decisively distinguishing patients developing PICs.

**PFI-79 Abstract id: 256.**

Surgical duodenal ampullectomy in the treatment of ampullary neoplasms: 12 cases experience

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Introduction: Duodenal ampullectomy is a technically demanding but effective surgical procedure for treatment of patients suffering from benign and malignant disease limited to Vater ampulla.

Aims: Evaluation of outcomes after surgical duodenal ampullectomy in a referral centre for pancreatic surgery.

Patients & methods: Between Jan-2010 and Feb-2013 we performed 196 consecutive surgical procedures for benign and malignant peri-ampullary disease, of which 12 Vater ampullectomies. Indication to ampullectomy was made depending on mandatory preoperative endoscopic ultrasound (EUS) with evidence of disease limited to ampullary wall and on biopsy results. In two patients with ampullary carcinoma we performed a palliative ampullectomy because of comorbidities which contraindicated pancreaticoduodenectomy. Mean BMI was 25.27±2.7. Mean age was 66±13. Three patients had preoperative jaundice and required biliary stenting.

Results: Mean operative time was 280±52.7 min and mean blood loss was 137±99 mL. Overall morbidity was 25%, of which a case of pneumonia and two duodenal fistulas requiring radiological drainage. Median length of hospital stay was 10 days (range 8–24); one patient needed readmission. No patient experienced reintervention. Histological diagnosis revealed 6 ampullary carcinomas, 1 neuroendocrine neoplasm, 5 ampullary adenomas. Two patients with ampullary carcinoma experienced local recurrence, of which one underwent pancreaticoduodenectomy, while the other received chemotherapy because of comorbidities. All patients are alive and in F-up, 11 are free from disease.

Conclusion: In an high volume pancreatic surgical center duodenal ampullectomy is feasible and shows good postoperative results. In selected cases it could be considered a valid alternative to pancreaticoduodenectomy. Preoperative EUS is mandatory for proper surgical indication.

**PFI-80 Abstract id: 61.**

Laparoscopic distal pancreatectomy: What factors are related to the learning curve?

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Introduction: Factors related to the learning curve for laparoscopic distal pancreatectomy have rarely been evaluated.

Aims: The primary endpoint was operative time. The secondary endpoints were conversion rate, reoperation rate, overall postoperative morbidity and mortality, postoperative pancreatic fistula, post-pancreatoctomy haemorrhage, length of hospital stay and unplanned splenectomy.

Patients & methods: A retrospective study of 32 patients who underwent a laparoscopic distal pancreatectomy performed by a single high volume pancreatic surgeon experienced in advanced laparoscopic surgery. Pre-, intra- and postoperative data were collected.

Results: The operative time and the cumulative sum of the procedures presented a significant logarithmic correlation (p = 0.048), but not a linear correlation (p = 0.091). The learning curve was said to have been completed after 17 procedures (AUC = 0.714; PR = 0.040). Multivariate analysis confirmed that the completion of the learning curve (a cut-off of 17 procedures) significantly reduced operative time by 18% (effect 0.82; CI: 95% ±0.71-0.95; P = 0.009) but extended resection increased it (effect 1.24; CI: 95% ±1.03-1.49; P = 0.023). Conversion rate, reoperation rate, overall postoperative morbidity and mortality, postoperative pancreatic fistula, post-pancreatoctomy haemorrhage, and length of hospital stay were not significantly related to completion of the learning curve. Unplanned splenectomy was significantly more frequent in the first 17 procedures.

Conclusion: Operative time seems to be the main factor related to the completion of the learning curve for laparoscopic distal pancreatectomy. The learning curve could be considered completed after 17 procedures if performed by surgeons experienced in advanced laparoscopic techniques and in high volume centres for pancreatic surgery.

**PFI-81 Abstract id: 71.**

Pancreatic resections: Are there preoperative factors related to a “soft pancreas” and are they useful in predicting pancreatic fistulas?

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Introduction: Soft pancreatic parenchyma is the most widely recognized risk factor for pancreatic fistulas.

Aims: Endpoints were to recognize preoperative factors related to a soft pancreatic remnant and to establish if they are useful in predicting a pancreatic fistula.

Patients & methods: Retrospective study of patients who underwent pancreaticoduodenectomy or left pancreatectomy. Factors considered...
were: sex, age, co-morbidities, body mass index, American Society of Anesthesiologists score, characteristics of the pancreatic remnant and preoperative diagnosis.

**Results:** Two hundred and eight patients were recorded. The pancreatic fistula rate was 29.3% and it was significantly related to the type of resection, the soft texture of the pancreatic remnant (P = 0.037), a Wirsung duct diameter <3 mm and the preoperative diagnosis. The risk factors predicting a soft pancreatic remnant, were BMI >24 kg/m² (P = 0.011), a Wirsung duct size <3 (P < 0.001) and patients with peripancreatic diseases (P < 0.001). Based on these 3 factors, we developed a risk score model that was validated by considering the pancreatic fistula rate. We noted that the overall and clinically relevant pancreatic fistula rate significantly increased with increasing score values (P = 0.002 and P = 0.028, respectively). Using a score cut-off value of 6 points, patients with a score <6 were considered to be at low risk; those with a score ≥6 were considered to be at high risk.

**Conclusion:** Body mass index >24 kg/m², Wirsung duct size <3 mm and preoperative diagnosis may be considered as preoperative factors related to a soft pancreas and they resulted useful in predicting the incidence of pancreatic fistulas.

**PII-82 Abstract id: 41.
Outcomes of pancreatic resection: Analysis of the french national database on 6436 patients

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**Introduction:** National reports on outcome after pancreatic resection are missing in Europe.

**Aims:** To analyze outcomes after pancreatectomy using a large national database.

**Patients & methods:** French health care database was screened to identify all patients undergoing left pancreatectomy (LP) and pancreaticoduodenectomy (PD) between 2009 and 2010. Parameters including age, medical history, indication and support structure were retrieved. Retrospective analysis were performed to measure morbidity and mortality rates.

**Results:** On LP (n = 2352), 461 centers performed at least one LP per year (<44 over 10 LP). Laparoscopy was used in 13% of cases. Indication was a malignant tumor in 80% of cases. The average duct diameter was 29.3% and it was significantly related to the type of resection, the soft texture of the pancreatic remnant (P = 0.037), a Wirsung duct diameter <3 mm and the preoperative diagnosis. The risk factors predicting a soft pancreatic remnant, were BMI >24 kg/m² (P = 0.011), a Wirsung duct size <3 (P < 0.001) and patients with peripancreatic diseases (P < 0.001). Based on these 3 factors, we developed a risk score model that was validated by considering the pancreatic fistula rate. We noted that the overall and clinically relevant pancreatic fistula rate significantly increased with increasing score values (P = 0.002 and P = 0.028, respectively). Using a score cut-off value of 6 points, patients with a score <6 were considered to be at low risk; those with a score ≥6 were considered to be at high risk.

**Conclusion:** Body mass index >24 kg/m², Wirsung duct size <3 mm and preoperative diagnosis may be considered as preoperative factors related to a soft pancreas and they resulted useful in predicting the incidence of pancreatic fistulas.

**PII-84 Abstract id: 286.
Interventional radiologic therapy for postpancreatectomy hemorrhage as the first line treatment


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**Introduction:** Postpancreatectomy hemorrhage (PPH) is a life-threatening complication after pancreatic surgery. Although the International Study Group of Pancreatic Surgery (ISGPS) established the definition and grading of PPH, there is no consensus of PPH therapeutic strategy because of a wide variety of clinical situation.

**Aims:** The aim of this study is to determine which treatment should be appropriate as the first line treatment for PPH.

**Patients & methods:** Three hundred thirty patients after pancreatic surgery at our institute were reviewed in this study. We examined patient backgrounds, characteristics and treatment of PPH, clinical outcomes.

**Results:** Eighteen cases (4.2%) had PPH and 11 cases of them (61.1%) were associated with postoperative pancreatic fistula. The distribution of ISGPS grades was: grade B = 5 cases, grade C = 13 cases. On first-line, interventional radiology (IVR) was performed in 13 of 18 cases. Since the past decade, interventional procedures have been undergone successfully in all cases. There was no mortality in patients receiving IVR treatment.

**Conclusion:** IVR treatment is considered to be the primary treatment for PPH because IVR is less invasive and more effective than surgery.

**PII-85 Abstract id: 300.
Outbreak of antibiotic-resistant klebsiella pneumoniae in a high-volume pancreatic surgery unit

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**Introduction:** The threat of infections due to multidrug-resistant organisms is increasing. No effective drugs are available for the therapy of
serious infections caused by multidrug-resistant gram-negative rods, including klebsiella pneumoniae. In 2012, a strain of klebsiella pneumoniae resistant to multiple antibiotics, including carbapenems, was identified in our hospital. Such outbreak impacted on postoperative outcome after major surgical procedures.

**Patients & methods:** During institutional morbidity and mortality audits, the frequency and the impact on postoperative outcome of multidrug-resistant klebsiella pneumoniae infections after pancreatic resections performed in 2012 was evaluated.

**Results:** In 2012, 261 pancreatic resections were performed at our institution. The rate of postoperative complications was 54.4%. There were 6 postoperative deaths (2.2%). Postoperative mortality doubled in comparison with 2011 (3/257, 1.1%), although this did not reach statistical significance (p=0.257). Among the six patients who died, five had a sepsis caused by a multidrug-resistant klebsiella pneumoniae, mostly superimposed to a grade C pancreatic fistula. Two other patients with a severe multidrug-resistant klebsiella pneumoniae eventually survived. No postoperative death in 2011 was owing to a sepsis from multidrug-resistant organisms.

**Conclusion:** Multidrug-resistant organisms, and in particular klebsiella pneumoniae, severely impacted on postoperative mortality after pancreatic resections performed at a highly experienced tertiary care centre. Adequate information among health care professionals and strategies to prevent the outbreak of these gram-negative rods, including hand washing and isolation of infected patients, are essential. No deaths from multidrug-resistant organisms occurred as of March 2013.

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**PPI-87 Abstract id: 246.**

**Clinical relevance and interventional-radiological management of early complications after pancreatic surgery: A 12-year single-centre experience on 1285 patients**

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**Introduction:** Despite the improvement in technique/expertise, major pancreatic surgery remains burdened with a high complication rate.

**Aims:** Our aim was to report our 12-year single-centre experience about the clinical relevance and the interventional-radiological management of the early postoperative complications (treatment/prevention) on 1285 patients submitted to pancreatic surgery.

**Patients & methods:** In 2000-2012, 1285 patients were submitted to pancreatic resections (pancreatoduodenectomy, total-pancreatectomy, distal-pancreatectomy). Patients were classified on the basis of the complication severity into 5 (Clavien-Dindo-classification): grade-0—none, grade-1/2—conservative treatment, grade 3a—endoscopic/interventional-radiological, grade-3b—surgery, grade 4—intensive care, grade 5—death. Interventional-radiological management was as follows: PTC/biliary-drainage in case of biliary-fistula under US/fluoroscopic-guidance (right approach, puncturing along the course of the sixth-segment portal branch with 21G Chiba-needle, or left approach if aerobilia/adequate volume of left hepatic lobe); embolisation (microcoils/PVA-particles) or covered stenting in case of bleeding of gastroduodenal/splenic arteries; percutaneous drainage (US/CT-guidance) of liquid/infected collections. Pancreatic-islet-intraportal autotransplantation was performed when a pancreatic portion was resected for technical reasons.

**Results:** Patients were classified as follows: 524/1285 (40%) grade-0, 210/1285 (16%) grade-1, 361/1285 (28%) grade-2, 72/1285 (6%) grade-3a, 55/1285 (4%) grade-3b, 24/1285 (2%) grade-4, 39/1285 (3%) grade-5. 72/1285 (grade-3a) and were successfully treated as follows: 30/72 PTC/biliary-drainages, 27/72 liquid/infected collection percutaneous-drainages, 9/72 bleedings (7 embolisations, 2 covered-stenting). 6/72 endoscopic procedures. 25/1285 underwent pancreatic-islet intraportale autotransplantation. One bleeding/t biliary-fistula needed 2 treatments.

**Conclusion:** In experienced centres of pancreatic surgery, complications can be successfully diagnosed and managed by interventional radiological procedures, limiting their clinical relevance and avoiding a high-risk surgical re-treatment.

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**PPI-88 Abstract id: 239.**

**Clinical features and outcome of pancreatic adenocarcinoma presenting with cachexia**

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**Introduction:** Pancreatic Ductal Adenocarcinoma (PDAC) frequently presents with weight loss/cachexia. Molecular mechanisms of cachexia are increasingly explained, but its clinical features and impact on prognosis are poorly investigated.

**Aims:** To evaluate the prevalence of cachexia as presenting symptom of PDAC, clinical features of patients with cachexia and their outcome.

**Patients & methods:** Retrospective analysis of a prospective cohort of incident PDAC cases. Features of patients with cachexia (C+) (defined as weight loss>5 kg in the 6 months before diagnosis) compared to those without it (C-).

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Results: Of 291 PDAC patients 144 (49.4%) had cachexia at presentation (C+), Ca 19.9 values and the rate of jaundice (43.7% vs 40%; p=0.5) at onset were similar in C+ and C-. C+ patients more frequently reported abdominal pain before diagnosis (56.4% vs 40.8%; p=0.004) and had longer diagnostic delay (4.8 vs 2.2 months; p=0.005). Age at diagnosis, and rate of diabetes were similar in C+ and C- patients, but C+ were more frequently male (61.1% vs 47.6%) and overweight (mean BMI 28.6 vs 25.9; p=0.001). Tumor site, grading and size were similar, but C+ patients were more frequently metastatic at diagnosis (44.4% vs 32.6%; p=0.004). Survival probability was lower, yet not significantly, in C+ patients (7 vs 11 months; p=0.84).

Conclusion: Weight loss resulting in cachexia is an onset symptom of some 50% PDAC patients, more frequently observed in male and overweight subjects. Cachexia is associated with abdominal pain and longer diagnostic delay, and with a higher rate of metastatic disease at diagnosis, which might have an impact on outcome.

P11-89 Abstract id: 165.
Disease spectrum of intraductal papillary mucinous neoplasm with an associated invasive carcinoma: Invasive IPMN versus pancreas ductal adenocarcinoma-associated IPMN
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Introduction: Current version of WHO classification introduced the concept of ‘intraductal papillary mucinous neoplasm (IPMN) with an associated invasive carcinoma’. However they include large spectrum of malignant disease from minimally invasive to similar to ductal adenocarcinoma.

Aims: The authors investigated the clinicopathologic characteristics and prognosis of this disease category according to tumor morphology and percentage of invasive component.

Patients & methods: Fifty-nine patients who underwent surgical resection of IPMN with an associated invasive carcinoma at Seoul National University Hospital were subgrouped according to the invasive component of <5% (minimally invasive IPMC; MI-IPMC), 5-50% (invasive IPMC; IPMC+), and >50% (Pancreatic ductal adenocarcinoma-associated IPMN; PDAC-IPMN). Prognosis was compared with 219 curatively resected conventional PDAC.

Results: Eleven MI-IPMN (18.6%), 24 IPMC+ (40.7%) and 24 PDAC-IPMN (40.7%) were identified. With the transition from MI-IPMC to IPMC+ and PDAC-IPMN, percentage of advanced T (P<0.001) or N stage (P=0.001), expression of S100A4 (P=0.004), p53 (P=0.028), and CD24 (P=0.009) increased and SMAD4 expression decreased (P<0.001). The overall 5-year survival rate for MI-IPMC, IPMC+ and PDAC-IPMN were 80.8%, 59.0%, and 50%, respectively. Survival probability was lower, yet not significantly, in C+ patients (7 vs 11 months; p=0.84).

Conclusion: PDAC-IPMN has different clinicopathologic characteristics compared with the IPMC-I. IPMN with an associated invasive carcinoma is composed of a wide spectrum of disease.

P11-90 Abstract id: 320.
Collected series of resected intraductal papillary mucinous tumours (IPMTs) of the pancreas and correlation between the mucin expression profile and the malignant potential
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Introduction: IPMTs have attracted attention as a new pathological entity. Behind the different appearance of the different subtypes, there is different behaviour.

Aims: The aim of our study was to present the different mucin expression and its correlation with the malignant potential.

Patients & methods: The resected specimens were examined twice by different pathologists and when either different or uncertain diagnoses resulted, was the sample excluded. 41 patients were proved to have IPMT between the period of 2002-2012. Samples were immunohistochemically labelled for MUC1, MUC2 and MUC5AC. The patients were grouped according to type of the tumour, i.e. main duct- (MD), branch duct- (BD) or mixed-type (MX) IPMTs. We also created subgroups based on the mucin expression profile, like intestinal (I - MUC1-, MUC2+, MUC5AC-), pancreaticobiliary (PB - MUC1+, MUC2-, MUC5AC-), gastric-type (G - MUC1-, MUC2+, MUC5AC+).

Results: 13 MD-, 10 BD- and 18 MX- type IPMTs were found. In total only 17.1% were found to be benign. The malignancy rate in the MD, BD and MX groups was 61.5%, 60%, 72.2%, respectively. Based on the mucin expression profile 17 I-, 11 G- and 13 PB- type IPMTs were found. All patients in the PB- group while 64.7% and 27.3% of the I- and G-groups were malignant, respectively.

Conclusion: The lack of MUC1 expression may be related to a less invasive characteristics of IPMTs, while the MUC5AC expression alone can be related to benign potential. In contrast, MUC2+ and MUC5AC+ or MUC1+ and MUC5AC+ expression can increase the rate of success of diagnosing invasive IPMTs.

P11-91 Abstract id: 249.
The carboxyl-ester lipase (CEL) gene - A risk factor for pancreatic cancer?
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Introduction: The CEL gene is known to be highly polymorphic. We have previously described a rare syndrome of exocrine and endocrine pancreatic dysfunction, caused by single-base mutations in the CEL gene. In addition, we have identified copy number variants (CNVs) of the CEL locus and variable number of tandem repeat (VNTR) length polymorphisms in CEL exon 11.

Aims: The aim of this study was to examine if the CEL CNV alleles predispose to pancreatic cancer. We also investigated the association between pancreatic cancer and the CEL VNTR-length.

Patients & methods: We examined patients with pancreas cancer in a Norwegian cohort (n=250), and Norwegian blood donors (n=190–233) were used as healthy controls. For screening of CEL CNVs, we used a duplex PCR assay. Genotyping of the CEL VNTR was performed using multiplex PCR and DNA fragment analysis.

Results: We have identified three CEL CNVs, two with gene duplication and one with a deletion. The carrier frequencies of the duplicated alleles were 4.6% and 2.9%, respectively, among the pancreas cancer patients, and 2.6% and 3.2% in the controls. The deleted allele was not detected in pancreas cancer, compared to 0.5% in the controls. When analyzing the CEL VNTR-lengths, we found alleles harboring from 11 to 23 repeats, with 16 repeats being the most frequent VNTR length. Alleles with more than 17 repeats were more frequent in patients with pancreatic cancer.

Conclusion: We observed no statistical significant association between the CEL CNV alleles and pancreatic cancer. However, there is a tendency of a positive association between pancreatic cancer and increased CEL VNTR-length.
PII-92 Abstract id: 64.

Efficacy of double pigtail stent as conservative treatment of grade B pancreatic fistula after pancreatoduodenectomy with pancreatic anastomosis


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Introduction: Despite improvements in surgical techniques and postoperative care, morbidity associated with pancreatoduodenectomy (PD) is still high. The grade B PF is defined by symptomatic pancreatic fistula, requiring a specific medical treatment also associated with radiologic drainage. This type of treatment is effective, but requires prolonged hospitalization and holding of external drainage.

Aims: The objective of this study was to evaluate the efficacy of internal endoscopic drainage using double pigtail stent (DPS) of grade B PF after PD with pancreatic anastomosis.

Materials & methods: Between 2008 and 2011, all patients presenting grade B PF after PD treated endoscopically (6 patients) were included. Diagnosis of PF was based on ISGPF criteria. Endoscopic treatment was standardized using DPS. Primary endpoint was the feasibility and efficacy of endoscopic procedures. Secondary endpoints were PF data, endoscopic procedures and short-term follow up data.

Results: Endoscopic treatment has been achieved in all patients without complications. Median time to onset PF after PD was 14 days. Median time to onset of endoscopic procedure after discover of PF was 6 days. Depletion of external PF was obtained 7 days after DPS. Median time of external drains removal was 7 days after DPS. Oral refeeding was performed 7 days after DPS for all patients. Median time of removal DPS was 60 days. Median length of hospital stay after DPS was 10 days. On a median follow-up of 21 months, there was no recurrence of perianastomotic collection.

Conclusion: Endoscopic treatment of grade B PF after PD seems effective, safe and associated with a shorter duration of hospitalization.

PII-93 Abstract id: 188.

Impact of diagnosis and treatment of pancreatic exocrine insufficiency (PEI) on survival of patients with unresectable pancreatic cancer (PC)

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Introduction: PEI is associated with malnutrition, weight loss and poor survival in patients with unresectable PC.

Aims: We aimed at evaluating the impact of PEI therapy on survival in these patients.

Materials & methods: Retrospective analysis of a prospective database of patients with unresectable PC confirmed by EUS and FNB. Patients with survival <30 days were excluded. All patients were evaluated for palliative chemotherapy and endoscopic bile drainage if needed. Those patients diagnosed in the Department of Gastroenterology (group 1) were further evaluated for PEI by 13C-MTG breath test and nutritional status, whereas other patients (group 2) were not. Group 1 patients with PEI were treated by pancreatic enzyme replacement therapy (Creon®, 50,000 Ph.U. lipase/meal and 25,000 Ph.U. lipase/snack). Survival (median and 95%CI) was analyzed by Kaplan-Meier test and Cox regression and compared by Log Rank Test.

Results: 66 patients with unresectable PC were included (mean age 69.3 years, range 28-100, 43 male, 50 stage IV), 21 (31.8%) in group 1 and 45 (68.2%) in group 2. Age, tumor stage and PS were similar in both groups. Survival in group 1 (301 days, 95%CI 151-451) was significantly longer than in group 2 (89 days, 95%CI 30-148) (p=0.002). Palliative chemotherapy and PEI and malnutrition therapy were independent factors associated with longer survival in a multivariate model controlled by age, gender and tumor stage.

Conclusion: Treatment of PEI and malnutrition has a relevant impact on survival in patients with unresectable PC. These results should serve as background for future clinical trials in this context.

PII-94 Abstract id: 257.

Primary pancreatic carcinoids

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Introduction: Primary pancreatic carcinoids (foregut) are very rare. Diagnosis is made in case of high urinary 5-HIAA (or high serum 5-HT) or immunostaining of 5HT in tumor cells.

Aims: To evaluate clinical presentation, endocrine tumor markers, histology, therapeutic approach and follow up (FU).

Patients & methods: From 1986 to 2011 in our Department 211 neuroendocrine (NE) pancreatic tumors were observed. Eight (3.8%) primary carcinoid tumors were found. Follow up (FU) to June 2012.

Results: Out of 8 cases enrolled (5 M/3 F, averaging 55.8 yrs), three were symptomatic. Seven high serum 5-HT or high urinary 5-HIAA, one asymptomatic with positive 5-HT immunostaining in tumor cells. Location: 6 body-tail. All cases malignant: 7 with liver and 1 with a single nodal metastases. Four patients had high serum 5-HT (up to 176 umol/L), seven high urinary 5-HIAA (up to 522 umol). Surgery: only 1 case resected (left pancreatectomy), 7 cases had only biopsy. Three patients treated with somatostatin analogues (SST-A) and chemotherapy (CT), one CT and radiometabolic therapy after hepatic artery embolization (HAE), one HAE and SST-A, and one only CT. Follow-up: 6 patients died for disease progression (mean survival 52 mo), 2 are alive (1 without disease 72 mo after surgery, 1 asymptomatic with high 5-HIAA 27 mo after SST-A and CT).

Conclusion: Most of primary pancreatic carcinoids are locally advanced tumors or have liver metastases at time of diagnosis, then not amenable to surgery. Patients may have high urinary 5-HIAA without carcinoid syndrome. In foregut carcinoids long term survival may be achieved with multimodal approach, including CT.

PII-95 Abstract id: 117.

Sarcopenia and survival in pancreatic ductal adenocarcinoma: A systematic review

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Introduction: Sarcopenia (skeletal muscle depletion) has been shown to predict worse survival in various cancers. The prognostic significance of sarcopenia in pancreatic cancer has not been systematically evaluated.

Aims: To perform a systematic review of data regarding sarcopenia and survival in pancreatic cancer.

Materials & methods: Two independent reviewers performed a systematic review of literature published in PubMed, EMBASE, Cochrane Database (January 2000-December 2012). The following MESH and non-MESH headings were used: (pancreatic neoplasm OR pancreatic cancer) AND (sarcopenia OR cachexia OR body mass composition OR denutrition
Introduction: Surgery is generally not indicated for metastatic periampullary adenocarcinoma because it does not appear to improve survival. Despite controversy, it is not suggested for most patients, and death may occur within the first 2 years and annually thereafter. Recurrence rate, time and site of recurrence were evaluated. Relevant Abstracts were read, eligible articles retrieved and a manual search of the bibliographies performed. The A-related article A-function in PubMed was used to identify missed studies. English language relevant clinical studies of any level of evidence were included. Unpublished data, Abstract or duplicate publications were excluded.

Results: Two articles were found of 343 articles and related research. Two retrospective trials included 152 patients with inoperable pancreatic adenocarcinoma. The prevalence of sarcopenia was 62(56%) and 26(63%) patients. All had advanced cancer and underwent chemotherapy/chemoradiation. Sarcopenia was assessed by means of CT-scan skeletal muscle calculation. Sarcopenia alone was not significantly associated with poor survival. In multivariate analysis sarcopenic obesity but not sarcopenia alone was associated with significantly lower survival.

Conclusion: The systematic review showed the lack of data about sarcopenia impact on survival in patients with pancreatic cancer. It justifies the need of further research.

PII-96 Abstract id: 85.
Liver resection for metastatic periampullary cancer: Is it (sometimes) worthwhile?
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Introduction: Surgery is generally not indicated for metastatic periampullary adenocarcinoma because it does not appear to improve survival.

Aims: Is metastatic periampullary cancer an absolute contraindication to surgery? Could someone benefit from liver resection?

Patient & Methods: Our prospectively collected database (2003-2012) lists 21 patients who underwent liver resection for metastases from periampullary adenocarcinoma. Resection was offered to young patients who were fit for surgery and had few synchronous or metachronous metastases. Potential prognostic factors were taken into consideration to design a score that was applied to the study population to predict survival.

Results: Duodenal carcinoma was the primary tumor in 15 patients; the remaining patients had ampullary carcinoma or distal bile duct carcinoma. One right hepatectomy, 2 bisegmentectomies and 18 atypical resections were performed. Simultaneous liver and pancreatic resection did not significantly improve postoperative morbidity and mortality compared to standard pancreatic resection. The median overall survival from liver resection (OS) of patients with synchronous and metachronous disease was 11.4 months (95% CI: 6.0-16.9) and 28.5 months (95% CI: 1.7-55.2), respectively (p=0.12). The proposed score was able to divide the subjects into three classes of prognosis, in which the estimated OS was significantly different.

Conclusion: Surgery for liver metastases from periampullary tumors is controversial. It is not suggested for most patients, and death may occur even earlier compared to palliative cure. However, a small group of highly select patients could benefit from surgery.

MMMP9 and S100A9 expression in peripheral blood mononuclear cells (PBMC) are correlated with PDAC and with PDAC-associated diabetes mellitus
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Introduction: Tumor-stroma-endocrine interactions favour pancreatic adenocarcinoma (PDAC) growth/progression and PDAC-associated diabetes mellitus (DM). S100A8/A9 and the matrix metalloproteinases (MMPs) 8 and 9 are overexpressed in PDAC stroma.

Aims: To verify whether S100A8, S100A9, MMP8 and MMP9 mRNA in PBMC is useful for diagnosing and staging PDAC and/or for detecting PDAC-associated DM. To study the impact of S100A8/A9 and of PDAC-associated growth factors and cytokines on MMPs expression.

Patients & Methods: S100A8, S100A9, MMP8 e MMP9 mRNA were quantified by qRT-PCR in 62 PDAC, 37 chronic pancreatitis, 23 pancreaticobiliary tract tumors (PBT) and 30 healthy controls (HC). PBMC (blood donors) were treated with insulin, EGF, TGFb1, S100A8/A9 before MMP8 and MMP9 mRNA analysis.

Results: MMP8 and MMP9 were higher in PDAC and in PBTC than in HC (Kruskal-Wallis Test: p<0.0001). S100A8 (p=0.902) and S100A9 (p=0.303) did not vary. PDAC stage was not correlated with any molecule. At binary logistic regression analysis (PDAC presence or absence dependent; S100A8, S100A9, MMP8, MMP9, age, gender, CA19-9, bilirubin, glucose, C-peptide, CRP, ALT predictors), only MMP9 (OR:0.69;95% CI:0.48-0.99; p=0.047) and CA19-9 (OR:1.74;95%CI:1.31-2.33; p=0.002) were independently correlated with PDAC. In PDAC, DM was independently correlated only with S100A9 (OR:8.16;95%CI:2.31-28.78; p=0.001) and age (OR:1.10;95%CI:1.01-1.21; p=0.028). Insulin, EGF and TGFb1 did not affect MMP8 or MMP9 expression. S100A8/A9 significantly induced MMP8 (F=23.68, p=0.002) and MMP9 (F=93.84, p=0.0001) mRNA in PBMC.

Conclusion: PDAC is associated with an increased MMP9, while PDAC-associated DM is associated with an increased S100A9 expression in PBMC. S100A8/A9 effects on MMPs support the hypothesis of an intriguing relationship between inflammation, diabetes and PDAC.

PII-98 Abstract id: 57.
The role of lymph node ratio in recurrence after curative surgery for pancreatic endocrine tumours
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Introduction: The prognostic role of lymph nodes metastasis and lymph nodes ratio in pancreatic neuroendocrine tumours is unclear.

Aims: The endpoint was to define the role of the lymph nodes ratio in recurrence after curative surgery.

Patients & Methods: Retrospective study of 53 patients who underwent a curative standard resection for pancreatic neuroendocrine tumours. The following data were considered as possible factors for predicting the risk of recurrence: gender, age, presence of symptoms, hormonal status, site of tumours, type of resection, size of the tumours, radical resection, pathological T, N and M stage according to the European Neuroendocrine Tumor Society, the Ki67 index, the number of lymph nodes harvested, the number of metastatic lymph nodes and the lymph node ratio. Follow-up examinations were conducted every 6 months for the first 2 years and annually thereafter. Recurrence rate, time and site of recurrence were evaluated.
Results: Twelve (26.4%) patients developed a recurrence of the disease with a mean time of 66.4±8 months. Recurrences were located in the liver in 8 cases (66.6%) and were local in 4 (33.4%). At multivariate analysis, the only factors significantly related to recurrence were: size of lesions (HR 1.1, CI. 95% 1.0-1.1, P=0.011), Ki67 >5% (HR 3.6 CI. 95% 1.3-10, P=0.014) and LNR >0.07 (HR 5.2, CI. 95% 1.1-25, P=0.045).

Conclusion: Our study confirmed that the lymph nodes ratio played an important role in the recurrence rate and suggested that a low number of metastatic lymph nodes reduced the disease free survival.

PII-99 Abstract id: 223.
The diagnostic value of pancreatic amylase analyses from prophylactic abdominal drainage in identifying pancreatic fistula following pancreaticoduodenectomy
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Introduction: Postoperative pancreatic fistula (POPF) remains the predominant cause of pancreaticoduodenectomy(PD)-associated morbidity and mortality. Prophylactic abdominal drainage following PD is controversial; the therapeutic value has been questioned, the importance of drain fluid analyses for POPF diagnosis emphasized.

Aims: To evaluate to which extent drain pancreatic amylase (DPA) contributed to the diagnosis of subsequent POPF formations.

Patients & methods: Prospective study of 315 standardized consecutive PD’s with prophylactic drainage 2008-2012. Daily samples of DPA, plasma pancreatic amylase (PPA) and C-reactive protein (CRP) were obtained concomitantly. Differences between ICGF-defined POPF and non-POPF were evaluated. ROC analyses were performed for the POPF-predictive values of DPA, PPA and CRP. Cut-off levels were determined; a risk profile for clinically-relevant POPF was constituted and related to the results of the intra-operative pancreatic risk assessment.

Results: 59 patients (19%) had clinically-relevant POPF. CRP, PPA and DPA levels for postoperative day (POD) 1-3 differed significantly between non-POPF/POPF-A and POPF-B/C. The POPF-predictive impact of DPA (POD1 1320U/L, OR25; POD2 428U/L, OR29) was superior to that of PPA (POD1 1320U/L, OR25; POD2 428U/L, OR29) was superior to that of PPA and CRP. Cut-off levels were determined; a risk profile for clinically-relevant POPF was constituted and related to the results of the intra-operative pancreatic risk assessment.

Conclusion: The peroperative classification of pancreatic characteristics forms the basis for POPF risk assessment. Prophylactic abdominal drainage is recommended for patients with intermediate- or high-risk glands from a diagnostic perspective. Postoperative DPA and CRP courses had a high accuracy in monitoring the initial pancreatic inflammatory response and predicting the subsequent development of clinically-relevant POPF.

PII-100 Abstract id: 314.
Prognostic Factors in Neuroendocrine Tumors of the Pancreas Category: Clinical science - pancreatic cancer.
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Introduction: Classification of potentially malignant pancreatic neuroendocrine tumors has gone through several changes.

Aims: We present the efficiency of clinicopathological parameters and different classifications (ENETS, UICC, WHO) from the viewpoint of prognosis.

Patients & methods: We analyzed the clinicopathological parameters (hormone production, mitotic activity, Ki-67 index, TNM) of 34 neuroendocrine tumors.

Results: The grade values obtained on the basis of the Ki-67 index and mitotic figures showed correlation. The Ki-67 proliferation index had a significantly higher value in case of tumors with lymph node metastasis. Based on grade and stage, insulinomas belonged to the group having significantly better prognosis, without giving distant or lymph node metastases. The stage according to either the ENETS or UICC classification was the same in case of localized tumors and distant metastases. However, we found differences in stage regarding tumors showing infiltration of surrounding structures. In case of tumors classified into the carcinoma group and giving lymph node metastases according to the WHO classification, the development of metastases at distant sites is to be expected.

Conclusion: The three classification systems customary in the diagnosis of neuroendocrine tumors of the pancreas (ENETS, UICC, WHO), the hormone production as well as proliferation index of the tumors are all prognostic factors. We suggest the parallel application of both grading systems when assessing the proliferative activity. In the pathological report it is essential to indicate the type of classification used.

PII-101 Abstract id: 254.
Role of morpho-histological features of pancreatic stump in prediction of postoperative pancreatic fistula (POPF) development after pancreaticoduodenectomy (PD)
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Introduction: PD is characterized by high morbidity, mainly represented by POPF and its further consequences. Wirsung diameter and pancreatic texture are notoriously related to POPF. Limited information is available about relationship between pancreatic stump histo-morphological features and POPF onset.

Aims: Evaluation of predictive role of intra-operatively assessed pancreatic stump histo-morphology on POPF incidence after PD.

Patients & methods: Between Mar-2011 and Feb-2013 we performed 187 consecutive PD; we prospectively recorded surgeon’s judgment about pancreatic texture, highlighting Wirsung diameter, its position, the whole stump area (approximately elliptic), POPF rate and its clinical impact. Our dedicated pathologist collected histological data about stump fibrosis and inflammation creating a specific score (6 progressive degrees considering fibrous substitution and lymphocyte’s tissue infiltration).

Results: POPF rate and clinically significant POPF rate (ISCGF B-C) were respectively 26.5% and 17%. Wirsung smaller than 4mm and soft texture resulted associated with higher POPF rate (respectively 37.5% vs.4.3%, p<0.001;78% vs.21%, p<0.001). Larger stumps were related with POPF (p=0.007); Wirsung decentralization was associated with lower POPF risk (more evident on stump’s antero-posterior axis than on crano-caudal, respectively p=0.019 and p=0.144). Our fibrosis-and-inflammation score correlated with surgeon’s judgment about texture (p=0.001); an increasing score was associated with lower POPF rate (p=0.001).

Conclusion: Wirsung diameter and pancreatic texture remain main determinants for POPF. Moreover, higher POPF risk is reasonably predictable in larger pancreatic stumps and when Wirsung is centrally located. POPF risk appears lower when at intraoperative histological analysis considerable fibrosis and inflammation are identified. These findings appear useful in tailoring management on patient individual risk (drains positioning-removal, octreotide prophylaxis, re-feeding).
Visceral fat and survival in pancreatic cancer: A systematic review

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Introduction: Visceral obesity has been shown to affect survival, surgical morbidity and chemotherapy efficacy in patients with colorectal, ovarian and lung cancer. However, the prognostic role of visceral fat in pancreatic cancer has not been systematically studied.

Aims: To perform a systematic review of literature regarding visceral obesity and survival in pancreatic cancer.

Materials & methods: Two reviewers independently searched PubMed, EMBASE, Cochrane Database, for English speaking studies published since 2000. The following search strategy was used: (pancreatic neoplasm OR pancreatic cancer) AND (obesity OR body mass composition OR visceral fat OR body mass index OR fat distribution). After exclusion of non-relevant Abstracts, full-text papers and their bibliographies were searched. Unpublished data, Abstract or duplicate studies were excluded.

Results: Finally, 4 papers out of 343 have been included in the analysis, all with retrospective design. The papers included 602 resected patients and 41 patients undergoing chemoradiation. Visceral fat was calculated by means of CT scan analysis without a unified methodology (retrorenal fat, total visceral fat area on the level of umbilicus or 3rd lumbar vertebrae). In two smaller studies (n=61 and n=41) higher visceral fat loss or higher visceral fat quartile correlated with worse survival. In the two larger surgical studies no correlation was found.

Conclusion: No consistent results regarding the role of visceral fat in pancreatic cancer survival are available. Therefore, new prospective studies with standardized methodology are needed to clarify this question.

Total laparoscopic pancreaticoduodenectomy: Is there a learning curve? Category: Clinical science - pancreatic cancer.

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Introduction: Laparoscopic pancreaticoduodenectomy (LPDE) is an alternative to traditional surgery for patients with tumor of the head of the pancreas and peripancreatic area. LPDE is considered as a technically feasible and safe procedure in selected patients. But at the same time a lot of surgeons stop performing total laparoscopic pancreaticoduodenectomy (TLPDE) after 5–15 procedures because of the difficulties of learning curve.

Aims: To assess the learning curve of total laparoscopic pancreaticoduodenectomy.

Patients & methods: The data of 54 patients who were planned for LPDE from January 2007 to January 2013 were analyzed. The same surgical team performed all the procedures. 46 patients were underwent TLPDE. Patients were divided in three groups. Group A, B and C (15:16:15 patients respectively).

Results: Among the 54 patients, 46 patients underwent TLPDE. The conversion rate was in the group A=26.7%(n=4), group B=18.7%(n=3) and C 0%(n=0). Median operative time of TLPDE for the group A was 540±43min, B 500±50min and B 350±60min (minimally -280min). Mean blood loss was for group A 663±35ml, B 612ml and C 590ml. Total postoperative complication rate (Claven-Dindo-Strasberg) for group A 66.6%(n=10), B 43.7%(n=7) and C 26.6%(n=4). Total rate of complications 45.6%(n=21). Total postoperative mortality was 4.3%(n=2) one of the patients died from insufficiency of the pancreatoyejunostomy, another one – because of acute heart failure without any surgical complications). The median operating time in early cases was longer than in the later cases and may represent the learning curve of TLPDE.

Conclusion: The results become significantly better after 30 procedures. The most difficult and potentially dangerous for intra and postoperative complications were: dissection along superior mesenteric and portal vein and performing of pancreaticojejunal anastomosis. Performing TLPDE by the same team, including nurses, is the very important factor quick learning curve and safety.

Post-operative effects of TPN compared to early enteral feeding after pancreaticoduodenectomy

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Introduction: Feeding after abdominal surgery is controversial, particularly in pancreatic surgery. This has become more important following the introduction of fast track surgery, the aim of which is to make surgery more efficient and minimise costs.

Aims: The aim of this study is to assess the impact of parenteral feeding after pancreateoduodenectomy.

Patients & methods: Retrospective analysis of patients undergoing pancreateoduodenectomy between March 2011 and November 2012 was carried out. Patients who were given total parenteral nutrition (TPN) were compared with those given early enteral feeding (EEF) as tolerated. Primary outcomes assessed were postoperative nutritional outcomes including albumin level, change in body mass index (BMI) as well as blood parameters including white cell count and C-reactive protein. Length of hospital stay and complication rates, according to the Clavien-Dindo classification, were also evaluated.

Results: 49 patients were included. 22 (45%) patients had TPN, 27 (55%) patients were fed enterally. There was no significant difference in nutritional outcomes in the two groups (p=0.814). The WCC was significantly higher in the TPN group (p = 0.037). Median length of stay was longer in the TPN group than the EEF group (21 days vs 15 days). Complication rates were similar in both groups. However, 2 patients had complications associated directly with TPN.

Conclusion: Patients initiated on TPN feeding after pancreateoduodenectomy had no benefits compared to those that are fed enterally. Overall complication rates were similar but TPN was associated with longer hospital stay. This evidence supports the idea that fast track patients should not be routinely fed parenterally.

The clinical impact of diagnostic errors in cystic tumors of the pancreas

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Introduction: Diagnostic errors in the preoperative evaluation of cystic neoplasms of the pancreas (CNP) are not uncommon. Only limited data is available regarding the impact of these errors on clinical management.

Aims: This study aims to evaluate the clinical impact of these diagnostic errors.
Patients & methods: A series of 141 patients undergoing surgery for CNP at Karolinska University Hospital was retrospectively analyzed. There were 60 males and 81 females; the mean age was 60.3 yrs. CT was performed in 138 patients (97.8%), MR in 85 (60.3%), and EUS in 31 (21.9%).

Results: Histology confirmed the pre-operative diagnosis in 60.5% of patients. The concordance rate between pre-operative diagnosis and histology was similar for asymptomatic and symptomatic lesions (60.5% vs 61.4%; p=NS). The rate of correct diagnosis increased over time (2004-2006: 54.5%, 2007-2012: 61.7%, 2010-2012: 63.5%). Lymphoepithelial cysts (2/2) were misdiagnosed most frequently, followed by serous cystic neoplasia (24/33, 72.2%), solid pseudopapillary neoplasia (5/8, 62.5%), mucinous cystic neoplasia (7/25, 28%), and IPMN (17/56, 33.3%). Reevaluating the surgical indication in view of the histological diagnosis, surgical resection was not required in 13 patients (9.2%). There was no mortality in this patient group, and morbidity amounted to 53.8%.

Conclusion: The results confirm that preoperative diagnostic errors are quite common in CNP; however, the percentage of patients who unnecessarily undergo surgery is low (9.2%). The error rate is similar for symptomatic and asymptomatic patients.

PII-106 Abstract id: 288.
Systematic review of the literature on the use of sealants in pancreatic surgery
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Introduction: A pancreatic fistula is a potentially life threatening complication of pancreatic surgery.

Aims: The aim of this systematic review is to evaluate the role of sealants in pancreatic surgery in terms of preventing pancreatic fistula.

Patients & methods: We performed a systematic search of the literature from January 2005 to December 2012. Inclusion criteria were studies on the use of local sealants in pancreatic surgery that reported mortality and the rate of pancreatic fistula (primary outcome). Animal studies, studies in non-English language, studies that use liquid or non topical sealants and studies not using the ISGPF classification for postoperative pancreatic fistula (POPF) were excluded.

Results: Seven studies were included: one randomized controlled trial, two prospective and four retrospective observational cohort studies. Distal pancreatectomy was performed in 436 patients (sealants n=258, controls n=178) and 121 patients underwent pancroctoduodenectomy (sealants n=94, controls n=27). Following distal pancreatectomy, 108 patients (42%) treated with sealants developed POPF versus 93 patients (53%) in the control group (p=0.03). Of these 22(9%) versus 22(12%) were clinically relevant (grade B and C fistula, p=0.19). Following pancroctoduodenectomy, 9 patients (10%) treated with sealants versus 3 patients (11%) in the control group developed POPF (p=0.81), of which 3(3%) versus 1(3%) were clinically relevant (p=0.89). There were no major differences in time to drain removal, hospital stay, morbidity and mortality.

Conclusion: The current data do not support the routine use of sealants in pancreatic surgery, because there was no effect on clinically relevant fistula. Larger well-designed studies are needed to determine the efficacy of local sealants in preventing pancreatic fistula after pancreatic resection.

Frequency and characterization of benign lesions in patients undergoing surgery for the suspicion of solid pancreatic neoplasm
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Introduction: A diagnosis of benign lesions is reported in 5-21% of patients undergoing pancreaticoduodenectomy for pancreatic neoplasm, whereas no data have yet been published for body-tail resections.

Aims: Aim of the study was to investigate the frequency and to characterize the benign lesions mimicking cancer in the head and in the body-tail of the pancreas.

Patients & methods: We retrospectively reviewed pancreatic specimens collected from 2005 to 2011 in the database of the Institute of Pathology of Mainz (Germany). Patients with final diagnosis excluding malignancy were analyzed by histology, imaging findings and clinical aspects.

Results: 373 patients were identified. Benign disease was diagnosed in 33 patients (8.8%), in 25 out of 298 (8.4%) in pancreatic head resections and in 8 out of 75 (10.7%) of the body-tail resections group. Para- duodenal pancreatitis (PP) was diagnosed in surgical specimens in 13 out of 373 patients (3.5%), autoimmune pancreatitis (AIP) in 11 (2.9%), “ordinary” chronic pancreatitis (CP) in 6 (1.6%) and accessory spleen in 3 (0.8%). In pancreatic head resections the most frequent diagnosis was PP (13 out of 298 – 4.4%) and AIP (9 out of 298 – 3%), whereas in the body-tail accessory spleen (3 out of 75 – 4%), CP (3 out of 75 – 4%), and AIP (2 out of 75 – 2%).

Conclusion: Benign lesions are observed with the same frequency in specimens of the head or body-tail of the pancreas. AIP accounts for 2.9% of all resections, 3% of pancreatic head and 2.7% of the body tail.

Cystic pancreatic lesions – Do we need radical surgery?
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Introduction: Despite improved diagnostic methods, correct diagnosis and treatment of cystic lesions of the pancreas (CLP) still constitutes a clinical challenge.

Aims: This study aimed at retrospective evaluation of diagnostic accuracy and surgical treatment of CLP.

Patients & methods: Patients with CLP referred to our institution for evaluation and treatment between 2001 and 2012 were retrospectively analyzed. Statistical calculations were performed with IBM SPSS Version 20.

Results: A total of n=234 patients of median age 63 (range 22-90) years were included in the study, of whom n=160 (68%) were operated, n=17 treated minimally invasive or interventionally and n=57 were observed only. Most frequent definite histologically confirmed lesions in the 160 operated patients were benign pancreatic pseudocysts (BPP, 30%) and intraductal papillary mucinous neoplasms (IPMN, 24%), followed by various rare entities like serous and mucinous cystic neoplasms, cystadenocarcinoma, neuroendocrine tumor and others. Of resected IPMN, 46% were invasive and multivariate analysis disclosed younger age, absence of symptoms or former malignancy and presence of diabetes as independent risk factors for invasive transformation. Clinical or preoperative classification as benign or malignant showed fair accuracy, as only 4% of lesions regarded as benign turned out to be malignant after resection and no patient without resection developed malignancy at a median follow-up of 8 months. In the subgroup of patients operated for suspected benign IPMN, malignancy rate was 13%.

Conclusion: Diagnostic accuracy regarding the biology of CLP is relatively high. We suggest that parenchyma-sparing techniques can be performed if benign CLP are suspected.

Are the new IPMN’s guideline effective to predict the presence of invasive IPMCarcinoma? A single center experience
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Introduction: In 2012 the IPMNs International Consensus Guidelines changed the criteria for surgery and the definition of “malignancy”, reserving this term only for invasive carcinoma

Aims: To evaluate the accuracy of surgical criteria to predict malignancy.

Patients & methods: From 2003 to 2012, data regarding 184 patients with IPMNs, were recorded. Forty-two (22.8 %) patients, undergoing surgery, were evaluated according to the new guidelines. Criteria for surgery (cyst size, Wirsung dilatation, symptoms and presence of solid endocystic component) were studied to assess the malignancy in patients affected by IPMNs. Multivariate analysis was carried out comparing the new (only invasive carcinoma) and old definition of malignancy (invasive carcinoma and high grade dysplasia).

Results: All operated patients presented criteria for surgery. Malignancy was recorded in 21 (50%) and 17 (40.5%) patients, according to the Sendai and Fukuoka definitions. At multivariate analysis no factors predicted malignancy according to Fukuoka definition, while presence of ESC (RR 14.2; CI 95% 1.8–113.5; P=0.012) and cystic size (RR 11; CI 95% 1.02–1.20; P=0.019) were related to malignancy according to Sendai definition. A dimensional cut-off of the cystic lesion of 26 mm was obtained with a ROC curve (AUC= 0.724; P=0.013). At the multivariate analysis, this cut-off resulted the strongest independent factor predicting malignancy according to Sendai definition (RR 8.0; CI 95% 1.13–56.95; P=0.037).

Conclusion: In our experience, surgical criteria seem to be inefficacy to predict presence of invasive carcinoma. ESC and cystic size were the only factors able to detect patients with high grade dysplasia or invasive carcinoma and to suggest the surgical approach.

P111 Abstract id: 331.
A unifying concept for periampullary adenocarcinomas

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Introduction: Periampullary adenocarcinomas comprise pancreatic, distal bile duct, ampullary and duodenal adenocarcinoma. The epithelia of these anatomical structures share a common embryologic origin from the foregut. With steadily increasing numbers of pancreaticoduodenectomies over the last decades, pathologists, surgeons and oncologists are more often confronted with the diagnosis of “other than pancreatic” periampullary cancers. The intestinal subtype of ampullary cancer has been shown to correlate with better prognosis.

Aims: clinical and histopathological evaluation of intestinal vs pancreatic ductal adenocarcinoma

Patients & methods: From n=198 cases of periampullary carcinoma with clinical follow-up, evaluation of histological subtype and immunohistochemical staining pattern for CK7, CK20 and CDX2 was done by two experienced pathologists. Routine pathological parameters were included in survival analysis performed with SPSS 20.

Results: In univariate analysis, intestinal subtype was associated with better survival in ampullary, pancreatic ductal and duodenal adenocarcinoma. Intestinal differentiation and lymph node ratio, but not tumor location were independent predictors of survival when all significant predictor variables from univariate analysis (grade, TNM stage, presence of precursor lesions, surgical margin status, perineural, vascular and lymphatic vessel invasion, CK7 and CDX2 staining pattern) were included in a Cox proportional hazards model.

Conclusion: Intestinal type differentiation of periampullary carcinomas and lymph node ratio are independent prognostic factors not only in ampullary, but also in other periampullary adenocarcinomas like pancreatic ductal adenocarcinoma. Differentiation is more important than tumor location for prognostic stratification in periampullary carcinomas.

P111 Abstract id: 114.
Diagnostic accuracy of contrast-enhanced computed tomography in assessing extra-regional lymphadenopathy in pancreatic and periampullary cancer: A systematic review

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Introduction: Computed tomography (CT) is the most widely used method for assessing resectability of pancreatic and peri-ampullary cancer. One of the contra-indications for curative resection is extra-regional lymph node (ELN) metastases.

Aims: The aim of this study was to determine the diagnostic accuracy of CT in assessing ELN metastases in pancreatic and peri-ampullary cancer.

Patients & methods: We systematically reviewed the literature published up to November 29th 2012, according to the PRISMA guidelines. Studies reporting on CT and histopathological assessment of ELN in patients undergoing pancreaticoduodenectomy were included. We excluded studies were data on CT and ELN were not reported. Data on baseline characteristics, CT-investigations and histopathological outcomes were collected. Diagnostic accuracy, positive predictive value (PPV), negative predictive value (NPV), sensitivity and specificity were calculated for individual studies and pooled data.

Results: After screening, 4 cohort studies reporting on CT-findings and histopathological outcome in 157 patients with pancreatic or peri-ampullary cancer were included. Histopathologically proven ELN metastases were present in 28/157 (18%) patients, which had been diagnosed on CT in 7 (25%) patients. CT falsely suggested presence of ELN metastases in 18 (12%) patients. Overall, diagnostic accuracy, specificity and NPV varied from 63-81, 80-100% and 67-90% respectively. However, PPV and sensitivity ranged from 0-100% and 0-38%. Pooled accuracy, sensitivity, specificity, PPV and NPV were 75%, 25%, 86%, 28% and 84% respectively.

Conclusion: CT has a low diagnostic accuracy in assessing ELN metastases in patient with pancreatic or peri-ampullary cancer. Therefore the suspicion of ELN metastases on CT should not be a contra-indication for explorative laparotomy and, when possible, pancreaticoduodenectomy.

P112 Abstract id: 121.
Clinical behavior in 63 patients with branch duct type of intraductal papillary mucinous neoplasm

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Introduction: An international consensus conference has recommended close follow-up in patients with branch duct type of intraductal papillary mucinous neoplasm (BD-IPMN), even if no symptoms, smaller than 30 mm in diameter and no mural nodules.

Aims: This study investigated whether the recommendation could be appropriate in a single-centre experience.

Patients & methods: Sixty-three patients who were diagnosed with BD-IPMN at our institute between 2000 and 2012 were enrolled in this study. At the first presentation, all patients were asymptomatic and had a
BP-IPMN lesion which was smaller than 30mm in diameter and had no mural nodes. The regular outpatient follow-up by a 6-month clinical-radiological protocol has been done.

Results: During the follow-up period, 7 out of 63 cases (11.1%) showed suspicion of malignancy in BD-IPMN lesion, presenting tumor growth (more than 3.5 cm in diameter), the presence of mural nodules and recent-onset or worsened diabetes. The mean follow-up time was 3.2 years (median 2.0 years). All these patients received pancreatic surgery. Pathologically, three out of 7 cases had adenocarcinoma. One case died of cancer 2.2 years after the procedure while 2 cases were alive with no evidence of recurrence and metastasis for more than 2.5 years (5.8 years, 2.6 years). 56 patients (8.9%) were asymptomatic and showed no evidence of malignant transformation.

Conclusion: This study revealed that close follow-up in patients with branch duct type of intraductal papillary mucinous neoplasm (BD-IPMN), even if smaller than 30 mm in diameter and no symptoms or mural nodules, should be recommended.

PIL-113 Abstract id: 258.
Prospective validation of microRNA signatures for detecting pancreatic malignant transformation in endoscopic-ultrasound guided fine-needle aspiration biopsies
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Introduction: Pancreatic ductal adenocarcinoma (PDAC) is a devastating disease, despite advances in imaging and surgical techniques, and a greater understanding of its molecular biology. Enhancing early detection and the development of novel methods of differentiating benign from malignant pancreatic disease should aid treatment decisions and improve patient outcomes. microRNAs (miRNAs) are potentially ideal diagnostic biomarkers, as they are tumor and tissue specific and are incredibly stable molecules. However many candidates are yet to be clinically validated.

Aims: The aim of this study was to prospectively assess the role of cancer-specific miRNAs in the detection of pancreatic malignancy in endoscopic-ultrasound fine-needle aspirates (EUS-FNAs).

Patients & methods: Between 2010-2011, 55 patients with a suspicious pancreatic lesion on cross-sectional imaging were referred for EUS-FNA evaluation. At endosonography, the first part of the FNA was sent for cytological assessment and the second part was placed directly into Trizol reagent for total RNA extraction. Eight miRNAs (miR-21, miR-155, miR-135b, miR-24, miR-210, miR-196a, miR-217 and miR-10b) were selected after careful review of the literature. miRNA expression was measured by qRT–PCR using Taqman assays.

Results: A 2-miRNA classifier (miR-21/miR-10b) was found to discriminate benign from malignant pancreatic lesions most accurately, with a sensitivity of 82.6% and specificity of 92% (area under curve 0.838).

Conclusion: We provide further evidence for the use of miRNAs as diagnostic biomarkers for PDAC. This study demonstrates the feasibility of using fresh EUS-FNAs to establish miRNA-based signatures unique to pancreatic malignant transformation with the potential future application for risk stratification and patient selection.

PII-115 Abstract id: 313.
Comparison of preoperative CT-based and intraoperative pancreatic risk assessment in predicting pancreatic fistula after pancreatoduodenectomy
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Introduction: Postoperative pancreatic fistula (POPF) remains the predominant cause of morbidity after pancreatoduodenectomy (PD). As previously shown, intraoperative evaluation of pancreatic texture and main pancreatic duct (MPD) size provides a reliable measure of risk for clinically relevant POPF (ISPGF grade-B/C (Ansorge Br. J.Surg 2012). Likewise, the preoperative CT-based determination of the remaining gland volume and MPD diameter can reliably predict the risk of POPF (Frozanpor WJS 2012).

Aims: To evaluate the predictive value of preoperative radiological features compared to intraoperative risk estimation for the development of clinically relevant POPF.

Patients & methods: In all 296 consecutive PDs at Karolinska University Hospital that had undergone preoperative CT determination of residual gland volume and MPD diameter were included. In 216 of these patients, a standardized intraoperative assessment of gland texture and MPD size were done. Both the preoperative and intraoperative risk assessments were conducted in three POPF-risk groups: low, intermediate and high risk. The risk estimates were calculated as OR (confidence interval-Cl).

Results: Results of the radiological arm exhibits: low risk 4.3% (OR 7.5; CI 3.1-18, p<0.001), intermediate risk 22% (OR 2.4; CI 1.2-4.5, p<0.001), high risk 41% (OR 5.0; CI 2.2-11, p<0.001). Results of the intraoperative risk assessment arm exhibits: low risk: 4.8% (OR 8.6; CI 3.4-22, p<0.001), intermediate risk 26% (OR 2.7; CI 1.3-5.7, p<0.01), high risk 39% (OR 4.7; CI 2.0-11, p<0.001).

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PII-114 Abstract id: 255.
Molecular and immunohistochemical subtyping of pancreatic ductal adenocarcinoma (PDAC): A step towards personalized treatment and individual prognosis
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Aims: To provide further evidence for the use of miRNAs as diagnostic biomarkers for PDAC. This study demonstrates the feasibility of using fresh EUS-FNAs to establish miRNA-based signatures unique to pancreatic malignant transformation with the potential future application for risk stratification and patient selection.

Materials & methods: Surgical resection material and detailed clinical data of 100 PDAC patients were collected. Conventional histomorphological analyses and immunohistochemistry for p53, SMAD4 and p16 were performed. Mutation analysis of KRAS (exon 2 and 3) was performed by combination of real-time polymerase chain reaction and direct sequencing. Results: KRAS mutations were identified in 88% of patients (76/86; 79% exon 2, 10% exon 3). Immunohistochemical loss of SMAD4 and p16 expression was identified in 40% (36/88) and 57% (48/84), respectively. Strong nuclear accumulation of p53 was detected in 51% (45/88). Most patients carried alterations in three or two genes (37% each; alterations in four genes: 10%, one gene: 8%).

Conclusion: Molecular alterations in key tumor suppressor and oncogenes (KRAS, CDKN2/p16, TP53 and SMAD4) are common in PDAC. Correlation with clinical outcome will provide further information about molecular subtypes with prognostic relevance.

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Conclusion: The preoperative CT-based risk assessment and the intraoperative assessment done by experienced pancreatic surgeons had comparable POPF-predictive impacts.

PII-117 Abstract id: 130.
Change in attitudes of surgical leaders regarding a national concentration of Whipples
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Introduction: In 1990-94, we found in a nationwide survey in Finland based on individual patient records that hospital mortality and re-operations were independently associated with annual hospital volumes. After that we have repeatedly promoted the centralization of Whipples.

Aims: To analyze current attitudes of surgical leaders, the centralization and the national results of Whipples.

Materials & methods: The same questionnaire was send to all surgical leaders in the country in 2002 and 2012. Whipples and hospital mortalities in different hospitals were searched from national databases in 2000-2001 and 2010-2011 and compared to the earlier results.

Results: 93% of the surgical chiefs in 2002, compared to 100% in 2012 were aware about the international results. 75% compared to 77% were aware about the similar national results. Centralization to all or only few university hospitals increased popularity in the attitudes (69% vs. 96%; p<0.05). Centralization has occurred slowly in Finland, with low nationwide hospital mortality (1990-1994 10%, 2001-10 4%, 2010-11 3%). Hospital mortality has remained lowest in the highest volume hospitals. Hospital mortality in volume >10/yr hospitals was 2%, 2% and 4% (in 1990-1994, 2001-10 and 2010-11) compared to 13%, 8% and 5% in volume <5/yr hospitals. The 150 annual operations in 2010-11 were performed in 14 hospitals (compared to 24 hospitals for 110 annual operations in 2000-2001 and 33 hospitals for 70 annual operations in 1990-94). In 2011, 55% of the operations were performed in two hospitals.

Conclusion: Despite good knowledge of benefits and favorable attitude in questionnaires, national centralization is a very slow process in a large European country with sparse population.

PII-118 Abstract id: 193.
Bleeding following pancreatic fistula is the leading cause for early mortality after pancreatic resections
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Introduction: High volume centers today report <5% so called 30-day or sometimes “in-hospital” mortality. However, the true post-operative mortality rate may be obscured by long hospital stays, late readmissions due to complications, or when patients are transferred to other institutions.

Aims: The aim was to evaluate 90-day postoperative mortality and underlying cause of death.

Patients & methods: All patients undergone pancreatic resection between 2004-11 (n=601) were retrieved from our prospective register: 433 pancreaticoduodenectomies (PD), 113 distal (DP), and 55 total pancreatectomies (TP). Dates of death were retrieved from the Swedish population registry and the cause of death retrospectively analyzed from hospital records.

Results: In total 27 patients (4.5%) died after pancreatic resections within 90 days. According to type of resection the 30-, 60- and 90-day mortality was 3.0%, 3.2%, and 3.5% respectively after PD, 0.9%, 2.7%, 3.5% after DP, and 7.2% after TP. Of 23 patients dying within 90 days after partial resection, 18 (78%) had a postoperative pancreatic fistula (POPF), and in 12 (67%) of these an intraabdominal and/or gastrointestinal bleeding was the cause of death. Bleeding as the cause of death without POPF was observed in 2 out of 9 patients (22%).

Conclusion: POPF is the leading cause of death, mainly due to secondary fatal bleeding. Efforts to decrease the incidence of POPF and to early diagnose and intervene on signs of bleeding are essential to decrease mortality after pancreatic surgery.

Is the pancreaticoduodenectomy for cancer in cirrhotic patients reasonable? Case-control study from the Surgical French Association report for pancreatic surgery 2010
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Introduction: The pancreaticoduodenectomy (PD) is the efficient treatment to obtain long-term survival for adenocarcinoma of the pancreatic head (APH). The presence of cirrhosis is usually considered a contraindication for surgery based on old data.

Aims: The objective of this study was to evaluate postoperative outcomes of PD for APH in cirrhotic patients compared to non cirrhotic.

Materials & methods: It was a French retrospective multicenter study in patients with APH with cirrhosis during the period from January 2004 to March 2012. Matching on demographic criteria in 2:1 with patients with APH but non-cirrhotic from Surgical French Association report 2010 was conducted in a selection of 1886 patients. We compared these 2 groups in terms of postoperative morbidity and mortality, specific and non-specific complications, and the overall survival rate.

Results: 32 cirrhotic patients were matched with 64 non-cirrhotic patients. Mean age was 62.1 years. 81.2% of patients in the cirrhosis were Child A. The overall complication rate was respectively 84.3% vs. 40.6% (p<0.001). The pancreatic fistula rate was 9.3% vs. 6.2% (NS). Fifteen patients developed specific complication of cirrhosis (46.8%) including 5 liver decompensation. The postoperative mortality rate was 15.6% vs. 4.7% (NS). The major complication rate (Clavien ≥3) was 50% vs. 22.2% (p<0.05). The recurrence rate was 28.1% vs. 48% (NS). Mean follow-up was 13.8 vs. 13 months (NS). Mean overall survival was 24 vs. 23 months (NS).

Conclusion: PD for APH in cirrhotic patients is feasible, but with an increased risk of complications not specific to pancreatic surgery, but to cirrhosis.

PII-120 Abstract id: 285.
Pylorus resection in partial pancreatic-duodenectomy: Impact on delayed gastric emptying
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Introduction: Partial pancreatic-duodenectomy (PD) as the standard treatment for pancreatic head pathologies is complicated by postoperative delayed gastric emptying (DGE) in up to 45% of all patients.
**Aims:** Aim of the study was to evaluate the impact of pylorus resection on DGE following PD.

**Patients & methods:** 40 consecutive patients undergoing PD were treated with resection of the pylorus under complete preservation of the stomach (prPD). They were compared with a pair-matched control group treated with resection of the pylorus under complete preservation of the stomach (ppPD) as the current surgical standard in a 1:1 ratio (age, gender, histopathology). Objectives were operative parameters, incidence of DGE, morbidity and length of hospital stay.

**Results:** Overall DGE incidence was significantly lower after prPD (15.0% vs. 42.5%, p=0.0066) with DGE grade A 7.5% vs. 20%, grade B 5.0% vs. 12.5% and grade C 2.5% vs. 10%. Operative parameters (blood loss, operation time) and surgical morbidity (other than DGE) were not different between the groups (27.5% prPD vs. 30.0% ppPD, p=1.000). There was a trend towards a shorter hospital stay in the prPD group compared to the ppPD group.

**Conclusion:** Resection of the pylorus with stomach preservation significantly reduces the frequency of DGE after PD without showing any disadvantage compared to standard ppPD. This finding could be of high relevance for the clinical practice in routine PD and should consequently be investigated in a large randomized multicenter trial to create further evidence.

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**Abstract:**

**P11-121 Abstract id: 142.**

**Postoperative recurrence in patients operated on for benign intraductal papillary mucinous neoplasms (IPMN)**

**Olivier Roux, Marie-Pierre Vuillerme, Jérôme Cros, Sofi Dokmak, Sebastien Gaujoux, Beatrice Assilhou, Vinciane Rebours, Olivia Henic-Dhomme, Frédérique Maire, Maxime Palazzo, Laurent Palazzo, Alain Aubert, Anne Couvelard, Alain Sauvanet, Pascal Hammel, Philippe Ruszniewski, Philippe Levy.**

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**Introduction:** Risk of postoperative recurrence in patients operated on for exclusively benign IPMN has not been extensively studied. Published studies mixed benign and invasive type, and data did not distinguish true recurrence from lesions left in place.

**Aims:** To evaluate the recurrence rate of IPMN after partial pancreatectomy for benign IPMN and to assess the need for reoperation.

**Patients & methods:** Data were collected for patients operated on in a single centre between 1998 and 2008. Recurrence of IPMN was evaluated on MRI performed during follow-up. Recurrence was defined as new cystic lesions communicating with main pancreatic duct. The evolution of IPMN cysts not resected during surgery was documented.

**Results:** 125 patients (63 males, median age 60 (20-77) years, low, moderate, high grade dysplasia in 47, 43 and 35 pts, respectively) were included. IPMN involved branch ducts (n=69), main pancreatic duct (n=5) or mixed-type (n=51). Median postoperative follow-up was 4(2-13) years. 83 pts had no residual lesion (group 1, median F/U: 4yrs (2-13)), while 42 had some residual lesions deliberately left in place (group 2, median F/U: 4 yrs (2-8)). 3 recurrences were observed in Group 1, all of them were invasive leading to total pancreatectomy. In group 2, no new lesion occurred ≥ 1 changes in persistent lesions were observed in 5 pts (0 invasive) leading to total pancreatectomy indication.

**Conclusion:** Postoperative relapse rate of benign IPMN is low (3.6%) after a 4-year F/U. Occurrence of invasive recurrence warrants carefull F/U in all operable patients. Residual lesions should be followed like de novo IPMN.

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**Abstract:**

**P11-122 Abstract id: 190.**

**Distal pancreatectomy in Italy: Results of a multicenter survey**


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**Introduction:** No data are available about distal pancreatectomy in Italy, regarding homogeneity of care among centers, or diffusion and results of minimally invasive distal pancreatectomy (MIDP).

**Aims:** To investigate current practice for DP in Italy.

**Patients & methods:** A survey was conducted among 20 institutions by the Italian Association for Study of Pancreas (AISP). Centers were asked to fill in two questionnaires about: 1. perioperative protocols for DP; 2. operative results of MIDP in the period 2010-2011.

**Results:** 1. Variability in clinical practice was observed among centers. Octreotide was used in 46% of centers, enzyme supplementation in 35%, nasogastric decompression in 85%, oral liquids on day 1 in 63%. All hospitals used at least one drain, removed between day 3-5 in absence of fistula. In case of splenectomy variability in type and timing of vaccinations was recorded.

2. In 2011-2012 18/20 centers performed at least one MIDP, accounting for overall 179 patients (148 laparoscopic, 31 robotic). Among different centers MIDP rate ranged between 0-51%. Overall MIDP rate doubled from 2007(15%) to 2011(28%). Main contraindications for MIDP were: organ invasion (83%), malignancy (33%), diameter>=5cm (28%); previous surgery (28%). Conversion rate was 16%. Mean operative time was 231 minutes, blood loss 288 ml. Morbidity was 57%, with 5% relaparotomy rate. Pancreatic fistula occurred in 51% (grade A 35%, B 16%). Mean postoperative stay was 9.9 days with 8% readmission rate.

**Conclusion:** There is a marked variability in clinical practice among Italian centers. MIDP is becoming more popular, but postoperative stay is longer than expected.

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**Abstract:**

**P11-123 Abstract id: 90.**

**Resection of locally advanced pancreatic cancer after neoadjuvant chemotherapy with modified FOLFIRINOX: A prospective phase II study**

Nelide De Lio 1, Enrico Vasile 2, Mario Antonio Belluomini 1, Francesca Costa 1, Carla Cappelli 1, Daniela Campani 1, Alfredo Falcone 2, Ugo Boggi 1.

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EPD become more simple modality of pseudocyst drainage. Excluding the intra cystic mass, and cystic wall vessels. Applying SEMS using doppler echo effect ideal puncture site could be localising by well known method to distinguish malignant formations. In caeses of EPD pancreas neoplasm were the cytological diagnosis. In other cases were found in several cases mostly females (60-75 yrs), were operated on. or because of septal structure of the pseudocyst. Mucinous cystadenoma cysts were not drained, because of small diameter in 15 cases (2-3,5 cm) fluid were only punctured for diagnostic goals. Neend biopsy and aspiration is a self expanded metal stent (SEMS) was used to emptying the pseudocyst (7 and/or 10 F) throw the gastric wall, using endosonography. In one case pseudocysts were drainaged with double pigtail endocystic plastic drain went throught on ERCP to exclude major ductal leakage. In 14 caeses the endoscopic pseudocysts drainage (EPD) were performed. Most of the cases by echoendoscop, 221 of them for pancreatic laesions. In 15 cases endo-

**Introduction:** 20% of the patients have a primary-resectable pancreatic ductal adenocarcinoma (PDAC), in 30-40% surgery is denied because of local tumor growth, in the absence of metastasis. These patients could be still be considered for resection, if responsive to neoadjuvant chemotheraphy (NACT).

Aims: We report the results of a phase-II-clinical-trial, coupling high-dose-multi-drug-NACT with aggressive surgery.

**Patients & methods:** All patients enrolled were selected by a multi-disciplinary workgroup. Selection criteria: stage-III-locally-advanced-PDAC (suspected arterial involvement), ECOG PS 0-1, age 18-75 years. A modified-FOlRIFIRINOX regimen was used. Tumor response was evaluated according to RECIST. The opportunity to add a local treatment, either surgery or radiation-therapy, was evaluated after every CT follow-up.

**Results:** Between 11/2010-11/2012, 26 patients (mean age 59 years) were enrolled: 9/26 celiac axis involvement, 11/26 superior mesenteric artery, 6/26 celiac axis and superior mesenteric artery. 9 had a partial response (34%), 15 stable disease, 2 progressed. 14/26 underwent to surgery, 11/26 to resection with curative intent (47.8%): 2 pancreaticoduodenectomy, 9 total-splenopancreatectomy.

Mean-operative time was 618 minutes. In hospital-mortality was 9%, overall-postoperative-morbidity 62%, surgical morbidity 12%, medical morbidity 50%. Mean-hospital-stay was 26 days. 11/11 were R0. Resected-lymph-nodes-mean-number was 67, nodal-metastasis-mean-number 4. 12% of resected venous segments and 33% of resected arterial segments weren’t involved on histology. Overall-progression-free-survival was 17.6 months, resected-patient-progression-free-survival 17.8, out-of-surgery-patient-progression-free-survival 10.3, median-overall-survival 24 months.

**Conclusion:** The modified-FOlRIFIRINOX protocol in PDAC allows extended resection in a relevant percentage of stage-III-PDAC with results comparable to those in primary-resectable-patients. New data from further studies are needed before any final conclusion may be drawn.

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**PII-125 Abstract id: 292.**

Comparison of chemoradiotherapy (CRT) and chemotherapy (CT) in patients with locally advanced pancreatic cancer (LAPC) controlled after 4 months of gemcitabine with or without erlotinib: Final results of the international phase III LAP 07 study

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**Background:** In patients with LAPC controlled with CT, CRT could be superior to continuing CT (Huguet, JCO 2007). The role of erlotinib is unknown.

Aim: To define: the role of 1) CRT after disease control with gemcitabine and 2) role of erlotinib in LAPC.

**Patients & methods:** LAPC PS 0-2 patients, 1st randomization: gemcitabine +/- erlotinib 100 mg/d for 4 months (R1, stratification: center, PS). 2d randomization: patients with controlled LAPC had 2 additional months of CT (Arm 1) or CRT (Arm 2) 54 Gy and capecitabine 1600 mg/m^2/d (R2, stratification: center, initial arm). Patients receiving erlotinib at R1 had maintenance therapy. Quality control for RT: dummy runs (assessment of treated patients, Primary objective: overall survival (OS) in R2 patients. Secondary objectives: role of erlotinib on OS (R1), tolerance, predictive markers. 722 patients required to observe 392 deaths to show a median OS increase from 9 to 12 m (HR=0.75) in the CRT arm with planned interim analyses. Kaplan-Meier, log rank and univariate Cox tests were used.

**Results:** From 442 pts included for R1, 269 pts reached R2 (arm1:136; arm 2:133). Main baseline characteristics in arms 1/2: female 44%/56%, mean age 63/62, head tumor 65%/62%, PS 0 56%/48%. After a median follow-up of 36 m, 221 deaths had occurred allowing the planned interim analysis. OS in R2 pts was 16.5 m [15.5-18.5] and 15.3 m [13.9-17.3] in arms 1 and 2, respectively (HR=1.03 [0.79-1.34], p=0.83). IDMC has confirmed that the futility boundary for the hypothesis of CRT superiority was crossed.

**Conclusion:** Administering CRT is not superior to continuing CT in patients with controlled LAPC after 4 months of CT.

Symposium Presentations

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**Symposium on Pancreatic Regeneration and Repair**

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**S-1 Abstract id: 83.**

Sirtuin-1 regulates acinar to ductal metaplasia and supports cancer cell viability in pancreatic cancer


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Introduction: The exocrine pancreas can undergo acinar to ductal metaplasia (ADM). ADM occurs in pancreatitis and can generate precursor lesions of pancreatic ductal adenocarcinoma (PDAC). Sirtuin 1 (Sirt1), a protein deacetylase, is an important regulator in cancer.

Aims: We aim to study the expression and the role of Sirt1 in different stages of pancreatic carcinogenesis. In addition, we analyse the expression of Sirt1’s key inhibitor Deleted in Breast Cancer 1 (Dbc1) and potential down stream targets.

Materials & methods: We analysed pancreatic samples from mouse models and patient tumours by immunostainings, Western Blot and real time RT-PCR. We used mouse ADM models and established human PDAC cells to manipulate Sirt1’s expression and activity.

Results: Sirt1 is co-expressed with Dbc1 in nuclei of normal acinar cells and loss of Sirt1 in normal pancreas has no apparent effects. In ADM however, Sirt1 but not Dbc1 undergoes a transient cytoplasmic shuttling, suggestive of a temporary decreased nuclear and increased cytoplasmic Sirt1 activity. Our observations indicate that this contributes to the ADM process.

In addition to suppressive effects of a Sirtuin inhibitor on ADM, we also found that interference with Sirt1’s expression or application of an inhibitor in PDAC tumours results in loss of cell viability. In addition, we show that in PDAC, Dbc1 expression is differentially down regulated and the sensitivity of a panel of PDAC cell lines to a Sirt1 inhibitor correlates with Sirt1/Dbc1 expression.

Conclusion: This is the first study to show that Sirt1 is a critical regulator and potential therapeutic target throughout pancreatic carcinogenesis.

S-2 Abstract id: 149.

Combined pharmacological inhibition of Notch and JAK/STAT pathways effectively suppresses conversion from acinar-ductal metaplasia to pancreatic ductal adenocarcinoma and is superior to monotherapy

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2 Institute of Pathology, University of Tuebingen, Germany

Introduction: Pancreatic ductal adenocarcinoma (PDAC) is an aggressive disease with a high rate of metastasis. Recent studies have indicated that Notch and JAK2/STAT3 signaling pathways are both important for the initiation and progression of PDAC.

Aims: The purpose of this study was to determine the outcome of targeting these two tumor signaling pathways simultaneously both in vitro and in vivo.

Materials & methods: We assessed the combinational effects of the g-secretase inhibitor IX (GSI IX) and JAK2 inhibitor (AG-490) on growth and epithelial plasticity of human pancreatic cancer cell lines, and in a genetically engineered mouse model (Pdx1-Cre; LSL-KrasG12D; p53 fl/fl) of PDAC.

Results: Dual treatment with GSI IX and AG-490 significantly impaired cell proliferation, migration, invasion, soft agar growth and apoptosis when compared to monotherapies. Notably, inhibition of Hes1 down regulated phosphorylation of STAT3 and reflects a synergistic effect. Most importantly, combinational treatment significantly attenuates tumor progression in vivo and suppresses conversion from acinar-ductal-meta-plasia (ADM) to PDAC.

Conclusion: Our results suggest that targeting Notch and JAK2/STAT3 signaling pathways simultaneously is superior to single inhibitions, supporting combined treatment by GSI X and AG-490 as a potential therapeutic approach for PDAC.

S-4 Abstract id: 231.

Antidromic NFATc1 and p53 signaling at the edge of differentiation and stemness in pancreatic cancer


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Introduction: The current concept suggests a direct link between EMT and stemness induction in pancreatic cancer, thereby coupling cell motility and de-differentiation with self-renewal capacities and drug resistance. Both key features of cellular plasticity are controlled by distinct intracellular signaling and transcription pathways. We have shown that NFATc1 activation promotes PDAC and metastasis through its ability to integrate extrinsic stimuli into coordinated gene regulation.

Aims: To assess whether NFATc1 controls transcription of EMT genes and stemness in PDAC, particularly upon p53 inactivation.

Patients & methods: We generated mouse strains with combined pancreas-specific expression of NFATc1, p53 fl/fl and KrasG12D. These mice showed a highly aggressive tumor growth. Mouse primary tumour cells were used to identify NFATc1 targets by gene expression profiling and pathway analyses (ChIP seq, miRNA analyses and GSEA). NFATc1 mediated...
EMT and stemness were assessed in human and murine pancreatic cancer models using migration/invasion and spheroid assay.

**Results:** Here, we identified antidiromic NFATc1 and p53 transcriptional network control over EMT and stemness. We show that p53 activation prevents cells from EMT in a miR200c dependent manner. However, disruption of the tumor suppressor pathway enables NFATc1/Sox2 chro-matin complex formation and transcription of EMT programmes, resulting in highly invasive and metastatic PDACs. Finally, re-expression of miR200c or NFATc1 inactivation suppresses EMT/stemness genes and re-sensitizes PDAC to chemotherapy.

**Conclusion:** Antidiromic NFATc1 and p53 signaling pathways control key features of cellular plasticity and tumor progression at the level of gene transcription. These findings implicate key roles for NFATc1 in transcriptional regulation of differentiation and self-renewal in PDAC.

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**S-5 Abstract id: 247.**

Serotonin regulates progenitor cell-based but not clonal regeneration in the adult pancreatic acinar cell

Enrica Saponara, Sabrina Sonda, Kamile Grabliauskaite, Theresia Reding, Rolf Graf.

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**Introduction:** Progenitor cell-based regeneration of acinar cells is activated during cerulein-induced pancreatitis. This process requires acinar de-differentiation via secretion of zymogen content, followed by expression of progenitor cell markers and formation of acinar-to-ductal metaplasia (ADM). Clonal regeneration without loss of zymogen content and cell de-differentiation is observed following 60% pancreatectomy.

**Aims:** We previously showed that serotonin (5-HT) is essential for acinar cell secretion with a strong impact on the pathophysiology of acute pancreatitis; we now investigate the role of 5-HT in pancreatic regeneration.

**Patients & methods:** Cerulein-induced pancreatitis and 60% pancreatectomy were performed in wild type (WT) and tryptophan hydroxylase-1 knock-out (TPH1−/−) mice, with reduced peripheral levels of 5-HT. The regenerative potential of pancreatic acinar cells was evaluated in vivo, over a period of two weeks.

**Results:** After experimental pancreatitis, WT mice showed an early up-regulation of 5-HT2A/5-HT2B receptors, amylase secretion and progenitor cell marker expression, indicative of acinar de-differentiation. These events were followed by the appearance of ADM lesions and acinar cell proliferation. Conversely, in TPH1−/− mice these early parameters were blunted and consequent formation of ADM and proliferation of acinar cells were inhibited. After 60% pancreatectomy, clonal regeneration of differentiated acinar cell was comparable in the two strains. Similarly to what was observed in vivo, 5-HT2A/5-HT2B receptor agonist promoted proliferation only in de-differentiated but not in dexamethasone-differentiated AR42J cells.

**Conclusion:** Our results indicate that 5-HT, likely via 5-HT2A/5-HT2B receptors, modulates progenitor cell-based but not clonal regeneration. Current investigations aim to elucidate the role of 5-HT in pancreatic proliferation induced by primary mitogen administration.

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**S-6 Abstract id: 19.**

Effect of cystathionine-gamma-lyase gene deletion in caerulein-induced acute pancreatitis in the mouse

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**Introduction:** Hydrogen sulfide (H2S) has been reported to be involved in the signaling of the inflammatory response; however there are differing views as to whether it is pro- or anti-inflammatory.

**Aims:** The present study was aimed to investigate if endogenously synthesized H2S via cystathionine-γ-lyase (CSE) plays a pro- or anti-inflammatory role in caerulein-induced acute pancreatitis

**Materials & methods:** Acute Pancreatitis was induced in CSE knockout (CSE−/−) and wildtype (CSE+/+) mice by hourly caerulein injections (50 µg/kg) for 10 hours. Mice were sacrificed 1 hour after the last caerulein injection. Blood, pancreas and lung tissues were collected and processed to measure the plasma amylase, plasma H2S, myeloperoxidase (MPO) activities and prostaglandin E2 and cytokine levels in pancreas and lung.

**Results:** CSE−/− mice showed significantly less local pancreatic damage as well as acute pancreatitis-associated lung injury in comparison to the CSE+/+ mice. There were also lower levels of pancreatic eicosanoid and chemokines in the CSE−/− mice when compared with CSE+/+ mice. Additionally, in CSE−/− mice, there was a greater level of pancreatic CSE expression and sulfide synthesizing activity in caerulein-induced when compared to the saline control. When comparing the two saline treated control groups, the CSE−/+ mice showed significantly less pancreatic H2S synthesizing activity relative to the CSE−/− mice.

**Conclusion:** These data provide evidence that endogenous H2S generated by CSE plays a key pro-inflammatory role in caerulein-induced pancreatitis and its genetic deletion affords significant protection against acute pancreatitis and associated lung injury.

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**S-7 Abstract id: 214.**

Acinar specific TGF-β signaling regulates acinar cell regenerationCategory: Basic science - chronic pancreatitis.

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Hospital Zurich, Switzerland

**Introduction:** TGF-β signaling is implicated in many pathophysiological functions of pancreatic cells, including regulation of regeneration and fibrosis. However, the function of TGF-β signaling is strongly context-dependent and an acinar cell specific role of this molecule in modulating regeneration has not been completely investigated before.

**Aims:** In this study we aim to determine the contribution of TGFβ signaling to acinar cell proliferation during pancreatitis by using mice deficient in TGFβ receptor II (TGFβRII−/−) exclusively in acinar cells.

**Materials & methods:** Pancreatitis was induced in control and PTF1-CreERT2, TGFβRII−/− mice by multiple injections of cerulein. The expression of proliferation markers, cell cycle regulators, and the severity of tissue inflammation and fibrosis were analysed by immunohistochemistry and qRT-PCR.

**Results:** Ki67 and BrdU analyses revealed increased number of proliferating acinar cells in TGFβRII−/− mice. Surprisingly, immunohistochemistry showed that expression of the cell cycle inhibitor p21/WAF1/Cip1, one of the main targets of TGFβ signaling, was comparable in WT mouse and TGFβRII−/− mice. However, the expression of the cell cycle inhibitor p16INK4a increased only in CSE−/− mice. This process requires TGF-β signaling inhibits activation of acinar cell cycle and prevents excessive ADM formation. Additionally, the loss of TGFβ signaling in acinar cells potentiates fibrogenic processes during pancreatitis, suggesting the existence of a regulatory feedback between acinar and stellate cells.

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**S-8 Abstract id: 147.**

Pancreatic stellate cells promote the hapto-migration of pancreatic cancer cells through collagen I mediated activation of alpha2beta1 integrin pathway

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**Introduction:** Pancreatic stellate cells (PSCs) mediate fibrogenic processes during pancreatitis, suggesting the existence of a regulatory feedback between acinar and stellate cells.
Introduction: Factors mediating the effects of pancreatic stellate cells (PSCs) on pancreatic cancer cells (PCCs) have not been clearly identified.

Aims: To investigate the role of PSCs in PCCs migration and to identify underlying mechanisms.

Materials & methods: Effects of conditioned PSCs supernatant (PSC-SN) and exogenous adhesive molecules on the biology of Panc1 and UlaPaCa cells were investigated by modified Boyden chamber assay, adhesion assay and single cell tracking assay, respectively. Integrin expression and focal adhesion kinase (FAK) phosphorylation were assessed by Western blot. Anti-integrin α2/β1 antibodies and FAK inhibitor (PF-573228) were used to demonstrate the involvement of collagen I.

Results: PSC-SN dose-dependently induced PCCs trans-migration, mainly by improving adhesion and motility. PSC-SN mediated adhesion was a prerequisite for the stimulation on PCCs migration. As pure chemokines, PSC-SN was not sufficient to stimulate the trans-migration or motility of PCCs. In contrast to poly-L-lysine or fibronectin, collagen I alone showed resembling effects to PSC-SN on PCCs, including polarized morphology, facilitated adhesion, accelerated motility and trans-migration. Both PSC-SN and collagen I induced haptokinesis of Panc1 and haptotaxis of UlaPaCa. Anti-integrin α2/β1 antibodies attenuated PSC-SN/collagen I-induced PCCs trans-migration and adhesion. PSC-SN or collagen I constantly enhanced FAK phosphorylation (Tyr397) in PCCs. PF-573228 diminished PSC-SN/collagen I-induced PCCs haptotaxis/haptokinesis.

Conclusion: Collagen I is the major mediator for PSC-SN induced hapto-migration of PCCs. Through collagen I binding to integrin α2β1 on PCCs, FAK signaling pathway is initiated.

Introduction: ATP is an extracellular signal released from all cells, including pancreatic acini. Released ATP may stimulate the surrounding pancreatic stellate cells (PSC).

Aims: Our aim was to characterize whether pancreatitis-associated stimuli induce ATP release from acini and investigate the importance of ATP in regulating proliferation of PSCs.

Materials & methods: Mouse acini and AR42J cells were studied and ATP release was detected with luciferase kit. PSCs were isolated from WT and the Pfizer P2X7 KO mouse using a selective attachment method. Proliferation was monitored with BrdU incorporation.

Results: The potential pathophysiological stimuli such as mechanical stress, hypotonicity and the bile acid chenodeoxycholate (CDC) all induced ATP release from acini. Alcohol, however, did not. CDC (1 mM) induced significant ATP release up to 20.4±7.4 nM/10^6 cells/ml. Basal ATP release supported PSC proliferation, as it was inhibited by apyrase, an ATP/ADP hydrolytic enzyme. The proliferation rate was lower in P2X7 KO PSCs compared to WT cells. Also the PSC number from P2X7 KO pancreas was 50% lower than from WT ones. Exogenous ATP further stimulated proliferation in a concentration-dependent and 100 μM gave max stimulation. ATP in mM concentration was lethal to PSCs, and this effect was absent in P2X7 KO PSC. Basal/stimulated proliferation and cell death could all be inhibited with the P2X7 antagonists.

Conclusion: Together, the study shows that ATP release and purinergic signalling should be considered as important factors in pathophysiological processes in pancreas. Importantly, ATP and P2X7 receptors are regulators of PSC proliferation and death, and could be potential targets in pathologies involving pancreatic fibrosis.
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